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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF ALAMEDA

COORDINATED PROCEEDINGS SPECIAL TITLE [RULE 3.550], ESSURE PRODUCTS CASES	JUDICIAL COUNCIL COORDINATION PROCEEDINGS No. 4887 ASSIGNED FOR ALL PURPOSES TO: Judge Winifred Y. Smith, Dept. 21
THIS DOCUMENT RELATES TO: *Macias, et al. v. Bayer Corp., et al.* Riverside Super. Ct., No. RIC171556 (regarding Plaintiff Katie Elder only) *Aispuro, et al. v. Bayer Corp., et al.* San Bernadino Super. Ct., No. CIVDS1716459 (regarding Plaintiff Summer Frost only) *Martinez, et al. v. Bayer Corp., et al.*, Los Angeles Super. Ct., No. BC662859 (regarding Plaintiff Valerie George only) *David, et al. v. Bayer Corp., et al.* San Bernadino Super. Ct., No. CIVDS1717506 (regarding Plaintiff Tathiana Gibeau only) *Dorsey, et al. v. Bayer Corp., et al.* Los Angeles Super. Ct., No. BC626412 (regarding Plaintiff Dena Sheldon only) *Quick, et al. v. Bayer Corp., et al.* Sacramento Super. Ct., No. 34-2017-00217315 (regarding Plaintiff Stefanie Trujillo only)	**DECLARATION OF ALYCIA A. DEGEN IN SUPPORT OF DEFENDANTS' MOTION TO EXCLUDE TESTIMONY OF DR. KIMBER C. RICHTER ON *SARGON* GROUNDS** [Filed concurrently with Motion to Exclude Testimony of Dr. Kimber C. Richter] Reservation ID: No reservation ID needed. Date: January 15-16, 2020 Time: 9:00 a.m. Place: Administrative Building 1221 Oak Street, Dept. 21 Oakland, California 94612 Judge: Winifred Y. Smith

Boyd, et al. v. Bayer Corp., et al.
Los Angeles Superior Court, Case No. BC676503
(regarding Plaintiff Shandra Walker only)

DECLARATION OF ALYCIA A. DEGEN

I, Alycia A. Degen, hereby declare as follows:

I am an attorney licensed to practice law in all the courts of the State of California. I am a partner with the law firm of Sidley Austin LLP, counsel of record for defendants and specially appearing defendants Bayer Corporation, Bayer HealthCare LLC, Bayer HealthCare Pharmaceuticals Inc., and Bayer Essure Inc. (collectively, "Bayer") in these coordinated proceedings, JCCP No. 4887, including the case listed in the caption to this declaration. This declaration is submitted in support of Defendants' Motion to Exclude Testimony of Dr. Kimber C. Richter on *Sargon* Grounds. The facts set forth in this declaration are within my personal knowledge. If called as a witness, I could and would competently testify as follows.

1. Attached hereto as **Exhibit A** is a true and correct copy of the Expert Report of Kimber C. Richter, M.D., served on Defendants on October 4, 2019.

2. Attached hereto as **Exhibit B** is a true and correct copy of certain excerpts from the certified transcript of the deposition of Kimber C. Richter, M.D., taken on October 16, 2019.

3. Attached hereto as **Exhibit C** is a true and correct copy of the Expert Report of Mary Weick-Brady, MSN, RN, served on Plaintiffs on October 4, 2019.

4. Attached hereto as **Exhibit D** is a true and correct copy of the United States Food and Drug Administration's *Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization: Guidance for Industry and Food and Drug Administration Staff*, dated October 31, 2016 and publicly available from FDA's website at https://www.fda.gov/media/96315/download.

5. Attached hereto as **Exhibit E** is a true and correct copy of the official transcript of the September 24, 2015 meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to the United States Food and Drug Administration, publicly available online at https://wayback.archive-it.org/7993/20170722212955/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM467456.pdf.

6. Attached hereto as **Exhibit F** is a true and correct copy of the Essure Problems' *For Immediate Release – January 12, 2015* web page, downloaded as it appeared on November 14, 2019 at https://essureproblems.webs.com/press-release-1-12-15.

7. Attached hereto as **Exhibit G** is a true and correct copy of the United States Food and Drug Administration's *FDA Review Document: Review of the Essure System for Hysteroscopic Sterilization*, dated September 24, 2015, and publicly available online at https://wayback.archive-it.org/7993/20170112002002/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM463486.pdf.

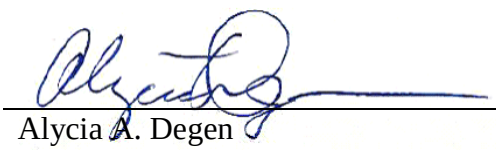
8. Attached hereto as **Exhibit H** are true and correct copies of all twenty-six slides of a presentation titled *Essure Problems: Utilizing Facebook and Mobile Apps in Pharmacovigilance*, posted online by Epidemico on August 27, 2015, and downloaded as they appeared on November 14, 2019 at https://www.slideshare.net/epidemico/essure-problems-utilizing-facebook-and-mobile-apps-in-pharmacovigilance.

9. Attached hereto as **Exhibit I** is a true and correct copy of a document produced by Plaintiffs in this litigation at Bates numbers ESSURE_JCCP_PLS00111262 through _PLS00111265.

10. Attached hereto as **Exhibit J** is a true and correct copy of the United States Food and Drug Administration's *FDA Activities: Essure* webpage, downloaded as it appeared on January 11, 2017 at https://wayback.archive-it.org/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452254.htm.

11. Attached hereto as **Exhibit K** is a true and correct copy of Essure Problems' *Call with the FDA 2-7-14* webpage, downloaded as it appeared on November 21, 2019 at https://essureproblems.webs.com/call-with-the-fda-2-7-14.

Executed on this 22nd day of November, 2019, at Los Angeles, California.



Alycia A. Degen

EXHIBIT A

KIMBER C. RICHTER, M.D.,

EXPERT REPORT

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I. QUALIFICATIONS

Kimber C. Richter, M.D.

I received my medical degree from the University of Cincinnati College of Medicine in 1979. As a licensed physician, I worked in industry for 15 years at firms that designed, manufactured, and sold medical devices, consumer products, drugs, and cosmetics. I advised on medical aspects of product design, safety, and marketing. I directed a clinical research facility that conducted studies assessing product safety and performance. I managed staff, wrote protocols and performed examinations. I served as a Clinical Instructor in the Department of Obstetrics and Gynecology at the Medical College of Wisconsin.

I served as the Vice President and global head of medical, safety, and regulatory affairs for a large company that sold devices for women in approximately 130 countries (Tambrands Inc.) I advised worldwide education programs and supervised consumer testing. My department handled consumer complaints and inquiries (up to 2 million one year). I made Medical Device Reporting (MDR) decisions and supervised submission of reports to FDA. I coordinated academic research programs on product issues and served as a corporate witness.

As Vice President of a large disability and life insurance company (Unum Life Insurance Company) I advised on emerging diseases and health conditions, conducted clinical assessments of claims, and guided firms in successful rehabilitation of employees. This experience provided unique insight into medical practices across the Unites States and beyond.

In 1995 I joined the Center for Devices and Radiological Health (CDRH) at the U.S. Food and Drug Administration (FDA). As a Deputy in the Office of Device Evaluation, I developed policies and processes for premarket review and served on inter-Center teams including steering committees for the Office of Women's Health. I supervised large review organizations, guided significant review decisions and led major projects.

In 2002 I transferred to the Office of Compliance, which was responsible for compliance and enforcement of device law and regulations. As Deputy for Medical Affairs, I conducted and supervised risk assessments for recalled devices and advised on recall strategies, industry letters and agency press statements. I supervised a staff of expert physicians and the Division of Bioresearch Monitoring. I evaluated emerging public health issues and potential product shortages. I represented FDA on international working groups and served on the Board of Directors of the Association for the Advancement of Medical Instrumentation (AAMI). During my tenure at FDA I developed and edited guidance documents, gave public presentations on FDA policy and practices, met with numerous firms, and sent official compliance/enforcement letters to companies and clinical investigators when appropriate.

I retired from FDA in December 2015 and have been consulting with a focus on medical devices, risk management practices, and risk assessments.

My resume with publications, and my standard fee sheet are provided in Appendix A.

II. BACKGROUND

Purpose of Assessment

The purpose of this review is to assess the post market regulatory compliance and corporate actions of Conceptus Inc. (Conceptus) and Bayer Pharmaceutical Corporation (Bayer) (collectively the "Manufacturer") with regard to the Essure System permanent contraceptive implants (Essure). Specifically, I was asked to review the Manufacturer compliance with 21 CFR §820 *et seq.* and 21 CFR § 803 *et seq.* to determine whether the Manufacturer was complying with the FDA requirements for investigating health and safety complaints that it received and whether it was complying with the attendant FDA requirements for reporting adverse events through a Medical Device Report ("MDR") filed with the FDA.

Sources of Information

This review has been conducted based on information provided by counsel as well as information I obtained independently from other sources including the FDA website. I have also considered the joint Expert Report of Anne Holland, Christine Brown and Cathy Arroyo and their analysis of the Manufacturer complaint files contained therein and I rely on that report as a basis of my opinions. A list of the documents I considered was prepared by counsel at my request and is provided in Appendix B.

Description of Product

The Essure System is a medical device that is intended to achieve permanent sterilization of women through bilateral occlusion of the fallopian tubes. It includes a permanently implantable insert and a disposable delivery system. Essure inserts are placed in both fallopian tubes through the cervix using a vaginally inserted catheter. Each insert consists of a Nitinol (nickel-titanium alloy) outer coil, a 316L stainless steel inner coil wrapped in polyethylene terephthalate (PET) fibers, platinum marker bands, and a silver-tin solder.[1] [2]

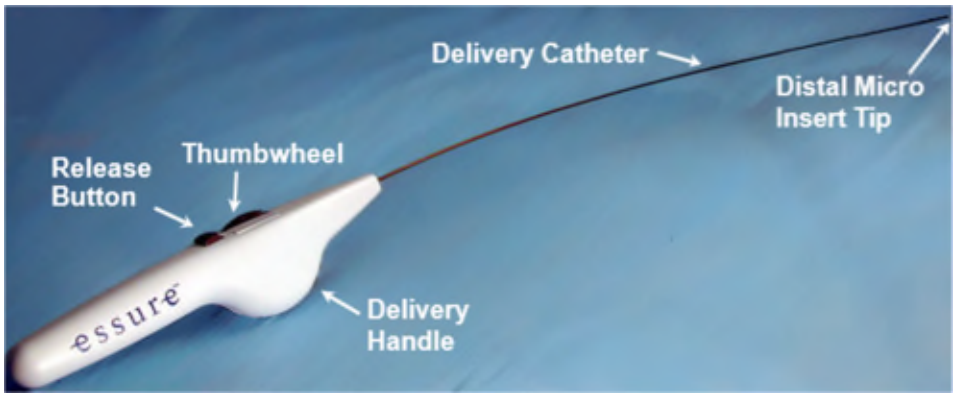
Figure 1 shows the Essure insert in a wound-down configuration attached to a release catheter. Figure 2 shows the insert after expansion. Figure 3 shows the delivery system.

Figure 1. Essure micro-insert wound-down and attached to release catheter (not to scale)[3]:

Figure 2. Essure micro-insert after expansion (not to scale):[4]

The disposable delivery system shown in Figure 3 consists of a delivery wire, a release catheter, a delivery catheter and a delivery handle. (The delivery wire and the release catheter are not visible in the diagram.)[5]

Figure 3. Delivery system for Essure micro-insert[6]



The Essure™ micro-insert comes wound down and attached to a delivery wire with a nitinol core. The device is constrained by a release catheter covered by a flexible delivery catheter. A black positioning marker on the delivery catheter aids in proper placement of the device in the fallopian tube.

The delivery handle controls the device delivery and release mechanism. The thumbwheel on the delivery handle retracts both the delivery catheter and the release catheter. The button allows the physician to change the function of the thumbwheel from retracting the delivery catheter to retracting the release catheter. The delivery wire is detached from the micro-insert by rotating the system. [7]

The intent of the Essure design is both to have the devices provide a physical barrier in the fallopian tube and to have the devices incite a localized chronic inflammatory response that causes fibrous tissue growth (like scarring) in and around the inserts. Over time, the fibrous tissue is expected to help hold the inserts in place and also block the fallopian tubes, preventing sperm from passing to reach and fertilize the eggs. It is recommended that patients have a radiologic imaging test performed three months after insertion to confirm that the Essure device is in the correct location in the fallopian tubes and that the fallopian tubes are occluded.[8] [9]

III. SUMMARY OF OPINIONS

Based on my review of the documents as well as my knowledge and experience, I have formed the opinions summarized below. They are discussed in subsequent sections of the report.

1) Medical device manufacturers, not the FDA, have primary responsibility for the quality, safety and effectiveness of their medical devices both pre-and post-marketing.

2) Medical device manufacturers are required to comply with the provisions of 21 CFR §820 *et seq.* and 21 CFR §803 *et seq.* These provisions are inextricably intertwined. 21 CFR §820 outlines the requirements for complaint handling, including intake, investigation, and documentation, plus the procedures, staffing, and training necessary to accomplish these tasks. Regulation 21 CFR 820 also requires manufacturers to evaluate complaints and determine if reporting to FDA is necessary. If so, the complaints shall be promptly reviewed, evaluated, investigated, and documented as specified. Regulation 21 CFR §803 governs the criteria for reporting complaints to FDA based on information obtained under §820 as well as the processes and timeframes for required reporting.[10] Failure to comply with the §820 requirements creates an inability for the manufacturer to make correct, complete, and prompt reporting decisions as required under §803.

3) The Manufacturer of Essure failed to comply with FDA regulations for complaint handling and adverse event reporting, including, but not limited to the provisions of 21 CFR §820 *et seq.* and 21 CFR §803 *et seq.* These failures were systemic in that they continued for almost a decade and were not simply isolated events. The Manufacturer's MDR violations reduced the number of known reportable events submitted to FDA significantly over time in at least three ways. First, the Manufacturer failed to report initially *known* events to the FDA. Second, the Manufacturer failed to adequately and/or timely investigate thousands of complaints that it had received to determine whether those complaints might potentially be reportable to the FDA. And third, the Manufacturer wholly excluded some events that came to firm attention from being processed as complaints, thereby eliminating any opportunity for investigation of reportability. To the extent the Manufacturer claims to have adequately and/or timely investigated, it failed to document and/or maintain documentation of such investigation as required by the regulations.

4) The extent of the underreporting of adverse events and malfunctions pursuant to 21 CFR §803.50 was severe. According to the statistical analysis performed by Ms. Holland, Ms. Brown and Ms. Arroyo, they identified 18.8% of complaints that should have been reported to the FDA but were not. Furthermore, the Manufacturer failed to investigate or did not follow-up on 57% of complaints and thus reportability could not be determined. Adverse event reporting numbers before and after a policy change by the Manufacturer, and an estimate of the reportable events not being submitted from a manager who was there, both support the conclusion that more reportable events were withheld from FDA by the Manufacturer than were submitted by all sources over the same time period.

5) Had the Manufacturer complied with complaint intake, investigation and reporting requirements under the FDA Regulations, it would have allowed the FDA to take actions to inform and protect the public about Essure safety issues much earlier than 2016. In my opinion, there could have been sufficient information to prompt FDA action requiring stronger warning labels for patients and physicians as early as 2006.

6) After acquiring Essure from Conceptus in 2013, Bayer had the knowledge, opportunity and obligation to correct the severe underreporting of MDRs to the FDA including systemic issues with Complaint intake, investigation and reportability assessment. Specifically, Bayer had knowledge of severe Conceptus MDR underreporting issues no later than three-six months after acquisition of the company in 2013. Despite this, Bayer failed to perform a comprehensive, adequate, and timely retrospective reassessment of complaints and MDR reporting decisions and update FDA accordingly. To date, Bayer has not reported to FDA complaints received prior to 2013 that are known MDRs and has otherwise failed to take actions to assure regulatory compliance and patient safety concerning Essure.

7) The Manufacturer also failed to comply with FDA medical device risk management requirements relating to the post-market sale and distribution of Essure. Despite increasing indications of safety concerns with Essure, the Manufacturer failed to recognize, investigate, and correctly evaluate the severity and likelihood of harm to patients. The failure to recognize and appropriately rate risks to patient safety from product use and malfunctions facilitated the significant and systematic under-reporting of MDR's.

8) The MDRs eventually submitted (most from sources other than the Manufacturer) were a cause of FDA convening an Advisory Committee meeting in September 2015. Specifically, the FDA stated that "As part of examining safety concerns about Essure raised by patients and cited in MDRs, the FDA convened a meeting of Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee on September 24, 2015." An Advisory Committee hearing like this is a rare and significant step for the FDA to take to monitor the safety of a marketed medical device.

9) FDA has also confirmed that the MDRs eventually submitted to it were a cause of requiring a Black Box Warning and Patient Decision Checklist (required informed consent document) for the Essure device. After in-depth review, interviews with patients, and careful consideration informed by the public advisory panel meeting, FDA concluded that the pre-2016 warning labels were inadequate and that patients and physicians were not receiving or understanding information regarding the risks and benefits of the Essure device.[11]

10) FDA has determined what actions Conceptus/Bayer needed to take to inform and protect Essure patients. These were demonstrated in a final public guidance document, in a required post market study, and in required label changes including a black box warning and patient/physician checklist. FDA ultimately made the checklist and patient/physician signatures mandatory as a condition of sale in the United States. The FDA Commissioner highlighted the importance of the mandatory patient/physician check list in a press statement on April 9, 2018: *The FDA plans to enforce these requirements and will take appropriate action for a failure to comply, including applicable criminal and civil penalties.*[12]

11) The Manufacturer had knowledge of and access to much of the information that FDA ultimately used to recognize the safety issues with Essure beginning as early as 2006. The Manufacturer had the opportunity and responsibility to identify these developing serious safety concerns, report as required to FDA, and take voluntary actions to inform and protect patients without the need for FDA intervention.

12) It is my understanding that material and information is still being discovered and that additional final testimony from the Manufacturer is expected. Accordingly, I reserve the right to supplement my opinions based on new information obtained subsequent to this report.

IV. FDA REGULATION OF MEDICAL DEVICES

A. The Food and Drug Administration

The U.S. Food and Drug Administration (FDA) is a major public health agency charged with implementing and enforcing the Federal Food, Drug, and Cosmetic Act[13] and related laws.
In 1906, Congress passed the Pure Food and Drugs Act that established initial FDA regulatory functions, prompted by growing awareness of dangerous dyes and preservatives in foods, worthless or fatal patent medicines, and unsanitary slaughterhouses.[14]

In 1938, The Federal Food, Drug, and Cosmetic (FDC) Act established regulatory oversight for cosmetics and therapeutic devices. It required that drugs be shown to be safe before marketing. It followed 107 deaths (including children) from an elixir containing poisonous diethylene glycol[15].
In 1976 the Medical Device Amendments created a framework for regulating medical devices and required FDA review of many devices before marketing.

Today FDA ensures the safety, effectiveness, and security of human drugs, animal drugs, medical devices, and biologics including vaccines, blood products, cells, and tissues. FDA is responsible for the safety of U.S. foods, cosmetics, animal foods, and radiation-emitting products such as laser pointers, X-ray machines and microwave ovens.[16]

FDA oversight extends from initial product testing through the end of marketing and sometimes beyond (i.e. permanent implants). The agency reviews clinical study protocols and pre-market submissions. FDA receives more than one million adverse event/incident reports each year that are monitored for emerging safety issues. The agency has the authority to monitor the manufacture, import, transport, storage, and sale of regulated products.[17]

FDA regulates a wide array of products with widely different purposes for users including infants, children, teens, pregnant women, middle aged or elderly adults in good health or suffering from serious or terminal diseases. Products may be used in rural or urban homes, businesses, schools, healthcare facilities, laboratories, ambulances, gyms, or airports.

U.S. consumers spend about 20 cents of every dollar (more than $ 2.5 trillion dollars per year) on products regulated by the FDA. Regulations cover approximately 35,000 produce farms, 300,000 restaurant chain establishments, and 10,500 vending machine operators. FDA regulates products

that are manufactured or handled at almost 270,000 registered facilities, many of them overseas. They account for 12 percent of all U.S. imports ($ 273 billion per year) and about 16 percent of U.S. exports ($ 233 billion per year).[18]

The agency cannot provide individual requirements or continuous scrutiny for every product it regulates. Instead, FDA issues regulations for large groups of products (such as drugs, devices, or foods) describing how the law will be applied. Regulations for different products may vary depending on the amount of oversight required, the nature and number of products involved, and the size and types of firms. FDA has authority to enforce these regulations.[19]

The FDA also issues guidance documents to inform industry about agency processes or expectations for specific products. In 2016 FDA issued a final guidance document for Essure and any similar products in the future.[20]

FDA also participates in writing standards, especially for medical devices. Standards are documents written by a group of experts from academia, industry and government that reflect current consensus thinking about processes, products, or testing that can affect product safety and performance. Standards are reviewed and updated every few years. If FDA determines that a standard has value, the agency can officially "recognize" it. If a firm can demonstrate that it complies with a recognized standard this may streamline premarket reviews or inspections.[21]

To maintain and optimize public health, a partnership between the manufacturer and FDA is essential. The agency has information about emerging research and adverse event experiences across manufacturers that may help identify safety concerns. FDA also has scientific and clinical expertise on staff that many companies don't have.

The manufacturer has in-depth knowledge of their specific products, manufacturing activities, and results of in-house testing. Manufacturers receive and review complaints from product users. To make use of this information, the manufacturers must investigate reports, assess the findings, monitor trends, and evaluate potential risks appropriately.[22]

In order to assure patient safety, the firm must share significant information with FDA in a timely way through adverse event reports required by regulation 21 CFR 803, as well as voluntary communications about emerging issues. FDA can then advise the firm on appropriate actions and notify the public if necessary. The firm benefits from early FDA input into the significance of these potential issues as well as support from the agency identifying and implementing actions to protect patients. These interactions can also help clarify the agency's regulatory expectations for manufacturers.

B. Medical Device Regulation

FDA is organized into several Centers that regulate major product areas. The Center for Devices and Radiological Health (CDRH) oversees the regulation of medical devices including Essure.[23]

Medical devices are used in the prevention, diagnosis and treatment of illness. They range from tongue depressors and bandages to syringes, surgical gloves, laboratory tests, ultrasound machines,

artificial joints, and cardiac pacemakers. FDA currently regulates approximately 190,000 different devices manufactured in more than 21,000 facilities worldwide.[24]

Technologies used in medical devices are diverse and evolving rapidly. Niche devices may be essential for specific patient/user groups. Success of treatment often depends on patient body size, and anatomy, as well as skills of the skills of the healthcare provider. Medical device regulation must accommodate these realities.

Congress created the framework for regulating medical devices in the Medical Device Amendments of 1976.[25] Section 513 of the FD&C Act established three classes of devices that provide increasing oversight as the risks of medical devices grow. This structure reflects both the need for patient safety and the desire for quick access to new products.

CDRH implemented the device framework through a series of regulations that describe broad general requirements for medical devices in Title 21 Code of Federal Regulations (CFR) Part 800 to 1299.

The Center also issues guidance documents describing FDA expectations for specific types of devices[26] and has recognized numerous standards that support product safety and effectiveness. CDRH educates companies through conferences, publications, email and telephone help desks, and staff are also available to address questions by email, in telephone calls and meetings.[27]

CDRH may request inspections of clinical study sites or company facilities before approving a product or after marketing if there is concern about product quality, safety, or compliance with regulations. Field offices also initiate inspections of medical device manufacturers.

C. Medical Device Classification

The three classes of medical devices are based on the potential risks to patients/users and the level of control FDA needs to provide reasonable assurance of safety and effectiveness.
General Controls are regulatory requirements authorized by the FD&C Act [28] that apply to all medical devices distributed in the United States.

Examples of General Controls include:

- The Quality System Regulation (QSR) also called Good Manufacturing Practices (GMP)
- Medical Device Reporting of adverse events
- Labeling of medical devices consistent with the regulations
- Reporting of corrections and removals (recalls)

Class I devices: Class I medical devices present low to moderate risk of harm to the user. They make up about 50 percent of all medical devices. Examples include arm slings, and hand-held surgical instruments. Class I devices are usually simple in design and have a history of safe use. They are usually exempt from premarket review. Risks are managed by General Controls and are usually exempt from premarket review.

Class II devices: Class II medical devices have known moderate to high risks. These devices make up about 43% of all medical devices. Examples of Class II devices include x-ray systems, glucose test strips, infusion pumps, and surgical drapes. General Controls are not sufficient, but the agency can require Special Controls that are considered adequate to assure safety and effectiveness.[29] [30]

Examples of Special Controls include:

- Special labeling requirements,
- Pre-market data requirements,
- Mandatory FDA guidance for the products,
- Post market studies or patient registries.

Many Class II devices require FDA review and clearance before marketing based on substantial equivalence to a legally cleared/marketed predicate device. These 510(k) pre-market notification submissions generally include extensive laboratory or bench testing data and sometimes clinical studies

The FDA review cycle for 510(k) submissions is 90 days. The Center provides guidance documents for 510(k) clearance processes and specific device types. Class II devices exempt from premarket review are identified in 21 CFR 862 through 892.

Class III devices: Class III medical devices are considered to have the highest risk. Information available is not sufficient to assure safety and effectiveness with General Controls and Special Controls. Class III devices require submission of a premarket application (PMA) and approval by FDA before marketing.[31] These devices usually support or sustain human life, are important in preventing disease, or have the potential for unreasonable risk of illness or injury to the patient. The design, materials, technology, or clinical purpose may be new and the risks may be unknown. Examples of Class III devices include replacement heart valves, silicone breast implants, and deep brain stimulators. In 2017 FDA approved only 64 PMA's. [32] After Class III devices are marketed a series of sequential PMA supplements may be submitted to FDA for approval of product, manufacturing, and other changes. The firm is also required to submit PMA annual reports keeping FDA apprised of new safety and effectiveness information as well as other updates.

PMA (Pre-Market Application): The threshold for approval of a PMA is reasonable assurance of safety and effectiveness based on valid scientific evidence.[33] FDA also weighs the risks and benefits to patients. PMA's generally include clinical study data and receive in depth review by a team of scientists. FDA usually performs an inspection of the manufacturing site to evaluate readiness for market. The PMA review cycle is 180 days. The contents required in a PMA are found in Section 515(c)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA often requests input from a medical advisory panel before making the decision to approve or not approve a PMA.

D. Manufacturer Responsibilities

Three post marketing requirements for industry are essential to the success of the regulatory framework for medical devices These include:

1. responsibility for assuring device quality, safety, and effectiveness,
2. responsibility to report required information to FDA in a timely way, and
3. responsibility to identify and assess the risks of potential safety issues and take voluntary actions to reduce or eliminate them.

These requirements are reflected in CDRH regulations, guidance documents, and recognized standards. Manufacturers have an obligation to implement them appropriately for their products.[34]

Manufacturers are Responsible for the Quality, Safety, and Effectiveness of Medical Devices

Medical device manufacturers are responsible for assuring the quality, safety, and effective performance of their products throughout commercial use as described in the General Control - Quality System Regulation 21 CFR 820, 21 CFR 7.40 and ISO 14971:2007 *Medical Devices – Application of Risk Management to Medical Devices.*

Companies independently design and evaluate their devices, establish and control manufacturing processes, select and monitor their materials, suppliers, and contract facilities. They decide the final content of labeling, advertising, and promotional materials. Manufacturers have access to complaint information and user feedback not known to the public or FDA.

Manufacturers have responsibility to identify emerging issues, interpret safety signals in the best interests of patients, and act promptly to protect health and welfare. This obligation goes beyond achieving FDA approval to market and submitting MDR reporting.[35] [36] [37] [38] [39]

FDA regulations indicate how manufacturers are expected to meet these obligations. Responsibilities of executive management are described in 21 CFR 820.20 and ISO 14971:2007 Section 3.2. Regulations note specifically when procedures are required for companies to document in detail expectations that will be applied for their particular device. [40] [41] [42]
FDA supports manufacturers in their responsibilities for product quality, safety and effectiveness. Guidance documents and recognized standards help companies independently optimize device designs, evaluate safety and effectiveness, and assess and address product risks. Manufacturers much succeed in these tasks for FDA to achieve its public health mission, since the majority of medical devices receive no FDA review before marketing.[43]

Manufacturers Are Responsible for Identifying, Assessing, and Acting to Reduce Potential Risks

Medical device manufacturers are required to have a process in place that monitors product related information and identifies potential hazards, harms, and emerging safety issues, assesses the risk of harm to patients, determines the acceptability of risk to patients, and acts to control (eliminate or reduce) risks if they are found to be unacceptable. This requirement originates in the Quality System Regulation 21CFR 820.30(g) which is a General Control. The standard ISO 14971:2007 has been recognized by FDA and provides the widely used process for meeting this requirement.

Sources of information manufacturers are expected to monitor include (but are not limited to) unpublished data, MDR reports from other sources, medical literature, new or revised consensus standards, new or updated FDA guidance documents, product complaints, manufacturing production data, and trend analysis.[44] [45]

Each manufacturer must create appropriate risk management procedures for their products and identifies and assesses changes based on new information over time. The firm decides what controls are necessary to reduce risk and makes a final valuation of residual risk and acceptability to market. Controls to reduce patient harm may include changes to design, production, distribution, labeling and marketing approaches when necessary.[46]

Quality systems and MDR Reporting are inextricably linked. More specifically, "complaint files are linked to MDR event files because a complaint must be evaluated to determine if it is a reportable adverse event."[47] Failure in the quality systems can lead to an underreporting of MDRs to FDA.

Summary of Key Documents

The three requirements of industry described above are addressed in the following documents:

1. **The Quality System Regulation (QSR) 21 CFR 820**

   The QSR is a General Control that establishes basic requirements for manufacturers of finished medical devices. It includes a range of processes and activities necessary to ensure that products maintain the quality, performance/effectiveness and safety described in premarket submissions and product labeling. The purpose of this regulation is described in 21 CFR 820.1 as follows: *The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act.*

   The QSR governs a wide range of processes from product design through the end of marketing for essentially all medical devices distributed commercially in the United States.[4849] It provides requirements for Executive Management and requires manufacturers to develop procedures for a number of activities, implement them and document the results. QSR requirements include complaint handling and investigation, corrective and preventive actions, prompt evaluation of complaints for reportability to FDA, and review and investigation of complaints that must be reported.[50] [51] [52] [53] [54]

2. **The Medical Device Reporting (MDR) Regulation 21CFR 803**

   This regulation is another General Control. It builds on the QSR, describing the criteria and required timeframes for reporting device-related deaths, serious injuries, and malfunction information to FDA. It clarifies what information must be reported, when and how to submit reports, options available to streamline reporting activities, and the process for follow-up reporting if necessary.

3. **Class III Device Post Approval Reporting Obligations**

Class III devices have some additional post market requirements described in the pre-market regulations, PMA approval orders, and the Conditions of Approval statement.[555657] If these requirements overlap with MDR reporting requirements then MDR reports receive priority.

4. **ISO 14791: 2007 Application of Risk Management to Medical Devices**

The international consensus standard *ISO 14971 Medical Devices – Application of Risk Management to Medical Devices* provides a process for identifying, assessing, and controlling risks for all devices. The 2007 version of the standard was officially recognized by FDA in 2016. It has been widely used to meet FDA risk management requirements for much longer and is currently considered state of the art worldwide.[58] A more recent version (2012) of the standard includes wording relevant specifically to the European Union [59]

ISO 14971:2007 supports the QSR, providing processes that help ensure continuing product quality, safety, and performance. It supports the MDR regulation by providing a process for manufacturers to identify known and potential failure modes, assess the risks such failures pose, and use this information to guide complaint handling processes and MDR reporting decisions. Post market surveillance processes also help companies identify when changes occur to known risks and any new emerging issues that occur. This standard describes how to estimate the risk to patients of various events based on severity and frequency scales, how to eliminate or reduce risks, and how to determine if any risks remaining are acceptable for marketing or continued marketing of the product. The identification and assessment of these harms can influence the criteria manufacturers use to make MDR reporting decisions.

The Medical Device Action Plan issued in 2018 by the FDA Commissioner and CDHR Director stated that "Once a device is on the market, risk-management planning is essential to manage any risks that might emerge and to reduce the likelihood of future risks."[60]

V. THE ESSURE SYSTEM

A. Class III Device Approval

The Essure System is a Class III device subject to both General Controls and the Class III pre-market and post market requirements described above. The PMA for Essure (# P020014) was filed by FDA on April 22, 2002. The agency granted approval to market the Essure System on November 4, 2002 based on clinical study data from 745 subjects and input from an expert advisory panel on July 22, 2002.[61] [62]

When FDA approved Essure it was already available in Australia, Canada, much of Europe, Indonesia, Singapore, and Turkey.

The FDA approval letter described the indication for the Essure System as follows: "This device is indicated for permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes." [63]

The approval letter and attachment identified conditions of approval including:

- Commercial distribution limited to prescription use,
- Training requirements for health care practitioners,
- Five-year follow-up for phase II and pivotal trials with updates submitted annually. Labeling changes, if required based on testing results, submitted in a PMA supplement.
- Post approval study in the U.S. monitoring the success of newly trained physicians in bilateral placement of the Essure System with first attempt,
- Annual reporting of published or unpublished non-clinical and clinical data with use of product (21 CFR 814.84),
- Requirement that a PMA supplement "must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification." unless it is already addressed through MDR reporting.[64] [65]
- Medical Device Reporting as described in 21 CFR 803.[66]

The PMA Summary of Safety and Effectiveness Data listed contraindications for use including recent pelvic infection, known allergy to contrast media, and known hypersensitivity to nickel confirmed by skin test.[67] Section V.3 also stated:

> *The long-term nature of the tissue response to the Essure micro-insert is not known. The majority of the clinical data regarding PET in the fallopian tube is based on 12-24 months of implantation, with little data at 36 months. Therefore, beyond 24 months, the nature of the cellular/fibrotic response and the ability of the response and the device to maintain occlusion are not known.*

B. Activity After U.S. Marketing

Sales

Use of Essure grew rapidly in the United States. By 2007 the Essure procedure had grown to 51% of all sterilization procedures not following pregnancy at Detroit Medical Center hospitals.[68] Hysteroscopic sterilization represented 38% of sterilization procedures in the U.S. not associated with pregnancy between 2005 and 2012 (including Adiana from 2009 - 2012).[69] [70]

In 2015, Bayer stated that the Essure device has been studied in more than 10,000 women since it was first developed and distributed to approximately one million women worldwide.[71]

Bayer Acquisition of Essure

Bayer acquired Conceptus and the Essure System in July of 2013.

Post Market PMA Supplements

Thirty-nine (39) PMA supplements were submitted to FDA for Essure by September of 2015. They addressed topics including product enhancements, changes in manufacturing facilities, and labeling updates. There were changes to the delivery system and then to the delivery catheter by 2007 in response to post market feedback.[72] The Manufacturer received approval to remove the contraindication for nickel sensitivity and revise the warning in physician labeling on July 1st, 2011.[73] FDA approved additional information for the patient information booklet on risks of chronic pelvic pain and device migration on October 30, 2013.[74]

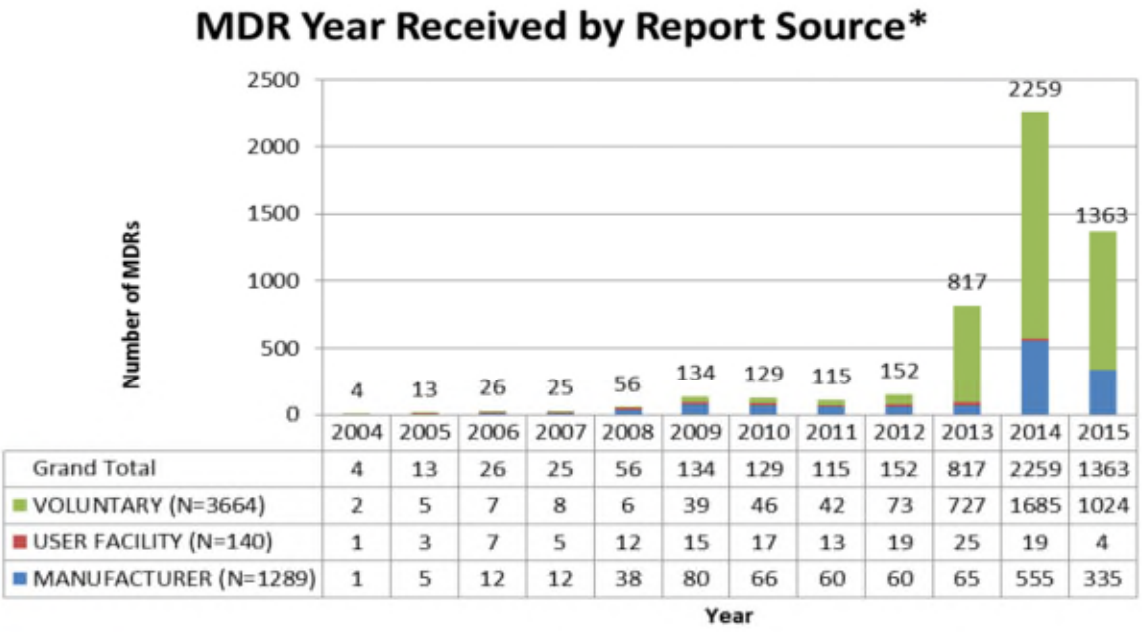
Increase in MDR Reports Received at FDA

The number of MDR reports received by FDA began increasing significantly in late 2013, mostly from patients filing voluntary reports directly with the agency. FDA had received a total of 5,093 MDR's from Essure approval in November of 2002 through May of 2015, captured in the Manufacturer and User Facility Device Experience MAUDE database from all sources.[75] A breakdown of the MDR's indicated that:

- There were 4,608 reports coded as patient injury, 474 as malfunctions, and 11 as deaths.
- Many of the MDR reports received after 2013 described events from previous years.
- Many of the MDR's received, especially after late 2013, contained multiple concurrent symptoms that the reporter believed were associated with or a consequence of Essure use.
- FDA sends a copy of any voluntary reports it receives from other sources to the device manufacturer. The firm is expected to evaluate the data and submit an MDR if the report appears to meet regulatory filing criteria. Therefore, there may have been duplicate reports (directly from the user and again from the firm) submitted for some events.[76]

In response to the increased adverse event reporting numbers and complaints discussed in traditional and social media outlets, the agency conducted an in-depth review of MDR reports received, met with consumers and advocates to hear their concerns about the Essure System, and scheduled a public advisory panel meeting.[77] [78] [79] The following table is reproduced from page 29 of a summary document FDA prepared before the meeting:

Figure 5 – Number of MDRs Received per Year, Prior to June 1, 2015, by Report Source



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Grand Total	4	13	26	25	56	134	129	115	152	817	2259	1363
VOLUNTARY (N=3664)	2	5	7	8	6	39	46	42	73	727	1685	1024
USER FACILITY (N=140)	1	3	7	5	12	15	17	13	19	25	19	4
MANUFACTURER (N=1289)	1	5	12	12	38	80	66	60	60	65	555	335

*Of the reports received, 4608 were coded as patient injury reports, 474 as device malfunctions, and 11 as deaths.[80]

After the acquisition of Conceptus, Bayer assumed responsibility for filing MDR reports for Essure in October of 2013.[81] The Bayer corporate practice differed from previous Essure MDR reporting processes. An immediate reporting decision was made if possible, the reporting clock started at the time of first contact, and submission proceeded within 30 days based on the information available. Physician confirmation was not considered essential. These new practices increased the number of events found to be MDR reportable,[82] This increase in Manufacturer reports is noticeable in blue on Figure 5 for 2014 and 2015, although most of the increase in MDR reports for those years was due to direct patient/consumer submissions.

Bayer acknowledged this on page 31 of their Executive Summary for the FDA Advisory Committee Meeting stating:

> *"Also, as a matter of general policy and in the attempt to facilitate comprehensive assessment by receiving Health Authorities and regulatory bodies, Bayer favors an assessment of reportability, which may be more comprehensive than with other companies."*

The Manufacturer also offered suggestions about causes for the substantial increase in MDR reports from patients directly to FDA including general trends of increased adverse event reporting across products, increased interest in Essure and potential liability activities following the acquisition, active online listening and outreach programs by the firm to facilitate reports from

users, and availability of new mobile adverse event reporting apps including the FDA MedWatcher, which facilitates direct consumer reporting of adverse events to FDA. [83]

FDA Post Market Advisory Panel Meeting

On September 24, 2015, FDA convened its Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to consider the safety and effectiveness of Essure sterilization. Both FDA and Manufacturer representatives provided written summaries and presentations.[84] [85] [86] The Open Public Hearing session provided an opportunity for Essure users to describe their experiences and written public input was also sent to the docket.

Summary of Advisory Panel Findings[87]

The panel discussed a range of clinical issues including persistent pain, perforation of the uterus or fallopian tubes, intra-abdominal or pelvic device migration, abnormal or irregular bleeding, allergy or hypersensitivity reaction, and pregnancy. The panel wanted to ensure that patients had access to healthcare services at all steps of Essure use including device removal.

Support for informed patient decision-making was another topic of interest. The panel addressed the need for better patient materials and recommended updates to patient labeling. The Committee discussed the use of various imaging modalities to identify and/or evaluate certain adverse events. The panel discussed the need for additional physician training on topics including device removal, aborting placement procedures, and when alternative options for contraception should be pursued.

The panel expressed a general desire to see additional post market data on the Essure system to better understand the adverse events that had been discussed and several panelists suggested a patient registry. The panel generally agreed that additional information regarding metal reactions/sensitivity is needed.

Finally, the panel discussed patient populations where the benefit-risk profile of Essure was acceptable and those where it might be less favorable. The panel stated that hysteroscopic sterilization is an important option for women who are not good candidates for laparoscopic or general surgery, as long as they are well informed about potential risks. The panel suggested that patients with a known hypersensitivity to metal, autoimmune disease, history of pelvic inflammatory disease, and those with a history of abnormal uterine bleeding may be less suitable candidates for Essure.

Subsequent FDA Actions

Following the panel meeting, FDA took actions to address Essure safety concerns and inform consumers. FDA indicated that input from patients led the agency to believe some women were not receiving or understanding information regarding the risks and benefits of Essure.[88]

On February 29, 2016, FDA ordered the Manufacturer to conduct a post market surveillance ("522") study to gather more data about benefits and risks of Essure.[89]

On March 4, 2016 FDA issued draft guidance seeking public comment on wording for a boxed warning and Patient Decision Checklist to help ensure that women received and understood the benefits and risks of the product. FDA issued the final guidance document in October 2016.[90]

In November 2016 FDA required a black boxed warning for Essure on the first page of the product labeling, to alert doctors and patients about "reported adverse events, including perforation of the uterus and/or fallopian tubes, intraabdominal or pelvic device migration, persistent pain, and allergy or hypersensitivity reactions.[91] [92]

FDA also required a mandatory patient-doctor discussion checklist that was an "acceptance of risk and informed decision acknowledgment." The new warning highlighted the risk of persistent pain, perforation of the uterus and/or fallopian tubes, intraperitoneal migration, allergy or hypersensitivity reactions, rashes, itching, chest pains, joint or muscle pain, hair loss, fatigue, weight changes, and mood changes on the first page of the patient information booklet, in all bolded, all capital letters.[93] [94]

On April 9, 2018, FDA restricted the sale of Essure to facilities and healthcare providers that agreed to review the Essure checklist with women considering use of the device and have both the patient and physician sign. An FDA press release on that date stated in part:

> *The U.S. Food and Drug Administration* today i*ssued an order to restrict the sale and distribution of the Essure device to ensure that all women considering use… are provided with adequate risk information so that they can make informed decisions. The FDA is taking this step after becoming aware that some women were not being adequately informed of Essure's risks before getting the device implanted, despite previous significant efforts to educate patients and doctors about the risks associated with this device. The FDA is requiring a unique type of restriction, using its authority to restrict the sale and distribution of a device to impose additional requirements needed to provide a reasonable assurance of its safety and effectiveness. The FDA is committed to continuing to use its full authorities to ensure the post-market safety of medical products.*
>
> *The new Essure labeling, which will now be legally required when this product is offered to a patient, restricts the sale and distribution of the device to only health care providers and facilities that provide information to patients about the risks and benefits of this device. Specifically, the patient brochure titled "Patient-Doctor Discussion Checklist – Acceptance of Risk and Informed Decision Acknowledgement," must be reviewed with the prospective patient by the health care provider to ensure the patient understands the risks, benefits and other information about Essure implantation. The patient must be given the opportunity to sign the acknowledgment, and it must be signed by the physician implanting the device. Bayer, the device manufacturer, is required to implement the restrictions immediately and ensure that the process going forward results in health care provider compliance with the sales restriction. The FDA will review and monitor Bayer's plan to ensure the company complies with the restriction. The FDA plans to enforce these requirements and will take appropriate action for a failure to comply, including applicable criminal and civil penalties.*[95]

Voluntary Removal of Essure From the U.S. Market

On December 31, 2018, Bayer discontinued selling and distributing the Essure device in the United States.[96] Health care providers could continue to implant Essure devices for up to one year after the date of previous purchases. Bayer agreed to continue implementing the FDA restriction on sale and distribution of Essure so that women would be fully informed of the risks associated with the device.

VI. COMPLAINT HANDLING FOR ESSURE

Quality System Regulations

The QSR in 21 CFR 820.20 requires management with executive responsibility for medical device manufacturers to assure that quality system processes are established and maintained, with adequate resources including trained personnel.

The QSR in 21 CFR 820.198 requires medical device manufacturers to establish complaint files and procedures, process and investigate complaints as appropriate. Requirements include:

- Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints,
- Such procedures shall ensure that all complaints are processed in a uniform and timely manner,
- Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer must maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.
- Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

Complaints are a primary source of adverse event reports to FDA. The QSR in 21 CFR 820.198 (a) (3) requires screening complaints for reportable adverse events as follows:

> *"Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 of this chapter, Medical Device Reporting."*

In 21 CFR 820.198 (d) the QSR further states:

> *"Any complaint that represents an event which must be reported to FDA under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise clearly identified…"*

Summary Findings Related to the Manufacturer's Quality Systems

Other experts have reviewed the Essure complaint handling procedures, processes, and files in detail. I concur with their findings. I have also personally reviewed documents provided to me. Based on all of this information and material, I have concluded that the Manufacturer failed to comply with FDA requirements for quality systems set forth in 21 CFR Part 820, including, but not limited to, complaint handling, in the following ways:

- Procedures were inadequate for processing complaints in a proper, uniform and timely way.
- Procedures for complaint processing were inadequate and/or not properly followed.
- Staffing was not sufficient and not provided with necessary training.
- Investigation of complaints was inadequate and inconsistent.
- Large backlogs of open complaints developed and persisted for years.

This systemic non-compliance with regulations related to complaint handling led to delays and, in many instances, outright failure to investigate complaints, identify reportable events and submit them to FDA, resulting in a lack of information available for the agency to monitor the safety of Essure in wide population use and delayed adequate warning of known risks associated with the product.

I have provided a few examples demonstrating the extent of problems below. Further discussion of complaint investigation related to MDR reporting below. I reserve the right to supplement as others are revealed.

The Manufacturer's Quality Systems Failures

21 CFR 820.198 (a) mandate that procedures be established and maintained to implement complaint handling and evaluate reportability of adverse events. The regulation in 21 CFR 820.5 requires that: *Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.* It is my opinion that the Manufacturer failed to comply with 21 CFR Part 820 and such failure led to an underreporting of MDRs to FDA under 21 CFR Part 803

The Manufacturer's complaint handling processes and procedures lacked information necessary for staff to intake, evaluate, investigate, document, and report to FDA, where necessary, process Essure complaints in an adequate, uniform, and timely manner consistent with the regulations. Information needed to adequately handle complaints was not included. Documents were revised frequently without clear explanations. The Complaint Handling Procedure 1360 was revised at least 30 times [97] and Work Instruction WI-03490 Monitoring and Reporting Complaint Metrics was issued in at least 18 versions.[98]

Robert McCarthy, Operations Director QE, QA, began supervising the Essure Product Surveillance function in 2008. In his deposition he acknowledged the inadequacy of complaint processes/procedures and noted that the process in place for managing complaints when he assumed responsibility did not allow acceptable performance. He stated:

"I think the procedures could have been clearer about how to make sure that we would not have a backlog of complaints."[99] *He also said: "At that time, the procedures did not provide enough instructions … to manage those activities effectively."*[100]

An internal audit performed by a former FDA investigator in August 2008 cited complaint procedures as a major deficiency: "There are numerous procedures which are required by regulation which are not currently in place at Conceptus. The needed procedures would codify practices already undertaken by Conceptus staff. The lack of such high-level procedures appears to have contributed to the large degree of variation in the performance of certain tasks undertaken by Conceptus employees."[101]

Further, complaint files were not consistent with procedure SOP 1630. Most files checked during the audit were missing records or incomplete, which the auditor considered another major deficiency.

Uniform and timely complaint processing was also limited because there was no list of the categories/levels of investigation to be performed for different types of complaints in use before 2012. The following exchange during Michael Reddick's, Senior Manager of Product Surveillance, fact witness deposition summarizes the situation:

Q. Prior to July 30th, 2012, does a document exist that tells us how Conceptus defined the very categories of complications like this?
A. So, I'm not aware of any document … that defined that.
Q. Okay. So, prior to July of 2012, was there any kind of documents at all that you used to train investigators into what they should be looking for and how to determine how to categorize the various complaints that were coming in?
A. Well, there was a list that was used but it was not -- you know, they were trained as on-the-job training basically.
Q. You didn't have something that defined it like this prior to 2012 that you're aware of?
A. That's correct.[102]

CFR 820.20(b)(2) requires Management with executive responsibility to "…provide adequate resources including the assignment of trained personnel..." The 2008 internal audit identified deficient training practices and training documentation as another major deficiency category.[103]

This lack of personnel is shown in a September 6, 2007 where Lois Pierce, Quality Control Supervisor/Technician/Product Complaint Manager, tells Ed Sinclair, Vice President of Regulatory Affairs and Quality Assurance, that they are in need of another temporary employee stating: *"I would like to have one person to work strictly with Shak in the product surveillance lab to catch up with the backlog of AR's…(There have been over 700 AR's submitted since Jan 2007, a record high, with bent tip being the number one problem)"*[104][105]

Edward Sinclair, Vice President of Regulatory Affairs and Quality Assurance, confirmed that employees were not adequately trained to intake and report complaints as follows:

Q. And do I understand from your testimony, then, that there were other people that just answered the main line that might have not been so well-trained?
A. Right. They certainly may not have been trained on interactions how to elicit information from a caller.[106]

21 CFR 820.198(a)(1) requires that "all complaints are processed in a uniform and timely manner" and 21 CFR 820.198(3)(d) that "Any complaint that represents an event which must be reported to FDA under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual (s)….". and 21 CFR 803 requires that internal systems must provide for "Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements."[107]

The Manufacturer's procedures provided no consistent or meaningful timeline for complaint handling in a timely manner. Instead, they allowed complaints to remain open for long periods in violation of with QSR and MDR regulations. In his deposition Robert McCarthy, Operations Director QE, QA, overseeing Product Surveillance including complaint handling and MDR reporting, confirmed that complaints could be held open indefinitely awaiting product return or information from physicians. When asked *"According to whom?"* He responded, *"Our procedures."*[108]

Bayer, by and through its designated PMQ witness, Michael Reddick, Senior Manager of Product Surveillance, testified to the timeliness of investigations in stating:

A. Well, I mean, we'd have to look at the procedures that talks about doing investigations
Q. Sure, you go ahead and tell me. That's fine
A. It doesn't assign a specific time frame for conducting -- conducting the investigation
Q. So you could start an investigation a year or two years or three years after you initially received a complaint, and you would still be timely in reports to the FDA?
A. I'm not aware of that ever happening
Q. I'm not asking you whether it happened or not. I'm saying under your theory, that would be okay; correct?
A. I would say that's not okay
Q. Why not?
A. To me that would not be timely
Q. What is timely?
A. I'm not sure how that is defined. I don't know that it is defined[109]

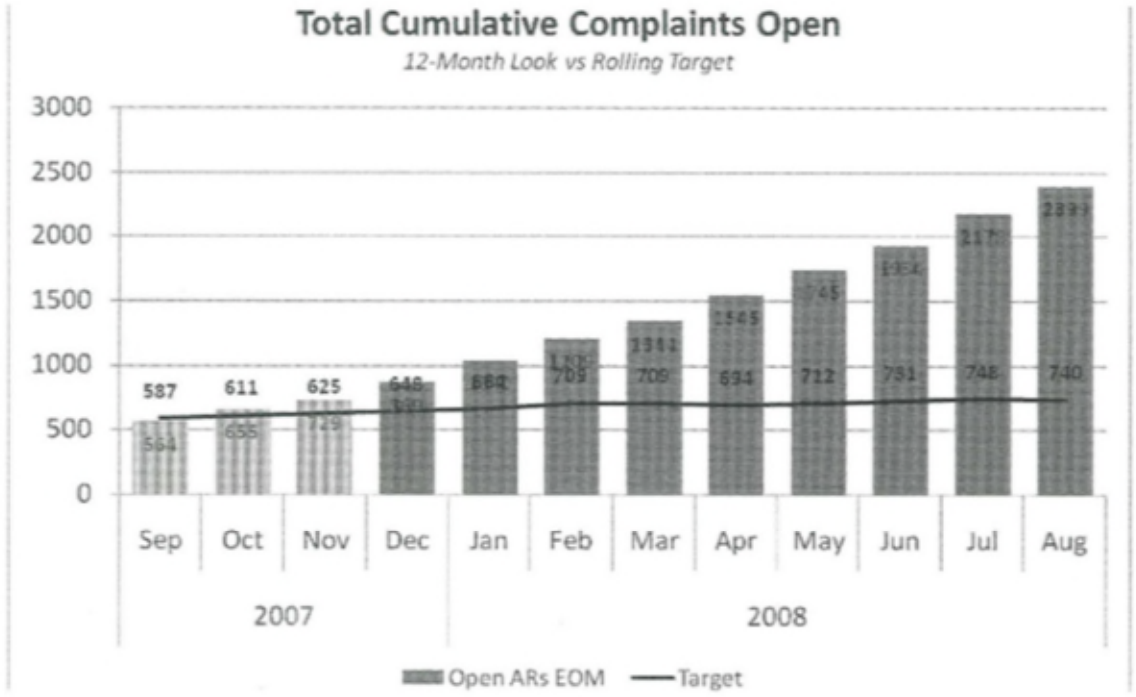
The 2008 internal audit cited complaint backlogs as another major category of deficiency noting that the very large backlog of open complaints serves as a signal to the FDA reflecting a violation of the requirements of 21 CFR part 820.198. Complaints are to be addressed in a timely fashion, according to the requirements of this section of the Quality System regulations so that MDRs are properly and timely reported in accordance with 21 CFR 803.50. Some of the currently open complaints were originally opened in March 2007. It seems likely that the complaint record would include even older open complaints if it were not for the fact that the current complaint handling system (CRM) was also activated in March 2007.[110]

Backlogs of Essure complaints continued over a period of years. During 2007-2008 they were growing from month to month and reached approximately 2,500 open complaints in October of 2008. An Operations Monthly Update report for October 2008 provided this Product Surveillance update*:*

> *"A[] team was assembled to start correcting the issues found in Product Surveillance System internal audits. An outside consultant was hired to rewrite the procedures. The team has generated and approved a timeline and a plan to perform all corrective and preventive actions. These will be recorded in CAPA."*[111]

And later, ***"There is currently a large backlog of AR's…. (***See Chart in Attachment 7). Currently there are approximately 2, 500 open complaints that need to be investigated and closed."[112]Attachment 4 to the report shows the 12-month history with 292 AR's received in Sept 2007 and 250 received in August 2008.[113] Attachment 7 shows that cumulative complaints open in September 2007 were 587 and had risen to 2,399 in August 2008.[114] See table below*:*

ATTACHMENT 7



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Robert McCarthy, Operations Director QE, QA, acknowledged in deposition testimony that the backlog included all open complaints and stated: "Complaints are continuing to add to that backlog as days go by. There could be MDR's in there that are still under evaluation."[115]

The extent of Essure complaint handling issues was documented in Robert McCarthy's Performance Review for 2008 with an overall performance comment by his supervisor:

> *"This has been [a] particularly challenging year with the identification of the compliance issues in the Product Surveillance department. This issue distracted his attention from the other areas in Operations during the second half of the year… I think the biggest disappointments were: a) allowing the Product Surveillance issues to continue to mount during 2008 even though a dire assessment would have been made as soon as he took responsibility for the department…"*[116]

Edward Yu, Director of Clinical and Regulatory Affairs in 2008, testified: "***Yes, I was very much aware that there was a backlog.*** Indeed, we had – we recognized it. We also had a third-party consultant come in to assess that particular area. And we opened up a CAPA, as per our quality systems, to assess that because it was a systemic issue, and we subsequently closed that CAPA."[117]

Internal Audit 2008 Reveals Quality Systems Failures

Robert McCarthy, Operations Director QE, QA, arranged for an internal audit and gap analysis of Product Surveillance systems by an outside consulting group, Reglera LLC. The audit was performed by Steve Yost, a former FDA investigator and internal auditor at Reglera, on August 5-7, 2008. Eight major categories were identified with deficiencies sufficient for each to result in FDA issuing a 483 notice of observations and possibly taking further action.[118] These categories included:

1. Good documentation practices were not being followed and this appeared to be a systemic issue. Training for all employees was recommended.

2. Unique requirements for Conceptus MDR reporting described and implemented by staff were not documented in writing or procedures. No evidence available that FDA had agreed certain events such as uncomplicated perforation or pregnancy did not need to be reported. Without this evidence the failure to file some types of events appears out of compliance.

3. Very large backlog of open complaints. At the time of audit there were approximately 2,000 open complaints out of about 4, 500 complaints received since the CRM system was activated in March 2007. This could be considered a violation of 21 CFR 820.198 timely fashion requirements. Some examples were opened in March 2007 and remained open at date of audit (17 months later). It is possible some open complaints are even older, but a new electronic system was implemented in March 2007 and files were apparently assigned the date of entry/transition.

   The report highlighted as a particular concern 702 complaints categorized as "Waiting for Product Return". The report stated:

   > *"The number of complaints in the "Awaiting Product Return" category is particularly indicative of a failing system. The oldest complaint in this category is*

dated 2/27/2007. If this complaint was actively addressed there would be no justification for remaining in this state for more than two years. The status should have been updated to indicate that the product was not going to be returned and the process of closing this complaint or performing a paperwork investigation should have been initiated months ago."

4. Various discrepancies noted in handling of MDR evaluation forms.

5. CAPA audit showed several significant concerns related to documentation of corrective actions.

6. Complaint files were not consistent with SOP 1630. The procedure dictates required contents and documents for each file. Most files checked were missing records or incomplete.

7. Numerous procedures required by the regulations were not in place which contributed to large variations in performance over certain tasks by employees.

8. Training program and related record keeping were deficient.

The audit confirmed the need for additional personnel and training and recommended restructure of the entire Product Surveillance department, as well as addressing inadequate and unclear procedures.[119]

Quality Systems Failures Persisted Even After the 2008 Internal Audit

Despite the findings of and recommendations from the 2008 Internal Audit, failures in the quality systems persisted for years. Robert McCarthy, Operations Director QE, QA, scheduled a meeting on February 23, 2009 with an invitation including the statement, *"There are multiple Complaint AR's sitting in clinical information and as was discussed previously this may be an issue if there was to be an audit."*[120]

A backlog of approximately 2,000 open complaints existed in January of 2010 that persisted for months.[121]

Robert McCarthy, Operations Director QE, QA, sent an email dated December 7, 2010 noting both high numbers of complaints and issues with delayed reporting by sales reps. He wrote:

"Ric stated that replacement products (and complaints including bent tips) in October represented about 8.5% of sales. Rob explained that if products were replaced, then ARs were created … and also that Mark observed that complaints are being reported late by sales reps, and asked how feedback can be received quickly…"[122]

Complaint volume and safety concerns continued in 2011. [123]An email chain from Ad Eikelenstam, Sigma-Medical, to Robert McCarthy and others with the subject line: "Continuing Complaints" stated on January 24, 2011:

> *"Today we got a complaint about bended tips again (4 from 1 hospital)! Too many customers are complaining about the quality of the devices. Has there been a change in assembling devices? … Complaints arc coming from very experienced gyn teams! Please advise asap."*[124] *And February 7, 2011: "Complaints do not stop. We got several new complaints last week and today about bended tips, detachment issues. Again from teams with a lot of experience. We are worried about the possible consequences of' all these complaints. Competition, recall, patients claims and so on. We need to discuss this shortly."*[125]

The Operations Monthly Update dashboard for August 2011 showed that sales staff were failing to meet the 3-day deadline for reporting complaints to Product Surveillance 27-28% of the time and the Manufacturer was failing to meet the 90-day complaint closure target 56.3% of the time.[126]

Complaint processing issues and significant complaint numbers continued into 2012. On January 11, 2012 Robert McCarthy, Operations Director QE, QA, send an email saying

> *"I was reviewing the AR Subjects in this months Log. I noticed several potential misclassifications in the data. Can you review and let me know what you think. If they mis classified, they should be corrected and Reglera needs to be notified of the issues."*[127]

On Jul 16, 2012, Mr. Reddick, Senior Manager Product Surveillance, sent a note to his team saying, *"I've noticed an increase in the number of Bent Tip complaints over the last two or three months."* He asks for their input on reasons.[128]

On October 1, 2012 Tracey Hughes, a nurse in Product Surveillance, began an email chain to Michael Reddick, Senior Manager Product Surveillance, regarding follow-up to AR-28674-ZF7L.[129]

The file begins with contact to Product Surveillance on June 7 and 11 asking if *"anyone has contacted patient and is this an MDR." On* July 19 the sales representative followed up with the doctor again. The physician expressed frustration that the Manufacturer would not contact patient to advise of past experience. On August 15 the representative called again – physician is upset as he felt he was misled with information about the number of patients that have experienced pelvic pain with the Essure devices. The Area Director has communicated with the physician. On August 21 the physician performed a surgical removal of both fallopian tubes with Essure implants for the patient who had pelvic pain. Following the operation, the patient was doing fantastic and pain free. The physician voiced concerns that patient contacted the firm and got no support or follow up call. He is upset with this process and feels someone should have reached out to him and to the patient. Product Surveillance indicates no record in file of the patient contacting Conceptus.

On August 24 the sales representative called saying MD attributes the patient's pelvic pain to Essure. On September 10, 2012, an MDR was submitted to FDA. Senior management is asking what went wrong that patient never got contacted even after July 19 discussion with physician expressing concern.[130]

On October 30, 2012 Robert McCarthy, Operations Director QE, QA, emailed Michael. Reddick, Senior Manager Product Surveillance, asking *"Can you please analyze the reported complaints this month. We are getting pretty high rate this month."* He follows up on November 5 saying: *"I am getting concerned with the volume of complaints we have been receiving over the last weeks. Please review the data and let me know if there is a concern."* The AR daily log below this statement shows 37 complaints in first two days of November (almost the total for entire month of October).[131]

On July 24, 2013, Michael Reddick, Senior Manager Product Surveillance, sent an email to Tom Lupo, Vice President of U.S. Quality, stating:

> *"We are still having IT/connectivity issues which are preventing utilization of our MasterControl complaint handling software. My team is currently recording initial complaint information in word templates and holding the information pending resolution of our IT issues, so we are still taking calls and incoming emails; however, this is creating a very large backlog of work that my team will need to address at a later date once our IT issues are resolved."*[132]

On October 22, 2013, Robert McCarthy emailed managers including Michael Reddick, Senior Manager Product Surveillance, stating:

> *"I am really concerned about our performance in Operations. We have missed multiple deadlines … in the last several weeks. I need your help to make sure we are addressing each task and project requirement with quality and diligence to meet each and every one of them*[133]*. The bottom line is that our recent performance has been UNACCEPTABLE and will no longer be tolerated. Please make the necessary adjustments in your areas to address these issues so that they do not continue to occur."*[134]

The National Standards Authority of Ireland (NSAI) performed an audit in 2014, which included Essure functions that resulted in a Non-Conformity Report. Cause of the Nonconformity included: *"Milpitas (Essure) personnel were not adequately trained on the overall global complaint handling process to adequately oversee and/or explain the complaint cases."*[135]

The Corrective Action section of this Audit, which was signed by the Manufacturer states:

- *Bayer Milpitas SOP 01044 "Regulatory Inspection Procedure" will be revised to ensure that appropriate support functions are made available or are present for inspections and audits.*
- *Bayer global and Milpitas local complaint handling procedures will be revised to ensure all medical device complaints are available in the complaint database (Dev@com) and are accessible by Milpitas personnel.*
- *Milpitas personnel will be trained on the overall global complaint handling processes delegated to outside functions in order to adequately oversee and explain complaint cases.*[136]

All of these quality system failures led to a delay and/or total lack of proper MDR reporting.

VII. MEDICAL DEVICE REPORTING GENERALLY

Overview of Medical Device Reporting Regulation

The Food, Drug and Cosmetic Act provides the authority for FDA to require Medical Device Reports (MDRs) from manufacturers, importers, and user facilities. The QSR in 21 CFR 820.198 requires prompt evaluation of complaints for reportability to FDA as well as review, investigation, and documentation of complaints that must be reported as MDR's. The MDR regulation CFR 803 describes the specific criteria, timeframes, and process for reporting of device-related deaths, serious injuries, and malfunctions. FDA also encourages voluntary submissions from patients, caregivers, healthcare professionals, and consumers.[137]

Summary of MDR Reporting Requirements

MDR reporting requirements can be summarized from 21 CFR 803.50 and 21 CFR 803.56 as follows:

A manufacturer is required to submit an MDR report to FDA within 30 calendar days after becoming aware of information that reasonably suggests their marketed device:

- May have caused or contributed to a death or serious injury, or
- Has malfunctioned and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction recurred.
- A manufacturer must also submit a follow-up MDR report to FDA within 30 calendar days if additional information is obtained that was not submitted in an initial report.

An MDR must be submitted within 5 working days if FDA has made a written request to the firm, or if action is required to prevent an unreasonable risk of substantial harm to public health based on any information including trend analysis.

Definitions

The regulation defines terms to help manufacturers understand their reporting responsibilities. Key definitions from 21CFR803.3 include:

> ***Caused or contributed*** *means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of: (1) Failure; (2) Malfunction; (3) Improper or inadequate design; (4) Manufacture; (5) Labeling; or (6) User error.*
>
> ***Malfunction*** *means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed...*

> ***Serious injury*** *means an injury or illness that: (1) Is life-threatening; (2) Results in permanent impairment of a body function or permanent damage to a body structure; or (3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.*

Information that Reasonably Suggests a Reportable Event has Occurred

Information that reasonably suggests a reportable event has occurred is described in 21CFR 803.20 (c)(1) as:

> *"Any information, including professional, scientific, or medical facts, observations, or opinions, may reasonably suggest that a device has caused or may have caused or contributed to an MDR reportable event. An MDR reportable event is a death, a serious injury, or a malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."*

A manufacturer does not need to report an adverse event if there is information that would lead a person who is qualified to make a medical judgment reasonably to conclude that a device did not cause or contribute to a death or serious injury, or that a malfunction would not be likely to cause or contribute to a death or serious injury if it were to recur. Persons qualified to make a medical judgment include physicians, nurses, risk managers, and biomedical engineers. Information that the qualified person used to determine whether or not an event was reportable must be maintained in the files as specified.[138]

MDR Reporting and Complaint Handling Are Linked

As stated above, complaint files are linked to MDR event files because all complaints must be evaluated to determine if it is a reportable adverse event.[139] An FDA PowerPoint presentation titled "Complaint Files" created by Stanley Liu, Consumer Safety Officer at FDA, outlines the importance of complaint investigations and how they lead to corrective and preventative action.[140]

Investigation of Reports

Manufacturers are responsible for conducting an investigation of each potential event that comes to their attention and evaluating the cause. If the firm cannot submit complete information, they must provide a statement explaining why this information was incomplete and the steps taken to obtain the missing information. Any required information that is obtained after the initial report must be submitted in a supplemental report.[141]

Documentation

Manufacturers are required to establish written or electronic event files[142] containing all information related to the event including the firm's evaluation of the event and decision-making

process for reporting/not reporting to FDA. The MDR event file must also contain an explanation of why a firm could not obtain or did not submit any required information. The file must include copies of all MDRs submitted, and acknowledgments from FDA in response to electronic MDR submissions. MDR Event files must be retained for the expected life of the device (permanent for Essure) even if the product is no longer distributed.[143]

MDR Submission

Manufacturers must submit known or reasonably known information about the patient, event, device, follow-up treatment and outcome, as well as who provided the initial information.[144]Form 3500A is completed and submitted electronically.

Importance of MDR Reporting

Industry post market surveillance of medical devices plays a key role in protecting public health. Manufacturers gather most of the information needed to recognize safety issues. Reporting it to FDA provides the agency, other manufacturers, and the public with information about the events and an opportunity to independently assess emerging safety or performance issues. It enables FDA to act in a timely way to protect device users when necessary.[145] [146]

The FDA Medical Device Safety Action Plan,[147] issued by the FDA Commissioner and the CDRH Center Director in 2018 states:

> *"Although medical devices provide great benefits to patients, they also present risks. FDA's public health responsibilities span the life cycle of medical devices and, at every stage, FDA must make well-supported regulatory decisions, taking into account the totality of the evidence, to determine whether the benefits outweigh the risks… not all information regarding benefits and risks of a device is available nor can be generally known before a device reaches the market. New information about the device's safety, such as reports of unexpected adverse events, may become available once the device is more widely distributed and used under real-world conditions (e.g., in routine clinical practice, in the home setting), in broader patient populations, and by a broader range of clinicians. Or, the risks associated with a device may change—for instance, if modifications to a device introduce new or increased known risks, or changes in manufacturing adversely affect the quality of a device…"*

The FDA Manufacturer and User Facility Device Experience (MAUDE) database contains the MDR reports filed by manufacturers, importers, user facilities, doctors, patients and other sources. Within FDA, these MDR's are used to help estimate the risk of defective products and classify recalls. They guide the wording of public health statements and the pre-market review of future products. The database is also available to the public for online searches and downloads. MDR information allows consumers and healthcare providers to make informed decisions about devices and procedures for specific medical conditions. Manufacturers of similar devices can identify hazards and reduce risks for their own products.

FDA Response to MDR Signals

When the FDA becomes aware of a possible emerging safety concern, the agency gathers information and assesses the nature and significance of the issue. A comprehensive MDR review may be conducted looking at reports for the device and sometimes for similar products. An inspection of firm facilities may also be initiated. Both the MDR review and inspection were performed as FDA considered the increasing number of adverse event reports with Essure use.

FDA actions to address potential safety issues may include posting public health notices, writing publications for medical journals, encouraging manufacturers to recall products or issue letters to healthcare providers and patients, updating product labeling, ordering manufacturers to conduct post-market 522 studies, issuing guidance documents, developing and recognizing standards, as well as laboratory and clinical research. Rarely the Center may call an advisory panel meeting to provide public and expert input into a post market issue and recommend appropriate actions.

VIII. MEDICAL DEVICE REPORTING FOR ESSURE

As discussed above effective MDR reporting is an important tool for assuring medical device safety and public health. Disruption of a manufacturer's required MDR processes can result in incomplete or inaccurate information provided to FDA and other users of the MAUDE database. It can also result in reporting delays and delays in the provision of adequate information getting to the public and medical community. Disruptions can occur at various stages of a manufacturer's processes, including, but not limited to:

- Selection of qualified MDR management and staff
- Establishment of procedures to implement MDR reporting activities
- Intake of all relevant complaints and product experiences
- Triage of known MDR's to immediate reporting
- Investigation of all known MDR's and potential MDR's/complaints to timely closure
- Establishing and applying suitable MDR reportability criteria
- Filing MDR's within FDA required timeframes

Summary Findings Related to the Manufacturer's MDR Reporting for Essure

Other experts have reviewed the Essure MDR reporting procedures, processes, and filing decisions in detail and I concur with their findings. I have also reviewed material. Based on all this information, I have concluded that the Manufacturer failed to comply with MDR reporting regulations for Essure at all stages of the process identified above. In particular:

- Management lacked the skills, knowledge and experience to set policy and oversee or conduct adequate investigations and make appropriate MDR reporting decisions.
- MDR reporting procedures were inadequate and non-compliant with regulations.
- Investigations were not initiated, conducted, and completed in a uniform and timely way, or documented as required

- Overly limiting processes and criteria consistently removed potentially reportable events from assessment and MDR filing.
- Perforations and migrations were not reported despite FDA written notification that they were MDR reportable.
- Underestimation of the severity of harms and patient risks of events described in complaints and published literature elevated the reporting threshold for MDR's and limited submission of reportable events.
- Apparent manipulation of data assignments such as complaint category, attribution of cause for events, and determination of malfunction to avoid MDR reporting and to artificially lower complaint numbers to avoid safety signals.
- Failure to submit many reportable events associated with Essure use to FDA.
- Lack of required MDR reporting delayed FDA action on Essure by several years.
- Bayer knowledge of serious MDR reporting issues with past Essure practices did not lead to in depth reassessment of past filing decisions and corrective submissions to FDA.

The Manufacturer's Failures Related to MDR Reporting

Management Lacked Skills,Knowledge, and Experience for MDR Activities

The Manufacturer selected, employed, and promoted individuals to conduct and oversee complaint handling and MDR evaluation and reporting processes for Essure who lacked the education, clinical knowledge, training and experience necessary to make MDR reporting decisions for a Class III permanently implanted medical device. The firm was non-compliant with 21 CFR 820.20 (b) (2*): "Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities…"*. Below are resume summaries of the individuals who oversaw complaint handling, MDR evaluation, and reporting processes for the Manufacturer.

Edward Sinclair (V.P. of Regulatory Affairs, Clinical Research, and Quality Assurance)

Mr. Sinclair worked for Conceptus in 2001-2008 as Senior Director of Quality and returned in 2003-2008 as Vice President of Regulatory Affairs, Clinical Research, and Quality Assurance. He had an MA in Management but no education or experience in a healthcare field. His previous positions had been in quality leadership for medical device manufacturers and start-ups, sometimes including regulatory responsibilities.[148]

Robert McCarthy (Senior Director of Operations and Quality)

Mr. McCarthy received an Associate's degree from West Valley College in Saratoga, CA and began his career as an operations receiving clerk. He joined Conceptus in 2001 and worked in positions of increasing responsibility on Essure in documentation, production, and quality from 2001 to 2016. In 2008 he was appointed Director/Senior Director of Operations and Quality including supervision of the Product Surveillance group responsible for complaint handling and MDR reporting. In late 2013 the responsibility for MDR reporting was reassigned. Mr. McCarthy

continued his other duties until leaving Bayer as Site Director and Senior Director of Operations and Quality in 2016.[149]

Mr. McCarthy had no experience performing complaint investigations, clinical event reviews, or MDR reportability assessments. He had no medical background and was not familiar with the FDA regulations. He delegated all complaint and MDR decisions to Product Surveillance subordinates, colleagues in Regulatory Affairs, and quality engineers that he considered technical experts.On his c.v. Mr. McCarthy identifies reducing "the Essure Product cost by 47%" as a Key Highlight of his career.[150]

Michael Reddick (Senior Manager of Product Surveillance)

Mr. Reddick served as Senior Manager of Product Surveillance for Essure from 2009-2016.[151] He directly supervised the Product Surveillance staff and was responsible for MDR reporting decisions until late 2013. He continued in a lead role for Essure complaint handling until 2016.
Mr. Reddick had a Bachelor's degree in Industrial Engineering and an MS in Industrial and Systems Engineering.[152] He had no medical background or clinical experience.[153] Before joining Conceptus he worked for a Class II medical device firm as a Quality Engineer.

Rachelle Acuna-Narvaez (Regulatory Affairs Associate /Manager/Director)

Ms. Acuna-Narvaez joined Conceptus in 2007 as a Regulatory Affairs Associate after earning her J.D. and working for a law firm on merger-related activities for almost a year. When she left the company in 2013, she described her position as Director of Regulatory and Clinical Affairs with responsibility for supervision of worldwide clinical trials and regulatory compliance for Essure. Ms. Acuna-Narvaez worked as a clerk in a medical office for several years and attended one year of medical school (1990-1999) before pursuing her law degree.[154] She had no training or experience with regulatory work, medical device regulations, or medical device manufacturers before she was hired.[155]

Edward Yu (Director of Clinical and Regulatory Affairs)

Mr. Yu joined Conceptus in July 2006 as Director of Clinical and Regulatory Affairs, and in 2009 became Vice President of Clinical and Regulatory Affairs, taking on additional responsibilities as a member of the executive management team. He spent much of his time overseeing post-market clinical studies and the rest on regulatory affairs, consulting with Product Surveillance as requested on MDR reporting issues.[156] He holds a bachelor's degree in biological science and a master of business administration degree.[157] Before joining Conceptus, he worked in Regulatory Affairs for Guidant in relation to its sale of cardiac stents and various other companies, but not implantable gynecologic devices.

Lois Pierce (Quality Control Supervisor/Technician/Product Complaint Manager)

Ms. Pierce joined Conceptus in February 2000 as a Quality Control Supervisor.[158] Her responsibilities included conducting regular employee training Good Manufacturing Process (GMP), ISO and Medical Device Directive (MDD) regulation, and writing SOPs.[159] Her role

included inspecting raw material that came in before it was time for final assembly. Ms. Pierce holds a bachelor's degree of science and a master of business administration degree.[160] Prior to joining Conceptus, Ms. Pierce worked with medical devices as raw material components.[161]

Ayesha Siddiq (Product Surveillance Clinical Analyst)

Ms. Siddiq joined Conceptus in July 2006 as a Product Surveillance Clinical Analyst, and was later promoted to Manager within the Product Surveillance group. Ms. Siddiq was involved in complaint handling related to the Essure device throughout her time at Conceptus. She holds a bachelor's degree in science, and obtained her certified medical assistant license in 1998.[162] Before joining Conceptus, she designed and developed software user training to maintain compliance in software and meeting FDA requirements at Kyphon Inc.[163]

Findings

It is my opinion that all of the managers and decision makers listed above lacked adequate training and education necessary to perform MDR related duties for the permanently implanted Class III Essure device. They also demonstrated a lack of basic understanding or concern about the purpose or application of FDA regulations, medical device risk assessment and risk management, as well as product safety issues or what a permanent implant can do in the body. This is shown in the examples throughout the following sections.

MDR reportability frequently involves assessing whether an event is a "***Serious injury"*** defined in the regulation as an "injury or illness that: (1) Is life-threatening; (2) Results in permanent impairment of a body function or permanent damage to a body structure…"

Individuals making these assessments, like those identified above, should have sufficient knowledge, training, and experience to interpret these regulations, including the definitions, in relation to the product at issue and the clinical impact the product may have on the patient over time while inside the body. Failure to understand these requirements and lack of these qualifications, can and did in this case lead to an underreporting of MDRs.

For example, these MDR decision makers failed to understand that an implant in the abdomen had the potential to be life threatening even if it was initially asymptomatic, despite reports of bowel perforations requiring surgery. (See perforation section below).

Perforation is a hole that develops through the wall of any body organ. Small or large bowel perforations may have symptoms including severe abdominal pain, fever and chills, nausea, vomiting and shock. Treatment generally involves antibiotics and often includes emergency surgery to repair the hole. Sometimes one end of the intestine may be brought out through an opening in the abdominal wall (colostomy or ileostomy) to allow the bowel to heal. Surgery is generally successful, but the outcome depends on severity of the perforation, how long it was present before diagnosis, tolerance of the patient to anesthesia, and the patient's underlying health status. Infection is a known complication of perforation and may occur inside the abdomen (abscess or peritonitis) or throughout the body (sepsis). These infections can be life-threatening or fatal. Bayer is aware of this information because it is a known risk for their IUD

product and listed in the labeling from 2008. (Warning # 3 for Sepsis references risk of death, and Warning #7 references risk of intestinal perforations and peritonitis).[164] A cursory library or internet search would also have made this information available to Conceptus management.[165] [166] [167]

The Manufacturer's MDR Procedures Fail to Comply With Regulations

In 21CFR803.17 the regulation requires that manufacturers develop, maintain, and implement written procedures for:

1. Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements;
2. A standardized review process or procedure for determining when an event meets the criteria for reporting under this part;
3. Timely transmission of complete medical device reports to manufacturers or to us, or to both if required.

However, the procedures for Essure failed to clearly describe appropriate processes and timelines for complaint reporting triage, investigation, and MDR reporting by the Manufacturer. Examples include:

a. Wording of definitions,
b. Criteria and processes for MDR activities were often lifted or paraphrased directly from the regulation with no explanation of how the terms would be applied for this device and firm,
c. Wording and content of documents changed frequently. Form QAF-2729 bounced back and forth between several criteria sets in revisions, and repeatedly removed "Chronic/Long-term Pain" from items to be reported.[168] [169] [170] [171]

There was ongoing confusion, not clarified in the procedures, about handling contacts from patients. On December 3, 2007 Jennifer West requested clarification after a call from a patient with constant bleeding post implantation and the Essure found in her uterus. She e-mailed Edward Yu and Laura Cases: *"Ed, I am not sure (once again) what to do with this. I am not sure who is going to contact this person..."* On December 7, 2007 she sent another request, *"Ed, I am not sure (once again) what to do with this. I am not sure who is going to contact this person…"*[172]

On February 7, 2008 Gaby Avina (Ask Gaby) emailed Jennifer West in response to a patient reporting perforation:

> *"What is Regulatory's process for handling these complaints. My role is really to answer questions for women interested in the procedure. I have been spending time 'putting out fires'. Please, let's discuss this again."*[173]

On March 6, 2009 a Product Surveillance staff member expressed uncertainty about how to handle a patient complaint and who was allowed to contact patients. Ms. Acuna-Narvaez responded on March 17: *"It's my understanding that if we receive a patient complaint about the product, it is a*

complaint that needs to be investigated according to the regulations. Thus, from a regulatory point of view, we should contact patients that have had the procedure and complain about the device…" Someone determined that the patient needed to sign a HIPPA form and Mr. McCarthy received the form on March 30, almost a month after first contact. It then had to be shared with the patient so complaint investigation could begin.

The CE mark for Essure was suspended on August 3, 2017.[174] The three root causes that were identified as contributors to the CE Mark Suspension included:

1. *The integration of the Complaint Handling Process was not effective*
2. *The original requirement to include language in BDP-SOP-017 was not included in the final released version*
3. *The effectiveness check of CAPA No. did not adequately verify that all actions were effectively addressed* [175]

The Manufacturer's MDR Reporting Criteria Was Too Restrictive

The regulation describes criteria for required Manufacturer MDR reporting in 21 CFR 803.50. There is no wording that limits MDR submissions to these circumstances. In fact, many MDR submissions received by the agency come from small manufacturers with limited regulatory knowledge, or physicians, healthcare facilities, patients, or consumers with very little to no regulatory knowledge. Manufacturers are at risk of regulatory penalties if they fail to report required events but submitting MDR's when reporting may not be necessary does not carry similar penalties.

Instead of taking the required reporting criteria and developing procedures explaining how they would be applied for Essure so that all appropriate events would be reported in a timely way, the Manufacturer developed a set of exclusions describing all the times reporting would not occur. These exclusions removed entire groups of contacts or complaints from potential MDR reporting and reduced the number of reports filed to the very minimum. These exclusions do not appear in the procedures but are consistently referenced in emails and deposition testimony. Because this process prevented submission of reportable adverse events to FDA it was both irresponsible from a public health perspective and failed to comply with the regulations.

On February 10, 2009, Rachelle Acuna-Narvaez wrote in an orientation email to Michael Voss that attached is *"My thoughts on medical device reporting so you know the nitty-gritty. This is my regurgitation of tribal knowledge here –* ***no work instructions or SOPs exist on this, nor should they IMHO****."*[176]

The failure to submit reportable events was described in an email dated October 28, 2013 from Cibele Rudge to Roland Graf and Ilona Weltrowski about differences between the Conceptus and Bayer approaches to MDR reportability. He notes that in the exemplar cases, Conceptus did not report the cases but he feels they are reportable. Weltrowski responds that the *examples "illustrate that the reportability criteria at Conceptus were far more reduced to interventions required to prevent serious injury..."*.[177]

The exclusion policies were sometimes carried to extremes, as in the case where a patient died from complications that developed during an Essure insert removal and no MDR was filed.[178] Some of these exclusions are as follows:

Exclusion #1: Will Not Pursue Investigation/Reporting if Intervention or Procedure Did Not Occur to Treat Symptoms or Remove Device

21 CFR 803.50 requires reporting of an injury or illness that "*… (2)Results in permanent impairment of a body function or damage to a body structure… (3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function… or permanent damage to a body structure….*

In some cases, significant symptoms may be treated by medical or surgical intervention before permanent loss of a body function occurs. These should result in an MDR report following subsection (3) above. However, intervention is not required to meet MDR reporting criteria. Subsection (1) requires only that the event be life-threatening, and Subsection (2) requires only that permanent impairment or damage occurred with no mention of intervention. An acute injury could lead immediately to permanent impairment, for example from severe bleeding, bowel damage before surgery, or nerve injury. Intervention may also depend on the ability of healthcare providers to correctly diagnose the cause before permanent damage has occurred, and on whether the patient's health is sufficient to tolerate the intervention. Situations that meet subsection (2) must be reported, will be valuable for FDA to consider, and exclusion from reporting appears violative. In fact, these women are likely to be more seriously ill or injured than those who underwent intervention.

Examples of statements made by the manufacturer regarding the confirmation of medical intervention include:

A November 3, 2013 email from Ayesha Siddiq, Clinical Analyst, to Shaw Lamberson, Director US Country Pharmacovigilance stating: "*The most critical investigations are needed for those where MDR reportability is the main factor and* ***we need confirmation of medical intervention from a doctor****."*[179]

Edward Yu, Vice President of Clinical and Regulatory Affairs testified to the necessity of medical intervention in stating:

> Q. So if a physician reported to you that a perforation occurred from Essure and that a surgery to remove the coil was being planned but had not yet occurred, would you consider that a reportable event?
> A. No, not until the event had happened.[180]

A June 28, 2011 email from Michael Reddick to Michael Voss states that a case should now be considered an MDR, because "the physician went back on a separate procedure (hysteroscopy) to examine the source of a patient's pain and he removed an object… Since the patient's pain resolved following the removal, we would consider this to be medical intervention."[181]

Exclusion #2: Will Not Pursue Investigation/Reporting Unless Physician Confirms Medical Necessity of Intervention

There is no requirement in the regulation that any information, including medical or surgical intervention, must be confirmed by a physician, or the treating physician, or be confirmed to be medically necessary. It is my opinion that, for purposes of MDR reporting, if a patient and physician together make a decision that medical or surgical intervention will be performed, they have concluded that it is medically necessary and the occurrence of intervention is sufficient to meet subsection (3). Considering the sensitivity of healthcare providers (and gynecologists in particular) to malpractice issues and legal actions, asking for a retrospective re-confirmation of the necessity of a completed procedure could potentially create barriers to good patient care and completing the investigation. This exclusion is not appropriate and appears violative.

An email from Shirley Reid, Product Surveillance temp, dated December 1, 2009 with subject line "Unresolved Complaints Please provide status" demonstrates that this Medically Necessary requirement was considered routinely. She is seeking information to close out overdue investigation files, hopefully well after the 30-day report/no report decision was made.

> *"…AR without information in CRM, on HSG List, MDR log or in Correspondence e-mail. AR-05632-JPOY Patient had Essure placement in 2006 and has experienced pain ever since. Patient blames pain on Essure device. Physician performed hysterectomy 2008.* ***Was the hysterectomy actually performed? Was it medically necessary.*** *Where is the 30 day MDR? What is the status of the patient? (Nov 2008)*
>
> *AR06271-2ZKR Patient had Essure procedure performed by different physician. She went to another physician because she was experiencing pain and wanted a second opinion. U/S revealed a perforation. No HSG was performed. What was the result of this situation? How was the perforation handled?* ***Was device removed? If so, was it medically necessary.*** *What is the status of the patient? Where is the MDR?"*[182]

Emails from the Complaint file for AR 20670-SWFF between Michael Reddick, Senior Manager of Product Surveillance and Michael Voss, Outsourcing Manager at Reglera, indicate the established use of various exclusions including requirement for confirmation of Medical Necessity.

> On April 18, 2011 Michael Reddick begins: *"I would like to get confirmation from the physician on this case. I.e. did removal occur? Did symptoms resolve?* ***Did physician feel Essure removal was medically necessary?"***[183]
>
> On April 19, 2011, Michael Voss responds: *"Removal has not yet been performed, but is scheduled. So we don't yet know if symptoms have resolved.*
>
> *I hesitate to wait until the actual procedure takes place (approximately 30 more days) to report this incident. To be conservative, I feel this is a reportable incident for the following reasons, but I would like to better understand the Conceptus policy. It seems to me, in this case, that since the physician is going to perform surgery, medical necessity is implied.*

Additionally, perforation with pain followed by device removal is an established reportable incident (ex: has been reported as MDR's many times in past), as such, physician collaboration is not a requirement for determining in the affirmative that this event is reportable.

I know Conceptus has a policy of getting collaboration from Dr.'s regarding medical necessity, *resolution of symptoms, etc. Please provide feedback"*[184]

Exclusion #3 Will Not Pursue Investigation/Reporting Unless Physician Attributes Symptoms / Need for Intervention Directly and Exclusively to Essure Device

The regulation does not require any statement from the patient's healthcare provider, including a statement attributing the symptoms reported or intervention taken specifically or exclusively to the device. The Manufacturer is encouraged to investigate and gather clarifying information about the event. The submission form includes space for how the device was involved (21 CFR 803.52 (b)(5). However, to require a specific statement in order to proceed with investigation or reportability assessment is outside the scope of the regulation and unduly limiting. In addition, medical/surgical intervention may be performed for symptom relief or resolution through removing inserts, and/or address contraceptive concerns at the same time.

None of these procedures would be needed without a failure or adverse event related to the Essure product. The information only needs to reasonably suggest that a device may have caused or contributed to and does not need to be decisively known at the time of an MDR reporting decision. Obtaining the statement from a physician may also not be practical. A temporal and/or anatomical association with the device may be sufficient to make the reporting decision in some cases. An exclusion removing complaints from investigation or reporting consideration may lead to non-reporting of legitimate issues and is not appropriate for MDR reportability assessment.

Ilona Weltrowski, Product Technical Complaints and Device Vigilance, confirms that medical intervention was part of the Manufacturer's reporting assessment stating:

Q. And what do you understand was the -- were the key differences between the way that Conceptus reported complaints and the way that Bayer reported complaints?
A. **Well, one of the key differences was that Conceptus did reach out** to the treating physician to obtain medical confirmation, but also **to discuss with the treating physician if the intervention was related to the Essure device**. So it was a medical confirmation including a relatedness assessment that was obtained from the treating physicians. In the Bayer organization, we, of course, also reach out to treating physicians to receive follow-up information, but our reportability assessment is done in-house by medical experts that we have in-house, and we do not necessarily have to have the medical – the confirmed assessment from the treating physician order to take the reportability decision.[185]

On August 14, 2006, Pamela Price, Medical Director, sent an email to Edward Yu, Vice President of Clinical Research and Regulatory Affairs, with the subject "MDR—filing due today" stating: *"I thought surgical intervention for device removal was reportable. The physician did not give an*

alternative reason for her pain…" Edward Yu, Vice President of Clinical Research and Regulatory Affairs, responded that same day stating:

> ***"As long as the treating physician believes that the pain is not directly attributed to the device, I don't believe that we need to treat this as reportable based upon our procedure/evaluation form****. That being said, it would be nice (per your comment Pam) to have an alternate reason from the physician, or update if the pain has resolved but overall I am comfortable from a documentation standpoint."*[186]

On October 22, 2013, Rachelle Acuna-Narvaez, Director of Regulatory and Clinical, sent an email to Shaw Lamberson, Vice President of US Pharmacovigilance, stating:

> *"We don't have a letter or document confirming that only medically confirmed MDRs have to be reported; it is an assessment that we made as a company to report in this manner.* ***As regulatory, we felt that it was a justifiable approach because we often found out in investigation that a complaint may initially have appeared to be reportable, but it may not be when information was gathered from the physician."***[187]

Exclusion #4: Will Not Pursue Investigation/Reporting If a Patient's Symptoms Did Not Resolve Following Surgical Removal of Device

Improvement after intervention is not required by the regulation and is not a clinically appropriate expectation. Patients with the most serious conditions may have symptoms that continue beyond intervention. The injury or illness may already have caused permanent injury with continued symptomology. Howard et al. reported on persistent pelvic pain over several years after an apparently successful retrieval of a perforating right-sided Essure implant. The authors noted that Essure fragments may have perforated the uterus and warned that Essure fragments are not always visible to the naked eye.[188]

Excluding patients with continuing symptoms from MDR reporting would eliminate the most severe cases. It is also possible that additional injury could occur during the intervention process causing new symptoms that could become confused with the original problem. Resolution of symptoms could be a factor considered in favor of reportability decisions. However, lack of resolution of symptoms should not be weighed as a factor against reporting and it should not be used as an absolute exclusion from MDR. Consistent use of such an exclusion is non-compliant with the regulation.

However, in his emails Michael Reddick repeatedly instructs Product Surveillance staff that this is a requirement for MDR reporting. As noted in the example for Exception #2 above, Mr. Reddick is asking for confirmation that the symptoms resolved following product removal before making the decision to report to FDA. He also explains the process to Alicia Lowery, Regulatory Affairs Associate, in an email dated September 11, 2012 with the subject "FDA MW Inquiry DUE 10/5" as follows:

> *"This is a case where we have information from the patient, but no information from a medical professional to corroborate the information. We always seek answers to 3 key*

*questions: (1) was device removal performed, (2) did physician attribute the cause to Essure, and **(3) did symptoms resolve after removal**. Since we couldn't contact the physician or any other medical professional, we couldn't make a proper assessment."*[189]

Rachelle Acuna-Narvaez, Regulatory Affairs Manager, confirmed the Manufacturer had a policy to determine whether a patient's symptoms resolved after [medical] intervention stating:

Q. And what Michael Reddick indicates is that: Historically the Conceptus process, when we received a complaint that was a potential MDR, we would investigate the case by contacting the physician involved and getting any additional facts about the case that would help us assess the reportability of the complaint. Specifically we would verify the facts that we had received, determine if medical intervention had been performed, **determine if the patient's symptoms resolved after intervention,** and get the physician's medical opinion of whether the Essure device caused or contributed to the issue. Based on information gathered during our investigation, we would file with FDA within a 30-day window.
Did I read that correctly?
A. Yes.
Q. And is that your recollection of how the Conceptus process went during your time at Conceptus with regard to filing MDRs with the FDA?
A. Yes, that is my experience on how the product surveillance department approached the issue.[190]

Exclusion #5: Will Not Pursue Investigation/Reporting of Events Occurring During Procedures Unless Essure Device is Confirmed Direct Cause

The regulation requires that manufacturers submit MDR reports to FDA after becoming aware of information that reasonably suggests their marketed device " May have caused or contributed to a death or serious injury, or …".[191] When procedures are being performed for purposes of implanting, removing, treating symptoms from, or replacing the Essure product the product is considered to have "contributed to" the serious injury and the manufacturer should track such events and report as appropriate.

During an FDA inspection from December 8, 2010 to January 6, 2011 the Investigator noted that the firm was not reporting complaints of injury occurring during insertion of the device (FDA 483-Observation #1).[192]

Observation 1:

An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury. Specifically, the following complaints from July 12, 2010 to Dec. 10, 2010 both report a bowel perforation that occurred during the procedure to place the firm's product.

1 – incident and aware date of 11/3/2010: ***Perforation from scope,*** *patient taken to hospital for exploratory laparoscopy. Resolution notes on 12/21/2010 states* ***patient had bowel perforation*** *with some hemorrhage. Patient had a hysterectomy.*

2- incident and aware date of 11/16/2010: When doctor attempted to place second device, ***she used graspers to locate the ostium. She perforated the patient's bowel****.*

In both complaints the firm's device did not directly cause the injury, but the procedure for use required the use of an hysteroscope and visualization of the tubal ostium

The Manufacturer routinely excluded procedural events that occurred with the use of devices other than Essure during insertions, removals, hysterectomies and other procedures/surgeries for treatment of symptoms. Tubal ligations were conducted to address symptoms or performance failures with Essure and I believe they should have been tracked and reported to FDA as well. Excluding these events from investigation and/or MDR reporting was inappropriate and violative.

Exclusion #6: Will Not Pursue Investigation/Reporting Unless Technical Defect is Recognized as Malfunction

A malfunction is defined in 21 CFR 803.3 (k) as "the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed..."

The Manufacturer failed to investigate and assess reportability of events where product did not perform as intended, showed technical defects or had issues that were not acknowledged as malfunctions, even if they were visibly obvious. The symptoms or events were then attributed to non-product factors and excluded from reporting.

For example, all perforations and migrations of the device should be considered malfunctions because the implant moved out of the fallopian tube where it was intended to create a physical barrier preventing sperm from reaching the egg.[193] [194] They should also be reported as MDR's because serious or life-threatening events have occurred with Essure insert migrations. (see below) Despite written instructions from FDA to report these events [195] and verbal guidance from an FDA investigator, the Manufacturer often failed to submit MDR's for perforations and migrations particularly if they were asymptomatic. For example, a CT scan showed an Essure device in abdominal cavity following abdominal pain. The device was removed and returned, but no device investigation was required by the Manufacturer.[196]

Devices that were either unable to be located, had migrated or broken in the patient's body post implant and were not removed were not treated as malfunctions and reported by the Manufacturer if the specific patient was currently asymptomatic.

On November 25, 2008, Mia Zhang sent an email to Rachelle Acuna-Narvaez, Regulatory Affairs Manager, with the subject "AR05730-4A9E_need review please" regarding an AR generated for

a physician who used graspers to remove a broken Essure device. Rachelle Acuna-Narvaez responds:

> *"Yes, this is how we treat these incidents. If a "broken" device is removed w/ graspers during the Essure placement procedure, it is considered as a part of the procedure. Additionally,* ***broken device, properly places doesn't require intervention- it can remain in the patient if asymptomatic****."*[197]

Note – a broken device indicates a failure to perform as intended, the definition of a malfunction and should be documented, addressed through root cause analysis (not labeling review) and tracked to open a CAPA if appropriate. Whatever stresses are provided during insertion, this possibility of breakage should be considered in advance or when it occurs, evaluated for risk to patient and future occurrences minimized through design or materials changes, improved instructions for use, or whatever other product improvements are appropriate.[198]

In another example, an Essure device that actually broke apart during insertion was attributed to procedure error not product related, and therefore not reportable.[199]

On January 20, 2011, Edward Yu, Vice President of Clinical Research and Regulatory Affairs, responded to the FDA regarding five instances he identified as examples of perforations where the Essure was found in the abdominal cavity. On page 3 of this letter, Edward Yu writes:

> *"Because none of the cited complaints of micro inserts being found in the peritoneal cavity resulted in pain or other symptoms****, the reports of the mislocated devices constitute mere trivial impairment or damage that does not rise to the level of serious injury****."*[200]

From a clinical perspective, allowing a foreign body to remain in the patient is not confirming that the foreign body is safe or causes only trivial impairment. Rather, it indicates that the healthcare provider has determined that the risk of removal is greater than the risk of retention. If the product had performed as intended, the patient would not be faced with either of these risks. A more appropriate assessment here is what risk does the broken fragment or migrated product pose that the patient would not otherwise be exposed to? (See the perforation/migration section below).

This same process weighing risks of removal vs. retention is used when bullets lodge in gunshot victims. The risk of removal is often considered greater than the risk of retention and the bullet is left in place, but that does not mean the bullet poses no or trivial risk. Dr. Alan Cook, Director of Trauma Research at Chandler Regional Medical Center in Arizona states: "Very often, the bullets are not removed in the (hospital) setting because doing so would potentially cause more harm to the patient than the bullet has already done," and Dr. Debora Weiss, an Epidemic Intelligence Service Officer at the CDC agrees: "Unless it is wedged in a vital organ, …or a blood vessel, a bullet is usually just left alone." She adds that exposure to the bullet in the body can have short- and long-term effects ranging from a small change in organ function to life-threatening.[201] [202]

Note that for mis-placed Essure inserts (or for bullets) the retention/removal balance can change, such as if a patient develops symptoms of infection, organ perforation, bleeding, nerve damage, toxicity or hypersensitivity to materials.

Exception #7: Will Not Record and Pursue Investigation/Reporting of Multiple Issues or Failure Modes

The MDR reporting regulation does not limit symptoms, events, failure modes or product malfunctions to one per product, one per event/incident, or one per patient. This restriction is violative and artificially lowers complaint rates or adverse event reporting rates, delaying recognition of safety concerns.

The Manufacturer did not record multiple symptoms or failure modes even in cases where additional issues were clearly identified or confirmed by product examination.

On May 8, 2012 Mr. McCarthy emailed Greg Lichtwardt and Keith Grossman, President and CEO, saying ***"We do not currently open and record multiple ARs for other issues seen in the physical review of the returned device."***[203]

Dr. Andrea Machlitt, MD Director of Global Pharmacovigilance Risk Management, testified to the challenges this type of practice poses stating:

> Q. She goes on to say that [as read]: As you know, the Conceptus only captured one event per case. Did I read that correctly?
> A. Yes. And that is in relation to what we discussed beforehand.
> Q. Right.
> A. So the Essure cases at Conceptus would have one coded entry in a failure mode. And the rest of the information would sit in the narrative, but not in a structured field.
> Q. And again, Dr. Monemi is saying if you want to capture all of the events, or you want to identify all the events, you have to check the narratives, right?
> A. Yes. And the point here is – that Ilona has not considered is that if you search for things that are not yet coded into a certain dictionary system, it will pose challenges. Because you can't rely that somebody has already coded it, and then you could look for standard metric queries, for example. So you could not do that here. You would need to apply other criteria, which would involve much more manual work.[204]

Exclusion #8: Will Not Consider Reporting Without Completed Investigation

Complaints can sometimes meet the threshold for MDR reporting based on initial information. How often reportability can be determined this quickly depends on the type of device, the nature of the adverse events, the source and consistency and completeness of complaints received, as well as the clarity and stringency of reporting criteria the firm applies.

The Manufacturer did not allow for this possibility. The requirements for follow-up and confirmation from a healthcare provider and resistance to a decision before investigation was closed limited the value of initial triage. In addition, the initial decision tree process used by the

Manufacturer almost always determined no for MDR reporting, so even cases where initial information reasonably suggested that the device caused or contributed to an event with required reporting the investigation was not prioritized accordingly.

A prompt and more appropriate triage process for new complaints would have allowed for rapid identification of obviously reportable events with investigation only to clarify reporting details. MDR reports for these known events could have been prepared immediately and submitted within the 30-day window, assuring regulatory compliance and freeing up staff for other investigations.

Essure adverse events often involved significant symptoms or patterns of symptoms recognized by patients and not requiring physician interpretations (such as might be necessary with laboratory tests or imaging studies, for example). The product also involves significant one-time interventions clearly known to patients. Examples of immediately reportable Essure complaints might have included significant symptoms of pain or bleeding, known damaged or inappropriately located inserts treated by medical intervention including insert removal, laparoscopy, hysterectomy or tubal ligation. Another example might have been injuries occurring from any cause during insertion or removal of inserts or follow-up intervention.

Rachelle Acuna-Narvaez, Regulatory Affairs Manager, opposed the idea of immediately reportable Essure complaints and testified:

> Q. So if a woman in whom the Essure device had been planted notifies Conceptus that she has suffered an injury that she relates to the Essure device, that triggers that 30-day requirement; right?
> A. Not necessarily.
> Q. Tell me why.
> A. In a case like that, we would actually look at all facts of the case. Even if a physician suggested it, we would do a – or sorry, reported such an event, we would actually examine the event in accordance with the procedures and work instructions that product surveillance has. And I saw "we," but it would be primarily product surveillance's department's responsibility. And they would look at the event and see if it seems to trigger the reporting requirements. And so I would say that in order to interpret the regulation that we become aware of information that reasonably suggests a device we market may have caused or contributed to a death or serious injury, we would actually examine each individual file to see if it meets that regulatory definition.[205]

The result was that numerous known MDR events were never filed or were submitted long after the due date in violation of FDA regulations. In late 2013 Bayer instituted an immediate filing process for known MDR's and also eliminated the requirement for physician confirmation. The number of MDR's reported rose immediately and significantly as described below.

Exclusion #9: Will Not Pursue Investigation/Reporting of Clinical Issues in Complaints

Complaint handling for Essure had a strong focus on the insertion process and time period, monitoring the product as a mechanical, single use disposable device rather than a permanent

implant. Procedures and the design FMEA process (SOP-01107), the investigation process, and safety considerations all seemed to prioritize the insertion timeframe technical product defects such as breaking, bending, or failing to insert, without adequately considering complaints of clinical symptoms and the potential long-term impact of permanent inserts in the body.

A spread sheet titled "Essure Follow-Up Clinical Investigations" outlines the clinical investigations that the manufacturer did and did not conduct.[206] This spread sheet does not consider clinical issues such as bleeding, cramping, or vaso-vagal response to be potential MDRs.[207]

The Conceptus Call Center Scripts for handling complaints (Revision A for example) asked no questions about patient history of nickel allergy, history of pain (headaches, menstrual cramps, hx of irregular bleeding) before or after the procedure was performed. The initial script focused on replacement of product and did not even ask about symptoms associated with the procedure or during use.[208]

The Manufacturer excluded incidents from MDR reporting if there was no obvious technical defect device function identified and confirmed as direct cause of the issue. Such events were attributed non-specifically to patient anatomy, doctor lack of experience, or problems with physician technique and not pursued. Under the regulation 21 CFR 803.3(c)(3), (5) and (6) these events were reportable because product design, labeling or user error may have caused or contributed to the problem. Design and labeling of the product are factors in success of product placement and use with atypical anatomy, success by inexperienced physicians, and success with variation in physician insertion techniques. In addition, the Manufacturer was required as a condition of approval to provide a new physician training program[209] , so the firm had regulatory responsibility for and directly influenced physician experience and techniques.[210]

Exception #10: Will Not Pursue Investigation/Reporting Based on Information From Patients

The Manufacturer had a long-standing practice of not accepting or following-up on complaints directly from patients. This was a very significant and inappropriate exclusion. It is not known how many complaints and reportable MDR's were lost due to failure to accept and pursue these clinical events. On August 3, 2006 Pam Price, Medical Director, wrote*:*

> *"Ed and Shelly, I think the call center needs to* ***aggressively direct these patients back to their physicians and ask that their physicians call the medical consult line*** *if they need additional info."*[211]

On February 12, 2008 Jennifer West, Medical Affairs Liaison, sent an email response to Gaby re: patient complaint that the Essure coils are nowhere to be found and that she has heavy bleeding for the last 2-3 months non-stop:

> *"This really isn't something that we would investigate further...****we have made the decision that we will not call patients so you don't need to ask the patient permission to contact her or her phone number****."*[212]

Mr. Reddick stated in an email dated September 11, 2012:

> *"**This is a case where we have information from the patient, but no information from a medical professional to corroborate the information.** We always seek answers to 3 key questions: (1) was device removal performed, (2) did physician attribute the cause to Essure, and (3) did symptoms resolve after removal. **Since we couldn't contact the physician or any other medical professional, we couldn't make a proper assessment."***[213]

Apparently, the file was closed and no MDR was filed.

Stan Fort emailed Ayesha Siddiq, Product Surveillance Clinical Analyst, with a potentially reportable case and on November 1, 2013 Ayesha responded*: "Hello, There will be no PTC opened for the social media case. This is not a confirmed patient report. Thanks."*[214]

Contacting healthcare providers to obtain clinical specifics of an event may be helpful as part of an investigation to understand how a product performed. However, confirmation from a healthcare provider is not necessary in many cases for reaching an MDR reportability decision. (Note the email from Michael Voss, Outsourcing Manager at Reglera, about requiring physician confirmation in Exclusion 2 above for AR # 20670-SWFF) and failing to investigate or closing a file prematurely without reporting for this reason is a violation of the regulation. Patients can inform an interviewer if they are several months pregnant, have pain, bleeding, or cramps. They know if a device removal procedure has been performed and in most cases are aware of the outcome from the healthcare provider. They know better than anyone if symptoms have or have not resolved.

Policy requiring physician confirmation is also not consistent with FDA's regulatory expectations. The agency accepts unconfirmed MDR reports for many devices directly from patients and actively solicits them. The FDA summary on Essure written for the Essure Advisory Panel showed in Figure 5 that the majority of MDR reports during 2013-2015 were self reports from women to FDA.[215] FDA provided a MedWatcher app to facilitate direct consumer reporting of adverse events to FDA.[216] During recalls FDA encourages manufacturers to provide MDR reporting information in Dear Doctor letters and other communications, so product users can report issues directly to the agency, and the agency solicits adverse event information directly from patients/consumers in public health notices.

Requiring confirmation from healthcare providers significantly delayed Essure MDR reporting decisions, since the Manufacturer started the 30-day MDR reporting window when investigation was complete. (see below). The exclusion of direct from patient information also led to closing investigations with no MDR filing, regardless of the severity of incident involved. The impact of this practice was demonstrated by the large increase in MDR filings when Bayer took responsibility for Essure MDR reporting. One manager indicated that the only change in reporting criteria that occurred was removal of the requirement for healthcare provider confirmation.

Limiting the acceptable source of information to healthcare providers can also limit recognition of safety issues for women's products. Complaints from women patients are consistently under-assessed for severity and clinical significance by healthcare professionals. This has been

established through a number of studies and occurs in both clinical trials and private healthcare situations. As a result, safety signals can be missed if a firm is overly reliant on data generated or only confirmed by healthcare providers.[217]

Exclusion #11: Will Not Pursue Investigation/Reporting Due to Changing Interpretation of Complaint Category

The Manufacturer pursued changes in categorization of complaints or events to avoid MDR reporting and/or reduce safety findings from trends. Such adjustments to avoid reporting are noncompliant and can lead to product safety risk. An example is the bent tip problem with Essure insertions.

The number of Essure System bent tip complaints was increasing in 2010. A Corrections and Preventive Action (CAPA) plan was opened and results of the investigation were emailed to the team on June 5, 2010, with Mr. Reddick and Mr. McCarthy both copied:

> *"During the course of our investigation, we observed a high degree of sample -to -sample variability in the tip bend angle exhibited by product manufactured in Tijuana, which in several cases failed to meet the admittedly subjective specification for kinks, gaps, and bend location. We have subsequently confirmed this variability as one of two repeatable causes for the "bent tip- introducer" failure mode. The other is a condition that can exist within the duckbill valve though normal process variation and is acceptable for the standard duckbill application; however, it has the potential to create a bent tip defect in our application, especially when combined with an exaggerated tip bend angle. Some minor contributors have been identified as well, but we are presently focusing our efforts on resolving these two key factors."*[218]

The bent tip complaints continued, and although the firm had identified causes related to failure to meet specifications and component design, Mr. McCarthy sent an email on May 11, 2012 suggesting that they recategorize this large number of complaints as physician error and no longer count them as device complaints. This would also inevitably take them out of the possible MDR pool. He stated that ***"Almost all bent tip complaints are currently classified as device complaints; however, a substantial number of bent tip complaints actually arise from clinical events caused by physician training or physician technique issues."*** He included a chart showing 479 bent tip complaints from January 1 to March 31, 2012.[219]

Another example of failure to capture accurate complaint numbers is reflected in the following email on January 20, 2013. The initial classifications of questionable placement or patency are not being correctly updated with final results of the film reviews to reflect perforation. Kathy Cassidy, Medical Liaison, states

> *"… regarding the quarterly report I have a few questions. For example, it seems like the* ***number of perforations is very low (4) for the quarter****. I know that I have reported several perforations during the 4th quarter through our film reviews and I have alerted product surveillance to these as well as copied Ayesha on the findings of these reviews.* ***I am wondering if the event (perforation) is not being captured after our film review (changed***

> ***from questionable placement or patency) and therefore not showing up on this report.*** *If our team needs to do something in addition to copying Ayesha and Tia on our HSG review results, we would like to know…"*[220]

In addition, the Manufacturer failed to investigate patient complaints voiced on the manufacturer's social media platforms such as Twitter or Facebook further avoiding their reporting responsibilities. A Power Point entitled "Essure Integration into GPV" created on October 29, 2013, outlines the Bayer processing of cases found on social media against the Conceptus process of "no activities" with regard to the reporting of complaints found through social media.[221]

Exclusion #12: Will Not Pursue MDR Reporting Because Information is Provided in Annual Report

The MDR reporting regulation is a General Control, the basis for regulating all Medical Devices and assuring public health. The FDA can grant an official exception to MDR reporting requirements on a case by case basis based on 21 CFR 803.19 (c-e). It is a significant violation of the regulation if manufacturers opt out of reporting without formal approval, or submit information elsewhere in the agency instead of filing MDR's. This is true even if the company believes there is no significant safety concern emerging or they have statements from a physician saying the product is safe. I have seen no evidence that the Manufacturer received an official exemption for summary reporting of any Essure events.

As indicated in the deposition testimony below, the Manufacturer failed to report MDR's as required by regulation and confirmed by specific correspondence from FDA. One justification for failure to report was apparently that summary information would be sent in through the PMA annual report. In addition to violating the requirements of 21 CFR 803, this approach is disingenuous.

The Conditions of Approval attached to the PMA approval letter/order for Essure in the ADVERSE REACTION AND DEVICE DEFECT REPORTING section required per 21 CFR 814.82(a)(9) include:

> *FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850* ***within 10 days*** *after the applicant receives or has knowledge of information concerning:*
>
> 1. *A mix-up of the device or its labeling with another article.*
> 2. *Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:*
>   a. *has not been addressed by the device's labeling; or*
>   b. *has been addressed by the device's labeling but is occurring with unexpected severity or frequency.*

3. *Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that* ***could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling****. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant.* ***When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Post approval Reports"*** *above unless specified otherwise in the conditions of approval to this PMA. This post approval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.*

This is followed by a section on required MDR reporting including the following statement:

> *"The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health."*[222]

The Manufacturer is not saying they filed reports to FDA within 10 days through the PMA report process. This would be more rigorous than the standard MDR 30-day reporting timeframe. It therefore appears that any annual submissions were made under Option 3 "*…**could not cause or contribute to death or serious injury" and "…are correctable by adjustments or other maintenance procedures described in the approved labeling**"*. This is not credible for several reasons. As noted elsewhere, FDA already indicated to the firm that MDR reporting was required for these events, including but not limited to two letters in 2004, the inspection in 2010-11, and clarification from the agency in 2011. The requirement for reporting indicates that the FDA believed serious injury is possible from use of the product and these events don't meet the reporting criteria for Option 3 in PMA annual reports. Causing or contributing to serious injury was also demonstrated in early clinical experience including a patient in the 2003 publication with pain and surgical intervention required. The reasons that perforations/migrations can cause or contribute to serious injury and should be reportable are addressed further in Exclusion #6 above and in the Perforation and Migration section below. Of note, in addition to a number of reports of serious or

life-threatening injuries with Essure use such as bowel perforation, the firm is aware of a death that occurred following procedural anesthesia during product removal.[223]

Although the Manufacturer chose not to report this event as an MDR, the awareness that death occurred following procedural anesthesia which is used with some surgical interventions or product removals, supports the potential for serious or life-threatening injury and the reportability of perforation/migrations. It disproves any assertion that the device "could not cause or contribute to death or serious injury."

The wording in the Conditions of Approval also state clearly that if there is redundancy in required filings the priority lies with the MDR regulation. To emphasize this prioritization further, FDA sent an email (in lieu of official letter) to the Manufacturer dated November 10, 2010 indicating that "In order to streamline the conditions of approval within the approval orders and **minimize duplicative reporting we've addressed "Adverse Reaction" and Device Defect reporting."** Device defect reports no longer need to be submitted directly to the PMA application as these are already covered under the recall reporting requirement in 21 CFR 806. **Likewise, adverse event reporting is covered under the MDR reporting requirements specified in 21 CFR 803. You may incorporate the above changes into the conditions of approval for P020014 as this is the current reporting expectation for all approved PMA's.**."[224]

MDR reports differ from annual reports. Medical Device Reports are captured and monitored for potential emerging safety trends on an ongoing basis by trained analysts. They are also accessible and available to the public on the FDA website. These reports provide critical information that not only helps improve patient safety, but also alerts the medical community to any potential issues with the device. PMA annual reports are required under CFR 814.82(a)(7) to provide product-related information generated or obtained following approval to the pre-market staff for continuity of regulatory oversight. It includes minor product updates, new published and unpublished data about product performance and sometimes labeling updates etc. This information is not entered into public databases for general use and is reviewed by the pre-market staff at their discretion.

MDR reports differ from annual reports. Medical Device Reports are captured and monitored for potential emerging safety trends on an ongoing basis by trained analysts. They are also accessible and available to the public on the FDA website. These reports provide critical information that not only helps improve patient safety, but also alerts the medical community to any potential issues with the device. PMA annual reports are required under CFR 814.82(a)(7) to provide product-related information generated or obtained following approval to the pre-market staff for continuity of regulatory oversight. It includes minor product updates, new published and unpublished data about product performance and sometimes labeling updates etc. This information is not entered into public databases for general use and is reviewed by the pre-market staff at their discretion.

Edward Yu, Vice President of Clinical Research and Regulatory Affairs, confirmed that after 2004, the manufacturer did not pursue MDR reporting for serious adverse events and instead filed them in the annual reports stating:

Q. Okay. And after receiving Ms. Kapsch's email in September 2004, am I correct that the company went on to not report perforations if those perforations did not result in medical or surgical intervention?
A. And the patients remained asymptomatic, yes, we do not file those as MDRs, but they are filed in the annual report[225]

Perforation and Migration of Essure Inserts [226]

"Perforation" is the penetration of an Essure insert partially or completely through the wall of the uterus, fallopian tube, or another body organ during or any time after the implant is placed. The device may then migrate into and around the abdominal cavity. An insert placed in the fallopian tubes may also work its way back down through the tube into the uterus (expulsion) or potentially move further along to the end of the tube and reach the abdominal cavity in that fashion. Perforation and migration are known risks with Essure due to the product design, method of insertion, and location of implants. Perforation due to the hysteroscope used for insertion is also possible. Essure kits distributed initially after product approval included a support catheter that appeared to increase the likelihood of perforation.

Often perforations and migrations are not detected. Symptoms that occur are frequently mis-diagnosed or migrated inserts may be asymptomatic. Perforations have been identified by X-ray on the day of placement, during 3-month post-insertion HCG or ultrasound, or months-years later during follow-up evaluation for symptoms such as pain or bleeding.

Essure perforations have been identified in 0.02% to 3.6% of patients in clinical trials and medical literature.[227] Patients may complain of abdominal/pelvic pain. Nausea and vomiting usually indicate perforation or entanglement with the small bowel and subsequent small bowel obstruction. In one case the insert perforated through the fundus of the uterus, into and through the wall of the small bowel to the mesenteric aspect, causing terminal ileum perforation requiring major surgery.[228] In addition to adverse events from perforation or migration of the insert, the lack of an implant in the fallopian tube can jeopardize contraception effectiveness.

Manufacturer filing of MDR's for perforation and migration has been extremely limited. However, reports are also submitted by other sources. FDA summarized all relevant MDR's in preparation for the Essure Advisory Panel meeting in 2015. At that time the agency had received 227 reports addressing migration outside the uterus. Locations included the uterus, fallopian tube, cervix, abdominal cavity, small intestine, ostium, terminal ileum, and ovary. Twelve MDR's described bowel perforation either due to free floating inserts within the abdomen or inserts within the uterus or fallopian tubes perforating through. One report described full thickness perforation through small bowel wall requiring ileo-cecectomy and other reports of the insert ensnaring a loop of small bowel causing obstruction in addition to perforation and the need for ileo-cecectomy.[229]

Literature review has also identified inserts in the abdominal cavity, omentum, small bowel mesentery or tissue, and large bowel mesentery, and cul-de-sac. Several complications or intra-operative observations were reported with migrated devices/fragments including small bowel obstruction due to insert entanglement or inflammation, small bowel perforation, adhesions and local inflammation.[230]

Organs in the abdomen can shift about with changes in position and activity, facilitating movement of foreign objects and creating opportunities for organs and objects to interact. There is a long history of foreign bodies in the abdomen causing harm. Uterine wall perforation is a well-recognized complication of Intra Uterine Devices (IUDs). About 1 per 1,000 IUD's migrate and about 15% of IUD migrations lead to complications including bowel obstruction or perforation, mesentery perforation, urinary bladder perforation, rectal strictures, and rectouterine fistula. Some of these complications are life-threatening.[231]

The Manufacturer did not initially consider perforations or migrations to be either malfunctions or MDR reportable events. FDA sent the firm a letter dated February 10, 2004 which stated in part:

> *"Since marketing of this device began, there have been four patients with tubal perforations (one patient listed as possible). Two of these patients underwent laparoscopic sterilization, one patient did not have any treatment, and the most recent case is still under investigation.* ***Please be advised that we consider tubal perforations to be MDR-reportable events (21 CFR 803), and all of these cases should have been reported to the FDA.*** *The last update received from the MDR analyst on February 3, 2004, did not include any adverse events associated with this device. Did these events occur in the United States or abroad? Please report the four cases of tubal perforation and any future adverse events to the FDA."*[232]

On March 30, 2004, Mr. Sinclair responded to the FDA, stating in part that *"Conceptus believes that tubal perforations (in general) are not MDR reportable events…"*[233] Mr. Sinclair went on to include a broader discussion of perforations generally, stating that Prof. John Kerin, the Principal Investigator of the Phase II clinical study, concluded in part that *"utero-tubal perforation with Essure is not associated with serious adverse clinical sequelae and should not be categorized in the same risk group as perforation of other organs that are associated with serious adverse clinical sequelae."*[234]

On May 3, 2004, the FDA wrote to Mr. Sinclair stating in part:

> ***"The FDA considers fallopian tube perforations in patients relying of the Essure device MDR reportable.*** *Any questions regarding MDR reporting to FDA should be sent to Sharon Kapsch, Chief, Reporting Systems Monitoring Branch, Office of Surveillance and Biometrics, Center for Devices and Radiological Health. She can be reached by phone at 301-827-2982."*[235]

On May 28, 2004, Mr. Sinclair wrote to the FDA in response to a MedWatch report, providing his justification for not reporting certain types of uterine and fallopian tube perforations as MDRs and he forwarded this letter to another FDA employee on August 10, 2004. His letter stated:

> *"Attached is a response originally sent to Diane Dwyer (at OSB) on May 28 in response to a Medwatch report. Specifically, our response provides a justification for not reporting certain types of uterine and fallopian tube perforations and pregnancies as MDRs. We have many medical opinions from practicing OB/GYNs*

that indicate most of these perforations are common and do not appear to meet the statutory definition of an MDR. In addition, we believe normal uterine pregnancies represent a contraceptive (effectiveness) failure and do not typically meet the definition of MDRs.

We certainly agree that perforations with complications (such as subsequent hypervolemia) or ectopic pregnancies would meet the criteria for MDRs and Conceptus would report such event to FDA. *To date, no ectopic pregnancies have been reported. Thank you for taking time to speak with me today. I look forward to working with you to clarify the reporting parameters for perforations and pregnancies because maintaining regulatory compliance is one of our highest priorities."*[236]

On August 20, 2004, the FDA responded, noting they were in receipt of Mr. Sinclair's message and stating, "*We hope to set up a telecom with you soon."*[237]

In September of 2004, three brief emails between the FDA and Mr. Sinclair were exchanged. On September 15, 2004, Mr. Sinclair wrote:

"I wanted to follow up with you regarding MDR reporting (see messages below). I know this is not a high priority but I would like to resolve the MDR categorization issues at some point. Perhaps we can schedule a teleconference toward the end of this month or early October?"[238]

On September 24, 2004, Mr. Sinclair wrote to the FDA:

"Thank you for your response. I appreciate the effort, particularly being shorted that, that was necessary for this determination."[239]

On September 24, 2004, the FDA responded to Mr. Sinclair, stating:

"I can give you an update on the progress of your request. Clarence Wilson was assigned to respond to your request. After a consultation with our clinical staff, he drafted a response, which I've recently reviewed. I expect his final to be ready early next week, at which time we will send it to you.

At this point, I do not believe that a telephone conference will be necessary. Basically, we agreed with you assessment of your MDR obligations for the events cited in Ms. Dwyer's letter to your firm, and your response back to Ms. Dwyer. Our letter explains our reasons for making that determination."[240]

The Manufacturer received no letter from FDA or other written follow up to this informal email, regarding either the specific cases or reporting policy generally. The firm proceeded with their practice of excluding perforations and migrations from MDR reporting. This approach was questioned during an internal audit performed by Reglera LLC in August 2008, performed by a former FDA investigator. He highlighted the practice of not-filing

perforations/migrations without presentable written support from FDA as a major category deficiency. Mr. Yost strongly advised the firm to obtain written documentation for any special reporting agreements from FDA and be able to produce it during audits.[241]

On October 7, 2009, Ms. Acuna-Narvaez wrote to the FDA requesting the letter:

> *"…it has come to our attention that Ms. Sharon Kapsch of FDA noted that a letter would be sent to Conceptus in 2004, however, we never received this. In reviewing our reporting procedures, we realized that the letter would be very helpful to us."*[242]

She sent a similar message to FDA again on November 10, 2008, noting that the Manufacturer never received the formal FDA letter regarding the evaluation of adverse events for reporting purposes.[243] The FDA responded to the Manufacturer on November 14, 2008, stating:

> *"I wanted to let you know that we received your request and will respond soon. Unfortunately, the person who drafted our original response in 2004, retired in 2006 and his records are no longer available. My records contain his response, but it is only in draft form. We can finalize this older draft, but the answers can only be used for application to the time period addressed in the original correspondence between your firm and our office in 2004. If newer information and/or even situations have occurred since that time, the answers may not apply. We are currently looking into this to see how best to address this situation."*[244]

On April 23, 2009, Ms. Acuna-Narvaez sent a follow-up email to the FDA once again requesting:

> "*In order to satisfy our quality division, would it be possible for you to send me an email stating that no letter was issued and there are no plans to issue a follow-up letter*?"[245]

During a 'for cause" FDA inspection on December 8, 2010 to January 6, 2011 the Investigator spoke with Manufacturer representatives including Edward Yu, Vice President of Clinical Research and Regulatory Affairs about findings in the complaint files. He noted that the firm was not reporting complaints of inserts in the peritoneal or abdominal cavity (FDA 483- Observation #2). He wrote that

> *"Such cases will be reported as MDR by the firm if the patient is complaining of pain and a second procedure is required to remove the coil. However, the firm will not report such complaints if an abdominal located coil is removed during a laparoscopic tubal ligation performed because of failure of the Essure procedure."*[246]

In the Establishment Investigation Report the investigator commented: *"I noted that none of the perforation complaints were reported as MDR's."* He spoke with Edward C. Yu who provided a copy of the Correspondence Conceptus had sent FDA on March 30, 2004. In initial complaint review the investigator found two complaints of coils in the abdominal cavity; one with patient pain and a planned removal to treat that pain that was not classified as MDR reportable.[247] He requested additional information from the firm and expanded his review.

The Establishment Investigation Report from this inspection included an Observation related to several complaints of perforations and migrations.[248]

> *"Observation 2: An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctions and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."*

Several examples were cited of devices in peritoneal cavity either asymptomatic or symptomatic. The investigator noted 45 complaints of perforation during his review, two for perforation of bowel, one bleeding, another had surgery to remove insert. None were reported as MDR's.

The investigator noted that during discussion ***"Mr. Edward Yu told me there was no evidence that the micro-insert posed a risk to injury if it was in the peritoneal cavity."*** Mr. Yu supported his view with two examples of perforation/migration of inserts from clinical studies, one patient had an intra-abdominal coil for 5 years without complication and when the other had the coil removed from the abdomen the surgeon noted no inflammatory reaction of surrounding tissue.[249]

In fact, the Phase II study published by Kerin 2003 described a case of perforation diagnosed after 2 years of placement. The patient requested that her micro-inserts be removed after a 6-month history of pain in her pelvic region, particularly on her right side. During the surgical procedure to remove the devices, the surgeon confirmed the perforation where one-third of the micro-insert was coiled under the peritoneum just below the right uterotubal junction. The surgeon performed a bilateral cornual surgical procedure to remove the coils. The patient's pain settled post-operatively and she remained pain-free after 18 months of follow up. This incident demonstrates that Mr. Yu's assessment that there is no evidence of any risk from a micro-insert in the peritoneal cavity was already outdated in 2003 and substantially flawed. This patient experienced six months of pain, risks of anesthesia, and surgical treatment of two sections of her uterus.[250] This example provides evidence of serious injury reportable to the FDA, and a device malfunction that would be likely to cause or contribute to at least serious injury if the malfunction were to recur.

Edward Yu later testified in his deposition:

> Q. But based on this document, Conceptus knew as of 2004 that an Essure insert that perforates a fallopian tube could attach itself to the lower bowel; correct?
> A. In this case it appears to be the fact. [251]
> Q. So were you aware during your time at Conceptus that as of 2006, some authors had published in peer-reviewed literature that Essure perforations can cause complications such as hemorrhage and bowel injuries?
> A. Yes. [252]
>
> Q. And did you know at the time (2006), you know, you were the director and vice president of regulatory and clinical affairs, that Essure perforations can cause complications such as hemorrhage and bowel injuries?
> A. Yes, that there's a possibility.[253]

Q. So even as of 2007 when physicians were reporting in published literature that physicians should be aware that they should not leave a dislodged implant in the abdomen, Conceptus was taking the view that as long as an Essure implant in a patient's abdomen was not at that time causing them symptoms, they did not need to report that as an MDR to the FDA; correct? . . . .
A. If they were asymptomatic, yes, I think in that case we would document the complaint, and but that would not be reported as an MDR if no surgical intervention was occurring.[254]

Q. Okay. Did you have an understanding in 2007 that an Essure implant that had perforated the bowel could cause peritonitis and sepsis?
A. Yes.[255]

Q. And it's not just that a perforation may require removal, it's that, you know, what these cases that we just went over show is that if a perforation occurs in a woman who gets Essure, it can result in one of these adverse events, peritonitis, sepsis, bowel injury, bloating of the stomach, and persistent pain, for example. Those adverse events could have happened in a patient who received Essure; correct? . . .
A. Yes, it could happen, but how likely it happens is the standard that's applied. One of these was actually reported as an MDR, the other ones were still reported to FDA.
Q. Not as MDRs though; correct?
A. No.[256]

Although the manufacturer had evidence of substantial risk of injury posed by Essure devices being located in a woman's peritoneal cavity, there was no policy to follow up with the women who reported such incidents to determine whether they were experiencing an adverse event:

Q. Okay. As to reports that Conceptus received and Bayer received that reported either a perforation or an Essure device located in the woman's abdominal or pelvic cavity, but did not report symptoms or a surgical intervention, what was the policy or practice at the company to follow up with those women to determine their health outcomes over time?
A. There was not a policy in place regarding those women in those situations that were asymptomatic. But on occasion, I believe the conversation would be with the physician or patient to let us know if anything changes, and they would let us know.[257]

A review of these facts demonstrates the substantial flaws in Edward Yu's statement to the FDA investigator in 2011 that there was no evidence of any risk from a micro-insert in the peritoneal cavity or that reports of the mislocated devices constituted mere 'trivial impairment or damage."

The investigator explained that the reason he found micro-inserts in peritoneal cavity likely to lead to injury was based on number of MDR's in the firm's database in which intra-peritoneal location led to complication. Mr. Bishop said he did not consider an insert falling out of the fallopian tube to be a be a malfunction because it does not involve malfunction of the micro-insert itself. The investigator responded that

> *"…because the micro-insert was designed to remain inside the fallopian tube. The coil migrating to a different location represented the device not functioning as it was designed. Mr. Edward Yu told me that there was no evidence that the micro-insert posed a risk of injury if it was in the peritoneal cavity. …* ***I said that the location of the micro-insert in the abdominal cavity was the condition that led to intra-abdominal coil becoming symptomatic in all cases in which an intra-abdominal coil had to be removed surgically."***[258]

The investigator also noted that there were "*41 complaints of perforation from July 12, 2010 to December 10, 2010…"*[259]

In January of 2011, Mr. Yu emailed the FDA asking for a few minutes to talk about the topic of the perforation-reportability.[260] The FDA responded that the Manufacturer's request was forwarded within the FDA to an employee who would be in contact shortly with a response.[261]

On January 20, 2011, Edward Yu wrote to the FDA in response to Observations made in the Form 483 from the recent inspection regarding perforation complaints.[262] Specifically, in one of the observations, the FDA cited five patient complaints in which there occurred perforation of the fallopian tube or uterus and the Essure device was found in the peritoneal cavity. The Manufacturer's reasoning for not submitting MDRs for those events was based in part on the fact that "*none of the cited complaints of micro-inserts being found in the peritoneal cavity resulted in pain or other symptoms****, the reports of the mislocated devices constitute mere 'trivial impairment or damage' that does not rise to the level of a 'serious injury.'"***[263]

On February 8, 2011, the FDA wrote to Edward Yu. The response clearly demonstrates that the Manufacturer's practice did not align with the reportability requirements Specifically, the FDA stated:

> *"Regardless of whether the perforation is due to a malfunction of the device or due to user error, a perforation would meet the definition of a serious injury, per 21 CFR 803.3, if medical or surgical intervention was necessitated to preclude permanent impairment of a body function or permanent damage to a body structure. For such events a serious injury MDR should be submitted to FDA, as required by 21 CFR Part 803.50(a)(1).*
>
> ***A perforation would meet the definition of a reportable malfunction per 21 CFR 803.3, if the device malfunction were to recur. For such events, a malfunction MDR should be submitted to FDA, as required by 21 CFR Part 803.50(a)(2)."***

The first paragraph confirms that perforations and migrations associated with symptoms and resulting in procedures to remove the insert or medical treatment for symptom relief must be reported as MDR's. The second paragraph clearly states that a perforation is a malfunction and meets the MDR reporting requirement for "*has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur."* Together, these statements confirm that all perforations and migrations must be reported to FDA regardless of the mechanism of occurrence, presence or

absence of recognized symptoms, and intervention that has or has not occurred. The Manufacturer's longstanding policy of systematically excluding migrations and perforations from MDR reporting was in violation of FDA regulation.

Findings

The Manufacturer's position on the reportability of complaints of perforation and migration was not substantiated by the post-market performance of the Essure device, as the clinical summary above indicates. It was also not supported by interactions with the Food and Drug Administration (FDA). The Manufacturer proceeded with their filing approach for a number of years citing informal communication with FDA regarding a small number of specific complaints and an anticipated decision that was not actually issued until 2011. The letter FDA issued ultimately did not support the Manufacturer's longtime position not reporting MDR's for all asymptomatic perforations and some symptomatic perforations/migrations as well.

As Edward Yu testified:

> Q. Are you aware of an explicit written statement by the FDA that approves your practice of not reporting any instances of micro-inserts in a patient's abdominal cavity as an MDR reportable event?
> A. There is not an explicit statement . . . .[264]

Unique reporting requirements described and implemented by staff were applied without documentation in writing or procedures. There is no evidence available or produced during inspections that the FDA agreed asymptomatic perforations were not MDR-reportable. The failure to consider perforations MDR-reportable is a violation of the Manufacturer's regulatory obligations and poses a significant risk to public health.

Manufacturer Failed to Meet Reporting Timeframes

Incorrect Interpretation of "Aware Date"

Consistent with MDR screening processes based on exclusions, the Manufacturer routinely began the MDR 30-day reporting timeframes when investigations were completed and the complaint passed the final exclusion threshold, rather than when the company received first notice of events. The words "…reasonably suggests…" were implemented as meaning after investigation has confirmed that a product defect or use error was the source of a reportable incident.

In a power point presentation for staff training dated November 21, 2013 (Bayer Global Pharmacovigilance BPD-017 Handling of Incident Reports Changes with V4) Slide # 10 discussed the start date for MDR reporting*:*

> *"**Clock start day 0: Company becomes aware of the information which constitutes a reportable case.** This may include the day a PTC investigation concludes a confirmed possible defect or use error which could lead to serious injury."*[265]

The same slide also noted:

> "I*ntervention: Planned/intended intervention does not make an event reportable (evidence from F/U information required that intervention had been conducted)* ➔ *revisit wording what is included as near-incident."*[266]

This documents the practice before and still in place during late 2013 of starting the reporting window when investigation was concluded and a specific possible defect or user error which could lead to serious injury was confirmed. It also confirms the policy of requiring confirmation of interventions and delaying reportability until interventions were completed.

On June 28, 2011, Michael Reddick, Senior Manager of Product Surveillance, sent an email to Michael Voss, Reglera, regarding the reporting of AR-21485-ZL36 to which Michael Voss responded:

> *"I used Vincetta's follow up date of 5/17/2011 here which puts this report past the 30-day window. Unless you have some other argument for utilizing a different date. I'm not sure how this was missed, we should discuss."*[267]

On June 30, 2011, Michael Reddick responds changing the aware date to the day the manufacturer confirmed resolution of patient pain stating:

> *"**I thought the MDR aware date should have been 6/15 since this was the day that we confirmed resolution of patient symptom (pain).** The 5/17 date was the date we confirmed that a follow-up procedure was performed, but we didn't (to my knowledge) know if the "potential catheter piece" was the cause of the pain at that point. The way I read the notes, **it appears we confirmed the patient was asymptomatic on 6/15/11**. Let me know if you disagree."*[268]

Robert Feyerherm, Manager, Quality Control & Product Surveillance, testified to this practice and his understanding of the aware date stating:

> Q. And do you recall what time limitations you were under?
> A. Once a medical device manufacturer is aware that a complaint is a reportable event, then they have 30 days.
> Q. So it's your understanding that it's not 30 days from when the complaint comes in; correct?
> A. That's correct.
> Q. And who told you that?
> A. Regulatory affairs.[269]

The way this policy was applied did not comply with the regulation. Many reportable events had enough information provided at first awareness to reasonably suggest they were reportable and the 30-day windows should have started on the date of initial notice. The Manufacturer's practice of not considering reportability until investigation was completed, and all exclusions had been

overcome, led to substantial delays in reporting of these cases, and often reporting never occurred because confirmation was not adequately pursued or was not provided for some other reason.

The best evidence of this is the substantial change in the number of MDR reports when Bayer assumed responsibility for submitting MDR reports for Essure and implemented their corporate practice with initial screening and immediate filing for known reportable complaints that did not require outside physician confirmation in late 2013. The Adverse Events reported per month globally rose from 3.2 cases per month previously to 55.0 cases per month on average following the new process.[270]

Disrupted investigation processes, documentation, and filing delays

MDR documentation and investigation activities were disrupted and delayed by the ongoing complaint backlogs and related process issues. In addition, Product Surveillance has difficulty tracking action requests, following up in a timely and consistent manner when additional information was needed, recording their activities related to information gathering and assessment, and documenting justification for decisions. Employee statements indicate that no one could tell months later whether or not an MDR had been filed. Some statements and testimony regarding this ongoing backlog include:

> A February 8, 2009 email from Rachelle. Acuna-Narvaez, Regulatory Affairs Manager, to Rob McCarthy, Operations Director, QE, QA, seeking an update on 7 possible MDR reports due for filing, can't even locate some of the forms: *"Rob - please note that I have not received a single AR that needs to be filed as an MDR from Mia or Nya --* ***I fear that some may have slipped through the cracks!"*** and she includes seven Medwatch numbers she needs AR's and investigations on and highlights three AR's she needs completed by Product Surveillance including one that is overdue.[271]
>
> An August 3, 2009 email from Gilbert Pinzon, Temp employee, to Rachelle Acuna-Narvaez, Regulatory Affairs Manager, regarding MDR not filed for two years: ***"This might be a reportable event that has been overlooked****. Please read the description… It's an AR from 2007 and it is an ESS205 device."*[272] On August 4, 2009 she responds: *"Thanks for your email! I agree with your assessment,* ***this should have been reported****…"*[273]
>
> A December 1, 2009 email from Ms. Shirley Reid with the subject line "*Unresolved Complaints* Please provide status" to Laura Casas, Medical Affairs Liason, [274] ***"Laura, I have four AR's without information in CRM, on HSG List, MDR log or in Correspondence e-mail.*** *(Two have dates November 2008 in parentheses)."*[275]
>
> Compliance with complaint investigation of potentially reportable incidents continued to be an ongoing issue in 2011. An internal audit of Product Surveillance on May 17, 2011 – June 6, 2011 made the following observation:
>
> > *"There is* ***no evidence to show that adequate efforts were made to follow-up with patients/physicians on several complaints that appear to have been reportable events****… One cite (AR-19488-6GFD) noted e-mail sent to patient on 1/5/11, no*

response from patient on 5/4/11- no evidence to show communication between 1/5/11 and 5/4/11."[276]

The NSAI Non-Conformity Report issued on June 25, 2014 for audit of the manufacturer's facilities citing a cause of the nonconformity to be that:

"The Bayer global procedure BPD-SOP-017 'Handling of Incident Reports' was inadequate in that ***vigilance reports were not reviewed for completeness prior to submission*** *to National Competent Authorities and the procedure did not specify the processes to ensure the fields on the form are properly populated according to the product specific information."* [277]

IX. REVIEW OF EXAMPLES FROM COMPLAINT/MDR STUDY

Michael Reddick, Senior Manager of Product Surveillance, testified in a person most qualified ("PMQ") deposition on behalf of the manufacturer on October 18, 2018. Plaintiff's counsel presented Mr. Reddick with 27 specific complaint files that were maintained by Conceptus, Incorporated. Mr. Reddick reviewed all of these complaints and policies/procedures that were in place at the time these records were created in preparation for this deposition.

I have compiled and reviewed the 6 complaint files that Mr. Reddick testified to in his PMQ deposition. The individual complaint information, Mr. Reddick's testimony, and my findings and opinions are summarized below.

AR #	Type/Date of Complaint	PMQ Deposition Testimony	Kimber Richter Review
AR-19522-NC57	Complaint 17871-7S0R was an earlier complaint and MDR for this patient with pain and device in uterus, removed. MedWatch 2010-00067. New complaint received for same patient 12/23/2010 patient experienced pain following placement of new/second Essure device, 2 weeks, persistently gotten worse. Patient is miserable with stabbing pain, expected implant removal. [278] Case opened 1/4/2011, notified	Unsure why initial assessment was no MDR, unsure why information is missing from file, unsure why Regulatory made decision to file as follow-up to first MDR (info not in file). He considers report date within regulations because clock starts when investigation is complete and information confirms the case is reportable. Michael Reddick testified: "Well, I can tell you what the regulations require. And it is the way the FDA set that up. They want you	Files and deposition reflect non-compliance with 21 CFR 820.198, 803.50, 803.52, 803.10. - Significant information missing from files, lack of follow up to obtain supporting documents, inadequate or incorrect MedWatch content. - Violation filing as follow-up instead of new MDR required for different devices. New MDR filing was appropriate since new device was implanted and especially since symptoms were associated with insertion of new device.

	1/5/2011 that implant removal was completed and tubes removed. MDR filed 2/3/2011 as follow-up to initial report.	to report within 30 days of you receiving information which indicates that you need to report the case."[279]	- Violation of MDR reporting timeframe: a. Bayer representative fails to consider the regulation wording "reasonably suggests" and "may have caused or contributed to" 21 CFR 803.50(a). b. Initial information was sufficient to reasonably suggest reportability on December 23, 2010. c. Confirmation of device removal was received January 5, 2011 one day after case opened. Delay in submitting report beyond 30 days from initial notice of complaint was unnecessary and non-compliant.
AR-19720-G65V	First notice 1/12/2011 Complaint opened 1/13/2011 date closed 3/14/2011 Right side perforation, device outside tube at HSG, patient asymptomatic no intervention. Dr. had just received results and had not talked to patient yet.	Michael Reddick testified as to why no MDR was reported: "But Conceptus had an agreement and had received guidance from FDA that all perforations actually were reported to FDA. So even though this case would not have resulted in a 30-day report to FDA, this case would have been included in an annual report, annual summary report that was submitted. And it would contain all perforations, regardless of whether they met the 30-day requirement or not." [280]	Files and deposition reflect non-compliance with 21 CFR 820.198, 803.50 - Significant information missing from files, lack of follow up to obtain additional information and supporting documents, missing reportability assessment, root cause identification. - Violation of MDR reporting: a. Bayer mis-represents the FDA MDR reporting regulation and instructions from FDA. All perforations meet criteria for reporting as 30-day events. Based on my reading, FDA expected asymptomatic events to be reported as malfunctions.

			b. The agency had authority to grant permission for the firm to submit some or all perforations in annual MDR summaries as a convenience, but that does not indicate those events don't meet reporting criteria. There is no evidence that an approval for annual summary reporting was ever granted.[281] c. There was never a regulatory option to submit perforation information in the PMA annual reports instead of filing MDR's, as letters from FDA indicate.[282] [283] The conditions of approval provided with the PMA approval order[284] and the letter from Dr. Corrado (FDA) to the firm also make it clear that PMA annual reporting cannot take the place of MDR reporting.[285] If the Bayer representative is suggesting that the Manufacturer intended/used PMA annual reporting as an alternative to MDR 30-day reporting that is inappropriate and a violation of 21 CFR 803.50. d. If Bayer is suggesting the Manufacturer intended PMA annual reporting as an alternative to MDR 30-

			day reporting, that is inappropriate and a violation of 21 CFR 803.50 Mr. Sinclair's responses on March 30 and May 28 of 2004 after FDA notified the Manufacturer that perforations must be submitted as MDR's (February 10 and May 3, 2004) provided the reasons he disagreed with the reporting requirement, but there was no indication he thought submission in the PMA annual report absolved the firm of responsibility for MDR reporting under 21 CFR 803. If he held that incorrect view originally, the initial letters from FDA in 2004 informed him otherwise. The idea that a PMA annual report eliminated the need for MDR reporting was not suggested in other documents from the Manufacturer reviewed either.
AR-19736-6J6Z	Implant date 7/7/2010, first contact 1/12/2011, complaint opened 1/13/2011, follow-up attempted 2/11/2011, talked to nurse in an Ob/Gyn office on 2/22/2011 who wasn't able to provide information, closed. Patient reached call center reporting pain with implantation down right leg and intermittently since, constant pelvic pain,	Michael Reddick, testifying as the Manufacturer's Representative, indicated the manufacturer would not accept information from patient even to prioritize the investigation or walk through initial decision tree until follow-up information was gathered. The manufacturer requires "some type of confirmation." They are "looking for some type of indication that there has been medical intervention	Files and deposition reflect non-compliance with 21 CFR 820.198, 803.50, 803.10, and 803.17(a)(2). a. Significant information missing from files, failure to investigate, no documented attempt to contact anyone with knowledge of issue. No or inadequate attempts to follow-up with patient. Lack of MDR reporting decision information and missing non-reporting rationale.

	confirmed allergy to Essure materials tested by allergist, frequent heavy periods, device migration into uterus, hysterectomy planned. Firm spoke with a nurse who did not know/could not provide information about allergy and said doctor did not plan to do the removal. No attempt to follow up with allergist or other Ob/Gyn who might be doing the surgery, no indication of further conversation with patient.	or the necessity for that." [286] When asked " Do you believe that this complaint was appropriately investigated and appropriately not reported to the FDA… based on the information that's present in this file? Did they do the right thing? " Michael Reddick testified "I believe they did."[287]	b. Record was classified as allergy, many symptoms reported. Investigator notes state: "Pain and allergy could not be confirmed, therefore no MDR should be filed". - Violation – Failure to Report MDR and Failure to Report in required Timeframe a. Initial information was sufficient to reasonably suggest device met reportability requirements on January 12, 2012. b. Unwillingness to report based on information from patient (Exclusion #10 above) was inappropriate and violated the regulation. c. Failure to consider reporting when initial information "reasonably suggests that a device may have caused or contributed to" without confirmation that device caused symptoms (Exclusion #3 above) that intervention occurred (Exclusion #1 above), and intervention was medically necessary (Exclusion #2 above). These exclusions from reporting consideration violate the MDR regulation. d. The firm did not investigate and try to obtain information to

			inform the reporting decision (as required in 21 CFR 820.198 and 803) or overcome these exclusions. Instead, the file was closed and MDR reporting was prevented. This was especially inappropriate when initial patient contact had addressed each of these factors. e. Non-complaint delay in initial follow-up based on complaint and MDR timeliness requirements. Thirty days before attempting to reach out and 41 days to follow-up contact (with no information) is also an inappropriate delay in follow-up from a clinical perspective for report of allergy to product content with significant symptoms and pain as described. - Violation of 21 CFR 803.17(a)(2) a. Regulation requires implementing a standardized review process or procedure for determining when an event meets the criteria for reporting, b. Decision not to report an MDR for this event is very inconsistent with the reporting decision for another complaint (AR-20847-Z9MH) based on information from files and deposition indicating this

			file has similar/equivalent or more substantial symptoms and was handled by the same Product Surveillance staff person during the same time period.
AR-20670-SWFF	Implant date 6/4/2009, first contact 3/4/2011, complaint opened 3/8/2011, additional information 3/10/2011 and further information on 4/12/2011. MDR filed 4/26/2011, 6/30/2011 decision tree revised to show MDR needed. Physician reported to sales representative that internal medicine doctor saw patient for pelvic pain and diagnosed perforation, device in abdominal cavity based on CT and X-ray. Follow-up note confirms information and plan for device removal.	Michael Reddick testified: Q: April 18, so six days after… the subsequent report had come from the doctor. And you said you would like to get confirmation from the physician on this case, i.e., did removal occur, did symptoms resolve, did physician feel Essure removal was necessary - medically necessary. Do you see that? Answer: Yes. Q. And are those some of the questions that you, as you were working in complaint handling …believe needed to be answered before a decision on whether to file an MDR could be made? A. Those were some of the questions, just as a standard rule, we would always ask. So just trying to get as much information as we could.[288]	Files and deposition reflect non-compliance with 21 CFR 820.198, 803.50, 803.10 File very incomplete, complaint handling records missing (appears to be emails only), there is no investigation information, missing reporting decision information and MDR records or non-reportable rationale. - MDR Reporting Decision a. Initial information was sufficient to reasonably suggest the device met reportability requirements on March 4, 2011. b. Bayer deposition indicates Product Surveillance manager was unwilling to submit report even after follow up confirmation of initial information, wanting additional confirmation that intervention had been completed (Exclusion #1 above), and intervention was medically necessary (Exclusion #2 above), and symptoms had resolved (Exclusion #4 above).

			- Violation of MDR Reporting Timeframe a. Initial information was sufficient to reasonably suggest device met reportability criteria so 30-day reporting window should have begun on March 4, 2011. MDR apparently reported April 26, 2011 about 22 days overdue. b. In this case, Reglera representative Michael Voss recommended filing MDR without further delay and the MDR report was just a few more days delayed but still submitted after the 30-day required timeframe.[289]
AR-20847-Z9MH	First contact 3/15/2011 Complaint open 3/16/2011 Implant date 6/7/2007 Incident date 3/15/2011 MDR reported 4/6/2012 Allergy, pain, multiple trips to ER Complaint investigation completed June 14. Woman called into call center 3/15/2011 , said she had nickel allergy and was not informed Essure had nickel in it, she was inquiring about a class action lawsuit. Investigator's note in file says "Called patient on 3/17, 4/7 and, 5/4 and 6/10 2011. Messages were left and no responses were received…"[290]	This file had a lawsuit acct referenced and the initial contact report was copied to senior managers Ed Yu and Greg Lichtwardt. Bayer representative acknowledges there is less information/less serious symptoms described than in previous complaint with allergy patient reported and more pain. Bayer representative can't explain why information about follow-up with patient in MedWatch form isn't in complaint file. Initial decision tree for this complaint was no MDR, doesn't know and can't tell from file why decision was made to file MDR. Initial information meets several	Files and deposition reflect non-compliance with 21 CFR 820.198, 803.50, 803.52, 803.10, and 803.17(a)(2). - Significant information missing from files, lack of follow up to obtain additional information and supporting documents, missing reportability assessment and decision files, inadequate MDR specific investigation, root cause identification and conclusions. Inconsistent content between files and MDR submission. MDR record filed incorrectly somewhere other than file. -Violation of 21 CFR 803.17(a)(2)

	However, MDR report states: "Follow up calls to patient to obtain additional information which was provided on 4/13/11."[291] Patient says her doctor recommends removal, but can't afford it and has chosen to live with pain. Won't provide physician's name. Says symptoms are pain during ovulation and body aches. Gone to ER 4-5 times, no follow up to allergist but knows she has allergy due to breaking out with earrings and cheap jewelry, inherited allergy from mother and grandmother.	of firm's reporting exclusions used during this time period for other complaints including patient report, no physician confirmation of symptoms, no confirmation of device cause, no indication of intervention planned or performed, no confirmation of allergy reported. Bayer Representative cannot explain difference in reporting decision vs. AR19736-6J6Z above handled by same Product Surveillance staff person, at same time period, with similar symptoms and different conclusion.	a. Regulation requires implementing a standardized review process or procedure for determining when an event meets the criteria for reporting, b. Decision to report an MDR for this event is very inconsistent with reporting decisions for other complaints based on what the file indicates are similar/equivalent or less substantial symptoms for this case than other files including AR19736-6J6Z. Note - This MDR filing suggests that senior management who were overseeing this case, and Senior Product Surveillance Manager Michael Reddick, who approved the decision, understood the appropriate MDR reporting thresholds and were able to apply them appropriately when a case was flagged for likely external legal involvement. -Violation of MDR reporting timeframe Initial contact 3/15/2011. MDR submitted 4/26/2011.
AR-34630-P2B7	Incident date 11/5/2010 First contact 4/9/2013, file refers to expulsion but physician also refers to bleeding with ablation in 4/29/2013 summary. HSG showed coils correctly in tubes	Michael Reddick, testifying on behalf of the manufacturer's policies, agrees that coils coming out into uterus "… might be considered to be a malfunction." [292]	Files, complaint chart from experts, and deposition reflect non-compliance with 21 CFR 820.198, 803.50, 803.52. - Significant information missing from files, lack of follow up to obtain additional

	2/10/2011 and at ablation physician saw coils hanging out into uterus. No evidence of MDR reporting.	Agrees that probable cause/root cause analysis lists information from IFU not relevant to the case.[293] There is no evidence of follow-up about additional modified HSG suggested by firm's medical liaison to determine if device is still functional as contraception.	information and supporting documents, lack of evidence for due diligence, probable cause/root cause analysis lifted from IFU and not relevant to case, missing/inadequate reportability assessment and decision files. inadequate. Decision tree showed no injury or malfunction despite expulsion. - Failure to recognize and pursue additional significant issue – bleeding – treated with ablation based on physician information. (Consistent with firm's reporting Exclusion # 9 above) - Violation of MDR Reporting Requirements and Timeframe a. Apparently no MDR reported b. Information known 4/29/2013 or earlier was sufficient to reasonably suggest device met reportability criteria based on bleeding with procedural intervention (ablation) and no information from follow-up that it wasn't device related.

Note: Answers throughout the deposition demonstrate a very limited specific interpretation of Complaint and MDR reporting regulations. For example, the Manufacturer's representative consistently cited intervention for serious injuries as the only justification for MDR filing. However, the regulation 21 CFR 803.3(w) provides two other options – is life-threatening, or permanent impairment or damage with no mention of intervention, as well as the malfunction with risk to patients from future use described. 21 CFR 803.50. The Manufacturer's representative repeatedly describes requirement for "confirmed" conditions rather than "reasonably suggests" and "may have caused or contributed to". Despite repeated questions, the representative acknowledges no timeliness requirements in regulation for complaint and MDR

handling/investigation activities except the 30-day reporting window. He also references company procedures which he notes have no specific timeline.[294]

Many Reportable Events Related to Essure Use Were Never Submitted to FDA

Approximately three months after the acquisition of Conceptus in 2013, Bayer assumed responsibility for MDR reporting decisions and filing for Essure, aligning the process with Bayer corporate practices. When initial information was sufficient to determine that reporting was necessary, Bayer made the reporting decision immediately and filed the report within 30 days of initial notice about the event, including whatever supporting information was obtained from investigation during that time.

Mr. McCarthy and Mr. Reddick expressed concern about this change, indicating they expected to see significant increases in the number of MDR's reported. Shaw Lamberson responded on October 22, 2013 that the only difference was they would now proceed without medical confirmation from an MD and file the MDR if it met Bayer criteria.[295]

In an email dated April 22, 2014, Robert McCarthy predicted that this change in MDR practice for Essure would increase the number of MDR reports to 120/month.[296] This suggests keen awareness of the significant and systematic under reporting occurring due to the reporting practices instituted by Mr. Sinclair, Mr. McCarthy, and Mr. Reddick.

On December 21, 2015 Mr. Bishop sent an email to Mr. Reddick and Mr. McCarthy indicating that during the last 15 months that Mr. Reddick made reporting decisions there were 48 case filed (3.2 cases filed per month in some country). Following the new process there were 1155 cases reported during the next 21 months (55.0 cases per month). Mr. Bishop *noted* ***"A greater than 17 times increase in filed complaints."***[297]

Other experts have reviewed the Essure complaint and MDR reporting processes and files in detail, and determined the likely extent and significance of under-reporting that occurred. I concur with their findings.[298]

Year	Quantity of Complaints that should have been reported as Initial MDRs in Sample Set but were not	Number of complaints reviewed in Sample Set	% of complaints reviewed that should have been reported (Sample Set)	Lower 95% Confidence Interval	Upper 95% Confidence Interval	Quantity of Complaints with Aware Dates in Total Population	Upper Confidence Interval	Extrapolated Quantity of complaints that should have been Reported	Lower Confidence Interval
2002	4	86	5%	N/A	N/A	86	4	4	4
2003	66	392	17%	13.30%	20.92%	448	60	75	94
2004	54	392	14%	10.50%	17.59%	672	71	93	118
2005	66	392	17%	13.30%	20.92%	813	108	137	170
2006	138	392	35%	30.50%	40.16%	1,748	533	615	702
2007	39	392	10%	7.20%	13.35%	1,167	84	116	156
2008	90	392	23%	18.90%	27.45%	1,301	246	299	357
2009	64	392	16%	12.80%	20.36%	2,398	307	392	488
2010	53	392	14%	10.30%	17.31%	3,645	375	493	631
2011	30	392	8%	5.20%	10.75%	4,351	226	333	468
2012	43	392	11%	8.10%	14.49%	4,735	384	519	686
2013	46	392	12%	8.70%	15.34%	4,338	377	509	665
2014	127	392	32%	27.80%	37.28%	3,228	897	1,046	1203
2015	154	392	39%	34.40%	44.31%	5,840	2009	2,294	2588
Total	974	5182	19%	17.70%	19.89%	34,770	6,154	6,535	6,916

It is my expert opinion, based on experience in medical device firms and FDA, as well as the documents reviewed, that the estimate they have offered is conservative, and under-reporting of MDR's by the Manufacturer may have been even more significant. Reasons I hold this view include:

- There was no direct avenue for receiving concerns from patients after Essure was implanted, and patient calls were not captured as complaints for the first several years.
- The increase in number of MDR reports after Bayer instituted changes (17-fold) suggests that under-reporting of MDR's prior to 2013 could have been greater than estimated.
- Firms with the compliance issues that Conceptus demonstrated with procedures, training, understaffing, investigation, and documentation often have gaps in gathering and retaining information that could have decreased the number of complaints available years later and the content with impact on reportability.
- Key managers with the most knowledge of Conceptus reporting practices expected the MDR numbers to rise even more than 17-fold with the changes in 2013, suggesting they may have believed under-reporting was very substantial.

The estimate indicates that there were several hundred removals of implants and other serious events known to the firm and not reported by the year 2005-2006, perhaps five times the number actually filed. It is reasonable to expect that if these additional significant events had been reported

to FDA, the agency would have taken action at that time, likely including patient and physician labeling changes. This is supported by the prompt action taken following the first PMA annual report when the FDA sent two letters in follow-up to just four reports of perforations without catastrophic outcomes.[299] [300] In addition, this product was novel and served a significant public health need, making it a priority for FDA ongoing oversight.

The Manufacturer Failed to Report MDRs Regarding Incidents/Near Incidents Determined from Legacy Data

Upon merging systems, Bayer had a difficult time discerning the differences in reportability criteria. The Conceptus-era cases were reviewed by the Pharmacovigilance department to clarify *"a discrepancy has been observed over the last months between Near-/Incident assessment in GPV Single Case Processing and the decisions of reportability made by the US MDR Review Committee."*[301]

For example, on October 28, 2013, Cibele Rudge, Global Pharmacovigilance Head of Single Case Processing, emailed Ilona Weltrowski, Product Technical Complaints and Device Vigilance, with the email subject being 'Essure legacy data-differences'. In this email Cibele Rudge pulls examples of complaint files *"checking the differences in terms of reportability (definition of incident criteria) of Bayer and Conceptus understanding"* stating:

> *"I'd say that the majority would be surgical removal of device; perforation in procedural related and embedment with surgical intervention (BUT NOT LIFE-THREATENING); miscarriage; Device ineffective + device removal and tubal ligation**: In all cases below, Conceptus did not report such cases. In my POV, these are reportable cases."***[302]

Cibele Rudge testified that the manufacturer, in fact, did not report these legacy cases to the FDA:

> Q. What I want to ask -- maybe you've answered my question, maybe you won't know this. Do you know whether Bayer went back and reported all 589 Conceptus Legacy cases that you had identified as incidents to the FDA in an MDR?
> A. To my knowledge, we have assessed the benefit-risk to check if there were any safety signals, any change in the safety profile of the product, and there was no change to the safety profile. And then the decision was taken in not going back and reporting, but considering that there was a different company in assessing a different way. So there was -- the decision was not to go back and report as individual cases.
> Q. Okay. So the answer is, no, Bayer did not go back and ensure that all 589 incidents from the Conceptus Legacy database that was identified by your department were actually filed with the FDA as MDRs; is that right?
> A. Again, we have reviewed everything. We have respect the decision taken by the previous company.
> Q. So you didn't report them under your -- here's what I'm trying –
> A. We have revised the cases, and we felt that there is no change in the safety profile of the drug, and the decision was taken not to report back, but to respect the decision and the process in place at that time by the previous company.[303]

The failure of the Manufacturer to submit incidents/near incidents that were identified as reportable to FDA from any historic data review is irresponsible, actually negligent regarding patient health and safety, and violative - it does not comply with FDA regulations (unless the firm requested and received a formal exemption). The purpose of the "become aware" 30-day reporting window in 21 CFR 803.50 is to accommodate just such situations. The decision not to file known legacy reportable events should also fail to comply with company procedures.

Choosing not to file known legacy MDR's also violates of 21 CFR 820.20 Management Responsibility and fails corporate responsibility. It validates and indirectly condones previous inappropriate practices. It sends a very harmful message to staff and management involved in both the original decisions and the file review. It also overlooks an obvious signal of serious regulatory gaps that went well beyond MDR reporting and should have been investigated and addressed through immediate actions including: in depth review of all complaint and MDR processes, procedures and records; review of all risk management and appropriate quality practices; training; substantial procedure updates; and immediate changes in key management and staff s appropriate, beyond the scope of MDR reporting. To be effective, the reviews and training should have been conducted by an outside consultant or group with substantial medical device experience. Most of these actions are steps that FDA would look for and even recommend or require when a medical device firm needs to address significant issues with regulatory compliance in the quality, complaint or MDR areas.

The federal regulations and the manufacturer's internal SOPs are in place to protect the public and ensure that medical devices on the market remain safe. FDA reporting regulations serve an essential purpose non-compliance cannot be justified by scientific or clinical views, potential benefits to business, concern about public media perception, or threats of litigation.[304]

X. RISK MANAGEMENT

Findings

Strong risk management processes are essential to assure safe and effective medical devices. The Essure risk management program was seriously flawed and not compliant with FDA requirements. Potential safety issues and failure modes were not identified and incorporated into complaint handling, investigation, and MDR reportability procedures and activities. These would normally be used to guide how manufacturers organize complaints for handling and the extent of investigation required. They help determine the appropriate trending thresholds for safety signals, and when incidents or product issues will be considered reportable as MDR's (either adverse events or malfunctions).

Risk management provides severity and risk ratings for all the various harms with product use and determines the acceptability of these risks. The ratings influence corporate culture and affect actions including response to complaints received, when to open a Corrections and Preventive Action plan, whether an event is "serious" and should be reported to FDA, how information about the product in medical literature and social media will be perceived, how documentation will be maintained, and what actions if any should be taken to prevent or minimize the risks to patients.

For example, if your risk management process indicates a product has no likelihood of serious injury, then MDR assessments might be minimal, with limited investigation and documentation, and less in depth review of incidents than might occur if the firm knew life-threatening events were possible. If your risk management process tells you that the risks with product use are broadly acceptable and not likely to harm anyone or need action to address them, then a manufacturer may become less responsive to complaints and possibly miss early signals. When the risk management process fails, manufacturers can make very serious safety errors.

Michael Voss, Reglera LLC, was involved in providing complaint handling and MDR report filing services to Conceptus. In his deposition he explained failure modes and the impact of risk management on MDR reporting stating:

> Q. Okay. So the second category of reportable events you mentioned were malfunctions that could cause serious injury if they were to recur; is that correct?
> A. Yes
> Q. Okay. So can you explain that to me a little bit more?
> A. Yes. If a company determines that a particular failure mode, if it occurred again could cause death or serious injury, if the answer to those questions are yes, they would report that event to the FDA. And if that event were to occur again, even if an injury didn't occur, they would continue reporting those things. Once you set the precedent of making a report you continue to report on that until the cause of that problem is eliminated.[305]

Michael Voss further testified:

> Q. Okay. And if a company's reporting criteria are too restrictive that will lead to underreporting, will it not?
> A. I'm not sure what you mean by restrictive. They should identify the failure modes that have adverse outcomes and, depending upon how they define that, you apply those failures to the decision tree and get to a yes or a no
> Q. And if a company defines the failure modes too narrowly that can lead to underreporting, correct?
> A. If a company defines a failure to be not reportable, then you wouldn't report on that type of event.
> Q. Is there any subjectivity in determining a reportability analysis?
> A. If your processes are designed to -- designed appropriately and robustly, then you want to take the subjectivity out so that the person who's going through the decision tree doesn't have to be subjective. I don't recall how robust or strict their risk files or their definitions of failure modes were. We would have just been trained to them and have applied them to the decision tree
> Q. But you had input on those processes you've 3 testified, correct?
> A. We would not have been involved in their risk management process, the process where they define their failures -- where they identify their failures, what the outcomes of those failures are and the risk profile of those…. the actual failures and the risks of those failures were all developed by Conceptus. We didn't do any -- anything in the risk analysis or determination of probability and severity.[306]

Definitions

Risk is combination of the probability of occurrence of harm and the severity of that harm.[307]

Risk Management is defined as the systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risks.[308]

The Conceptus SOP 1830 Risk Management (Revision G) Section 4.0 defined Risk Management as:

> *An organized, systematic decision making process that efficiently identifies, analyzes, plans, controls, communicates, and documents risk* ***to increase the likelihood of achieving project goals.***

Background

The concepts of risk management are universal. The military uses them to identify and manage hazards with the potential to impact mission effectiveness.[309] Banks use them to assess and manage financial risks,[310] power companies use them to assess and manage insurance and regulatory risks,[311] car companies use them to address manufacturing and car safety risks and guide business decisions.[312]

The primary purpose of FDA requirements for medical device risk management is preventing or reducing harm to patients and others.

The authority for these requirements comes from the quality system regulation.[313] [314] Risk management activities build on quality system complaint handling, corrective and preventive action plans, and management reviews to protect patients. The QSR and MDR programs benefit because risk management can strengthens design controls and continuous quality improvement efforts, support post market surveillance MDR signal identification and MDR reporting.

FDA has officially "recognized" ISO 14971:2007 which describes general requirements for risk management in Section 3.1 as follows:

> *"The manufacturer shall establish, document and maintain throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling those risks, and monitoring the effectiveness of the controls."*

This process can be summarized as follows:

Risk identification and assessment process must be repeated as new information becomes available throughout the product lifecycle. Manufacturers are expected to review and update risk assessments regularly. ISO A.23.2.d. states*: "risk management is an evolving process and periodic review of the risk management activities is needed to ascertain whether they are being carried out correctly…to adapt to changes."*

Risk Assessment

ISO D..3.1 states: "…If a risk chart or risk matrix is used for ranking risks, the particular risk chart or risk matrix and the interpretation used should be justified for that application."

The level of risk that is considered acceptable for a medical device depends on the type of product involved. Factors that influence the threshold for acceptable risk often include:

- The intended use of the product,
- Expected impact of device on length and quality of life,
- Age and health or illness of users,
- Nature of the harms both potential and known,
- Other options available for diagnosis, treatment, or prevention of the condition.

Examples

A firm that makes teething rings may decide that one infection from the product in 300,000 infants is not acceptable. This product offers temporary comfort but no significant health benefits to young children who are well. Similar products or other options for teething distress are available at markets and drugstores.

A company that produces a unique device expected to extend life for patients with heart disease or terminal cancer when no other option is available might conclude that one serious adverse event in 5,000 patients is acceptable to market.

FDA demonstrates the concept of different acceptable risks when it classifies medical device recalls. Recall risk classification, like the risk assessments conducted by manufacturers, determine what actions will be taken and what priority is given to prevent or correct patient exposure to the risks from devices. The highest class of recalls (Class I) involves products considered to have a *"reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death."*[315] The threshold for frequency of serious harms considered to meet this reasonable probability level has varied from 1/1,000 patients to 1/500,000 patients depending on the purpose of the device, patient population and other factors.

XI. RISK ASSESSMENT FOR ESSURE

Manufacturer Knowledge of Risk Management

Conceptus was familiar with risk management for medical devices and had documents in place before FDA market approval of Essure in 2002.[316] Bayer continued to use these documents after the acquisition, adding the Bayer logo and making some additional revisions over time.[317] [318]

Conceptus and Bayer had knowledge of ISO 14971 and referenced both ISO 14971:2000 and ISO 14971:2007 in their risk management documents over time.[319] [320]

Conceptus Employees continued to be actively involved in key risk management functions for Bayer. Mr. Reddick authored Revision F of R1831 and both Mr. Reddick and Mr. McCarthy were listed as custodians on the Metadata file created 8/14/2014. [321]

Senior Management Responsibility

ISO 14971:2007 describes management responsibilities in section 3.2 as follows:

> *"Top management shall provide evidence of its commitment to the risk management process by:*
>
> - *Ensuring the provision of adequate resources and*
> - *Ensuring the provision of qualified personnel for risk management.*
>
> *Top management shall:*
>
> - *Define and document the policy for determining criteria for risk acceptability; this policy shall ensure that criteria are based upon applicable national or regional regulations and relevant International Standards, and take into account available information such as the generally accepted state of the art and known stakeholder concerns;*
> - *Review the suitability of the risk management process at planned intervals to ensure continuing effectiveness of the risk management process and document any decisions and actions taken; if the manufacturer has a quality management system in place, this review may be part of the quality management system review."*

ISO A.2.3.2.c. states*: "*…because this International Standard does not define acceptable risk levels, top management is required to establish a policy on how acceptable risks will be determined."

Risk Management Documents

Risk management processes and procedures written by device manufacturers are tailored to the products and the company.[322] Senior management is responsible for how the company selects severity and frequency scales and the risk charts that determine what levels of risk will be considered acceptable for marketing. The scales and risk chart for each device are selected and documented in a formal plan. They may vary from product to product.

The commitment of top management is critical for an effective risk management process. These individuals should take responsibility for overall guidance of the risk management process and this subclause is intended to emphasize their role. In particular:

1. in the absence of adequate resources, risk management activities would be less effective, even if complying, to the letter, with the other requirements of this International Standard;

2. risk management is a specialized discipline and requires the involvement of individuals trained in risk management techniques (see A.2.3.3);
3. because this International Standard does not define acceptable risk levels, top management is required to establish a policy on how acceptable risks will be determined;[323]

Product Factors Considered

Known information about the product is considered when selecting severity and frequency scales and risk charts. It is also considered in planning and conducting post market surveillance risk management. Known information about Essure and long-term implants that might be relevant in these decisions includes:

- The nature of long-term tissue response to Essure inserts is unknown (as noted in the Summary of Safety and Effectiveness Data).[324]
- Long term implants can be associated with local or systemic symptoms and illnesses in patients well after placement and even if the product appears to be functioning well. Delayed, non-specific complaints with long term implant use may sometimes have a legitimate diagnosis with serious consequences.[325] [326] [327] [328]
- For permanent implants all risks from treatment, procedures, or surgery to address chronic symptoms/adverse events, or to remove or replace implants must be attributed entirely to the product for risk assessment purposes.
- Essure materials were intentionally selected to irritate body tissues causing local reactions and fibrous growth could potentially injure other tissues if they are misplaced[329] [330]
- Essure contains nickel and there is a high rate of hypersensitivity to nickel in U.S. women (estimated at 17%-25% of women vs. 3% of men) with symptoms known to occur locally and systemically.[331] [332]
- Long term pain syndromes have been known to occur in women that may be associated with longer term pain following procedures or surgeries.
- Clinical studies identified an increasing number and significance of adverse events associated with Essure use. The Manufacturer did not take these findings into account in assessing reportability and determining if information reasonably suggests that a device "May have caused or contributed to a death or serious injury (21 CFR 803.50 (a)(1) or "has malfunctioned and this device or a similar device…would be likely to cause or contribute to a death or serious injury if the malfunction were to recur." (21 CFR 803.50(a)(2).

Serious Gaps in Risk Management Procedures

For each potential issue, manufacturers are required to estimate the most severe levels of harm that could reasonably occur.[333] These scores determine where the product falls on the Risk Chart – in the acceptable risk zone or in a higher risk zone that requires reducing risk to continue marketing. Manufacturers are encouraged to voluntarily reduce even low risks as much as possible.[334]

Risk management procedures SOP 1830 Risk Management, R1831 Risk Analysis Procedure, and SOP 01107 Failure Mode Risk Analysis had serious flaws that continued across versions, were not

compliant, and jeopardized the firm's ability to correctly determine the severity and acceptability of patient risk. For example:

- SOP 1830 Risk Management failed to provide a clear and appropriate process for recognizing and assessing the severity of harms/events associated with Essure use.
- SOP 01107 Failure Mode and Effects Analysis failed to provide a clear and appropriate process for assessing the harm reflected by complaints of product design and evaluating and controlling them accordingly.[335] [336]
  - No descriptions are provided for the severity scale in SOP 1830 until Revision P (after 2012).[337]
  - Scales after Revision P of SOP 1830 include only one-word terms with no explanation, instructions, or descriptive wording of the levels. This allows staff very broad discretion in assigning low severity to events described in complaints or reported in medical literature, artificially raising the threshold for MDR reporting.
  - R1831 (Revision G in use mid-2013 or later) has no severity scale provided or referenced and there is no discussion of how to determine severity of events and frequency scores that are essential to risk analysis and evaluation following the ISO 14971 process. There is no mention of harms to patients or instructions about how to identify and assess them. The document jumps from identifying hazards to determining risk acceptability. Section 5.2.1 talks about documenting the acceptability of the hazard and 5.2.2.2 refers to determining the acceptability of hazards. No risk chart is provided or referenced and there are no instructions for how to evaluate acceptability of risk.[338]
  - R1381 (Revision G) describes considering use of overall residual risk to determine risk acceptability (Section 5.2.2.2 (a) final bullet) but does not provide any indication of how to perform that assessment.
- R1831 (Revision G) comments on determining risk acceptability are inconsistent with SOP 1830. R1831 does not provide or suggest a risk chart but offers points for consideration. A risk chart is provided as the only measure of risk acceptability in most revisions of SOP 1830.
- The severity table in SOP-01107 appears to mix the measurement of patient, business, and regulatory harms and risks. The document does not make it clear that different types of harms or risks (patient, business, regulatory, etc.) should always be assessed and documented completely separately to prevent diluting the ratings for patient risk.
- Risk assessments, especially patient severity assessments, benefit significantly from clinical input. This product was a Class III permanent implant, but there is no indication that clinical participation in risk assessments was recommended, required, or occurred.
- The ranges for frequency of harms provided in later versions of SOP 1830 are not appropriate for Essure or consistent with the ISO 14971:2007 example. They allow a relatively large number of events to occur at the acceptable risk level. Someone using the scale could easily determine that an issue involving quite a few deaths did not require further attention.

Severity Scale, Frequency Scale, and Risk Chart Are Not Appropriate

Risk Charts are the visual display of how much risk the firm considers acceptable to patients and also when the company must take to reduce or eliminate risk from a potential safety issue. The

Risk Chart for Essure shows a very high tolerance for risk that is, not appropriate for a Class III permanent implant. Based on the large number of patient adverse event reports, it also does not reflect known stakeholder concerns.

SOP 1830 divides risk into three levels. Descriptions of the categories vary in different revisions. These have been compiled from Revisions G, M, and S hand edited a bit for clarity:

- Broadly acceptable – tolerable risk, should be reduced where possible but acceptable without further action
- ALARP - undesirable but acceptable risk if mitigated to the extent possible without reducing clinical/functional utility of product
- Intolerable risk – unacceptable risk, redesign or reduction in occurrence of harm required

The Risk Chart for the Essure System in SOP 1830 (Revision G) is provided below:

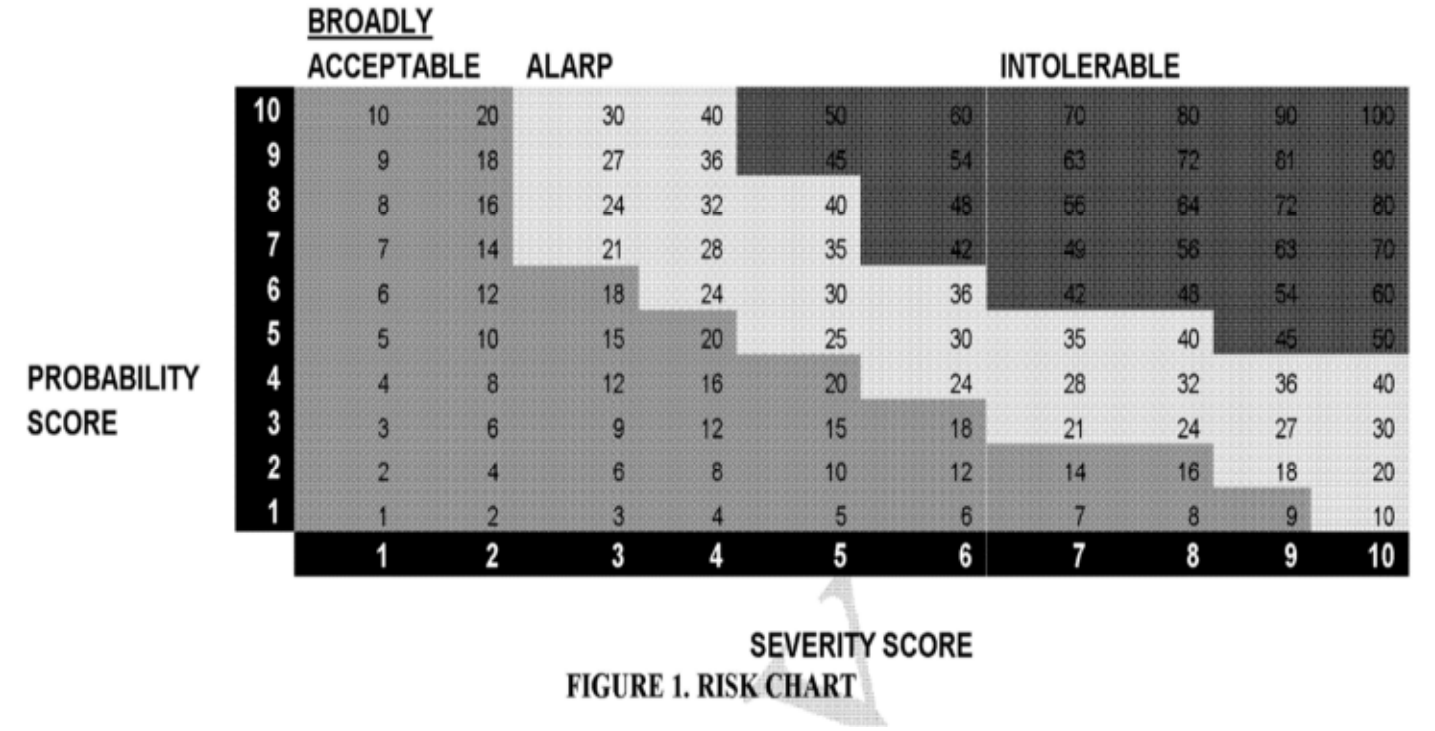

FIGURE 1. RISK CHART

In this version of the procedure, the severity and frequency levels were totally undefined. The risk chart shows that highest severity possible (which must include death) at a probability score of 4 out of 10 (near the middle of possible frequencies) would be considered acceptable if no control has been found to reduce it (ALARP). Severity scores of 8 and 9 (ratings likely to represent life-threatening injury, permanent organ damage, or long-term disability) would be considered broadly acceptable at the lower frequency scores, and acceptable if no control has been found at frequency ratings up through level 4 for Severity # 9 and frequency up through level 5 (including half the

frequency scale) for Severities # 7 and #8. This chart also indicates that patient harms with low severity (#1 and #2 probably reflecting inconvenience or minor injury) are broadly acceptable if they occur at the highest frequency score #10. Depending on how the frequency scale is defined, this could include all users.

This chart is not appropriate for the Essure device or many other devices. It shows that risks involving death or serious injuries can be acceptable across a range of frequencies of occurrence with no action required. How many deaths would be acceptable depends on how someone might read the probability scale which comes with no explanation.

The acceptable risk limit for contraceptive products should be low. Manufacturers need to seek ways to minimize or prevent risks before users are harmed. Many of the users are healthy young people who have long lives ahead and may have other birth control options available.

If the product risk falls in the (yellow) ALARP or Intolerable (red) zones on an appropriate risk chart, after all possible controls have been applied, it may still proceed with marketing if the firm can demonstrate that benefits outweigh the risks.

A later version of the Risk Chart for Essure from SOP 1830 (Revision S) is shown below. The 10-point severity and frequency scales have now been reduced to five-point scales. The chart includes one word for each level of the scales along with a range of numbers describing the frequency scale:

FIGURE 1 RISK CHART (Commercialized Products)

			Broadly Acceptable		As Low As Possible		Intolerable
PROBABILITY of OCCURENCE SCORE	Frequent >2.0%	P5	ALAP	ALAP	INT	INT	INT
	Probable >1.0% to ≤2.0%	P4	ALAP	ALAP	ALAP	INT	INT
	Occasional >0.1% to ≤1.0%	P3	BA	BA	ALAP	ALAP	INT
	Remote >0.001% to ≤0.1%	P2	BA	BA	BA	ALAP	ALAP
	Improbable ≤0.001%	P1	BA	BA	BA	ALAP	ALAP
			S1	S2	S3	S4	S5
			Negligible	Minor	Serious	Critical	Catastrophic

SEVERITY

The relative distribution of risk categories appears to be very similar, and the concerns about finding risks of death acceptable without action required remain. Frequency ranges have now been provided that offer context. However, these ranges appear much higher than appropriate for Essure and many other devices. They allow relatively high numbers of deaths or serious injuries to be acceptable if no control has been found to reduce risk. The range of events described as “Remote” (up to 1/1,000 patients) is higher or consistent with what FDA would generally consider “Probable” for defective product as noted previously. The result of this chart will be to place many

potentially significant issues (especially as they are first emerging) into the lower two categories where recognition of an important issue or appropriate follow-up actions may not occur. ISO D.3.4.2. Table D.4 provides an example scale of probability levels with ranges and the same one-word terms found in the Essure risk chart. The ISO example defines the highest level (frequent) as equal to or greater than 1/1,000 products. The Essure chart places frequency that high at the upper end of the "remote" range. The Essure Risk Chart has not been modified to account for the high frequency of events included in the lower probability ranges. In fact, it goes the opposite way, expanding the acceptable range to include both the acceptable zone and most of the ALARP zone from the ISO example risk chart (ISO D.8.5).

Senior Management Failed Regulatory Obligations

Conceptus SOP 1830 (Revision G) describes the purpose of risk management as: "to increase the likelihood of achieving project goals". This goal focus is consistent with programs addressing financial and business risks but not patient risks. Bayer provided a more direct statement on page 29 of their Risk Management Document[339] noting that "levels of risk and acceptability" set for the product were determined by the company's "appetite for risk."[340] These two statements might explain the choice of frequency scales and a risk chart with high tolerance for patient harm. Selection of a patient risk chart should be based on benefits to patient, not the financial/legal risk a company will accept to make money.[341]

Resources for effective risk management were not provided. Severe weaknesses in the risk management procedures demonstrate that Essure programs were not staffed by individuals with adequate risk management skills. ISO 14971:2007 states: "*risk management is a specialized discipline and requires the involvement of individuals trained in risk management techniques.*"

Management failed to identify potential patterns and pursue safety issues, including breakage and migration that was described known by August 2009 emails,[342] reportable event due to the patient's pain experience, broken pieces of insert migrating to bowel, and the fact that she went to the ER.[343] Emails in 2009 where Health French Agency requested an Expert Statement after piece broke off outer coil of insert, apparently during perforation/migration. Robert McCarthy stated in his deposition that he "*never asked anyone to look into safety issues with pieces breaking off.*"[344] In 2012 the firm had indications that the device was not designed to withstand removal so if a fallopian tube spasmed and the physician had to pull back the implant, breakage might occur.[345] On October 21, 2013 an email was forwarded to Robert McCarthy showing a breakdown of 838 complaints filed with FDA by women and doctors directly since 2004. It also showed 150 reports of coils breaking loose.[346]

In 2015, the Health Authority for France ANSM sent the Manufacturer a draft policy decision to pull Essure from the market in France. They cited approximately 1,000 adverse events reported for 2,600 women. Although the firm was apparently successful in avoiding Essure removal, they failed to recognize the significance of product safety and regulatory concerns that prompted considering the action.

Management also had knowledge of complaints about Essure safety and side effects on social media beginning as early as 2006. When a supplier emailed in 2013 asking if a Yahoo article about

Erin Brockovich pressing safety issues with Essure was affecting business. Robert McCarthy responded *"Nothing noticeable"* and *"Don't believe everything you read."*[347] When asked in a deposition about the advisory panel meeting if he believed the women describing problems with Essure were telling the truth, Mr. McCarthy responded *"I have no reason not to believe them."*[348]

Bayer relied on Conceptus procedures and management (including Michael Reddick, Robert McCarthy, and Henry Bishop) for activities related to risk management long after the differences in MDR reporting policies and their notable lack of good judgment in basic regulatory matters should have raised concerns about the decision-making and procedures established by this group.

Senior management failed to obtain the expertise needed to successfully address the situation when adverse event reports on Essure were increasing and FDA began discussing possible safety issues in 2013. Management could have reached outside the firm if necessary to clinical, regulatory, and risk management experts to re-think and optimize the Manufacturer's corporate approaches to Essure clinical issues.

The Manufacturer prepared an Executive Summary for the advisory panel meeting that offered several possible explanations for the increase in adverse event reports to FDA from patients. It included no consideration of possible device-related cause(s), risk management assessment by the firm, or actions/controls considered or taken. It concluded **that *"… the numerical increase can be explained by factors influencing post marketing safety reporting***. *Reporting rates remain compatible in line with the data generated in clinical studies."*[349]

In the presentation and written summary for the advisory panel the Manufacturer concluded that the benefit/risk ratio for the product remained positive. This demonstrates a very basic lack of understanding. As noted above, benefit risk analysis can be used to determine acceptability to market if risks remain high **after all efforts to reduce and control risk have been implemented.** A positive benefit/risk balance does not allow a firm to avoid investigating potential safety issues or fail to reduce them when possible.[350] In the months and years of complaints, published adverse reports, information on social media, MDR's reported to FDA, and the agency escalating concerns, the firm did not take all possible actions to minimize the risk with Essure use.

The Manufacturer failed to comply with FDA requirements and fulfill their risk management responsibilities. The firm failed to act to inform and protect patients and potential consumers. Conceptus did not anticipate significant potential safety issues or recognize them from early information. The company failed to recognize significant safety issues despite an increasing number of adverse event reports to FDA and visible and escalating concern from the agency.

There is no question what conclusions effective risk management programs should have reached or what actions should have taken. FDA demonstrated exactly what appropriate risk management included. When the manufacturer learned of increasing patient reports to FDA, they found ways to justify and discount them. FDA gave the situation priority over many other important safety issues. The agency gathered information and took action.

FDA responded with requirements for a new Essure post market surveillance study and labeling changes including a black box warning and a patient check list for physician/patient discussion

and signature before the procedure. All of these or similar actions could have been voluntarily initiated by the firm years before FDA required them. Patients could have been better informed and the risks of potential safety issues could have been minimized. In 2018 FDA determined that some patients were continuing to receive Essure devices without adequate understanding of the risks and potential issues. The agency took the rare action of restricting sale of the device to healthcare facilities and providers who would implement the patient checklist and signature as a required step before implanting Essure. The Manufacturer withdrew the product from the U.S. market at the end of 2018.

XII. CONCLUSION

The Center for Devices and Radiological Health at FDA screens numerous potential post market safety issues each year that are identified through MDR reports and other sources. A limited number receive follow-up investigation and actions by cross-functional teams. Involvement by agency level leadership such as the Office of Women's Health or the FDA Commissioner is unusual, especially involving direct interaction with patients/consumers. It is rare for the Center to convene an advisory panel meeting to obtain clinical input on the significance of a post market issue and request recommendations. Adding a black box warning to the label post market is uncommon. Requiring voluntary patient and physician check lists is very unusual. Restricting sale to force mandatory use of a patient/physician check list or consent form with mutual doctor/patient signatures is extremely rare and suggests a high level of concern about the product safety and the lack of reliable information sharing in patient care situations. The FDA Commissioner's strong comments in the press release reinforce the unusual nature of this situation. The Manufacturer indicated at the advisory panel meeting in 2015 that they had identified no concern and did not believe there was an issue. That demonstrates a major failure of risk management and a serious lack of compliance with FDA expectations and requirements affecting interconnected complaint handling, MDR reporting, and risk management activities.

Essure placement is an elective procedure undergone at the patient's discretion after physician counseling on the risks and benefits, alternative birth control options, and informed consent. As stated in the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Sterilization of Women (2017), "Obstetrician-gynecologists should provide pre-sterilization counseling that includes a discussion of a woman's reproductive desires and places her wishes at the center of care." "The decision among various methods is ultimately a matter of patient preference."

For the informed consent discussion to be meaningful, physicians and patients need complete, accurate and current benefit and risk information available on the device under consideration. Information entering into the public forum must be accurate and timely so the medical establishment will share with patients to reach the best conclusions for their situation. In this regard, physicians routinely rely on the medical device manufacturer to disclose up-to-date risk information about their devices since the benefit and risk analysis can change over time as newer data arises.

When a firm violates that trust, abdicates their corporate responsibilities and fails to comply with federal regulations the public is placed at unacceptable and unnecessary risk. Essure presents just such a case.

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[105] Deposition of Lois Pierce, dated September 14, 2019 at 138:10-20 (Q: Can you read the first sentence of the second paragraph, please, for the record starting with "Nothing." A. Okay. "Nothing new is going on around here, we are still receiving AR's at an astronomical rate. It seems as" if "it is a never ending battle." Q. Okay. What did you mean by "receiving AR's 16 at an astronomical rate"? A. By this time it had already hit the market, so of course once it hit the market we had more complaints coming in.)
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[134] BAY-JCCP-0680171
[135] BAY-JCCP-0435844
[136] BAY-JCCP-0435844
[137] 21 CFR 803
[138] *See* https://www.fda.gov/media/86420/download at 13; FDAPUB0001638
[139] *See* http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm; *See also* Appendix D to Executive Summary from 2015 Meeting of the Obstetrics and Gynecology Devices Panel (https://wayback.archive-it.org/7993/20170723124202/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM463486.pdf)

[140] 21 CFR 820.198; https://www.fda.gov/files/about%20fda/published/Complaint-Files---Printable-Slides.pdf (Slide 16)
[141] 21 CFR 803.56
[142] 21 CFR 803.18
[143] 21 CFR 803.18 (c)
[144] 21 CFR 803.52
[145] ISO 14971 Section A.2.9
[146] Advanced Medical Technology Association. (2018). Postmarket. Retrieved October 2, 2019, from https://www.advamed.org/postmarket.
[147] BAY-JCCP-1594367-1594384
[148] Edward Sinclair Dep. Exh. 17.
[149] BAY-JCCP-1616995-1616996
[150] BAY-JCCP-1616995-1616996
[151] Deposition of Michael Reddick, dated March 13, 2019, at 33:1-6.
[152] Deposition of Michael Reddick, dated March 13, 2019, at 36:6-20.
[153] Deposition of Michael Reddick, dated March 13, 2019, at 38:13-39:2.
[154] Rachelle Acuna-Narvaez, Dep. Exh. 286.
[155] Deposition of Rachelle Acuna-Narvaez, dated March 29, 2019, at 62:5-63:3.
[156] Deposition of Edward Yu, dated September 17, 2019, at 24:9-25:24.
[157] BAY-JCCP-4314711
[158] BAY-JCCP-7402159
[159] *Id.*
[160] *Id.*
[161] Deposition of Lois Pierce, dated September 14, 2019, at 12:8-19.
[162] BAY-JCCP-4810040
[163] BAY-JCCP-4810038
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[169] BAY-JCCP-0085097
[170] BAY-JCCP-0085097
[171] BAY-JCCP-0085104
[172] BAY-JCCP-0314376

[173] BAY-JCCP-0314405
[174] BAY-JCCP-0680219
[175] BAY-JCCP-0680220
[176] BAY-JCCP-1029597
[177] BAY-JCCP- 5529306
[178] BAY-JCCP-0722678
[179] BAY-JCCP-1546353
[180] Deposition of Edward Yu, dated September 17, 2019, at 271:10-14.
[181] BAY-JCCP-0180760
[182] BAY-JCCP-0416533
[183] BAY-JCCP-0089483
[184] BAY-JCCP-0089482
[185] Deposition of Illona Weltrowski, dated June 27, 2019, at 83:20-84:15.
[186] BAY-JCCP-0953875
[187] BAY-JCCP-0269314
[188] David L. Howard, MD et al., Use of Intraoperative Fluroscopy During Laparotomy to Identify Fragments of Retained Essure Microinserts: Case Report, 19 Journal of Minimally Invasive Gynecology 667 (2012).
[189] BAY-JCCP-0185912; *See also* Deposition of Robert McCarthy, dated March 19, 2019, at 363:7-13 ("Q: So to be clear, the patient's symptoms had to resolve after the intervention in order for the MDR to be reportable; right? MS. CURTIN: Object to form, vague. A: Based on what he has written here, that would be one of the factors that they would have evaluated.").
[190] Deposition of Rachelle Acuna-Narvaez, dated March 29, 2019, at 358:17-359:17.
[191] 21 CFR 803.50 (a) (1)
[192] BAY-ESSURE-0056223
[193] Bayer Healthcare. (2002). Essure permanent birth control: Instructions For Use. USA: Bayer.
[194] FDAPUB0000323
[195] BAY-EDPA-0798679-0798681
[196] BAY-JCCP-0140526
[197] BAY-JCCP-0366729
[198] ISO 14971:2007; 21 CFR 820.100 (a) (3)
[199] BAY-JCCP-0140336
[200] BAY-JCCP-0912002
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[203] BAY-JCCP-0242985
[204] Deposition of Andrea Machlitt, dated June 25, 2019, at 93:21-94:21.
[205] Deposition of Rachelle Acuna-Narvaez, Regulatory Affairs Manager, dated March 29, 2019 at 90:13 – 91:14
[206] BAY-JCCP-1546361
[207] *Id.*
[208] BAY-JCCP-0085313
[209] BAY-JCCP-0009265
[210] FDAPUB0000323
[211] BAY-JCCP-0209418
[212] BAY-JCCP-0314411
[213] BAY-JCCP-0185912
[214] BAY-JCCP- 1532946
[215] FDAPUB0000616
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[219] BAY-JCCP-0184850
[220] BAY-JCCP-0154726
[221] BAY-JCCP-5445325

[222] BAY-JCCP-0009265
[223] BAY-JCCP-0722678
[224] BAY-ESSURE-0054484-.
[225] Deposition of Edward Yu, dated, September 17, 2019, at 189:9-19.
[226] FDAPUB000032324 at 54-63.

[227] FDAPUB0000588
[228] FDAPUB0000588
[229] FDAPUB0000588
[230] FDAPUB0000588
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[232] BAY-JCCP-0912075
[233] BAY-JCCP-0912075
[234] *Id.*
[235] BAY-JCCP-0912096
[236] BAY-JCCP-0038735_R
[237] BAY-JCCP-0038735_R
[238] BAY-JCCP-0038735_R
[239] BAY-JCCP-0038735_R
[240] BAY-JCCP-0038735_R
[241] BAY-JCCP-0220343
[242] BAY-JCCP-0038735_R
[243] BAY-JCCP-0017541
[244] BAY-JCCP-0017541
[245] BAY-JCCP-0017541
[246] BAY-JCCP-0000008
[247] BAY-JCCP-0000008
[248] BAY-JCCP-0000001
[249] BAY-JCCP-0000011-12
[250] BAY-JCCP-0000012
[251] Deposition of Edward Yu, dated, September 17, 2019, at 221:24-25 – 222:2-5 (Discussing Exhibit 809 – AR04793 – BAY-JCCP-6806720 – an October 2004 event for which Conceptus the listed aware date is December 2004).
[252] Deposition of Edward Yu, dated September 17, at 209:3-8 (Discussing Exhibit 807 - Thoma, Véronique, et al. "Tubal perforation by ESSURE microinsert." Journal of minimally invasive gynecology 13.2 (2006): 161-163).
[253] Deposition of Edward Yu, September 17, 2019, at 209:10-14 (Discussing Exhibit 807 - Thoma, Véronique, et al. "Tubal perforation by ESSURE microinsert." Journal of minimally invasive gynecology 13.2 (2006): 161-163).
[254] Deposition of Edward Yu, dated September 17, 2019, at 214:9-23 (Discussing Exhibit 808 - Pyke, Robert, and Lisa R. Blackwood. "Complication of the Essure implant sterilization procedure: a case report." Journal of Gynecologic Surgery 24.1 (2008): 37-42).
[255] Deposition of Edward Yu, dated September 17, 2019 at 214:25 – 215:4 (Discussing Exhibit 808 - Pyke, Robert, and Lisa R. Blackwood. "Complication of the Essure implant sterilization procedure: a case report." Journal of Gynecologic Surgery 24.1 (Nov. 1, 2008): 37-42) (the incident happened in 2007, according to the published case report).
[256] Deposition of Edward Yu, dated September 17, 2019 at 230:6-25 (summarizing the above exhibits).
[257] Deposition of Edward Yu, dated September 18, 2019 at 292:2-14.
[258] BAY-JCCP-0000012-13
[259] BAY-JCCP-0000010
[260] BAY-JCCP-0017541
[261] BAY-JCCP-0017541
[262] BAY-JCCP-0911999
[263] *Id.*
[264] Deposition of Edward Yu, dated September 17, 2019, at 304:21 – 307:11.
[265] BAY-JCCP-0692941
[266] *Id.*

[267] BAY-JCCP-0289084
[268] BAY-JCCP- 0289084
[269] Deposition of Robert Feyerherm, dated May 21, 2019, at 168:22-169:7.
[270] BAY-JCCP-0438119
[271] BAY-JCCP-1028086
[272] BAY-JCCP-0686137
[273] BAY-JCCP-0686137
[274]BAY-JCCP-0416533
[275] BAY-JCCP-0416533
[276] BAY-JCCP-0180618; *See also* BAY-JCCP-0289742 (An email chain regarding adverse events in March 2012 received by the manufacturer in May or earlier the past year. Decision to file made August 28, 2012. Several month delay in MDR decision and reporting due to error in recording information and/or failure to follow up)
[277] Roberts, M. (2014). *Non-Conformity Report.* National Standards Authority of Ireland. Page 2. BAY-JCCP-0435843; See also BAY-JCCP-0053129_R (An external audit in 2015 found similar administrative issues. Eight (8) out of 25 MDRs did not have the date of event field completed. The event date was found another place on the form, in the field "Describe Event or Problem". Fifteen of twenty-five MDRs reviewed did not follow the MedWatch instruction in regards of coding the event and section H (Evaluation Codes) had not been completed).[277]
[278] BAY-JCCP-0089364
[279] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 93:18-22.
[280] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 115:15-24.
[281] BAY-JCCP-0912068
[282] BAY-JCCP-0912075
[283] BAY-JCCP-0912096
[284] BAY-JCCP-0009265
[285] BAY-ESSURE-0054484
[286] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 176:6-10.
[287] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 156:24.
[288] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 243:18-244:13.

[289] BAY-JCCP-0089482
[290] Reddick Dep Exh. 120 (October 18, 2018).
[291] Reddick Dep Exh. 120 (October 18, 2018).
[292] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 258:3-6.
[293] PMQ Deposition of Michael Reddick, dated October 18, 2018, at 259-260.
[294] PMQ Deposition of Michael Reddick, dated October 18, 2019 at 249:4-250:20.
[295] BAY-JCCP-0680167
[296] BAY-JCCP-0238009
[297] BAY-JCCP-0438119
[298] Complaint Handling Report, Section VI
[299] BAY-JCCP-0912075
[300] BAY-JCCP-0912096
[301] BAY-JCCP-2613733
[302] BAY-JCCP-5529306
[303] Deposition of Cibele Rudge, dated July 2, 2019, at 473:23-475:5.
[304] BAY-JCCP-0153781 (August 2, 2012 email from Michael Reddick to Greg Lichtwardt and Rob McCarthy: "Discuss need for escalation process for certain types of complaints: threatening litigation, requesting reimbursement, discontent patients requesting call backs")
[305] Deposition of Michael Voss, dated September 27, 2019, at 43:4-18.
[306] Deposition of Michael Voss, dated September 27, 2019, at 77:23-79:24.
[307] ISO 14971:2007 2.16
[308] ISO 14971:2007 2.22
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[313] 21 CFR 820.30 (g)
[314] comment 83 of the preamble to the 1997 rule
[315] Center for Devices and Radiological Health. (2015, April 25). Recalls, Corrections and Removals (Devices). Retrieved from https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices
[316] Risk Analysis R1831 Revision A, R1831 Revision G Revision History
[317] Conceptus R1831 Revision G. BAY-JCCP-7302767
[318] Bayer Healthcare. SOP 1830 Revision M. BAY-JCCP-0412483
[319] Conceptus, Inc. SOP 1830 Revision G. BAY-JCCP-0082571
[320] Conceptus R1831 Revision G. Section 3. BAY-JCCP-7302767
[321] Conceptus R1831 Revision G. Section 3. BAY-JCCP-7302767
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[323] ISO 14791-2007. A.2.3.3.a-c
[324] US Food and Drug Administration. (2002). *Summary of Safety and Effectiveness Data.* USA: FDA. Section V.3. FDAPUB 0000564.
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[335] Conceptus, Inc. *SOP 1830 Revision G.* BAY-JCCP-0082571
[336] Conceptus, Inc. *SOP 01107 – Failure Modes and Effects Analysis (FMEA). Revision L.* BAY-JCCP-0227514
[337] Bayer Healthcare. *SOP 1830 – Risk Management. Revision P.* BAY-JCCP-137
[338] Bayer Healthcare. *R1831 – Risk Analysis Procedure. Revision G.* BAY-JCCP-7302767
[339] Bayer Healthcare. *Risk Management Document XXX*. Page 29.
[340] Bayer Healthcare. *Risk Management Document XXX.*
[341] ISO 14971:2007
[342] BAY-JCCP-0686136
[343] BAY-JCCP-0953875
[344] Deposition of Robert McCarthy, dated March 19, 2019, at 223:4-25.
[345] BAY-JCCP-0242985
[346] BAY-JCCP-0242166
[347] BAY-JCCP-0237508
[348] Deposition of Robert McCarthy, March 20, 2019, at 443:1-5.
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[350] ISO 14971:2007.

Kimber C. Richter, M.D.

Kimber C. Richter M.D.

APPENDIX A

Kimber C. Richter, M.D.

Address: 310 Janesville Street
Oregon, WI 53575

Phone: 304-995-6071

E Mail: KRichter@KRClinicalConsulting.com

Work Experience:

K.R. Clinical Consulting, LLC

President (2016 – Present)

Consultant specializing in clinical product safety for medical devices. Experience with consumer products, drugs, and combination products as well. Advises on pre-market regulatory strategy, product development, human factors, clinical studies, hazard analysis and harm severity, health hazard evaluations, recall strategy, complaint and adverse event reporting issues. Writes and revises policies, procedures, clinical summaries, harms lists, benefit/risk documents and reports. Coordinates work of other consultants and specialist clinicians. Educates clients on regulatory requirements, processes, and expectations. Background includes in vitro diagnostics, women's products, and regulatory needs of start-up firms.

HireGenics

Part-Time Medical Director (October, 2017 – Present)

Provides clinical risk and regulatory expertise and support to a global drug and combination product company, with focus on risk management/risk assessment in post market surveillance and quality organizations. Leads and participates in cross-functional teams. Writes and updates corporate risk management, health hazard assessment and hazard analysis procedures. Advises on complaint and adverse event reporting issues. Provides training as requested.

U.S. Food & Drug Administration
Center for Devices and Radiological Health

Office of Compliance
Deputy Director for Medical Affairs (2002 – 2015)

Clinical lead for the Center on compliance and enforcement activities related to post market quality and safety of medical devices (prescription and over the counter), including more than 1,000 recalls per year. Identified significant public health issues, conducted risk/benefit

assessments, proposed plans to minimize public harm and bring products into compliance with regulations. Advised on industry communications, FDA public notices and press releases. Developed policies and procedures, drafted guidance documents, conducted training. Advised Center management on clinical aspects of enforcement actions including potential shortage impact of warning letters, import alerts, seizures, and injunctions.

Provided leadership on the use of science in regulatory activities. Identified emerging knowledge likely to affect safety and performance of current or future devices. Led regulatory policy updates to let industry benefit from new technologies while minimizing patient risks. Reviewed research proposals for scientific and regulatory merit. Served on inter-Center science-based policy groups including the Tissue Reference Group and the Drug Safety Board. Represented FDA on the Board of Directors of the Association for the Advancement of Medical Instrumentation (AAMI).

Supervised the Division of Bioresearch Monitoring responsible for policy setting, public education and enforcement of regulations on the design and conduct of medical device clinical studies. Participated in development of Center and Agency policy on clinical research. Served as US Co-Chair on the work group that drafted the global standard for clinical trials of medical devices (ISO 14155). Represented the Center on recent Agency-wide activities to optimize inspections of clinical studies.

Served on Office, Center and Agency groups for strategic planning, management and awards, reorganization, communication processes, and IT services. Represented the Center on the Peer Review Promotion Board for Medical Officers, and the Physician Compensation and Credentialing Board for FDA. Served as Acting Director for the Office of 160 – 200 people when the Office Director was anavailable. Advised and mentored staff and managers at all levels of the organization, and assisted supervisors with difficult personnel issues.

Office of Device Evaluation
Deputy Director for Clinical and Review Policy (1995-2002)

Provided clinical and process leadership on the review of medical device submissions including 510(k)s, PMA's and IDE's. Led major projects, streamlined procedures, and participated in key meetings with industry. Supervised four divisions at various times, with up to three divisions at one point including approximately 200 people. Handled Office budget and personnel activities. Represented the Agency to professional associations, Advisory Panels, Congressional staff, the press and the public.

Served on Agency policy setting groups including the Office of Women's Health Steering Committee. Represented the Agency on Global Harmonization Study Groups One and Five. Served as the Co-Czar of Center Re-engineering from 1997 – 1999. Five of my six teams received awards from Vice President Gore.

UNUM Life Insurance Company of America (First UNUM – New York)

Vice President and Officer (1994-1995)

Clinical adviser to First UNUM senior management. Conducted medical reviews of disability claims and life insurance applications. Coordinated work of nurses and consulting physicians to

provide a high volume of routine and specialty reviews on disability claims. Worked with physicians and employers tailoring rehabilitation plans to return claimants to productivity.

Tambrands, Inc. (Palmer, MA)

Vice President of Medical and Regulatory Affairs, Officer (1992 – 1994)
Director of Medical Affairs (1987 – 1992)

Global medical, safety and regulatory lead for a Fortune 500 company conducting business in approximately 150 countries. Product lines included Tampax tampons, First Response in vitro diagnostic products, Hygeia Sciences in vitro diagnostics, and Physician's Formula cosmetics.

Supervised four departments. Advised the company on clinical aspects of product design, claim support, and marketing. Provided worldwide regulatory strategy. Met with government officials, handled press inquiries, served as expert witness. Designed and coordinated basic research programs and Phase II, III, and IV clinical studies. Selected and monitored clinical and laboratory sites. Managed staff that designed and conducted consumer testing including focus groups, labeling reviews and surveys. Coordinated a research program on toxic shock syndrome at major universities. Advised on employee health issues.

Supervised a department handling up to 2 million consumer complaints and inquiries per year. Supported education programs for teens and adults around the world. Served as Chairman of the in-house Institutional Review Board. Supervised adverse reaction assessment and MDR reporting to FDA. Handled OSHA compliance and biohazard prevention issues.

Procter & Gamble Co. (Cincinnati, OH)

Physician, Special Products Group (1980 – 1981)
Physician, Food New Product Development (1985 – 1987)

Clinical lead for topical and systemic drugs under development and a novel food additive product. Project lead for topical drug approaching FDA submission. Designed, conducted, and monitored Phase I, II, and III clinical studies and consumer tests.

Kimberly-Clark Corp. (Neenah, Wisconsin)

Group Leader, Clinical Information Group (1983 – 1985)
Research Scientist Feminine Care R&D (1981 – 1983)

Advised on medical affairs, safety and design issues for consumer products and medical devices. Directed Clinical Research Center, designed and conducted studies to evaluate consumer preference, product performance and safety for medical devices, women's products, and diapers. Developed creative ways to test new concepts with limited subject risk. Coordinated academic research including toxic shock syndrome studies. Coordinated a network of medical consultants.

Education:

University of Wisconsin — 1972 – 1975
Biochemistry Major

Medical College of Wisconsin — 1975-1976
First Year Medical Student

University of Cincinnati — 1976-1979
College of Medicine
Cincinnati, OH
Doctor of Medicine

Resident in Internal Medicine — 1979 – 1980
The Christ Hospital
Cincinnati, OH

Medical License: State of Wisconsin (current)

Special Training, Honors, and Awards:

Clinical Instructor, Medical College of Wisconsin (1983 – 1985)
Federal Executive Training Course – "Leadership for a Democratic Society" (1998)
Three HHS Level Awards for Distinguished Service
Numerous FDA / CDRH Honor Awards

Publications:

Association for the Advancement of Medical Instrumentation. (25 August 2015). *Risk Principles and Medical Devices: A Postmarket Perspective (White Paper).* Arlington, VA.

Gutman, S., Richter, K., & Alpert, S. (1998). Update on FDA Regulation of In Vitro Diagnostic Devices. *Journal of the American Medical Association*, *280*(2), 190–192. doi: 10.1001/jama.280.2.190

Gutman, S., & Richter, K. (1999). New Directions in the FDA Regulation of In Vitro Diagnostic Devices. *Laboratory Medicine*, *30*(12), 782–785. doi: 10.1093/labmed/30.12.782

Kessler, L., & Richter, K. (1998). Technology Assessment of Medical Devices at the Center for Devices and Radiological Health. *The American Journal of Managed Care*, *4*, SP125–SP139. Retrieved from https://www.ajmc.com/journals/issue/1998/1998-09-vol4-n2sp/sep98-1095psp129-sp13

APPENDIX B

Materials Relied Upon

Depositions
Description
5/25/2017 Keith Abrams [PMQ] deposition and exhibits
1/11/2018 Michael Reddick [PMQ] deposition and exhibits
2/7/2018 Michael Reddick [PMQ] deposition and exhibits
2/13/2018 Christina Dickson [PMQ] deposition and exhibits
3/20/2018 Christina Dickson [PMQ] deposition and exhibits
4/18/2018 Michael Reddick [PMQ] deposition and exhibits
10/10/2018 Christina Dickson [PMQ] deposition and exhibits
10/18/2018 Michael Reddick [PMQ] deposition and exhibits
10/19/2018 Terry Mank [PMQ] deposition and exhibits
11/30/2018 Jamie Brown [PMQ] deposition and exhibits
2/13/2019 Lisa Mancer [PMQ] deposition and exhibits
3/13/2019 Michael Reddick deposition and exhibits
3/14/2019 Michael Reddick deposition and exhibits
3/19/2019 Robert McCarthy deposition and exhibits
3/20/2019 Robert McCarthy deposition and exhibits
3/21/2019 Randy Trimble deposition and exhibits
3/21/2019 Robert McCarthy deposition and exhibits
4/9/2019 Edward Sinclair deposition and exhibits
4/9/2019 Michael Reddick deposition and exhibits
4/10/2019 Michael Reddick deposition and exhibits
4/10/2019 Michael Reddick [PMQ] deposition and exhibits
4/10/2019 Edward Sinclair deposition and exhibits
4/16/2019 Edward Sinclair deposition and exhibits
5/1/2019 Alicia Lowery deposition and exhibits
5/10/2019 Laura Casas Abrignani deposition and exhibits
5/21/2019 Robert Feyerherm deposition and exhibits
5/22/2019 Ayesha Siddiq deposition and exhibits
5/23/2019 Ayesha Siddiq deposition and exhibits
5/31/2019 Gregory Lichtwardt deposition and exhibits
6/19/2019 Ayesha Siddiq deposition and exhibits
6/25/2019 Andrea Machlett deposition and exhibits
6/27/2019 Ilona-Maria Weltrowski deposition and exhibits
7/1/2019 Cibele Rudge deposition and exhibits
7/2/2019 Cibele Rudge deposition and exhibits
7/3/2019 Cibele Rudge deposition and exhibits
7/26/2019 Rachelle Acuna-Narvaez deposition and exhibits
8/13/2019 Roberto Chaves deposition and exhibits
8/14/2019 Roberto Chaves deposition and exhibits

9/5/2019 Edio Zampaglione [PMQ] deposition and exhibits
9/6/2019 Steve Yost deposition and exhibits
9/14/2019 Lois (Pierce) Price deposition and exhibits
9/17/2019 Edward Yu deposition and exhibits
9/18/2019 Edward Yu deposition and exhibits
9/18/2019 Terry Mank deposition and exhibits
9/23/2019 Wesley Gerber deposition and exhibits
9/24/2019 Christina Dickson [PMQ] deposition and exhibits
9/27/2019 Michael Voss deposition and exhibits
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12/20/2018 Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to strengthen the long-term safety oversight of the Essure device following discontinuation of its U.S. sales, https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-strengthen-long-term-safety-oversight-essure
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FDA Activities: Essure, https://www.fda.gov/medical-devices/essure-permanent-birth-control/fda-activities-essure (and any links related thereto)
FDA Essure Permanent Birth Control Website, https://www.fda.gov/medical-devices/implants-and-prosthetics/essure-permanent-birth-control (and any links related thereto)

EXHIBIT B

SUPERIOR COURT OF THE STATE OF CALIFORNIA
COUNTY OF ALAMEDA
JCCP No. 4887
Hon. Winifred Y. Smith
Dept. 12

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COORDINATED PROCEEDINGS SPECIAL TITLE (RULE 3,550),

ESSURE PRODUCT CASES

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THIS DOCUMENT RELATES TO:

KATIE ELDER v. Bayer Corporation;
Case No. RIC1717556 (Riverside)
SUMMER FROST v. Bayer Corporation;
Case No. CIVDS1716459 (San Bernardino)

VALERIE GEORGE v. Bayer Corporation
Case No. BC662859 (Los Angeles)
TINA GIBEAU v. Bayer Corporation;
Case No. CIVDS1717506 (San Bernardino)

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VIDEOTAPED DEPOSITION OF KIMBER RICHTER, M.D.
TAKEN AT: Godfrey & Kahn
LOCATED AT: One East Main Street
Madison, WI
October 16, 2019
9:21 a.m. to 7:19 p.m.

REPORTED BY ANITA KORNBURGER
REGISTERED PROFESSIONAL REPORTER

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in the report?

A. I'm going to say I don't know.

Q. Less than 20?

A. Possibly.

Q. Does that sound about right?

A. Possibly, yeah.

Q. Did you have any conversations with individuals other than lawyers to prepare your report or for your deposition today?

A. To prepare my report?

Q. Yes.

A. I had one brief discussion with the complaint experts.

Q. With Ms. Holland, Brown, and Arroyo?

A. Yes, uh-huh.

Q. Did you talk to all of them at the same time?

A. I think they may have been on the -- a couple people on the call.

Q. Okay. How long did you talk to them?

A. 20 minutes, maybe.

Q. When did you talk to them?

A. I'm not certain exactly when we talked. It was one conversation.

Q. What did you talk about?

about how they assessed reportability?

A. What their approach was, yeah.

Q. Okay. And what were your questions?

A. Basically, you know, what criteria they were using, how they were making that assessment, and --

Q. Did you tell them you agreed with their assessment or did you suggest that they modify it?

A. I agreed with -- I told them that I agreed with some of what they were doing, and the rest I didn't offer an opinion. I just was there to get information, basically.

Q. What did you agree with that they were doing?

A. I agreed with the approach that they were taking with their assessment and with the way they were looking at reportability, what should be reported, what not.

Q. And what is your understanding of how they were looking at reportability that you were agreeing with?

A. I don't believe that I would want to characterize their process. I guess I would refer you back to their report. I concur with the process that they followed.

Q. Well, you testified that you agreed with --

A. Yes, I did and I do.

Q. -- their process. And I'm asking you what the process was that you agreed with. I'm asking you from your perspective, Dr. Richter, what did you agree with?

A. I'm saying it's been a period of time, and I'd refer you back to their report.

Q. So you're not in a position today to tell me what you agreed with with their process?

MR. WALLACE: Objection, asked and answered. She already answered that. But if you want to --

THE WITNESS: No.

BY MS. CURTIN:

Q. You can't do that today?

MR. WALLACE: I think she's told you that she concurs with their report.

MS. CURTIN: I think I can ask her what she's concurring with, Ed.

MR. WALLACE: Well, do you have the report to show her as to if she disagrees with something? It's not really a memory test. And I will tell you I told her it's not going to be a

Q. But you consider all perforations to be MDR reportable; right?
A. Actually, yes, I do.
Q. Okay.
A. Unless you're given specific guidance from the FDA that says it's not necessary to report them.
Q. Okay. Did you take any notes from that call?
A. No.
Q. Did you take any notes on the six complaint files you reviewed that are described in your report?
A. I took my notes right into my report. That's sort of how I operate. It's fairly cumbersome, but it's -- it's the only way to keep --
Q. Understood. So your notes on the six complaint files that are described in your report starting on page 61 -- if you could turn there.
A. Uh-huh. Okay.
Q. Your notes are captured in this table?
A. Yes.
Q. Okay. Did you select these six complaints because they were used at a deposition

of a corporate witness, Michael Reddick?

A. Yes.

Q. Let's turn to pages three and four of your report. In your summary of opinions at the bottom here, you say, "Based on my review of the documents, as well as my knowledge and experience, I have formed the opinion summarized below." And then it goes on to list out some of your opinions. And I just want to focus on that.

Based on your review of the documents -- based on my review of the documents. Is that based on your review of the documents that are captured in your appendix B?

A. Yes.

Q. Okay. And you give opinions in your summary about whether Conceptus and Bayer properly handled and reported complaints; correct?

A. Let's see. Yes.

Q. You conclude that the companies violated FDA regulations with respect to thousands of complaints and reportability; correct?

A. Yes.

Q. And just to be clear, you reviewed less than 20 complaints, but are still willing to say that Conceptus and Bayer violated FDA regulations

regarding thousands of complaints?

A. Yes.

Q. Okay. Let's go back to your table of complaints. Which was on --

MR. WALLACE: 72.

MS. CURTIN: -- 61.

MR. WALLACE: 61.

THE WITNESS: I'm going to need a break soon. I'm just letting you know.

BY MS. CURTIN:

Q. Okay. Well, let me get through this table and then we'll take a break.

A. That's why I'm telling you now.

Q. Thank you. I appreciate it. So of the six complaints in this table that you put in your report -- and these are the only complaints you describe in detail in your report; right?

MR. WALLACE: Objection to form, report speaks for itself.

BY MS. CURTIN:

Q. Let me ask it this way. These are the only six complaints in your report where you give your personal analysis of potential issues with the complaint files; right?

MR. WALLACE: Again, same objection.

THE WITNESS: Let's see. I believe in this -- in this depth, yes.

BY MS. CURTIN:

Q. Yeah. Okay. And of the six reports that we have starting -- or the six complaints that we have starting on page 61, three of them were actually reported to FDA as MDRs; right?

A. Let's see.

Q. Let's look --

A. The first one was --

Q. -- at it this way. The first one was; right?

A. Uh-huh.

Q. The second one wasn't?

A. Okay.

Q. The third one wasn't. The fourth one was. Are you with me?

A. I'm not sure, actually. Which one is the first one? They're so long.

Q. 20670.

A. All right. I didn't get to that one yet. 2670. All right. Let's see here. MDR was filed.

Q. Okay. And 20847, an MDR was filed; right?

A. Uh-huh.

explain their processes.

Q. Okay. And do you know how they selected a random sample?

A. I'll refer you back to their report.

Q. Okay. Do you have an opinion on whether their sample is representative of all complaints that were held by Conceptus and Bayer?

MR. WALLACE: Objection to form.

THE WITNESS: I believe it's representative of the complaints that Conceptus put into their system.

BY MS. CURTIN:

Q. Okay.

A. I don't believe that was all the complaints that came in.

Q. Do you know if they excluded certain types of complaints from their sampling?

A. I'll refer you back to their report.

Q. Okay. Do you think it's methodologically appropriate to exclude types of complaints from a sample?

A. I'm going to refer you -- just refer you back to their report.

Q. You have no opinion?

A. They'll --

what happened here in this table that you've reflected on page 72?

A. I think it was probably more -- more rigorous and comprehensive in this case than what we might have done in FDA as part of understanding a potential situation.

Q. Okay.

A. Okay.

Q. So the analysis, this extrapolation that we see on page 72 in your table, was more rigorous and different from what FDA would have done?

A. I believe it was more rigorous and comprehensive.

Q. Okay. And just to be clear, you yourself never did a calculation where you extrapolated from a number of unreported complaints to reach a total number of complaints that must have been reportable and were not? You yourself never did that?

A. I may well have done that informally internally within the agency as part of trying to assess the significance of -- potential significance of an issue and determine the actions. Yes, I probably have.

Q. You remember doing that?

A. Yeah.

continue going through your summary of opinions. And I'm looking at paragraph four, which goes to the underreporting of adverse events. I want to look at your statement in here. "Furthermore, the manufacturer failed to investigate or did not follow up on 57 percent of complaints, and thus reportability could not be determined."

A. Okay.

Q. Middle of paragraph four.

A. Uh-huh.

Q. Did you do your own calculations to determine that 57 percent of complaints involved a failure to investigate or lack of follow-up?

A. No. This says specifically that this is according to the statistical analysis of the complaint experts, as it were.

Q. Okay. So you're relying on the analysis --

A. For that number.

Q. Let me finish my question.

A. Sorry.

Q. You're relying on the analysis of Ms. Holland, Brown and Arroyo for this opinion that the manufacturer failed to investigate or did not follow up on 57 percent of adverse events?

A. Yes.

Q. Okay. You do not yourself have a basis for this opinion?

A. Well, no, that's not -- I'm sorry, I may not have been clear. I do have a basis for accepting this. You know, the procedures were poor, the -- you look at the e-mails and in the e-mails that Mr. Reddick, particularly, is talking about how he's making decisions, or all of the other documentation of things that were not investigated properly, I feel that this number is quite credible.

Q. Okay. So you can look at e-mails and policies and procedures and come up with a number 57 percent?

A. I can determine whether or not it's in a reasonable range, yes. In that -- in addition to my experience in industry and my experience at FDA, yes.

Q. Okay. But you didn't do any calculation yourself for this 57 percent; right?

A. No. I was focused -- my report was focused in different directions.

Q. Do you know how they calculated 57 percent of complaints?

A. I'll refer you back to their report.
Q. So you don't know?
A. I'll refer you back to their report.
Q. So the answer to my question is you don't know?
A. I understand conceptually how they did it, and I'm comfortable with it, but I'm not going to describe it. I think that's for them.
Q. And you don't know what they reviewed to get to that 57 percent?
A. I'm going to refer you back to their report.
Q. Okay. Is it your opinion today that all 57 percent of those failure to investigate or did-not-follow-up complaints were in fact MDR reportable complaints?
A. I think we don't know because they weren't investigated.
Q. Okay.
A. That's a concern.
Q. We don't know how many of those complaints should have been reported or involved MDR reportabilities?
MR. WALLACE: Objection, form, asked and answered.

A. And based on review of their process and review of their report, which reassures me substantially that they did an excellent job.

Q. Okay. So you're comfortable that they did an excellent job?

A. I am.

Q. But you person --

A. And I have concurred in my report, which means I've put my personal credibility out there.

Q. But you personally have not reviewed any complaint files other than the six referenced in your report and some others in e-mails and documents?

A. Actually, I reviewed all of the 27 or whatever it was that were related to the six. So I reviewed others than those six that were -- there was -- there were a few more that I had as part of that that I did look over also.

Q. Okay. So you looked at the 27 from Mr. Reddick's PMQ deposition?

A. Yes, I did.

Q. Sorry, that's a legal term.

A. It was very depressing.

Q. Okay. So now we're up to, I think earlier you testified that you thought it was less

than 20, but now we're up to more than 20?

A. I know I did look at those.

Q. Okay.

A. So --

Q. So we are in the neighborhood of 30 complaint files that you reviewed?

A. Yeah, possibly.

Q. And other than those 30 complaint files, you cannot say whether any particular complaint file itself was reportable or not?

MR. WALLACE: Objection to form.

THE WITNESS: I'm -- I mean, I come back to I'm confident of the work that -- the processes that they used, I'm comfortable with their report. Yeah.

BY MS. CURTIN:

Q. Do you think, from your experience at FDA, that the most reliable way to determine whether a complaint is reportable is to look at the complaint file itself?

MR. WALLACE: Objection to form.

THE WITNESS: The problem here is that the complaint files were so bad that I'm not sure that that's the best source of determining whether something is reportable.

made a statement, you gave testimony that the complaint files were so bad --

A. Uh-huh.

Q. -- that maybe it's not reliable to look at them. And I'm asking you how many complaint files do you have firsthand knowledge of the state of?

A. Enough to know that complaint handling case records were poor.

Q. Okay.

A. And problematic. You know, as you pointed out, FDA can come in and do a -- we've talked about this, look at a small number and begin to see things. You know, one -- when you see major problems in a few, you know that there's an issue. And then when you see other audits coming in and confirming the same, when you see e-mails from the people involved and -- you know, there's a pattern here.

Q. How many of the 30 or so complaint files that you reviewed did you see major problems with?

A. I thought they were all awful.

Q. All of them?

A. Yeah.

Q. All 30?

A. Yeah. I thought they were -- there's just -- yeah, they're bad.

Q. But you have no personal knowledge of whether any of the other tens of thousands of complaint files that the companies had were similarly challenged?

MR. WALLACE: Objection to form, asked and answered several times.

THE WITNESS: I'm sorry, I'm rolling over my coat here.

BY MS. CURTIN:

Q. Can you answer my question?

A. I'm sorry, what was your question?

Q. You have no personal knowledge of whether any of the tens of thousands of complaint files that the other -- that the companies had were similarly challenged?

A. I'm confident, based on the procedures, the other audits that were done, and the e-mails, that that's the case, but --

Q. Okay. But you have no personal knowledge? That's what I'm asking you.

A. I have not read them, yes.

Q. You're assuming, based on what you saw in the 30 and other documents, that all the rest of

the complaint files are problematic?

A. I'm concluding that there are systemic problems.

Q. Okay. Do you know whether Ms. Holland, Brown or Arroyo reviewed the complaint files themselves for the 974 that they reviewed, or whether they reviewed narratives about the complaints?

A. I'm going to refer you back to their report for their processes.

Q. Do you know whether any individuals reviewed the complaint files for Arroyo, Brown and Holland, or whether they were the sole reviewers?

A. My understanding is that they had additional trained individuals that conducted some of the reviews.

Q. Do you know what the qualifications and training were of those trained individuals?

A. Not specifically. I would refer you back to the report.

Q. Did you assume they were qualified to review those complaints?

A. My understanding was.

Q. Okay. But you don't know what their qualifications were?

A. I don't recall the specifics. That was actually something we discussed in the call.

Q. Do you recall generally what their qualifications were?

A. Adequate for doing the complaint reviews.

Q. Who were they?

A. I don't know. I would refer you back to the report. I don't recall the specifics. I don't recall names.

Q. Okay. So you don't know who -- today who reviewed the complaints Ms. Arroyo, Brown --

A. No. I would refer you back to the report.

Q. What qualifications do you believe are necessary for someone to review complaints for reportability?

A. For reportability? So -- just a minute.

MR. WALLACE: How close are we getting to food?

THE WITNESS: I don't think I'll -- I don't think I'll address that. I think that probably the authors of the report were in the position to have that experience and know what was necessary to complete the work successfully. I'm going to refer you back to that.

about just kind of the overall numbers that come into --

Q. Let me do it this way.

A. Okay.

Q. From FDA's perspective, does a med watch form or medical device report have some limitations?

A. Yes.

Q. And what are some of those limitations?

A. Well, as you've mentioned, sometimes we don't know the sales numbers or the distribution numbers or the numbers of product out there when we look at a form. Sometimes information will be incomplete. Sometimes you end up with duplicate reporting, issues like that.

Q. Is the content of MDRs always reliable?

A. Is the content of MDRs always reliable. I would say the content of individual adverse events reports to the FDA can vary.

Q. Do MDRs permit FDA to make an assessment of causation in an individual case?

A. Depends how much information is in the -- the report.

Q. Does FDA use MDRs to -- in isolation to reach conclusions about medical device safety?

A. I think FDA would say that they use them in conjunction with other information.

Q. Do they use them in conjunction with clinical trials?

A. If that information is available.

Q. What other information does FDA use MDRs in conjunction with?

A. In some cases, additional information from the manufacturer.

Q. What type of information from a manufacturer?

A. About their investigation of an issue, their knowledge of the product, their manufacturing processes. That sort of thing might be taken into account.

Q. Does FDA receive information relevant to its analysis of safety of a product from published medical literature?

A. Can you just repeat the question real quickly? I'm sorry.

Q. Sure. Does FDA receive information -- actually, strike that.

Does FDA consider information from published medical literature in its analysis of safety of a product?

real quickly? Can you do that?

COURT REPORTER: "Did you see anything, public or otherwise, that suggested that FDA found the increased risk -- or the increased MDR reports after the Bayer acquisition to be a regulation violation on either company's part?"

THE WITNESS: Not directly, but FDA took substantial actions after they received the additional information. That certainly indicated to me that there were issues with the way things had been proceeding. So --

BY MS. CURTIN:

Q. So --

A. -- there was some kind -- are you talking about specifically MDR regulations, or any violations?

Q. Either.

A. Okay. Yeah, I think the actions that FDA took indicate significant risk management violations and --

Q. Okay. So it's your opinion that FDA's actions were evidence of a regulation violation?

A. Yes.

Q. But you haven't seen anything, either from FDA or otherwise, that FDA concluded that the

companies had violated the regulations?

A. I didn't see FDA say that. What they said is that we have serious issues and we are requiring change in labeling, labeling changes, then we are mandating changes in labeling and we are threatening you with civil and criminal penalties if you don't comply. That's -- that's a down-the-line extreme kind of FDA response.

So I interpret that, in addition to the fact that these -- there weren't voluntary actions taken by the firm, to indicate to me regulation noncompliance, yes.

Q. Okay. Your conclusion is that those FDA actions mean that a regulatory violation occurred?

A. Yes.

Q. Did --

A. Well, in combination with the lack of the action by the firm, lack of voluntary action by the firm, yes.

Q. Did FDA initiate a recall for Essure at any time?

A. Now, recalls almost always are voluntary. I think the question would be did Essure -- did Bayer or Conceptus initiate a recall. And to my knowledge, there weren't recalls. That was one of

looked for.

Q. Okay. And with respect to complaints coming in, would you have expected the complaint language in the label, if it had been changed in 2006, as you think it should have been, to look like the complaint references in the 2016 IFU?

A. I think generally.

Q. Okay. So --

A. In 2016, after -- after FDA recommended that.

Q. Okay.

A. That what you're asking?

Q. Yes.

A. Yeah, I think a lot of that could have been anticipated.

Q. Okay. So the language on patient complaints that FDA approved in the 2016 label you think should have been in the 2006 label?

A. Quite a bit of it voluntarily, yes.

Q. Do you know whether the company had received complaints that resembled, in frequency or severity, the complaints that FDA reviewed prior to the 2016 label change?

A. No. I can't speak -- I'm not speaking to that exactly. But if they had monitored their

complaints more comprehensively, I think that would have helped to inform the labeling that -- changes that maybe should have been made, is what I'm saying.

Q. So you think they might have seen complaints similar, prior to 2006, to what FDA saw in patient reported med watches in 2013 to 2015; is that fair?

A. Yes. And I think a number of those reported by -- by patients were patients that had previously tried to contact the firm one way or another and perhaps, you know, hadn't been captured. I don't know. So it's difficult. If you look at the example e-mails that come along, you'll see patient -- you know, something will come and say well, this lady called in and she said she's having all these symptoms, blah, blah, blah.

And then if the decision is, well, we don't -- we don't record that kind of thing or we don't report that kind of thing or we don't -- that's not a complaint because we don't take input that way, then, you know, just based on the e-mails that I've read suggest that quite a few of those things would have been identified. Yeah.

Q. How do you know that med watches reported

Q. Can somebody have an event in a previous year and not record it in a med watch until several years later?

A. Yes.

Q. Does that say anywhere that FDA concluded that women had attempted to report the same events to the company prior to 2013 and the company had not accepted those events?

A. I don't recall if there was any comment about the company's handling of them, no. Many of the MDRs received, especially after late 2013, contained multiple symptoms. And then they sent a copy of -- the FDA sent a copy of voluntary reports it receives to the device manufacturer. No. So I would have to say not right here, that wasn't exactly what I was thinking of. But -- so what was your question again? I'm sorry.

Q. I'm trying to understand the basis for your testimony. And I see you've read from advisory committee comments about when the events actually occurred that were reported in 2013 through 2015.

And my question for you is whether you've seen anything from the FDA to support your testimony that women that reported med watch events

in 2013 through 2015 had previously reported the same events to the company in the complaints.

A. No, I'm not certain that FDA would know that.

Q. Do you have any basis for that opinion?

A. Let me just -- let me stop and think for a minute. So Conceptus received -- nothing I could point my fingers on right now.

Q. And other than the 30 or so complaints that we have discussed that you reviewed prior to writing your report, you haven't reviewed a substantial number of complaints from prior to 2006 when you think the label should have changed?

A. That's correct.

Q. So you don't know whether, if we looked at a set of complaints from prior to 2006, compared to a set of med watches submitted by patients between 2013 and 2015, they would have provided the same information on adverse events?

A. I do know that information in some of the correspondence within Conceptus that I reviewed described, or quoted, specific complaint information that was significant that was not reported. So I do know that.

Q. Do you know whether, in terms of the type

or frequency of adverse events seen in the patient reported med watches between 2013 and 2015, and how that would compare to complaints received by the company in 2006 and earlier?

A. All right, now I'm confused. Can you repeat your question one more time?

Q. Well, I asked you about a set --

A. Yeah, I know.

Q. You gave the opinion, as I understood it, that the labeling should have changed --

A. Yes.

Q. -- to essentially look like the 2016 labeling in 2006; right?

A. Yes.

Q. And I am asking you, and if I understand you correctly, is that opinion based on your opinion that the complaints received by the company prior to 2006 would have been sufficient to trigger a label change similar to what triggered a label change in 2016?

A. Okay. First of all, I believe the label should have been voluntarily changed. It shouldn't have required a trigger similar to what occurred in 2015. So that's one point. Secondly, then, I think that the examples that I reviewed as I was

it's time to start reassessing. That's -- that's what I think.

Q. Time to start reassessing --

A. Yes.

Q. -- the labeling?

A. What should be in the labeling, yes. And while we're at it, any other actions to take to make sure that you're capturing information from patients directly and minimizing any risk to future patients. And that's -- I don't see that here.

Q. Do you think that FDA's decision to -- well, let me back up. Do you think that the label change in 2016 is solely a result of the MDRs that FDA had received between late 2013 and 2015?

A. I think it was a significant trigger.

Q. How -- what else was a trigger for FDA's actions in 2016?

A. Well, I think it was the trigger. As -- after the trigger, then I think they went back and looked at other information and talked -- then they had eventually ended up talking to some consumers and doing other things. But I think that the trigger was MDR numbers, yeah.

Q. So the FDA received a significant increase in MDRs that came directly from patients

between 2013 and 2015; right?

A. Yes.

Q. And by the middle to end of 2015, FDA had received in the neighborhood of 9900, 10,000 MDRs; does that sound about right?

MR. WALLACE: Objection to form.

THE WITNESS: I'm not certain about that. Say that again.

BY MS. CURTIN:

Q. Well, you know what, that's okay. It can -- I can do that specifically with a document. Okay. So you believe that the increased -- significant increase in med watches received between late 2013 and 2015 was the reason for the label change in 2016?

A. No, it was the trigger.

Q. Okay. So describe what you mean by trigger.

A. A trigger or a signal is something that there is a flag that there needs to be further consideration, further investigation within FDA and within the firm. So when the MDRs increase like that, then -- then the center says oop, we've got this here, we need to look at what's going on, we need to consider if any, you know, actions

having -- if there had been a huge increase in sales or something else that explained some of that, then they would take that into account. But before they made the decision then on what actions, they also looked at publications and talked to other people and so forth. But it's the MD -- the purpose of the MDRs is that trigger.

Q. Did the MDRs trigger the -- the increase in MDRs between 2013 and 2015 trigger the advisory committee meeting in September of 2015?

A. The agency says that was a factor, yes.

Q. Was that the only factor?

A. Well, I'm not -- I wasn't in those discussions, so I couldn't say for sure, but it was a significant factor. I think that another factor might be that they wanted additional input and information about possible controls, you know, possible actions to take to -- you know, that's the purpose of the advisory panel, is to get additional input from different stakeholders.

Q. Where does the agency say that the MDRs received between 2013 and 2015 were a significant trigger for or a significant factor in their decision to hold an ad com?

A. That I believe that they did say in

their -- their write-up, or in the press releases. I'll have to go back and look. You want -- I think I cite it in my report. You want --

Q. No, that's okay. The press releases related to their decision to hold an ad com?

A. Yeah. Somewhere within the agency discussion they talk about the fact that it was -- they didn't -- you know, they did a look in 2013, and then they ultimately decided to do the advisory panel meeting. And it ties that into the MDRs, I believe.

Q. And MDRs can come from a variety of sources; right?

A. Yes.

Q. They can come from a manufacturer?

A. Yes.

Q. They can come directly from patients?

A. Uh-huh.

Q. From physicians?

A. (Witness nods.)

Q. And patients can report their adverse events directly to FDA in a medical situation?

A. Yes.

Q. Are you aware of -- well, are there any other triggers for the advisory committee meeting

advisory committee meeting much earlier than 2015?

A. I believe FDA might have acted without an advisory panel meeting. I don't know that, if they had had that information at that time, they would have considered the advisory panel necessary. They might have. But it was not -- not an option in quite the same way earlier on to have postmarket advisory panel meetings. And I think -- again, we don't know exactly what the results of that -- those complaints would have been.

Q. So we don't know whether FDA would have had an advisory committee meeting in 2006 or thereabouts?

A. No. I mean, the alternative would have been to simply proceed to action.

Q. All right. And do you think FDA would have ordered a label change in 2006 that resembled the ultimate label change in 2016 --

A. I feel --

MR. WALLACE: Object to the form.

BY MS. CURTIN:

Q. Let me finish my question.

MR. WALLACE: Asked and answered.

BY MS. CURTIN:

Q. -- based on the complaints received by

committee meeting?

A. Yes. Whether it was adequate is another question.

Q. But FDA concluded that women were not receiving or understanding information on Essure's risks and benefits after the advisory committee meeting?

MR. WALLACE: Objection to form.

THE WITNESS: Well, wait. Now let's -- let's -- let me hear that question again. I'm sorry, I --

BY MS. CURTIN:

Q. No, no, no --

A. There's a lot of nuances in these things.

Q. Despite the fact that there was an instructions for use and a patient information booklet in effect prior to the advisory committee meeting in 2015, FDA heard testimony at the 2015 ad com that led FDA to believe that women were not receiving or understanding the risks and benefits of Essure; right?

MR. WALLACE: Objection to form.

THE WITNESS: Yes. But I think that earlier, if the complaints had come in, the firm should have reached that conclusion voluntarily and

permanent implant being put in healthy young women is not clearly communicated to the women what to expect, then that's an issue. I think companies should get right on that. I think you should -- you know, four years is generous. You know, they had sales start-up; it took a little time. So, you know, I understand that, but that's -- I consider that ongoing business.

BY MS. CURTIN:

Q. And to be --

A. Right, okay.

Q. -- clear, that is not based on a number of complaints that are captured or extrapolated in this table on page 72, but rather on your review of company documents?

A. Yes, primarily.

Q. And I think -- I think we're talking about the same thing here. But if you could just turn to -- back again to page 72 of your complaint. I'm sorry, of your report.

A. Okay.

Q. Okay. You with me?

A. Yes.

Q. Okay. At the bottom of page 72 you say, "It is reasonable to expect that if these

additional significant events had been reported to FDA, the agency would have taken action at that time, likely including patient and physician labeling changes." Is this what we've been talking about here?

A. Well, I think we've been talking about the firm's responsibility to take action. But I think that the agency also, had they seen those -- that information, would have stepped in.

Q. Okay. And again, this is based on the -- your review of company documents and not on the number of -- number of complaints that you reflect in this table on 72?

A. Well, I think it also includes information from that -- my conclusion, as I said, stands, but I think that this information and information that -- yeah, I'm sorry, I'm wandering a bit. I'll stop there and you can ask for further clarification.

Q. We talked about the change that you think would have happened with the physicians labeling. And just to be clear, the instructions for use is written for physicians, right, it's not intended for patients?

A. I think for this type of product, that's

correct.

Q. Have the instructions for use for Bayer always included a recommendation that doctors discuss risks of Essure with their patients?

A. I don't know if it's always said that specifically, but there's patient information provided.

Q. Okay. I also wanted to look at, just back to -- sorry, I should have told you to leave it open. So if you could stick with me on 73.

A. Okay.

Q. I wanted to understand your -- this is the language, after what we just read, this is supported by the prompt action taken following the first PMA annual report, when the FDA sent two letters in follow-up to just four reports of perforations without catastrophic outcomes. Tell me about why that supports your opinion that the agency would have taken prompt action.

A. I think that the fact that FDA was already asking for information, and in fact they were highlighting the need to report through the MDR process in those letters, indicates that they were concerned about even a small number of events.

Q. This is an example of FDA reading and

taking action based on a PMA annual report; right?

A. Right. But that is not the same as MDR reporting. And in fact, that was pointed out in two letters, that this was not -- that these should have been reported to -- you know, through the MDR process. Right. So yes, in this case they followed up, yes, but then let's look at what the firm did, all right? When the firm got those letters, they sent back a note saying we disagree with you, and they did not proceed to follow the guidance FDA had provided.

So you have a situation where, yes, there was quick action. So your questions previously if the agency had known all this in 2006, would they have taken action, you know, yes, they might have. But the company was not doing what they were asked to do to help make that happen. See?

Q. This is an example of FDA prioritizing review of a PMA annual report; right?

A. Yes. To say -- exactly. And I -- and I -- you know, I agree that it is. This was a new product, it was an important product. They did not see MDR reporting happening, and they flagged it.

Q. Did FDA prioritize review of the PMA

probability on that when you say reasonable to expect?

A. Well, the threshold for labeling changes is based on either the number of incidents or new types of events. And I think if the number of incidents had gone up significantly, FDA would have required labeling changes. And I don't mean significantly as in, you know, very large changes. You know, I think they would have required some kind of update if it had been statistically significant. And, you know, then what action they took would depend on what they saw.

Q. If there was a statistically significant increase in the number of reportable events, FDA would have taken action?

A. I think that that was often a threshold for labeling changes, yes.

Q. Okay. Well, let's talk about it in the context of Essure.

A. Okay.

Q. Is it your opinion that FDA would have taken action based on a statistically significant increase in the number of reported events?

A. Possibly in the context of sale, sale numbers.

the rate of adverse events could predict a label change; is that fair?

A. I think that might generally be true, yes.

Q. Okay. And I'm going to go back to your summary of opinions on page 4, if you could, of your report. I'm looking now at paragraph five. This is tied again to your opinion about a label change in 2006. And I just want to make sure I understand. Is it your opinion that FDA would have made a label change in 2006, or that the company should have made a label change in 2006?

A. Well, I think the company should have. And barring that, I think it's very -- it would be expected that FDA would have taken some action to address that.

Q. And when you say stronger warning labels for patients and physicians, we've talked about how the instructions for use would have looked like the 2016 instructions for use. Tell me how the patient labeling would have changed as early as 2006 with different information provided to FDA.

A. I think it would depend on what was in the complaints that the company didn't track and manage. So it might have been more information,

and it might have been differently worded or explained information. Might have included more information about the range of reports received as far as maybe length of pain or those sorts of things.

Q. And you just don't know without looking at specific complaints?

A. No. I mean, based on what I've read, I have a few thoughts. But it would depend on -- you know, that's the company's responsibility to do that.

Q. What are your thoughts on what it should have looked like? And I'm speaking of the patient labeling now.

A. All right.

MR. WALLACE: You mean other than what she's testified to already?

MS. CURTIN: She hasn't testified what the patient labeling should have looked like in 2006.

MR. WALLACE: All right. I disagree. Objection, asked and answered.

THE WITNESS: Okay. I think it perhaps would have benefited from additional information about the process, the reported side effects, the

nickel allergy issues, what women could do to report if they had an issue. All those things probably enhanced in the patient information booklet would have been useful.

I would have liked to have seen the firm create an 800 number for patients after receiving the product so that they could bring their questions to the company and their reports that way. Something like that.

BY MS. CURTIN:

Q. And when is your understanding of when the firm had a 1-800 number for patients to report complaints?

A. I don't think they did. That's my point.

Q. Okay.

A. Okay. I think that that would -- might have been something to fold into that kind of a patient information change.

Q. A responsible manufacturer would have included a 1-800 number for reporting complaints in a patient information booklet?

A. It seems reasonable to me, you know, and -- yeah.

MS. CURTIN: Let's take a break.

THE WITNESS: Okay.

MS. CURTIN: Thanks.

THE VIDEOGRAPHER: We're off the record at 3:47.

(Break taken.)

THE VIDEOGRAPHER: We're back on the record at 4:09.

BY MS. CURTIN:

Q. Did FDA determine, two years after the 2016 label changes were implemented, that patients were still not being adequately informed of known risks of the Essure device?

A. That's what they indicated.

Q. In 2018, when they ordered a sales restriction; right?

A. Right.

Q. Is it your opinion that FDA would have ordered a sales restriction earlier than 2018 with different information from the company?

A. They might have.

Q. Would that have been at the same time as a label change, or would it have been several years later?

A. Well, looking at what actually happened, they did the labeling change as -- required the labeling changes, and then two years later felt

that things were still not going -- proceeding adequately, and they took additional action with the restriction. So you could think that it would have happened in a similar way earlier. I like to think, and hope, that along with other voluntary actions by the firm, we don't know if that would have happened.

Q. We don't know --

A. We just don't know.

Q. We don't know --

A. That's right.

Q. -- when a sales restriction would have come in?

A. That's right.

MR. WALLACE: Object to the form.

THE WITNESS: Sorry.

BY MS. CURTIN:

Q. Did FDA have information about a greater -- greater frequency or severity of adverse events reported between 2016 and 2018?

A. Greater frequency or -- I would have to go back and look at exactly what the agency said.

Q. Are you offering an opinion that the 2018 sales restriction was a result of MDR reporting?

A. Well, ultimately, yes, because the MDR

of my report, okay?

Q. Can you say whether there is a category of complaints within the 974 in your table on page 72 that FDA did not have knowledge of until the time period of 2013 to 2015?

A. Are you talking about the different types of --

Q. Yes.

A. -- incidents or injuries?

Q. Yes. Is there a type of injury the FDA did not know about until 2013 to 2015 that was included in this 974 in your table on page 72?

A. I would have to double-check that.

Q. Okay. So you don't know that today. Okay. Are you planning to offer or are you offering an opinion that the companies had -- either company had knowledge of a different frequency or severity of adverse events than was included in the Essure instructions for use?

MR. WALLACE: Objection to the form. Report speaks for itself.

THE WITNESS: Do you want to do that again?

MR. WALLACE: I said objection to form, and the report speaks for itself as to what she's

offering.
BY MS. CURTIN:
Q. Do you have an opinion as to whether either company had knowledge of a higher frequency or severity of adverse events than is included in the Essure instructions for use?
MR. WALLACE: Objection. Same objection, her report speaks for itself.
THE WITNESS: Let's start with the fact that I think they should have, all right? Did they have the opportunity to have? Yes. What they actually pulled together and how they interpreted it, I'm not certain.
BY MS. CURTIN:
Q. What types of events do you believe, types of injuries, do you believe the companies should have had knowledge of a different frequency or severity than was included in the instructions for use?
A. I think the incidents related to procedures, possibly. Perforations and the risks of perforations. I think the pain-related complaints. And I think possibly surgical interventions and the risks of that are things that come to mind just looking at the way they handled

their reviews.

Q. This is based on your review of the company e-mails and documents; right?

A. And the examples of complaints, yes.

Q. Okay. Did the examples of complaints that you reviewed enable you to conclude that there was a different frequency of an adverse event type than was included in the instructions for use?

A. That, plus the various audits. You know, the Reglera, the Acorn, that sort of thing, led me to conclude that they would likely have found that if they had looked.

Q. Okay. So you don't know whether there was a higher frequency or severity of adverse events than the labels say?

A. That responsibility lies with the company.

Q. Okay.

A. That's my feeling.

Q. Okay.

A. All right.

Q. You think that if the company looked, they would have found a higher frequency or severity --

A. Yes.

reported to FDA because the procedures were out of compliance, in your opinion?

A. Not specifically. But I don't think that compliance is determined by whether -- by that kind of number. I think you comply with the regulation because that's a responsibility to comply with it.

Q. You offer an opinion that Conceptus and Bayer didn't properly investigate complaints; is that right?

A. Uh-huh.

Q. And do you have an opinion on the number of complaints that were not reported to FDA because of a failure to investigate complaints but should have been reported to FDA?

A. I would --

MR. WALLACE: Objection. I'm sorry.

THE WITNESS: Sorry.

MR. WALLACE: Objection to form.

THE WITNESS: Yeah, I would refer you to the report that the complaint experts prepared.

BY MS. CURTIN:

Q. Okay. You'll defer to Holland, Arroyo and Ms. Brown on that point?

A. They've done some of those estimates.

Q. Okay. And you're not offering your own

opinion on the number of complaints that were not reported to FDA because of a failure to investigate?

A. No. No.

Q. Incorporating their opinions.

A. Yeah.

Q. Okay. You offered an opinion that there were issues with how Conceptus maintained complaint files under Section 820.198 --

A. Yes.

Q. -- is that right? Do you have an opinion on the number of complaints that were not reported to FDA because of concerns under 820.198 with how the complaint files were maintained?

A. Well, I would refer you to the complaint handling experts and their report. And then I would also say that in addition, the lack of capturing them I think indicates that the number was higher than their estimate, probably.

Q. But the answer -- but --

A. Do I have a specific number? No.

Q. -- do you have a specific number? And your views on this are based on your review of e-mails and the 30 complaint files that we've talked about, and nothing more?

Q. If he found noncompliance in the procedures that he reviewed at an inspection, would you expect him to issue a finding?

A. In many cases, yes.

Q. Do you have your own independent opinion on how many perforations should have been reported to FDA but were not reported to FDA?

MR. WALLACE: Objection to form.

THE WITNESS: I believe they all should have been reported to FDA.

BY MS. CURTIN:

Q. Do you know how many perforations that is?

A. Do I have the number? No, not laid out.

Q. Okay. Do you have an opinion on the number of migrations that should have been reported to FDA?

A. I believe those should all have been reported as well, based on the information I've reviewed and in my experience.

Q. And in terms of the numbers, can we rely -- or did you rely on the numbers of perforations and migrations that Ms. Arroyo, Brown and Holland say should have been reported to FDA and were not?

someone saying sorry we didn't get back to you, we're in the progress, we hope to respond with an answer in the near future.

Q. Who is -- who is Sharon Kapsch, based on this signature line on the first page in the e-mail that I'm talking about?

A. Sharon Kapsch is a branch chief who was involved in interpreting reportability policies for OSB.

Q. So when Sharon Kapsch, branch chief, says, "At this point, I do not believe a telephone conference will be necessary. Basically, we agreed with your assessment of your MDR obligations for the events cited in Ms. Dwyer's letter to your firm, and your response back to Ms. Dwyer. Our letter explains our reasons for making that determination."

Is it your testimony that until that letter is received by the company, they cannot rely on Ms. Kapsch's stated agreement with the company's position?

A. Yes, that is my -- my clear opinion. And any branch chief of mine who wrote a letter like that would have been disciplined. Oh, excuse me.

Q. You would have disciplined Ms. Kapsch for

writing this e-mail?

A. It's caused a substantial amount of potential confusion.

Q. Okay. All right.

A. To send a note saying that we haven't -- we may have an answer, we may be getting back to you, I'm sorry, I --

Q. Troubles you?

A. Well, I'm sorry that I expressed my view about that, but yes.

Q. No, we're here to hear your views.

A. Well, but just troubles me. Well, all right.

Q. So you would have disciplined Ms. Kapsch for this e-mail?

A. I said if someone on my staff wrote an e-mail like this, I would have disciplined them, yes.

Q. At this point in time Ms. Kapsch is in the office of surveillance and biometrics? And you were never in --

A. No.

Q. Let me finish my question.

A. I'm sorry.

Q. You were never in the office of

Q. So your opinions on exclusions are based on company e-mails that you reviewed before your report and not on written policies and procedures?

A. Well, she says in her e-mail that they are not to be written down because she thinks it's not appropriate, which actually is, in my opinion, a noncompliance with 820. You know, you're supposed to put those into procedures. Yeah.

Q. And I'm not asking about Ms. Acuna-Navarez's e-mail.

A. Yeah.

Q. I just want you to give me a yes or no answer, if you can --

A. Okay. What was the question?

Q. -- to -- my question is, are your opinions on exclusions in your report from pages 36 to 51 based on company e-mails and communications as opposed to written policies and procedures?

A. I believe there also was one written policy that -- document that she prepared. I don't have it with me. But I do think she had one summary of policies.

Q. Okay. Apart from that one --

A. Okay.

Q. -- Acuna-Navarez summary of policies,

your exclusion opinions are not based on written policies and procedures?

A. Correct.

Q. Okay. And your exclusions on pages 36 to 51 are not based on your review of complaint files?

A. They're consistent with the complaints I did review. The complaints I did review support them. And I did identify in a few places under the six, even, where various exclusions were demonstrated.

Q. But you can't say with any degree of certainty how these exclusions apply to the broader group of 6,500 and something complaints that your table on 72 says should have been reported and were not?

A. I can tell you that this is noncompliant.

Q. Numerically you cannot tell us how many of those 6,500 or so complaints that you say should have been reported but were not, were failed to be reported because of the exclusions you've identified?

MR. WALLACE: Objection to form. Report speaks for itself.

THE WITNESS: Yeah. The process of the exclusions I believe was not compliant.

complaints --

Q. Yes.

A. -- in that report.

Q. And you don't know how many of the complaints not reported involved the types of events that FDA never added to its labeling?

A. That's correct.

Q. Okay.

A. But that raises a very interesting question, being possibly if there had been more that would have been, those things would have been added to the labeling. We don't know.

Q. But as we sit here today, you cannot offer an opinion to any degree of certainty that MDRs that did not, by type, end up in the 2016 labeling led to regulatory change?

A. MDRs -- say that again, please.

Q. MDRs that the company -- let me strike that. You cannot offer an opinion to any degree of certainty that an MDR of the type cardiovascular, autoimmune, respiratory, or one of these other types that does not end up in the 2016 labeling, that that event led to any kind of regulatory change?

MR. WALLACE: Objection to form.

A. Considered a significant.
Q. That's significant to you?
A. Yes.
Q. Are you giving the opinion that anything in the boxed warning is new information about risks that hadn't previously been included in labels?
A. And if we look at an earlier version, I'll be happy to confirm that for you.
Q. But is it your understanding, just for now, that what's new is the fact that it's in a box, not that the content is new?
MR. WALLACE: I would object to that. I think she asked and answered. She asked for the opportunity to compare it.
THE WITNESS: Yeah.
BY MS. CURTIN:
Q. Okay. Well -- let's read, if you could --
MS. CURTIN: Can we go off the record while she reads the label?
MR. WALLACE: Well, let's not go off the record. How about this, I won't count the time that she's taking to read it right now as a courtesy.
THE WITNESS: Okay. So --

Q. So we talked about formatting differences.

A. Okay.

Q. Can you tell me whether there is any new risk information in this boxed warning that was not in the 2002 label?

A. I think the way it's described is different than in the 2002 label. I think the 2002 label minimizes, in certain cases, the information that's here laid out in a little bit different way.

Q. So it's differently framed, but it's the same risk information; fair?

MR. WALLACE: I would object, asked and answered.

THE WITNESS: No. I think that saying a very small risk, or putting something at the end of a long sentence, is -- in the context of a procedure, is different than this warning.

BY MS. CURTIN:

Q. Is there a type of injury or risk in this boxed warning that, by type, doesn't appear in the 2002 label?

A. I don't believe so, from my cursory review.

Q. Okay.

And my question for you is, having reviewed this document prior to your opinion, do you think FDA is in the best position to describe why they are taking regulatory action?

A. I think FDA can represent what their thinking is, yeah.

Q. Okay. If you could turn to page 5. Turn to page 5, please.

A. Uh-huh.

Q. I'm going to read starting at the bottom. "And based on the 2015 panel meeting, including comments made during the open public hearing portion of the meeting and comments made in the associated public docket, FDA believes that some women are not receiving or understanding information regarding the risks and benefits of permanent hysteroscopically placed tubal implants that are intended for sterilization."

And FDA goes on to describe the labeling changes it's making related to the fact that women are not receiving or understanding information regarding the risks and benefits of Essure. Does that look right?

A. Yes.

Q. Does FDA say in any -- at any point in

time that it made label changes in 2016, including the patient checklist, and the addition of a boxed warning to the physician labeling, because it found a higher frequency or severity of adverse events in Essure from the MDRs it reviewed from 2013 to 2015?

MR. WALLACE: Objection to form.

THE WITNESS: I think in the press release where Dr. Gottlieb talks about the restriction of sale and the need for action in order to consider the product safe and effective, that that is essentially saying that.

BY MS. CURTIN:

Q. That's in 2018, though; right?

A. But you said at any time.

Q. Okay. Well, let me ask about 2016 then.

A. Okay.

Q. In 2016, when FDA issues its final guidance, do they say anything about changing the Essure labeling for physicians because of a change in the frequency or severity of adverse events?

A. Their concern, as they describe it primarily, is the communication of issues, information.

Q. The communication of issues with women?

A. Yeah, information sharing. And I thought

it was with physicians as well, but that may not be what they say.

Q. So the answer to my question is the FDA does not, in this guidance document, say that it is changing the label for physicians because of an increased frequency or severity of any adverse events?

MR. WALLACE: Objection to form.

THE WITNESS: Okay.

BY MS. CURTIN:

Q. They don't?

A. They talk about patient information.

Q. So they don't say that they're changing the label because of a change in frequency or severity of adverse events?

MR. WALLACE: Objection, asked and answered.

THE WITNESS: In this document, that's how I read it.

BY MS. CURTIN:

Q. They don't say it?

A. Correct. As I read it, yeah.

MS. CURTIN: Okay.

MR. WALLACE: All right.

E X A M I N A T I O N

EXHIBIT C

Mary Weick-Brady, MSN, RN
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Owner, MedDLI LLC
Consultant to NSF International

Expert Review and Report

SECTION A: BACKGROUND

I am the founder and principal of MedDLI LLC (Medical Device Labeling and Instructions), a consulting company that I started in January 2016. MedDLI provides consulting services related to the regulatory requirements for (1) medical device labeling; (2) devices being designed, developed, and moved into the non-clinical environment; and (3) medical device adverse event reporting decisions using the quality systems regulation (QSR) under 21 CFR 820 and medical device reporting (MDR) under 21 CFR 803. MedDLI has been retained for this litigation through NSF International.

I started my career as a registered nurse at the Mayo Clinic in Rochester, MN. I worked on the thoracic/endocrine, ENT/plastic surgery, and hematology/oncology units at Methodist Hospital in Rochester. I was accepted into the Peace Corps and moved to Ecuador in the remote Bolivar province, where I worked primarily as a public health nurse. With the Peace Corps, I also provided services in a clinic, including birthing babies, and treating tropical and rare diseases. I moved to Washington, DC and worked as an evening clinical supervisor for a long-term care facility and hospice in a private facility. I then joined the public health branch of the DC government to provide care, education, and other services, including on the topic of HIV/AIDS, to DC residents in clinics, schools, and on the streets. During this time, I also worked as a visiting nurse for a private home care agency in northern Virginia. I provided numerous types of treatments for many patients such as peritoneal dialysis and hemodialysis, care for newly diagnosed diabetics, wound care, ventilator therapy, and care for the dying. I also volunteered as a registered nurse for the Medical Reserve Corps in northern Virginia to provide nursing services during public health emergencies. I volunteered as the band nurse during my daughter's high school years in the marching band. I gave out medications on the band trips and assessed and treated students for illness while on marching band tours.

In late 1989/early 1990, I began my tenure at the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH).

I joined the FDA as part of an effort by CDRH's Office of Compliance and Surveillance (OCS) to hire nurses and other medical professionals to review and interpret the adverse event reports being sent to the FDA under the medical device reporting regulation. I was responsible for reviewing reports regarding general hospital medical devices; many of the reports were for various types of infusion therapies (large volume, patient controlled analgesia, insulin, and implanted). My responsibilities at the FDA included reviewing, evaluating, and analyzing individual MDRs to determine if known events were occurring with a greater frequency than expected, if there were unusual (non-labeled) events, or if there was a pattern noted across a device family or across manufacturers.

At the FDA, I performed follow up on reports. I followed up on approximately 10,000 reports per year for the general hospital devices, including manufacturer and voluntary reports. Part of my review of MDRs included monitoring and trending the many reports I received. When appropriate, I would recommend that the FDA issue or consider issuing recalls, public health advisories, and safety alerts if I determined that MDRs revealed a potential safety signal. While at the FDA, I regularly communicated with medical device manufacturers through (1) letters requesting additional information on individual reports; (2) telephone conferences; (3) in-house meetings; and (4) trips with investigators on inspections of facilities. Additionally, I wrote numerous directed inspections and worked with investigators when they were inspecting manufacturer facilities.

During my time at the FDA, I had responsibilities related to a number of implanted medical devices. For example, I was put on a special project to review thousands of patient events that came in regarding silicone breast implants. I was on the team working with the Commissioner, Office of the Inspector General, and investigators to determine if the complaints could have been associated with the breast implants. We held public meetings, listened to patients, and provided the Commissioner with data from the events submitted. The Commissioner eventually ordered manufacturers of silicone breast implants to stop their manufacture and worked with industry to develop quality systems that would assure a safe and effective product when reintroduced through the PMA application process.

In the early 1990s, I was a representative from the Office of Compliance and Surveillance ("OCS") to the newly formed FDA MedWatch team that developed the MedWatch reporting form.

In the early 1990s, OCS was divided up into two separate offices and I was promoted to Branch Chief for MDR in the new Office of Surveillance and Biometrics (OSB). I supervised a team of medical personnel that reviewed MDRs in OB/Gyn (briefly), dental, ENT, general hospital, surgical, physical medicine, anesthesia, orthopedics, and GI/GU.

I became the Deputy Division Director for the Division of Surveillance Systems (DSS) in 2001. The DSS is responsible for communications with manufacturers regarding potential MDR reportability determinations. The DSS was also responsible for drafting guidance and necessary regulations. I helped write the user facility (UF) reporting regulations after Congress mandated user facilities to report adverse events.

While at the FDA, I was also asked to develop a policy on home health (non-clinical) use of medical devices because more and more devices were being used in the home environment. At this time, I was promoted to the GS-15 level, the highest level in the federal government outside of the Senior Executive Service. I developed a committee on home health device issues, including labeling and premarket development. I started this work as a policy analyst for the Office Director in OSB in 2008, and eventually was requested by the new Center Director in 2010 to join the staff in the Center Director's office to continue this policy development. At this time, I was also the representative to the Global Harmonization Task Force (GHTF) on postmarket issues. I represented the US FDA on this committee for 6 years, developing global documents for postmarket activities including a unique coding system for adverse events. I was the representative on international standards for symbols and home use. I chaired the Association for the Advancement of Medical Instrumentation (AAMI) standards group on devices used in non-clinical environments. I retired in 2015 after 25 years with the FDA.

Through my different experiences at CDRH, I developed expert knowledge in the areas of MDR reporting, non-clinical use of medical devices, collaboration in international environments, holding public meetings to engage patients and health care professionals, and regulation and guidance development. I developed strong knowledge in the MDR and quality system regulations, as well as in other areas of compliance, labeling, and clinical research in the FDA labs.

The opinions expressed in this report are based on my background, knowledge, and experience gained at the FDA, international committee work, and my work through MedDLI as a consultant. My opinions are also based on the documents, deposition transcripts, and other materials that I reviewed, including all documents and regulations referenced in this report. I reserve the right to amend or supplement my opinions if new information is presented to me in this case, including the right to respond to any other experts within my area of expertise.

My company is being paid for this work through NSF International. NSF International is being paid $350/hour for me to provide regulatory consulting and testimony. In addition to my background noted above, I have provided my CV as Exhibit A. I have not been an expert witness in any trial nor have I provided an expert report or testimony in any case previous to this. Attached as Exhibit C is a copy of all materials I considered in forming my opinions in this report. Attached as Exhibit D is a list of my publications within the past 10 years.

SECTION B: OVERVIEW OF OPINIONS

Below is an overview of my opinions regarding the Essure device. Each of these opinions is based on a reasonable degree of certainty and is discussed in more detail throughout this report.

B.1. **<u>The Essure Device and Approval (Section C of this document).</u>** Essure was approved through the FDA's pre-market approval (PMA) process, which is the most stringent type of device marketing application required by the FDA for the evaluation of new medical devices or technologies. The Essure PMA included all components required by the regulations including study protocols, safety and effectiveness data, over seven years of clinical

trials and results, and reported adverse events. Upon recommendation by an independent advisory panel, the FDA approved Essure as a safe and effective permanent birth control device in November 2002.

B.2. Instructions for Use (Section D of this document). The Essure device is a safe and effective device, as designed and labeled, when placed properly in appropriate patients. Essure is a prescription device, available only when ordered and used by a licensed and trained physician. Essure was packaged with the FDA-approved Instructions for Use ("IFU"), which provided information to the physician on indications, warnings, precautions, contraindications, risks and benefits, and potential adverse events. The IFU instructed the physician to counsel patients on the risks and benefits of Essure prior to having the procedure. Updates to the IFU related to the safety and effectiveness of Essure were submitted as PMA supplements to the FDA for approval. The original IFU (and all subsequent versions) were approved by the FDA, indicating that they contained appropriate information for physicians to use the device in a safe and effective manner.

B.3. Post-Approval Monitoring of Essure (Section E of this document). The FDA monitors the safety and effectiveness of medical devices after they enter the market. The FDA monitored Essure in a variety of ways, including by reviewing reports of post-approval and post-market studies, analyzing annual reports, reviewing device defect reports, and approving PMA supplements. The FDA also monitored Essure by conducting inspections of both Conceptus and Bayer. In my opinion, the FDA closely monitored the safety and effectiveness of the Essure device following its approval, and the data and information from that monitoring continued to support the FDA's decision to approve Essure as a safe and effective device.

B.4. Product Complaints and MDR Determination (Section F of this document). A device manufacturer has the responsibility to develop procedures to receive, review, evaluate, and, if necessary, investigate complaints (21 CFR 820). For certain complaints that meet the regulatory requirements, manufacturers are required to provide MDRs to the FDA (21 CFR 803). While MDRs provide valuable information, they have limitations. As part of the quality systems in place at each company, Bayer and Conceptus had processes in place to receive, review, evaluate, and investigate complaints. My review of standard operating procedures (SOP) and work instructions (WI) showed that both Bayer and Conceptus had appropriate processes in place to allow them to follow the quality system regulation for complaint handling and the MDR regulation for reporting adverse events.

B.5. What Happens to a Report When It Comes to the FDA? (Section G of this document). The FDA takes the reports it receives seriously and reviews each one for significant information. The FDA relies on science-based data to support its review. The analysts are typically medical professionals and biomedical engineers who have experience handling and using medical devices in the healthcare arena or at a manufacturing facility. The FDA reviews MDRs in the context of the known risks and benefits of the device that are reflected in the device's labeling.

B.6. The FDA's Response to Increased Adverse Event Reports About the Essure Device (Section H of this document). Following an increase in adverse event reports, social and news media interests, and Congressional inquiry, the FDA (1) conducted a 2013 review of scientific literature, clinical trials, and adverse event reports relevant to Essure, and (2) in 2015, held a public Advisory Committee Meeting. As a result of these inquiries, the FDA confirmed that the overall safety profile for Essure remained the same. However, the FDA

recognized that some women felt that they had not received or understood the risk/benefit information from their physicians, and instituted changes to highlight the importance of doctor-patient communication. After this additional FDA scrutiny of Essure, the FDA continued to conclude that the benefits of Essure outweigh the risks, when used as labeled.

B.7. <u>Analysis of the Complaints Identified by Plaintiffs (Section I of this document).</u> I have reviewed a summary of the complaints that plaintiffs allege should have been reported as MDRs but were not. Based on my review of these complaints, the majority of them would not meet the regulatory requirements to be reported as MDRs as viewed. Additionally, even if all these complaints had been submitted to the FDA as MDRs, I do not believe that the additional MDRs would have caused the FDA to take any different or earlier action because these complaints do not change the risk/benefit profile of Essure.

SECTION C: THE ESSURE DEVICE AND APPROVAL

C.1 THE ESSURE DEVICE

Essure is a permanent birth control method. On November 4, 2002, Essure was approved under the FDA's PMA process (PMA P020014) as a Class III medical device.[1]

The Essure device is considered a less-invasive method of permanent birth control than tubal ligation, which requires incisional surgery. The Essure device is inserted into both fallopian tubes via an hysteroscopic non-incisional route. The device is expected to provide permanent birth control by occluding the fallopian tubes; follow-up in three months is needed to ensure that the fallopian tubes are occluded. Different forms of birth control are needed during this three-month period to prevent pregnancy.

C.2. FDA DEVICE REVIEW AND APPROVAL

The FDA reviews and clears or approves medical devices through three different categories of stringency: Class I (least stringent), Class II, and Class III (most stringent) as required by the Food Drug & Cosmetic Act (the Act), Section 513 (21 U.S.C. § 360(c)) to assure they are safe and effective for use (21 CFR 860.7).

Class I devices are typically considered to be very low risk or their risk is well known. Device manufacturers for these products must follow General Controls for adulteration, misbranding, registration, banned devices, notification, records and reports and general provisions of the Act. If the General Controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device and the device is not life-supporting or life-sustaining, the device can be placed into the Class I category. The manufacturer must still follow the law and regulations, and the devices are still subject to recall, inspections, and safety notices; however, the device does not go through a clearance or approval process at the FDA. Examples of Class I devices include surgical gauze, exam gloves, and thermometers.

[1] FDA Letter dated Nov. 4, 2002 [BAY-JCCP-0009265].

Class II devices are subject to Special Controls under Section 510(k) of the Act and are cleared by the FDA as being substantially equivalent to another device already on the market that has been shown to be safe and effective. A device is in Class II if General Controls are insufficient to provide reasonable assurance of its safety and effectiveness and there is sufficient information to establish Special Controls, including performance standards, post-market surveillance, patient registries, guidance documents, recommendations, and any other action needed to assure the device is safe and effective. If one of these devices is life-supporting or life-sustaining, more Special Controls can be put into place for the premarket submission to provide assurance and describe how the device is safe and effective. Examples of Class II devices are dialysis machines, external infusion pumps, and glucose meters.

Class III devices are devices that need premarket approval (PMA) in accordance with Section 515 of the Act (21 CFR 814). A device falls under the auspices of the PMA if there is insufficient information that exists to determine that General Controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of Special Controls would provide assurance. Many Class III devices are life-supporting or life-sustaining. Many of these devices are implants, new technologies, or are demonstrating new intended uses. This category requires manufacturers to submit a PMA application to the FDA for review and approval. The Essure device is a Class III device. Other Class III device examples include heart valves, breast implants, and electrotherapy stimulators.

A PMA application includes scientific information in the form of clinical data to demonstrate that a device is safe and effective.[2] PMA applications are given the FDA's most intense scrutiny and evaluation. The clinical data includes the study protocols, safety and effectiveness data, adverse reactions or effects, complications, device failure, device replacement, patient complaints, statistical analyses, biocompatibility, toxicology, wear and tear, shelf life, and any other information the manufacturer may have, or the FDA requests, to meet the regulatory requirements for premarket approval.[3] The studies must be performed under the FDA's Investigational Device Exemption (IDE) under 21 CFR Part 812 of the regulation. The FDA performs investigations during the IDE process to ensure the approved protocols are being followed. The studies and application process can take years until the device is approved.

The original PMA application for Essure was based on seven years of testing including concept, feasibility, verification, biocompatibility, animal studies, and shelf-life testing. Four clinical trials were also part of the application process: peri-hysterectomy, pre-hysterectomy, a Phase II study, and a Pivotal Trial. Each test and clinical trial provided information to the FDA that enabled the FDA to make a determination about the safety and effectiveness of the Essure device.[4] The FDA considers clinical trial data to be highly reliable and dependable because the data is obtained in scientific studies conducted under controlled conditions pursuant to preapproved protocols.[5]

[2] 21 CFR 814.20.
[3] https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma.
[4] Summary of Safety and Effectiveness Data [BAY-JCCP-0861055].
[5] See 21 CFR 860.7.

The FDA must approve the PMA application before a manufacturer may market a Class III device. The FDA reviews the clinical data, the draft labeling, and manufacturing specifications. Investigators also inspect the manufacturing facility, and the manufacturer's quality systems, and they did so with the Essure device, to assure the manufacturer is meeting the requirements under the Quality Systems regulation (21 CFR Part 820). In July of 2002, an Independent Advisory Committee reviewed the data on Conceptus and voted, unanimously (with a single abstention for religious reasons), to recommend approval for Essure.[6]

The preapproval data provided the clinical basis for the FDA's understanding of Essure's risks and benefits and the foundation for the FDA's continuing evaluation post-approval, including its assessment and updating of the IFU. The FDA evaluated Essure's premarket clinical data and approved the device and labeling with those known benefits and risks.[7]

SECTION D: INSTRUCTIONS FOR USE

When the FDA reviews a device for approval under a PMA, it also reviews and must approve the labeling.[8] Any subsequent changes to the labeling relating to the safety and effectiveness of a device must be approved by the FDA through a PMA supplement.[9] The FDA has the authority to inform a manufacturer of labeling changes it believes may be appropriate based on new information, including the results of ongoing studies and other scientific data. The labeling can be made more restrictive or less restrictive depending on the information received. An example of a less-restrictive label change approved by the FDA is the 2011 removal of the nickel hypersensitivity contraindication from the Essure IFU.[10]

Because Essure is a prescription device, the IFU is specifically written for the physician. It discusses in detail the indications for use, the contraindications, warnings, precautions, patient counseling, patient selection, and how to properly place the device.[11] I have reviewed Essure's original IFU and subsequent changes to the IFU made up to the present. In my opinion, the original Essure IFU and all subsequent versions approved by the FDA complied with the FDA regulations and adequately conveyed all known risks and benefits associated with the Essure device.

D.1. ORIGINAL INSTRUCTIONS FOR USE AFTER APPROVAL FOR PHYSICIANS (2002)

The original IFU, to be used by the physician, provided information about the Essure device, detailed the results of prior clinical studies (along with adverse events observed during those

[6] July 22, 2002 FDA Advisory Committee Transcript at pg. 299 [BAY-ESSURE-0019966].
[7] See July 22, 2002 FDA Advisory Committee Transcript.
[8] https://www.fda.gov/medical-devices/premarket-approval-pma/pma-labeling ("Approval will be based on the condition that the applicant incorporates the specified labeling changes exactly as directed and submits to FDA a copy of the final printed labeling before marketing.").
[9] 21 CFR 814.39.
[10] PMA Supplement No. 34 [BAY-ESSURE-0055994; BAY-ESSURE-0056509; BAY-ESSURE-0056531; BAY-ESSURE-0056746; BAY-ESSURE-0056070].
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/device-labeling-guidance-g91-1-blue-book-memo

studies and even potential adverse events not observed in the studies), and contained instructions for physicians regarding counseling potential patient candidates about the risks and benefits before the procedure. The IFU appropriately disclosed the known risks and benefits of Essure. The FDA approved changes to the IFU as new data and information became available. Some of these changes are detailed in section D.2.

Below is a summary of selected sections of the original IFU:[12]

Intended Use: Essure is intended for placement into the fallopian tube.

Indication and Effectiveness: Essure is a prescription device indicated for women who desire permanent birth control by bilateral occlusion of the fallopian tubes. Essure is highly effective when properly placed. The original IFU advised physicians: "Although the effectiveness rate established in the clinical trials of Essure was 100%, no method of contraception is 100% effective, and pregnancies are expected to occur in the commercial setting."

Contraindications:[13] The original IFU lists a number of contraindications, including for women who:

- are unsure about whether they will want to have more children,
- have undergone tubal ligation,
- in whom only one device can be placed,
- are pregnant or potentially pregnant,
- have delivered a child or terminated a pregnancy within 6 weeks of desired Essure placement,
- have active or recent pelvic infection,
- have known allergies to contrast media, and
- have known hypersensitivity to nickel confirmed by a skin test.

Warnings:[14] The original IFU lists several warnings, including:

- The patient must use alternative contraception until an HSG is performed three months post-placement to assure occlusion of the tubes; there may be an increased risk of ectopic pregnancy during this time.
- A small percentage of women reported recurrent or persistent pelvic pain.

[12] 2002 IFU [BAY-ESSURE-0000036].

[13] A contraindication is defined in 21 CFR 201.57(c)(5) as: "any situation in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed."

[14] A warning is defined in 21 CFR 201.57(c)(6) and in the 2001 CDRH guidance titled "Guidance on Medical Device Patient Labeling: Final Guidance for Industry and FDA Reviewers." The guidance defines it as "a written, pictorial, and/or audible alert to a hazard." Specifically, a warning "alerts the reader about a situation which, if not avoided, could result in death or serious injury." It may also describe potential serious adverse reactions and safety hazards. The designation of a hazard alert as a "warning" is reserved for the most significant problems. The term "warning" is generally used as the signal word for this type of hazard alert.

- To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilation.
- When introducing the Essure device into the fallopian tube, never attempt to advance the device against excessive resistance.
- If tubal or uterine perforation occurs or is suspected, immediately discontinue the Essure placement procedure.
- Device removal will likely require surgery including an abdominal incision and general anesthesia and possibly a hysterectomy.
- Patients with suspected nickel hypersensitivity should undergo a skin test to assess their hypersensitivity prior to placing the Essure device.

Precautions:[15] The original IFU provided precautions with the use of the device. Precautions included:

- regret by the patient;
- how far to advance the device;
- the physician should use a visualization process, such as hysteroscopy, to assure placement instead of blind placement;
- assure that the fallopian tube is accessible and patent; and
- terminate the procedure if the patient complains of extraordinary pain or discomfort.

Patient Counseling: The Essure IFU contains information necessary for doctors to have risk-benefit discussions with appropriate patients. The Essure IFU also referenced the Patient Information Booklet (PIB), which was intended to provide information to patients about the procedure, placement, and use of the device.

D.2. IFU CHANGES

Any changes to an IFU related to the safety and effectiveness of the device must first be approved by the FDA.[16] In my experience, IFU changes are common and expected with any PMA medical device because as the device is used in a commercial population, new information may become available. Labeling changes for Essure were minimal and continued to reflect a risk/benefit profile that was consistent with the original IFU. Some of the labeling changes include:

- June 2004 (PMA Supp. 5) – The FDA approved IFU and PIB updates to include three-year effectiveness results.[17]

[15] A Precaution is defined 21 CFR 201.57(c)(6) and in the CDRH Guidance on Patient Labeling as noted in the section on "warnings." A precaution, in the guidance, is "used for the statement of a hazard alert that warns the reader of a potentially hazardous situation which, if not avoided, may result in minor or moderate injury to the user or patient or damage to the equipment or other property. It may also be used to alert against unsafe practices. This includes the special care necessary for the safe and effective use of the device and the care necessary to avoid damage to a device that may occur as a result of use or misuse."

[16] 21 CFR 814.39.

[17] BAY-ESSURE-0027817; BAY-ESSURE-0031613.

- July 2005 (PMA Supp. 9) – The FDA approved IFU and PIB updates to include four- and five-year effectiveness results.[18]
- October 2006 (PMA Supp. 10) – The FDA approved IFU and PIB updates to include results of Post-Approval Study for newly trained physicians.[19]
- June 2009 (PMA Supp. 27) – The FDA approved IFU updates to address hypervolemia and perforations.[20]
- July 2011 (PMA Supp. 34) –The FDA approved IFU updates to remove nickel sensitivity contraindication, and revise the nickel sensitivity warning. In support of this supplement, Conceptus provided the FDA with all 92 previously received complaints that described events potentially related to nickel sensitivity.[21]
- March 2012 (PMA Supp. 35) – The FDA approved revision of IFU and PIB to add results of five-year Post-Approval Studies and information on pregnancies that occurred in the commercial setting (i.e., outside of clinical trials), and to make PIB understandable on an eighth grade reading level.[22]
- October 2013 (PMA Supp. 40) – The FDA approved revisions to the PIB, to address reports of chronic pelvic pain and device migration. The FDA completed a review of Essure's safety data in the post-market setting, and did not identify new safety risks based upon that review. The FDA did not request changes to the IFU based on their 2013 safety review.[23]
- June 2015 (PMA Supp. 41) – The FDA approved an IFU supplement to add an alternative confirmation test to the previously approved hysterosalpingogram confirmation test with the transvaginal ultrasound/hysterosalpingogram confirmation test algorithm.[24]
- November 2016 (PMA Supp. 46) – The FDA approved changes to the IFU and PIB, including a boxed warning and patient decision checklist.[25] In a 2016 guidance document, the FDA explained these changes would "ensure that a woman receives and understands information regarding the benefits and risks."[26] In the same guidance, the FDA provided the rationale for the boxed warning, "noting that these risks should be conveyed to the patient during the decision-making process."[27]

D.3. THE ESSURE PIB

The PIB is not written for medical professionals. It is designed to provide information about a device for a patient. PIBs are not intended to be a substitute for talking with a medical professional; they are designed to provide information and answer basic questions about a device in a way that a patient can understand.[28] The PIB must be approved by the FDA before use.

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[18] BAY-ESSURE-0032670; BAY-ESSURE-0034194.
[19] BAY-ESSURE-0034368-744; BAY-ESSURE-0040407.
[20] BAY-ESSURE-0049518; BAY-ESSURE-0049797.
[21] BAY-ESSURE-0055994; BAY-ESSURE-0056746.
[22] BAY-ESSURE-0056096; BAY-ESSURE-0059034.
[23] BAY-ESSURE-0062888-91; BAY-ESSURE-0063247.
[24] BAY-ESSURE-0064957; BAY-ESSURE-0084264.
[25]; BAY-ESSURE-0091652.
[26] FDA, *Labeling for Permanent Hysteroscopically-Placed Tubal Implants for Sterilization*, Oct. 31, 2016.
[27] *Id.*
[28] FDA, *Guidance on Medical Device Patient Labeling*, April 19, 2001.

The PIB for Essure provides general information about the device, as well as benefits and risks of this method of birth control. The PIB asks "Is Essure right for you?" and discusses when a patient should not use Essure.

SECTION E: POST APPROVAL MONITORING OF ESSURE

After approval, the FDA continues to monitor and review the safety and effectiveness of medical devices in a variety of ways.

The FDA's purpose in post approval monitoring is to ensure the continued safety and effectiveness of the device. If the FDA determines, looking at post market data, that the device is no longer safe and effective, it can withdraw the PMA. The FDA "relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective." 21 CFR 860.7(c)(1).

A manufacturer must comply with all post market requirements or it can be found in violation of the FDA regulations. The FDA could then initiate various enforcement actions against the manufacturer through the Office of Compliance and the regional FDA offices. Depending on the potential violation, manufacturers could be subject to FDA enforcement actions, including warning letters, product recalls, injunctions, criminal prosecution, and monetary penalties.

The FDA closely reviewed Essure post approval study data and regularly inspected both Conceptus and Bayer. The FDA never initiated any enforcement action against either Conceptus or Bayer regarding Essure. Nor has the FDA ever issued a recall or otherwise removed Essure from the market. This history demonstrates that Conceptus and Bayer followed the post-market requirements for Essure. The FDA closely monitored the safety and effectiveness of the Essure device following its approval, and the data and information from that monitoring continued to support the FDA's decision to approve Essure as a safe and effective device.

E.1. POST APPROVAL STUDIES (21 CFR 814.82)

Studies Required By PMA Approval

The FDA can require manufacturers to perform post-approval studies at the time of the PMA approval to help assure that the device remains safe and effective. In the case of Essure, the FDA required several post-approval studies.

Phase II and Pivotal Five-Year Follow-Up Studies: The FDA required Conceptus to continue to follow up on patients from the Phase II and Pivotal trials for five years. More specifically, the FDA required Conceptus to continue to collect data on pregnancies; patient satisfaction and tolerability; adverse events; and data from removal surgeries. The data from these trials were reported annually by Conceptus to the FDA. The five-year period concluded in 2008, and Essure's IFU was updated to include the five-year effectiveness data.[29]

[29] FDA Letter dated Nov. 4, 2002 [BAY-JCCP-0009265].

Newly Trained Physician Study: The FDA also required that Conceptus conduct a trial to study the bilateral placement rate for newly trained physicians.[30] The data from this study was to be used to evaluate the training procedures and to later update the labeling. Conceptus conducted two studies for this request utilizing model ESS205 for one study and model ESS305 in the other study.[31] Results were added into the IFU in 2010.

Other Post-Approval Studies:

Conceptus and Bayer also performed additional studies following PMA approval.

Novasure: Conceptus began a study (P020014 S017/PAS001) evaluating pregnancy rates in women aged 21-50 who have Essure micro inserts properly placed and who have also had the Novasure procedure to treat menorrhagia at up to 15 US sites. Based on my review of the FDA website, the study is ongoing and progress is adequate to meet the FDA regulatory requirements.

Transvaginal Ultrasound: Conceptus initiated a study to evaluate the use of transvaginal ultrasound (TVU) to confirm the effectiveness of Essure placement. Ultimately, this study was used to support PMA Supplement 41, which allowed TVU as an alternative test to confirm proper placement of the Essure devices in the fallopian tubes.

Other Studies: Conceptus and Bayer conducted their own clinical trials, including a "Survey on Use and Characteristics of Definitive Contraception with Essure" (SUCCES II) from 2008-2016. A total of 2593 women were enrolled in the study; the five-year satisfaction rate was 94%. Additionally, as discussed in more detail below, the FDA required Bayer to perform a 522 Study to compare the risks and benefits of Essure with tubal ligation. This study is ongoing.

E.2. ESTABLISHMENT INSPECTION REPORTS

Another way the FDA monitors the performance of medical devices is by conducting inspections of a device manufacturer's facilities. There are different types of inspections that can be conducted, including routine quality system inspections, clinical trial inspections, premarket approval inspections for PMAs, and directed inspections that are more specific to a potential problem or issues. FDA investigators collect data and information through in-person interviews, tours of facilities, reviews of files, and according to the Quality System Inspection Technique (QSIT). The FDA investigators must review complaint handling at each visit and review the MDR reporting with a goal of understanding a company's complaint handling procedures and identify any deficiencies.

[30] FDA Letter dated Nov. 4, 2002 [BAY-JCCP-0009265].

[31] In March 2006, Conceptus submitted PMA Supplement 12 requesting approval from the FDA for an Essure design change (from the ESS205 to the ESS305 model) to improve bilateral placement, ease of use, and reliability. The FDA approved PMA Supplement 12 regarding this model change on June 15, 2007. [BAY-ESSURE-0034785; BAY-ESSURE-0043186].

When an inspection is concluded, the FDA investigator details what occurred in an Establishment Inspection Report ("EIR"). The FDA investigators are thorough in their investigations and trained to identify deficiencies that may require further attention or potential correction. If there are deficiencies or potential violations observed during the investigation, the investigator will document them on a FDA form 483. A form 483 is used to communicate observations on a wide range of issues and may lead to further FDA action.

The FDA conducted regular inspections of Bayer and Conceptus, including the following dates:

June - July 2003: This was a post-market approval inspection. The investigator was on-site for six days and reviewed Conceptus's Action Request (AR) log, which included all Essure complaints received between July 2002 through June 2003.[32] The investigator also reviewed 14 sample ARs and several policies, procedures, and CAPAs, including SOP-1630 Rev D (addressing complaint handling) and QAF 2290 Rev A (MDR Decision Tree).[33] While a form 483 was issued regarding manufacturing, there was no form 483 issued that related to complaint handling.

September 2005: An inspection at Conceptus took place over two days. The inspection covered Conceptus's CAPAs, MDRs, and Management Controls. The inspector reviewed, among other things, Conceptus's complaint files from 6/2003 through 9/2005. The investigator reviewed Conceptus's CAPA logs for 2003-2005, as well as several policies and procedures, including specifically SOP-1630L and SOP-01045E (which relate to complaint processing and MDR) and CAPA 03-035 and SOP-01007F (which relate to risk management). The investigator also reviewed the AR Log and reviewed more closely 23 sample ARs, six of which had been reported as MDRs.[34] After this review, the investigator concluded that the "[r]eview of the complaint and MDR files from June 2003 to September 2005 noted no significant deficiencies or observations."[35] The investigator observed that the corrective actions from the previous inspections were verified through data, record, and procedural review. This inspection was determined to be No Action Indicated (NAI)[36] which means "no objectionable condition or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action)."[37]

July 2008 : This inspection was for quality systems review including CAPA and design controls for the ESS305 device model. Over three days at Conceptus, the investigator reviewed a list of all MDRs submitted by Conceptus and then requested and reviewed more closely 13 ARs that were submitted as MDRs.[38] The investigator then reviewed a list of all complaints received by Conceptus between September 2005 through July 2008 and randomly selected 13

[32] September 18, 2003 Inspection Memorandum [BAY-JCCP-1154987-89].
[33] *Id*.
[34] FDA QSIT Inspection Summary Report dated Sept. 26, 2005 [BAY-JCCP-1161658-60].
[35] 2005 FDA Establishment Inspection Report.
[36] *Id*.
[37] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions
[38] FDA Establishment Inspection Report dated July 11, 2008 [BAY-ESSURE-0056241-43].

from the list for review.[39] The inspector also reviewed the AR log and the CAPA log and requested to review all CAPAs from September 2005 through July 2008.[40] This review included CAPAs 05-004, 05-005, and 05-006, as well as SOP-1630 (which governed complaint handling).[41] Six Conceptus employees were interviewed, and the investigator stated "my review did not show any unreported reportable complaints."[42] This inspection was determined to be NAI.

December 2010 - January 2011: This was a directed inspection by the Office of Bioresearch Monitoring at CDRH based on a finding from an FDA foreign inspection of a contract manufacturer where product lots failed specification testing. A thorough inspection was done over 12 days on site at Conceptus and "covered all major quality subsystems."[43] The investigator reviewed the AR log, a spreadsheet with more than 16,000 action requests, and 182 MDRs submitted by Conceptus between January 2008 and December 2010.[44] The investigator also reviewed Conceptus's policies on complaint handling, including SOP-1630 (complaint handling), WI-03303 (medical device vigilance reporting), and WI-03306 (MDR processing).[45] The inspector also interviewed eight Conceptus employees.

The investigator found eight complaints that he noted as observations on a Form 483.[46] He stated that three complaints should have been filed as serious injuries and did not meet the reporting timeframe of 30 calendar days as required.[47] He also noted that five complaints identified as malfunctions were not reported to the FDA within the 30 calendar days as required in the regulation.[48] Conceptus disagreed with the observations and submitted its response to the FDA. After the FDA reviewed the complaints that were on the 483, it determined that seven of the eight events were not reportable; the final event was reported by Conceptus as an MDR, within the 30-day timeframe. In its letter in May 2011, the FDA stated that "the corrective actions which you propose, once they are fully implemented, should adequately address the observations."[49]

May - June 2013: This was a quality systems inspection that covered complaint handling, CAPAs, and design controls. The inspection noted that the Form 483 observations from the previous inspections were corrected. During the on-site inspection over 14 days, the inspector again reviewed Conceptus's procedures for complaint handling, including SOP-1630, WI-03306, and CAPAs 0019 and 0020.[50] The inspector requested and received an AR log listing all complaints (which was more than 16,000) received by Conceptus between January 2011

[39] *Id*.
[40] FDA QSIT Inspection Summary Report dated July 17, 2008 [BAY-JCCP-0009137-39].
[41] *Id*.
[42] FDA Establishment Inspection Report dated July 11, 2008 [BAY-ESSURE-0056241-43].
[43] FDA Establishment Inspection Report dated May 18, 2011 [BAY-ESSURE-0056223-40].
[44] *Id*. at 0056230-31; BAY-JCCP-0001109 (ARs); BAY-JCCP-0001110 (MDRs).
[45] BAY-ESSURE-0056231.
[46] BAY-ESSURE-0056233.
[47] *Id*.
[48] *Id*.
[49] FDA Letter to Conceptus [BAY-JCCP-0912070].
[50] FDA Establishment Inspection Report dated June 10, 2014 [BAY-JCCP-000019-22].

through May 2013, as well as a list of all MDRs.[51] The inspector then requested and reviewed 11 randomly selected complaint forms and 18 additional complaint forms that related to migration of Essure to the peritoneal cavity.[52] The inspector also reviewed all CAPAs from January 2011 through May 2013 and selected 11 random CAPAs for closer review, four of which were opened in response to the prior inspection.[53] The EIR noted that "[t]he current inspection found no objectionable conditions with CAPA system."[54] This inspection was NAI.

August - September 2015: This was a quality systems inspection of the facility that related to Bayer's communications with the FDA about an ongoing study in France. The inspection was conducted on-site for 13 days and involved the review of multiple policies and procedures, as well as the interviews of 10 Bayer employees. The investigator issued a Form 483 relating to the study, but no Form 483 was issued related to complaint handling.

These inspections support my conclusion that Conceptus and Bayer had sufficient complaint handling procedures in place at all times. Through these inspections, the FDA was in regular communication with Conceptus and Bayer and reviewed the complaints they received, as well their decisions for MDR reporting.

E.3. ANNUAL REPORTS

Annual reports build on the pre-approval data and are required for PMA approvals. Annual reports submitted for Essure included an updated review of the unpublished reports of data from any clinical investigations involving the Essure device and scientific literature involving the device and its safety and effectiveness.

Starting in 2004, the FDA requested that Conceptus include in its annual reports data tables to reflect instances of tubal perforations.[55] Complaints involving pregnancies were also included in annual reports beginning with the amendment to the 2003 annual report.[56] Conceptus, without being required by the FDA, also included within its annual reports a summary of all MDRs submitted the previous year; in 2010, the FDA told Conceptus they no longer needed to provide MDR information in annual reports.

From 2003-2007, the Conceptus annual reports provided data on patients in the Phase II and Pivotal studies who had hysterectomies. In its 2008 and 2009 annual reports, Conceptus provided data on detachment and deployment difficulties which was required as part of the Conditions of Approval letter for PMA P020014/S12 (the ESS305). The FDA notified Conceptus in 2010 that it no longer needed to provide this data.[57]

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[51] *Id*.
[52] *Id*.
[53] *Id*.
[54] *Id*.
[55] February 10, 2004 Letter from FDA to Conceptus [BAY-ESSURE-0029786-87].
[56] 2003 Annual Report Amendment [BAY-ESSURE-0029789].
[57] Nov. 10, 2010 Email from FDA [BAY-ESSURE-0054483].

The annual reports also contained Reports of Changes Described in 21 CFR 814.39(a) such as labeling changes, change of manufacturing site, new indications for use, changes in procedures, changes in performance or design, or an extension of the expiration date.

Under 21 CFR 814.39(b), the FDA requires that annual reports contain information about any changes to a device after the PMA approval that do not affect the device's safety and effectiveness. This information was included in all of the Essure annual reports. For example, Conceptus notified the FDA about changes to its labeling artwork in an annual report.

E.4. PMA SUPPLEMENTS

A PMA supplement, as noted by 21 CFR 814.3 is a supplemental application for an approved device seeking the FDA's approval of a change or modification to the device.

Any changes that affect the safety or effectiveness of a device after approval must be sent to the FDA as a PMA supplement for approval by the FDA. PMA supplements are often submitted to request the FDA approval for changes to the manufacturing facility, the labeling, design, or technology of a device.

Conceptus complied with post-market requirements, including submitting over 50 PMA supplements for the FDA's review and approval. I was given access to every Essure PMA supplement, many of which requested approval for IFU and/or PIB changes as described in section D.2. above.

E.5. DEVICE DEFECT REPORTS

As a requirement of Essure's approval, Conceptus provided the FDA with device defect reports (DDRs) whenever it received information concerning "[a] mix-up of the device or its labeling with another article; or any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to a death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling."[58] These reports specifically provided the FDA with information about potential Essure defects, including bent tips and deployment or detachment problems, as well as Conceptus's resulting actions. The FDA instructed Conceptus in 2010 that these reports were no longer needed, and Conceptus complied with that instruction.

F. PRODUCT COMPLAINTS AND MDR DETERMINATION

Another way that the FDA monitors a device's safety and effectiveness after approval is through adverse event reporting. Adverse events can be submitted to the FDA by (1) manufacturers and user facilities that must report certain events to the FDA as explained in the MDR regulation (21 CFR Part 803), and (2) from any other person or entity that wants to submit a device complaint directly to the FDA. Complaints are submitted to the FDA using MedWatch

[58] May 31, 2006 Device Defect Report [BAY-JCCP-0459019].

forms. The FDA's Manufacturer and User Device Experience (MAUDE) database houses the MedWatch reports that are submitted by manufacturers, importers, user facilities, health care professionals, and the public.

While adverse event reports have inherent limitations, the FDA uses these reports to monitor performance, unusual events, trends of known risks or complications, use error, and potential safety concerns.

For manufacturers, determining when an event should be reported to the FDA as an MDR can be a difficult task. When the manufacturer receives a complaint that is potentially related to its device, it must review and evaluate that complaint to determine whether it is an MDR reportable event under the applicable regulations (21 CFR 803.17, 803.18(e) and 820.198). Different manufacturers may reach different conclusions about whether particular types of events are reportable because regulations are general and applying them to individual complaints is not always straightforward. Because of this, the regulations focus on requiring that manufacturers have and follow sufficient procedures to consider and, if necessary, investigate complaints that come to them, as well as to document how and why they determined an event to be reportable or not reportable. Different manufacturers with compliant procedures could reach different conclusions about the reportability of similar complaints.

In my opinion, Bayer and Conceptus created appropriate systems designed to comply with these regulatory requirements and these systems had the necessary procedures in place to determine whether events were reportable.

F.1. THE MDR REGULATION

Manufacturers are required to submit events to the FDA as MDRs that are related to the manufacturer's device and that result in a death, serious injury, or for certain malfunctions (as defined by the regulations, 21 CFR 803.3). MDRs are submitted to the FDA through MedWatch on a 3500A form.

A reportable death, serious injury, or malfunction (per 21 CFR 803.3) is based on information a manufacturer receives, or becomes aware of, from any source, which reasonably suggests[59] that one of its marketed devices:

- may have caused or contributed[60] to a death or serious injury;
- or, malfunctioned and the malfunction of the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

[59] The term "reasonably suggests" includes any information, including professional, scientific, or medical facts, observations, or opinions that would cause the manufacturer to come to a reasonable conclusion that a device has caused or may have caused or contributed to an MDR reportable event. (21 CFR 803.20).
[60] The term "caused or contributed" means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure; malfunction; improper or inadequate design; manufacture; labeling; or user error. (21 CFR 803.3).

As noted above, determining whether a particular event is reportable and falls within this definition is not always straightforward.

Submitting an MDR is not an admission that the manufacturer's device caused or contributed to the reportable event (21 CFR 803.16); it means that the event met the reporting requirements of 21 CFR 803. As the FDA's website states, "Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report."[61]

MDRs must be submitted to the FDA within the regulatory timeframe, which is typically thirty calendar days, depending upon the event (21 CFR 803.10). The clock starts once the manufacturer has "become aware"[62] that they may have a reportable event. This could be the same day that the manufacturer receives the complaint or it could be after the initial reporting date when the manufacturer "becomes aware."

When submitting MDRs to the FDA, the manufacturer must include all information required by the MedWatch 3500A Reporting Form, if available.[63] If it believes that the data received through the reporting process requires it, the FDA may issue, as appropriate, directed inspections, recalls, safety alerts, and public health notifications.

F.2. COMPLAINT HANDLING

Manufacturers are expected to establish processes to ensure complaints are appropriately analyzed for reportability when they are received by the manufacturer. The FDA does not want a manufacturer to simply submit all complaints; the FDA wants reports that meet the MDR reporting criteria. If every complaint was passed onto the FDA, it could mask the information the FDA does need for further monitoring, safety issues, recalls, or other potential actions. Moreover, the regulations provide enough generality for manufacturers to develop processes for their particular medical device(s).

Conceptus, for example, had formal SOPs and WIs in effect, which described its processes for receiving, logging, evaluating, and investigating of complaints, as well as submitting MDRs to the FDA.[64] Bayer, too, had formal procedures in place, including Argus User Letter 67 and its own SOPs and WIs. Each company also updated those procedures as needed. Even though the companies' specific procedures differed, this is what the regulations allow—each manufacturer is permitted to develop its own procedures to comply with MDR reporting requirements. As part of the routine inspections described above, the FDA would have access to the companies' SOPs, WIs, complaint data, and complete complaint files. None of the inspection reports found any issues with the companies' complaint handling systems and MDR determinations.[65]

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[61] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

[62] The term "become aware" is defined at 21 CFR 803.3.

[63] 21 CFR 803.52.

[64] For example SOP 1630 and SOP 3180; WI-03304, WI-03306, and WI-03429.

[65] While the 2011 inspection resulted in a Form 483 regarding eight specific complaints, the FDA agreed with Conceptus that one complaint was timely reported and the remaining complaints were not reportable.

It is my opinion that both Bayer and Conceptus had the appropriate and necessary processes in place and undertook appropriate efforts to follow them.

F.2.a. COMPLAINT FOLLOW-UP

One of the primary problems a manufacturer faces in determining whether a complaint is reportable is a lack of information. An appropriate follow-up is therefore usually needed to determine if a report meets the criteria for reportability, but this is a multi-faceted and complex approach and depends on the complaint and the manufacturer. Typically, if complaint follow-up is necessary, at least three follow-up attempts to the complaint reporter are suggested. Due diligence, or good faith efforts (FDA Reporting Guidance 2016) are needed to show that the manufacturer has done what they can do to determine if an event is reportable to the FDA. However, the limited information given to a manufacturer, even after attempts at follow up, can make it extremely difficult to determine whether an event is reportable.

Because processes for follow up will vary among manufacturers, they are regularly analyzed during FDA inspections. An investigator for the FDA will assure that the individual procedures and processes meet the letter of the law while also providing the manufacturer the ability to individualize how they are going to develop their processes. As I describe above, the FDA inspected the complaint handling systems of Bayer and Conceptus on multiple occasions (see Section E.2 of this document).

The materials I have examined in this case demonstrate that both Bayer and Conceptus had appropriate processes in place to analyze complaints received and to make reportability determinations. Each company had the required processes in place and the materials I have seen demonstrate the companies followed those processes.

F.2.b. TRACKING AND TRENDING

Even if a particular complaint is not a reportable event under the regulation, manufacturers are expected to track and trend those complaints. The manufacturer should also track and trend complaints that are reported as MDRs. Tracking and trending allows the company to see if there is anything unusual happening in frequency or severity of adverse event reports or malfunctions.

It is my opinion that Bayer and Conceptus had procedures in place to continually trend complaints and adverse event reports and that they followed these procedures. Conceptus had quarterly internal trending reports titled “Post Market Surveillance Report” that provided detailed information on overall complaint data, distribution information, device complaints, clinical complaints, MDRs, and pregnancies. Typically, the report provided data related to the prior 12 months. Bayer generated reports titled “Device Risk Management Report”, which provided detailed information on post market surveillance, product supply, sales and marketing, regulatory issues, complaint review, post market clinical follow up, and evaluation of post market surveillance. Bayer created these reports on a semi-annual basis. These reports would be available

to the FDA inspectors during quality systems inspections or upon FDA request outside of an inspection. Based on my review of these reports, it appears that both Bayer and Conceptus were regularly tracking and trending the complaints they received regarding Essure. Further, the Essure tracking and trending reports I reviewed did not reveal any new safety issues.

F.2.c. COMMUNICATIONS WITH THE FDA

The FDA, Conceptus, and later Bayer, openly communicated about what might be reportable under the MDR regulation. This type of communication is what the FDA expects and is an important part of the continued monitoring of a medical device.

As an example, the FDA and Conceptus had discussions about the reportability of perforations and pregnancies. Initially, the FDA considered perforations to be reportable events; Conceptus reached out to the FDA to discuss this issue further. Conceptus, in a March 30, 2004 letter to the FDA and in response to a MedWatch voluntary report (MW1031305) in May 2004, provided its reasoning for why perforations and pregnancies would not qualify as reportable. Specifically, they stated that the complaints relating to tubal perforations resulting from placement of the Essure device did not cause or contribute to any deaths, no serious injuries were described, and, as a result were not reportable. Additionally, Conceptus cited an FDA Talk Paper released in 2002 regarding two Essure clinical studies. While there were tubal perforations reported in the studies, the FDA Talk Paper stated that "no serious adverse events were reported from either clinical study." Conceptus also stated its position that intrauterine pregnancies do not meet the reporting requirements for MDRs; however, pregnancies would continue to be trended and reported in the annual report.

On September 24, 2004, Sharon Kapsch, branch chief for the FDA's Reporting Systems Monitoring Branch, responded in an email to Conceptus that she agreed with their reporting decisions and a formal response would follow.[66] On October 7, 2008, Conceptus sent an email to the FDA following up on the FDA's formal response.[67] The formal response was received in 2011, which supported the position that neither uterine pregnancy nor asymptomatic perforations were reportable as MDRs. In the FDA response to Conceptus in 2011, the FDA determined that perforations are reportable, regardless of whether they are due to malfunction or user error, if they meet the serious injury definition or if intervention was needed. The FDA also stated "[a] perforation would meet the definition of a reportable malfunction, per 21 CFR 803.3, if the device malfunction would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."[68] Furthermore, perforations are reportable as a malfunction if the event were to recur and could cause or contribute to death or serious injury. The FDA concluded that a (uterine) "pregnancy is a failure of the device or the failure of the patient to follow instructions for the 3 months check post-placement (of the device)" and is not reportable. At no time did the FDA request a retrospective review of the perforations that were not reported as MDR in this time period.

[66] Sept. 24, 2004 Email from Sharon Kapsch to Ed Sinclair [BAY-ESSURE-0032552].
[67] Oct. 7, 2008 Email from D. Dwyer to FDA [BAY-JCCP-0366696].
[68] MDR Policy Branch Letter to Conceptus [BAY-ESSURE-0055379].

Similarly, Conceptus and the FDA communicated regarding the reportability of complaints involving pain, expulsions, and perforations. On August 30, 2012, the FDA requested that Conceptus provide additional information regarding MedWatch reports received by the FDA.[69] On October 5, Conceptus responded and explained its position as to why each of the MedWatch reports at issue did not meet the requirements for MDR reportability.[70] As part of its response, Conceptus provided the FDA with trending information regarding pain and expulsion: "Since January 2012, there have been 83 reported cases of pain and 92 reported cases of expulsions out of 178,984 devices sold; a total of 0.046% and 0.051% respectively. The Essure IFU reports pain in the Pivotal Trial as 12.9% and expulsion as 2.9%." Conceptus also gave the FDA trending information on perforations: "Since January 2012, there have been 52 reported cases of perforations out of 178,984 devices sold; a total of 0.029%. The Essure IFU reports perforations in Pivotal Trial as 1.1%." Additionally, Conceptus provided the FDA with a list of all MDRs reported from January 2009 to September 2012 with failure modes of pain, perforation, and expulsion.

The FDA and Conceptus communicated about the reportability of several potential device issues which might be categorized as malfunctions. For example, as discussed above, Conceptus was transparent with the FDA concerning its position on the reportability of perforations and the FDA accepted this position.[71] Conceptus also addressed detachment and deployment issues in communications with the FDA on multiple occasions including device defect reports filed between 2003-2006, Medwatch additional information letters from 2011, and the 2008 and 2009 annual reports.[72] In these communications, Conceptus was clear that the risk of serious injury or death was remote and the FDA accepted Conceptus's reporting position. Conceptus

[69] Aug. 30, 2012 FDA letter to Conceptus [BAY-ESSURE-0059943].
[70] Oct. 5, 2012 Letter to FDA [BAY-JCCP-0187441].
[71] For example, FDA Letter to Conceptus dated Sept. 24, 2004 [BAY-ESSURE-0032552]; Correspondence between FDA and Conceptus dated Jan. 6, 2011 and Jan. 20, 2011 [BAY-JCCP-0730255; BAY-JCCP-0726936; and BAY-JCCP-0912070]; 2011 FDA Establishment Inspection Report [BAY-ESSURE-0056223-40]; 2013 FDA Establishment Inspection Report [BAY-JCCP-000019-22]; and 2004-2015 Annual Reports [BAY-ESSURE-0033136; BAY-ESSURE-0039654; BAY-ESSURE-0044602; BAY-ESSURE-0045038; BAY-ESSURE-0055424; BAY-ESSURE-0058718; BAY-ESSURE-00559055; BAY-ESSURE-0065857; BAY-ESSURE-0082038; BAY-ESSURE-0095230].
[72] For example, March 28, 2003 Device Defect Report [BAY-JCCP-0495231]; Aug. 1, 2003 Device Defect Report [BAY-JCCP-0495235]; Feb. 8, 2005 Device Defect Report [BAY-JCCP-0495250]; Nov. 2, 2005 Device Defect Report [BAY-JCCP-0495265]; May 31, 2006 Device Defect Report [BAY-JCCP-0459019]; March 12, 2004 Device Defect Report [BAY-ESSURE-0029958]; Correspondence between FDA and Conceptus regarding certain MedWatch Reports [BAY-ESSURE-0056074]; Correspondence between FDA and Conceptus regarding certain MedWatch Reports [BAY-ESSURE-0056262]; Conceptus' response to FDA's 2011 Form 483 Observations [BAY-JCCP-0726936].

and the FDA had similar conversations about bent tips[73], breakage[74], and migration/expulsion issues.[75]

I believe that the companies were performing due diligence to make reporting decisions, many times in the absence of information from the complainant. Based on my review of the communications between the FDA, Conceptus, and Bayer, it is my opinion that Bayer and Conceptus had compliant complaint handling systems.

F.2.d. USE OF MEDICAL PERSONNEL

A manufacturer is not required to submit an MDR when it has information that would enable a person who is qualified to make a medical judgment to reasonably conclude that their device did not cause or contribute to a death or serious injury, or that a malfunction would not be likely to cause or contribute to a death or serious injury if it were to recur. Persons qualified to make a medical judgment include physicians, nurses, risk managers, and biomedical engineers. Medical personnel who were involved in the actual event can also be used to make determinations for reporting or not reporting an event. The information that the qualified person used to make the reporting decision must be kept in the MDR file and the determination not to report should be supported by sufficient documentation to justify the decision (21 CFR 820.198 and 803.18).

The FDA requires that people with medical knowledge of the device make determinations for reportability of a complaint. Bayer and Conceptus appropriately utilized medical staff and others knowledgeable about the Essure device to make these determinations. When Conceptus did not receive a formal response from the FDA in 2004 regarding perforations and pregnancies, they used experienced personnel internally to make medical determinations and they used opinions from outside medical personnel. For example, Professor John Kerin, a principal investigator of the Phase II clinical study provided his clinical perspective on tubal perforations to the FDA in response to a 2004 additional information letter.[76] In summary, he stated "the clinical experience of utero-tubal perforation using the Essure delivery system is not associated with serious adverse clinical sequelae and should therefore not be categorized in the same risk group as perforation of other organs which are associated with serious adverse clinical sequelae."

F.3. INTERNAL AND EXTERNAL AUDITING

In addition to establishing the processes noted above, the FDA expects manufacturers to continually monitor their complaint handling processes to ensure they satisfy the manufacturer's

[73] For example Conceptus's responses to MedWatch reports and communications with FDA regarding bent tips [BAY-ESSURE-0056285, BAY-ESSURE-0062044].
[74] For example Bayer's response to FDA's request for additional information regarding certain MedWatch reports [BAY-JCCP-0546996].
[75] For example Bayer's response to FDA's request for additional information regarding certain MedWatch reports [BAY-JCCP-0187441].
[76] Conceptus's response to FDA's request for additional information regarding a certain MedWatch report [BAY-JCCP-0912098].

regulatory obligations. I believe that Bayer and Conceptus were both diligent in their efforts to monitor their complaint handling procedures and that they acted appropriately in implementing necessary changes as part of those efforts. These efforts included not only self-monitoring efforts and audits, but it also included voluntary audits by third parties to evaluate each company's processes and help identify areas of improvement.

Conceptus, for example, hired a third party in 2008, Reglera, to perform an audit of its processes. Reglera issued a report on August 8, 2008, and it found some areas in which improvement was needed. Again, it is expected and normal in my experience that an audit will identify areas of improvement. One of the issues that was addressed through these corrective efforts was that Conceptus had a backlog of complaints that had not been closed. The FDA does not want backlogs and a responsible manufacturer will address problems by doing any of the following: initializing a CAPA, increasing staffing, or developing a better triage system to determine the severity of the complaint and move it to the personnel who can evaluate and investigate it for reportability. In response to Reglera's report, Conceptus initiated two CAPAs: (1) CAPA 08-010 to make changes to SOP 1630 and QAF-2729 with subsequent work instructions, and (2) CAPA 08-012 to address the backlog. This is how the process is supposed to work. The FDA requires manufacturers to continually assess their quality systems with their SOPs, procedures, and work instructions. These actions by Conceptus demonstrated that Conceptus was following the regulations to assess and revise their quality systems as appropriate under 21 CFR 820.100.

To help ensure that complaints were analyzed and resolved in a timely manner, Conceptus hired Reglera as a contractor to handle complaints from 2008-2013 though Conceptus maintained responsibility for MDR reportability. I reviewed the policies, procedures, and work instructions for handling complaints and sending a complaint for further evaluation and investigation to determine reportability. The SOPs, procedures, and WIs appear to be well documented and in compliance with FDA regulations for quality systems and MDRs.

F.4. LIMITATIONS OF MDR AND VOLUNTARY REPORTING

MDR data and voluntary reporting have inherent limitations. For example, because the reporting system is a passive one—relying on information provided—it can be difficult for the FDA to immediately determine the veracity of each report it receives. The reports also often have incomplete information. Voluntary reporters may state they have product problems or symptoms they believe are caused by a device with no supporting scientific data. Even the most thoroughly investigated reports submitted by a manufacturer may still be inaccurate because the manufacturer does not have access to complete medical records and event information.

Adverse event reports may often be duplicative, as well, as voluntary reports or user facility reports may be referencing the same event that a manufacturer reports as an MDR. Or one person may send in many separate reports, each with one symptom or problem, to increase the number of reports noted in the MedWatch system. It is extremely difficult to identify duplicate

reports in the MAUDE database. As a result, looking at the total number of adverse event reports alone will not reflect the actual number of incidents, devices, or patients involved in device events, nor will it accurately show the severity or frequency of a potential problem.

The FDA makes clear that the MedWatch system is not a reliable source of information when used by itself. The reports received in MedWatch have a disclaimer to make clear that a report of an event, standing alone, is not an admission that the manufacturer, its employees, or the device caused or contributed to the reportable event. As the FDA makes clear: "Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to under-reporting of events, inaccuracies in reports, lack of verification that the device caused the reported event, and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources."[77]

Dr. Jeff Shuren, Center Director for the FDA's Center for Devices and Radiological Health, recently made a public statement titled "Statement on Agency's Efforts to Increase Transparency in Medical Device Reporting and included a comment about the MDR system: "…it's important to note that medical device reports submitted to the FDA are only one source we use to monitor marketed medical devices. While such reports are a valuable source of information, this type of reporting has limitations, including the potential submission of incomplete, inaccurate, untimely, duplicative, unverified, or biased data."[78] The FDA has recognized these limitations generally and specifically with respect to Essure MDRs. (FDA Activities: Essure, FDA website).

A study published in 2001 (Berniker) acknowledged that the MedWatch system is unreliable. In her study, titled "Why MedWatch is Problematic", Berniker states in I.B.2. "MedWatch does not verify or validate reaction reports to determine whether or not they actually occurred or could plausibly have been caused by the drug or device. This would require significant resource expenditure."[79] She goes on to discuss reporting biases in III. A.2: "Some suggest that spontaneous reporting systems like MedWatch are inherently biased toward collecting certain reactions. For example, it makes sense that promotional claims, reports in the medical literature, and the media affect reporting."

The quality of an MDR and voluntary reports is another aspect that is very important to assuring that the data can be used to determine causality with a medical device. Berniker states in III.B. of her report: "The quality assessment has two parts. The first is whether the reaction

[77] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM
Statement from Jeff Shuren, M.D., J.D., director of the FDA's Center for De3vices and Radiological Health, on agency's efforts to increase transparency in medical device reporting (June 21, 2019), available at https://www.prnewswire.com/news-releases/statement-from-jeff-shuren-md-jd-director-of-the-fdas-center-for-devices-and-radiological-health-on-agencys-efforts-to-increase-transparency-in-medical-device-reporting-300872726.html

[79] Jessamyn S. Berniker, *Spontaneous Reporting Systems: Achieving Less Spontaneity and More Reporting* (2001), available at https://dash.harvard.edu/bitstream/handle/1/8846816/Berniker.html?sequence=2&isAllowed=y

should have been reported at all; for example, the MedWatch system solicits serious and unexpected events only. The fraction of reports that meet the desired reporting qualifications determines how 'selective' a system's reports are. The second part of the qualitative assessment is whether the report includes the essential information. . . . This can be described as 'comprehensiveness.'"[80]

SECTION G: WHAT HAPPENS TO AN MDR WHEN IT COMES TO THE FDA?

I am very familiar with and knowledgeable about the complaint handling process under 21 CFR 820.198 and MDR reporting under 21 CFR 803. The FDA takes all reports seriously and reviews every one that is submitted. The FDA is a scientifically-based agency and relies on science-based data to support their review and analysis of adverse events and product problems. MDR analysts are medical professionals and biomedical engineers who have experience handling and using medical devices in the healthcare arena or may have previously worked at a device manufacturing facility. They typically review and analyze reports from their area of expertise; for example, a registered nurse with a background in obstetrics and gynecology would be assigned the reports for Essure. Analysts are aware that MAUDE data is a small piece of a larger story and cannot be used alone to make a determination for a safety issue. They will use the MDR and voluntary reports to help them get a better understanding of a bigger picture.

G.1. DEVICE EVENT PROCESSING

Once a manufacturer sends an MDR to the FDA, those reports are routed to the CDRH database and are assigned to an analyst for review. The analyst receives reports typically within a day of the report coming to the FDA.

G.2. REPORT REVIEW

Once the analyst receives the report, he or she reviews the event description, looks for patient involvement and what happened to the patient, the type of event (and if it matches the event description), and reviews the patient codes, device codes, and the three evaluation codes. An important part of this analysis is that the reported information is compared with the information provided in the approved labeling. The analyst will review the current labeling for the product to see if the event reported falls within information already known about the device and described in the labeling.

Analysts also review any user facility, importer, or voluntary reports that are similar to the event in the reports or may be the same report. These reports usually are forwarded to the manufacturer for their review and analysis.

The analyst will trend the codes or keywords in the event across similar devices, similar codes, and/or across the same serial, lot, or model number. They will trend over a period of time to

[80] *Id*.

assess frequency of reports of an event. As needed, the analyst may consult with the pre-market reviewers, scientists in the CDRH lab, or the compliance officers to obtain additional information. Analysts are also able to review past inspections or remedial actions.

G.3. POTENTIAL ACTIONS

Once the analyst has reviewed and analyzed the report, they have numerous options for further action. The analyst can close the report; however, the report always remains available for future trending.

If the analyst believes more information is needed, he or she can contact the manufacturer either by telephone or through an additional information (AI) letter. The AI letter can request anything that is on the MedWatch report; the analyst can also customize the letter to ask for trending or determinations from the manufacturer as to why an event may not have been reported. The manufacturer is required to respond within 45 days of receipt of this letter with a MedWatch supplement. AI letters are typically the most common and frequently used action used by the analysts.

Analysts can request or make recommendations to the Office of Compliance (OC) for a directed inspection of the manufacturer. Analysts provide the specific questions they need answered in the inspection request. If no directed inspection is needed, analysts can request that specific questions be added to the next routine inspection.

If an analyst determines that a serious safety signal may exist or a recall may need to be initiated, he or she will elevate that issue to the appropriate department within the CDRH for potential action. In taking a course of action, the FDA will consider the benefits and the risks of the device.

SECTION H: THE FDA'S RESPONSE TO INCREASED ADVERSE EVENT REPORTS ABOUT THE ESSURE DEVICE

In response to increasing adverse event reports for Essure, as well as increased social media, traditional media, and political and social interest in Essure, the FDA has repeatedly scrutinized the data about Essure's safety and efficacy—and has repeatedly affirmed that Essure's benefits outweigh its risks. As the FDA's Essure website states, the "FDA continues to believe that, for the majority of women, the benefits of the device, when placed by an experienced health care provider, outweigh the risks."[81]

H.1. INCREASED REPORTS AND 2013 FDA SAFETY REVIEW

[81] https://www.fda.gov/medical-devices/essure-permanent-birth-control/fda-activities-essure (last visited Sept. 19, 2019).

Beginning in 2013, there was an increase in reports to the FDA related to Essure, with the majority of the increased reports in the form of voluntary reports. Based on my review of the evidence, this increase appears to have been due to a number of factors, including social media activity, media activity, congressional involvement, and Bayer's acquisition of Conceptus (including due to differences in the companies' reporting practices).

I reviewed the work of Dr. Maral DerSarkissian, who analyzed Essure adverse event reports from the MAUDE database. For most devices, the vast majority of the reports in the MAUDE database are submitted by the manufacturer. However, between 2004 and 2015, nearly 69% of all Essure MADUE reports were voluntary.[82] Dr. DerSarkissian also noted a spike in voluntary reports submitted for Essure. Between 2004 and 2012, there were a total of 212 voluntary reports submitted regarding Essure. In 2013 alone, there were a total of 725 voluntary reports, which is a threefold increase in one year compared to the prior 8 years combined. In 2014, the number of voluntary reports increased to 1,681. That voluntary adverse event reporting related to Essure is so far out of line with typical patterns of reporting supports my opinion that increased reporting was likely due to external factors such as press and political attention.

As a result of the increased reporting and media attention, in 2013, the FDA decided to conduct an analysis of information they had on the Essure device. This action from the FDA was caused by increased complaint reporting and media attention surrounding the Essure device. I have seen nothing that shows the 2013 analysis was prompted by the reporting of complaints containing unknown risks or known risks that occurred with increased frequency.

The FDA reviewed the scientific literature, clinical trials, and adverse event reports. The FDA concluded that the labeling adequately addressed the known risks associated with the device and that "although there is evidence of complications, as there are with all medical devices, overall results from this study did not demonstrate any new safety problems or an increased incidence of problems already known."[83] As to other events not previously shown to be linked to Essure, but reported as adverse events related to Essure, the FDA concluded that "none of the above information the FDA reviewed has established a causal connection between Essure and certain reported problems, such as extreme fatigue, depression, and weight gain."[84] Following the FDA's safety review the FDA approved PMA Supplement 40, which added references to rare reports of chronic pelvic pain and device migration to the PIB.

H.2. 2015 FDA ADVISORY COMMITTEE MEETING

Also in response to increased reporting, in 2015 the FDA convened an Advisory Committee meeting on Essure with a subsequent report of safety and efficacy of the device. Again this meeting appears to have been caused by increased reporting, but not by reporting that contained unknown risks of risks occurring at a greater-than-expected frequency. The FDA typically initiates an Advisory Committee meeting to obtain insight and perspective from independent experts. The Advisory Committee meeting for Essure was held on September 24, 2015,

[82] DerSarkissian Report at ¶ 43.
[83] FDA Essure Activities (Nov. 4, 2013).
[84] *Id*.

"to review and discuss current information related to the effectiveness of the Essure System, adverse events associated with, or suggested to be associated with, the Essure device, and the overall benefit-risk profile of the device."[85] The meeting included presentations by the FDA, Bayer, and members of the public.

In preparation for the meeting, the FDA again evaluated both the adverse event reports related to Essure from the MAUDE database and over a decade of scientific literature about Essure, including the ongoing postmarket studies by the company.[86] As it had in 2013, the FDA did not find evidence to conclude that there were "new or more widespread complications definitely associated with Essure."[87] The FDA explained during the hearing that many of the adverse events reported "are known complications" of the device "and are already included in Essure labeling."[88] After its comprehensive review, the FDA determined that Essure remained safe and effective for the majority of women when used according to the labeling.

Before the meeting, the FDA invited members of the public to submit comments and received thousands of comments in response. Members of the public were invited to present to the committee, and many women spoke about their experiences with Essure, including that some had not been fully informed about the disclosed risks of Essure before having the devices placed.

H.2.a. BOXED WARNING AND PATIENT DECISION CHECKLIST

Despite finding no new risks of using Essure, after the Advisory Committee meeting, the FDA directed Bayer to add a boxed warning and a decision checklist for the patient to sign after discussing the procedure with their physician to the labeling.

In October 2016, final CDRH guidance was issued for "Labeling for Permanent Hysteroscopically Placed Tubal Implants Intended for Sterilization." The guidance is based on feedback from advisory panel members and the public who felt that medical device labeling for Essure is not clear and many patients do not receive enough information before making a decision. As the guidance states, the purpose of the changes to Essure's labeling was to "help to ensure that a woman receives and understands information regarding the benefits and risks of [the Essure] device."[89] This boxed warning was not based on new or unknown information; all of the risks described in the boxed warning were disclosed in Essure's original 2002 IFU. Nor was it based on adverse event reporting (including MDRs). These labeling changes for Essure were made to draw attention to the need for physicians and patients to communicate about risks and benefits prior to having the procedure performed.

H.3. THE FDA'S RESPONSE TO CITIZEN PETITION

[85] FDA Review Document at 3.
[86] FDA Executive Summary (Sept. 24, 2015).
[87] FDA Essure Activities Webpage (July 1, 2017).
[88] Advisory Committee Tr. at 67 [BAY-ESSURE-0019966].
[89] Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization (Oct. 31, 2016).

In February 2015, a Citizen Petition seeking to have Essure's PMA revoked was submitted to the FDA. The petition included allegations that records from Essure's clinical trials had been changed to be more favorable to the device. The petition was later converted to a trade complaint (i.e., a claim that a device manufacturer may be marketing a product in a way that violates the law) and investigated by the Office of Compliance within the CDRH. In 2016, the Office of Compliance issued findings from its investigation, in which it reevaluated case report forms from the original clinical trials for the Essure device to assess patient allegations of study misconduct. The study by the Office of Compliance was extremely detailed and found that, "although occasional modifications to CRF data items pertaining to key outcome measures were identified, this analysis did not find evidence of systematic or intentional modification of study subject responses in an effort to falsify (provide a more favorable device profile) the data relied upon by the FDA to make the original PMA approval decision in 2002." Overall, 96-98% of women in the pivotal study related their comfort wearing the device as excellent or very good, and 94-96% rated their satisfaction as "very satisfied." A small minority of women reported pain, sometimes moderate or severe in intensity. The presence or absence of pain did not appear to be the sole determinant of a woman's report of comfort or satisfaction with the device.

H.4. 522 STUDY

In February 2016, the FDA directed Bayer to conduct a postmarket surveillance study to obtain more data about Essure's benefits and risks. 21 CFR Part 822.1 provides the regulatory portion of Section 522 of the Act, which gives the FDA authority to order post-market surveillance of Class II and Class III products. This section of the law was added to allow for extra scrutiny by the FDA for devices where the failure of the device would reasonably be likely to have serious adverse health consequences; or, the device is intended to be implanted for more than one year; or, the device is intended to be used outside a user facility to support or sustain life. If a manufacturer fails to comply with requests for post-market surveillance studies, it can be considered to have a misbranded device, which could lead to enforcement actions by the FDA.

Currently, Bayer is working with the FDA on a post-market study involving Essure (PS160001/PSS001). The study is an open-label, non-randomized, prospective observational cohort study of subjects who chose to undergo either Essure placement or laparoscopic tubal ligation. As of March 2019 (most recent data), the post-market surveillance study schedule was on time and considered to be adequate—meaning, the manufacturer is following the regulatory requirements for this study.

H.5 ADDITIONAL ACTIONS

Sales Restriction: Despite the addition of the boxed warning and the checklist to Essure's labeling, the FDA in April 2018 restricted the sale and distribution of Essure, limiting it to doctors and hospitals that review the FDA-approved "Patient-Doctor Discussion Checklist - Acceptance of Risk and Informed Decision Acknowledgement" with patients and obtain their signature's on the checklist before placing the device. The FDA also approves Bayer's new labeling (PMA Supplement S051) that includes the following statement: "the sale and distribution of this device are restricted to users and/or user facilities that provide information to patients

about the risks and benefits of this device in the form and manner specified in the approved labeling provided by Bayer." Also, the FDA approves Bayer's Patient-Doctor Discussion Checklist - Acceptance of Risk and Informed Decision Acknowledgement, which is part of the PIB, and has key information about the device, its use, and safety and effectiveness outcomes, which the patient should be aware of as they consider permanent birth control options.

Voluntary Discontinuation of Sales: In July 2018, Bayer announced that, for business reasons, it would no longer sell Essure in the United States and in December 2018, Bayer stopped selling the device in the United States. Health care providers have up to one year to implant the device. This was not a recall, and the discontinuation of sales was not the result of any enforcement action by the FDA. Bayer must continue with the 5-year postmarket study (discussed above at H.4.). Study enrollment will continue as long as Essure remains available in the United States, i.e., through December 2019.

SECTION I: REVIEW OF COMPLAINTS

I am aware that plaintiffs in this case have identified 946 complaints (Exhibit A) received by either Conceptus or Bayer that plaintiffs contend should have been reported as MDRs but were not. I have reviewed these complaints as part of my analysis for this report.

I have reviewed key information for all 946 complaints, including AR log incident descriptions and/or Argus narratives. Most of these complaints describe injuries that appear not to meet the requirement for reportability. Further, most contain reports of adverse events that have been disclosed in the Essure IFU.

Based on the analysis done by Dr. Maral DerSarkissian, it appears that approximately 52% of them were submitted to the FDA in some way (for example, as MDRs, in annual reports, during FDA audits, in PMA supplements, in device defect reports, in correspondence with the FDA, and in MedWatch forms).[90]

I have also reviewed the Level 1 and Level 2 Classifications provided by plaintiffs with their Exhibit A complaints. In general, these Level Classifications describe potential adverse events listed in the Essure IFU for many years. For example, 252 of the 946 Exhibit A complaints are categorized as perforations by Plaintiffs, and 37 are categorized as pregnancies. As discussed above, the FDA agreed that asymptomatic perforations and uterine pregnancies were not reportable. Additionally, many of Plaintiffs' classifications relate to device issues (e.g., breakage, dislocation/migration/expulsion), which the FDA agreed were likely not reportable as MDR.[91] Based on my review of the information contained in the AR log descriptions and Argus narratives, I did not identify any serious injuries (as defined by the MDR regulations) relating to new events not included in the Essure IFU.

[90] DerSarkissian Report at ¶ 58.
[91] Section F.2.c. above.

In my opinion, even if each Exhibit A complaint was submitted to the FDA as an MDR, I do not believe this would have caused the FDA to take any enforcement action related to Essure. Additionally, because there were not any serious injuries (as defined by the regulations) included in the Exhibit A complaints that were not already listed in the Essure IFU, I do not believe the FDA would have changed the IFU based on these complaints. Likewise, if all the complaints contained in Exhibit A were reportable as MDR, it would not have caused the FDA to hold an Advisory Committee meeting prior to 2015 or change the IFU regarding doctor-patient communication earlier than it did.

I have also been informed about complaints listed in Exhibit B that Plaintiffs believe were not fully investigated. There are 2,918 complaints in Exhibit B; I have only had time to review a sample of these complaints and the analysis by Dr. DerSarkissian. Based on Dr. DerSarkissian's review, 18% of these complaints were provided to the FDA in some way.[92]

Based on my review of Dr. DerSarkissian's work, most of the complaints involve device-related complaints (e.g., migration, expulsion, breakage). While some appear to have clinical issues (e.g., pain, perforation, bleeding), there do not appear to be any specific adverse events that meet the regulatory definition of serious injury, which were not already in the Essure IFU.

In my opinion, even if every Exhibit B complaint should have been submitted as an MDR, I do not believe it would have caused the FDA to make any changes to the IFU for Essure or take any other action.

I have also reviewed Plaintiffs' list of 236 MDRs that that they believe were not submitted to the FDA on time. Based on Dr. DerSarkissian's analysis of these MDRs and the aware date and report date information provided by Plaintiffs, it appears that 127 (54%) of these MDRs were submitted timely.[93] I have not had a chance to review the complaint files in Exhibit D, but it would not be uncommon for the "aware date" under the regulations to be significantly later than the date that the company first received the complaint due to new information coming in. A full analysis of these complaint files would confirm if this is in fact the case with the MDRs that appear to have been submitted late based on Plaintiffs' chart.

With regards to Exhibit D, it is important that all 236 reports were submitted to the FDA as MDRs. Even if the other 109 MDRs were submitted late over this 15-year period, the FDA would not have addressed this as a significant compliance issue. And because the FDA had each of these MDR reports, we know that they did not take any enforcement action with Conceptus or Bayer regarding the timeliness or substance of the MDRs.

SECTION J: CONCLUSIONS

From 2002 to the present, Essure has remained, in the eyes of the FDA, a safe and effective option for permanent contraception. The FDA considered carefully the risks and benefits of Essure as part of the PMA process in 2002, and it ensured that the appropriate risks were

[92] DerSarkissian Report ¶ 64.
[93] DerSarkissian Report ¶ 72.

communicated to physicians in Essure's approved label. The FDA has continued to monitor the device's safety and effectiveness through a variety of methods, including through the analysis of data from clinical trials and annual reports, regular inspections of Conceptus's and Bayer's complaint handling procedures, and review of adverse event reports. Through this monitoring, the FDA has never changed its position on Essure's PMA approval and Bayer's ability to market the device.

I do not believe that the reporting of complaints identified by Plaintiffs as MDRs would have prompted the FDA to take any additional or earlier action against Essure. The FDA is aware that some adverse events likely will occur with the use of a device, particularly a Class III device such as Essure. The critical determination to the FDA is whether the observed events are either unexpected or are more frequent with the use of a device than anticipated. I have seen nothing to indicate that was the case with Essure. In fact, even after increased reporting began in 2013 and an Advisory Committee Meeting in 2015 to review additional data from the public and from independent experts, the FDA affirmed Essure's safety profile and that it is a safe and effective device when it is used according to the labeling.

Date: October 4, 2019

Mary Brady MSN RN

EXHIBIT A

RESUME

Mary Weick-Brady, MSN, RN

EXPERIENCE

Current

Principal Consultant
NSF Health Sciences

Previous Positions

2015-Present Independent Consultant

Contracted through Alaska Universal Services to the Office of the Center Director (OCD) in the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA). Helped coordinate the agenda and speakers for the Patient Labeling Workshop held in September 2015. Facilitated a session and presented at this workshop that was designed to solicit the public's input on a standardized content, proper definitions, and plain language for laypersons using medical equipment.

Started the background and reference materials for updated patient labeling guidance.

Worked with current CDRH labeling coordinator to develop and initiate Phase III of the labeling research for medical device instructions for use (IFUs). This study is for health care practitioner IFUs only. The third phase is to test a standardized Table of Contents (ToC) developed by FDA against an existing ToC for manufacturer labeling. Ten devices are being tested and vary in their complexity from a simple use device to a device system. Worked with health care practitioners to develop appropriate scenarios and internally tested the scenarios with other practitioners to time how quickly they could find the information in either the manufacturer ToC or the FDA standardized outline. The study is ongoing in March and April. Results are expected before the end of the calendar year.

Project Leader for the Association for the Advancement of Medical Instrumentation (AAMI) to look at the process from hospital to home for infusion therapy, focusing on the medical device and how it impacts the user and the environment in which it will be used.

2010-2015 Senior Policy Advisor
Food and Drug Administration, Center for Devices and Radiological Health,
Office of the Center Director

Reported to the Deputy Center Director for Regulatory Affairs

Requested by the Center Director to move to the Office of the Center Director to develop Center-wide policy on labeling and on the home use of medical devices. Developed a strategic plan with Deputy Center Director to determine the proper course of action for health care professional (hcp) labeling and eventually for patient labeling.

Labeling Initiatives:
Announced and presented the plan to develop a standardized content of labeling December 2010. Gathered representatives from each office to review current standards, global initiatives, and internal work on labeling. Mapped each of the processes to the other to find what was common in all products and what was missing. Processes that were mapped included: labeling contents from international standards, the Global Harmonization Task Force (GHTF) document on labeling, labeling regulations from the Center for Drug Evaluation (CDER), labeling regulations from the CDRH In Vitro Diagnostics (IVD) office, and policy for the premarket submissions for Class III products in CDRH.

As a contract office representative (CORII), I received funding for a phased research study to determine what health care professionals look for in labeling, how they search for what they need, where they find the labeling, and what they really want out of labeling. The first phase of this study was with focus groups in three major cities on the east coast. The specialties and medical background varied in each group. Responses were consistent – they want labeling in an easy-to-read format, accessible electronically, or in a "quick guide" if it is physical labeling. The second phase of the research centered around development of a "quick guide" for an infusion pump. We tested 600 health care professionals to assess the format, the content, and the definitions. Having a standard way of finding information was key. This led to Phase III which is ongoing.
Presented findings of the research at a Labeling Public Workshop in 2013. Coordinated all panelists, presentations, and post-workshop public comments.

Received a small amount of money to conduct a survey of caregivers regarding labeling and instructions for use. This was coordinated through the National Family Caregivers Association (NFCA). Over 100 respondents stated similar issues and concerns with current labeling as that of the health care professionals. They want a standard content to find information easily and they want a "quick guide" for most devices.

Co-wrote the Symbols rule and subsequent guidance. The proposed rule published for comment and I responded to the comments that were sent in response to the proposal. The final rule will publish with the draft guidance.

Home Use Initiatives:
Worked with the Center Director to develop a strategy for the Home Use Initiative. This was announced in April 2011 as a Center policy initiative. Developed a website for the initiative. The initiative covered: guidance for premarket review, postmarket reporting, education, and work with accrediting bodies.

Held a public workshop on what is needed in a guidance for devices going into the home environment. Wrote and published the draft guidance on Design Considerations for Devices Intended for Home Use. Reviewed and responded to over 600 comments. Final guidance was published in 2012.

Developed a Cooperative Research and Development Agreement (CRADA) with Kwikpoint, a visual language developer. The intent was to find out if visual images, when properly tested, could substitute for language in IFUs. After testing two devices, we found it was possible. Published a Quick Guide on patient lifts using visual language and also started a sharps initiative based on the results of the study. This was placed on the FDA educational site.

Wrote a proposed rule on Electronic Submissions for Devices Labeled for Home Use. Wrote the draft guidance for the electronic submissions rule.

Along with participating manufacturers, I tested a method to submit labeling electronically through the current FDA system. After internal discussion, we then tested a new method in the CDRH registration and listing system.

Co-chaired the AAMI committee on devices used outside of a clinical environment. We developed a Technical Information Report (TIR 49) on how to develop proper training and instructional materials for devices going into a non-clinical environment.

Wrote a proposed rule on standard definitions that currently do not exist.

Worked with AAMI on their first Summit for devices used outside of a clinical environment. I was on the board and was a co-director of the summit. We developed the priorities and the panel sessions. Due to the government shutdown, I was unable to participate. It occurred October 2013.

Selected to be on the National Research Council's committee for Human Factors in the Home Environment. Served on the committee for 2 years.
{NOTE: If an individual holds multiple positions within one company, list each position separately as described above. If the responsibilities for each separate position within one company are not clearly defined in the Original CV, then follow the format below, listing both titles separately within one entry for the company, and include details associated with the individual's tenure at the company, not delineated by position.}

2008-2012 Senior Policy Analyst
Food and Drug Administration, Center for Devices and Radiological Health,
Office of Surveillance and Biometrics

Worked for the Office Director to develop postmarket policy focusing on the migration of devices going into the home and problems that occur.

Determined the status of policy, guidance, and practice in CDRH and FDA as it related to medical devices going into the home to be used by laypersons. Proposed a Total Product Life Cycle concept to promote the approval of products for use in the home. The objectives were to : develop and implement effective methods for communication with users and stakeholders; develop and implement a focused regulatory plan; adapt human factors policies; adapt postmarket surveillance systems; and encourage stakeholder involvement.

Named as the FDA representative to the Global Harmonization Task Force (GHTF) Study Group 2 to develop consensus documents for postmarket surveillance activities with medical devices. Developed 5 consensus documents during this tenure.

Project officer for an AHRQ contract to review all labeling regulations within FDA to do a comparison of what labeling states in CDER, CBER, OCP, and CDRH for home use.

2001-2008 Deputy Division Director
Food and Drug Administration, Center for Devices and Radiological Health,
Division of Surveillance Systems, Office of Surveillance and Biometrics

Supervised staff that provided regulatory guidance and interpretation of the postmarket reporting, including the Safe Medical Device Act. Supervised the Freedom of Information staff in postmarket, and the contractors who handled the data entry of the adverse events.

Managed the budge for contractors, the branches, the IT staff, and the division.

Developed the quarterly and division reports. Wrote responses to Congressional inquiries.

Chaired the Center Home Health Care Committee; initiated an action plan for the committee. Spoke at conferences and interviewed with the press on homecare issues. Worked with professional health care organizations and caregiver associations to bring the issue of home care to the forefront at FDA.

1993-2001 Branch Chief/Supervisory Nurse Consultant
Food and Drug Administration, Center for Devices and Radiological Health,
Office of Surveillance and Biometrics, Division of Postmarket Surveillance,
Product Evaluation Branch II

Provided regulatory guidance for the Safe Medical Device Act to industry, health care professionals, consumers, and agency professionals by leading training sessions, writing articles, advising on panels, and speaking at conferences. Developed a new reporting form for FDA as it pertained to SMDA.

Led the transition from an old office (Office of Compliance and Surveillance) to a newly formed office (Office of Surveillance and Biometrics) as part of the managerial team selected from the old office.

Supervised 8 professionals to monitor adverse events with medical devices.

Center representative to the reuse of single devices team and reengineering or postmarket activities.

1990-1993 Nurse Consultant
Food and Drug Administration, Center for Devices and Radiological Health,
Office of Compliance and Surveillance, Division of Postmarket Surveillance,
Product Evaluation Branch II

Reviewed mandatory and voluntary medical device adverse events in general hospital and general surgery. Identified and conducted analyses of devices to detect short-term problems, trends, and recurring problems.

Part of the special task force working on the silicone breast implant issue. Presented findings to the FDA Commissioner.

1986-1990 Public Health Nurse
District of Columbia Commission of Public Health
Washington, DC

Screened, referred, and performed preventive health services to 2600 elementary students. Collaborated with DC private organizations in outreach to provide medical care to poor families, and the homeless. Worked in various DC clinics including maternal/child, STD, TB, pediatric, methadone, and adult. Washington DC AIDS charter member to provide services to the people affected by the AIDS virus.

1988-1994 Visiting Nurse/Home Care
Visiting Nurse Association of Northern Virginia
Alexandria, VA

Provided clinical care in patients' homes throughout northern Virginia. Substituted as the evening clinical supervisor and night coordinator.

1985-1986 Evening Clinical Supervisor
The Washington Home and Hospice
Washington, DC

Managed 150 residents and 30 clinical staff during the evening shift. Scheduled, hired, disciplined staff. Taught professional development classes. Performed clinical tasks as needed.

1982-1984 Public Health Nurse
US Government/Peace Corps Ecuador

Varied positions including health inspector, labor and delivery, vaccination campaigns, sanitation, and educational activities for first responders. Wrote a grant proposal to the Pan American Health Organization to study neurological problems in my community. This was funded.

1981-1982 Registered Nurse
The Mayo Clinic
Rochester, MN

Performed clinical duties on thoracic/endocrine unit, ENT/plastic surgery unit, and hematology/oncology unit. Supervised the night shift on the heme/onc unit.

ADDITIONAL SKILLS

- Spanish, FSI 3++/5 (fluent in speaking, writing, and reading)
- French, basic comprehension, speaking, and reading

EDUCATION

1989	MS, Nursing/Administration, George Mason University, Fairfax, VA
1989	Post-Graduate Certificate, International Nursing, George Mason University, Fairfax, VA
1981	BA, Nursing, Augustana College, Sioux Falls, SD

PROFESSIONAL AFFILIATIONS

ISO/IEC 60601-1-11, Representative on the committee

AAMI 60601-1-11, Representative on the committee to determine the changes needed for the US version

AAMI Committee on Devices Used in the Non-Clinical Environment, Co-chair until May 2015

ISO Committee on Symbols, Alternate Representative until June 2014 and then Main Representative

Global Harmonization Task Force Study Group 2, FDA Representative, 2005-2012

ISO TC 210 Work group on medical device problem codes, Representative, 2006-2012
National Research Council (NRC) task force on Independent Living for the Aging and Disabled, Member

PUBLICATIONS / PRESENTATIONS

Presentations on Labeling

- CDRH Labeling Initiative – to senior staff in CDRH – December 2010
- CDRH Labeling Initiative – Office of Device Evaluation – May 2012
- CDRH Labeling Initiative – Office of In Vitro Diagnostics – June 2012
- CDRH Labeling Initiative – Office of Science and Engineering Laboratories – July 2012
- CDRH Labeling Initiative – Office of Surveillance and Biometrics – November 2012
- Health Care Professionals and Labeling – Office of Special Health Initiatives – January 2013
- Health Care Professionals and Labeling – Innovative Publishing webinar – February 2013
- Labeling at CDRH – Food and Drug Law Institute (FDLI) – February 2013
- Use of Symbols on Medical Device Labeling – FDA Public Workshop – April 2013
- Accessible Medical Device Labeling in a Standard Content – FDA Public Workshop – April 2013
- Recent Labeling Efforts at CDRH – Center for Tobacco Public Workshop – December 2014
- OCD's Work on Labeling – Center Science Council Forum in CDRH – December 2014

Presentations on Home Use

- Medical Devices in the Home: What FDA is Doing – Office of Special Health Initiatives – January 2013
- Home Use: Draft Guidance – Coalition of Wound Care Manufacturers – February 2013
- Medical Device Labeling and the Home Use Environment – FDLI – March 2013
- Batteries in the Home Use Environment – Battery Public Meeting – July 2013
- Kwikpoint CRADA update – CRADA Review Board – July 2013
- Draft Guidance on Design for Home Use Devices – SOQA – September 2013

- Update on Home Use and Labeling – Wound Care Stakeholders Association – February 2014
- Update on Home Use to Laypersons and Consumers – OSHI webinar – February 2014
- Using the Home Use Guidance – Human Factors and Ergonomic Society – April 2015

Presented "Wearables and User Impact" at the Regulatory Affairs Professional Society (RAPS) October 2015 in Baltimore, Maryland.

AAMI Technical Information Report (TIR 49) – Developed with the Committee on Devices Used in the Non-Clinical Environment, 2012.

IEEE-USA Geriatric Technology Symposium on Home Care Initiatives for Public Policy, Regulatory and Legislative Issues, June 2004

Updated March 2017

EXHIBIT B

PRIOR TESTIMONY

Mary Brady, M.D.

List of Prior Testimony

- This witness has not provided testimony in the last 4 years.

EXHIBIT C

Appendix C: List of Materials Considered

I relied on the materials cited in my report in forming my opinions. I also considered the following materials:

Pleadings

Master Long Form Complaint for Damages and Jury Trial, *In re: Essure Products Cases*, No. JCCP 4887 (Cal. Super. Ct. – Alameda)

Discovery

Further Responses of Specifically Identified Plaintiffs In Response to Defendants' First Set of Contention Interrogatories Nos. 1, 13, 35, 36, 37, 41 and 42, *In re: Essure Products Cases*, No. JCCP 4887 (Cal. Super. Ct. – Alameda July 22, 2019)

Exhibit C to Plaintiff's First Response to Defendants' Contention Interrogatories, *In re: Essure Products Cases*, No. JCCP 4887 (Cal. Super. Ct. – Alameda July 22, 2019)

Further Responses of Specifically Identified Plaintiffs In Response to Defendants' First Set of Contention Interrogatories Nos. 2, 5, 6, 7, 8, 9, 10, 11, 12, 14, 45, 52, 53, 54, 55, 56, and 57, *In re: Essure Products Cases*, No. JCCP 4887 (Cal. Super. Ct. – Alameda July 26, 2019)

Keith Abrams, Deposition Transcript and Exhibits (May 25, 2017)

Rachelle Acuna-Narvaez, Deposition Transcript and Exhibits (March 29, 2019; July 26, 2019)

Laura Casas, Deposition Transcript and Exhibits (May 10, 2019)

Christina Dickson, Deposition Transcript and Exhibits (February 13, 2018; March 20, 2018, October 10, 2018)

Andrea Machlitt, Deposition Transcript and Exhibits (July 25, 2019)

Lisa Mancer, Deposition Transcript and Exhibits (February 13, 2019)

Rob McCarthy, Deposition Transcript and Exhibits (March 19, 2019)

Michael Reddick, Deposition Transcript and Exhibits (January 11, 2018; February 7, 2018; April 18, 2018; October 18, 2018, March 13, 2019; March 14, 2019; April 9, 2019; April 10, 2019)

Cibele Rudge, Deposition Transcript and Exhibits (July 1, 2019; July 2, 2019; July 3, 2019)

Ayesha Siddiq, Deposition Transcript and Exhibits (May 22, 2019; May 23, 2019; June 19, 2019)

Ed Sinclair, Deposition Transcript and Exhibits (April 9, 2019; April 10, 2019; April 16, 2019)

Illona Weltrowski, Deposition Transcript (June 27, 2019)

Ed Yu Deposition Transcript (September 17, 2019; September 18, 2019)

Production Documents

BAY-ESSURE-0000052 – BAY-ESSURE-0093270	JCCP Production 05: Essure Regulatory File
BAY-JCCP-0868005	2002 Form FDA-483
BAY-JCCP-0009278 – BAY-JCCP-0009288	2003 Response to Form FDA-483
BAY-JCCP-0338036 – BAY-JCCP-0338044	2003 Internal Memo re Phone call from Mark Chan – FDA Inspector for 2003 Inspection
BAY-JCCP-1154987 – BAY-JCCP-1154989	2003 Internal Memo re Documents Reviewed and / or Retained by FDA Investigator
BAY-JCCP-1161658 – BAY-JCCP-1161660	2005 Memo to File re FDA QSIT Inspection Summary Report
BAY-JCCP-1163179 – BAY-JCCP-1163181	2005 Memo to File re FDA QSIT Inspection Summary Report
BAY-JCCP-0009137 – BAY-JCCP-0009139	2008 Memo to File re FDA QSIT Inspection Summary Report
BAY-JCCP-1155227 – BAY-JCCP-1155248	2008 and 2011 Establishment Inspection Reports
BAY-JCCP-0730255 – BAY-JCCP-0730257	2011 Form FDA-483
BAY-JCCP-0726936 – BAY-JCCP-0727004	2011 Response to Form FDA-483
BAY-JCCP-0912070 – BAY-JCCP-0912072	2011 FDA Response to Conceptus Response to Form FDA-483
BAY-JCCP-0000019 – BAY-JCCP-0000022	2013 Establishment Inspection Report
BAY-JCCP-0050302 – BAY-JCCP-0050322	2015 Establishment Inspection Report
BAY-JCCP-0866858	2015 Form FDA-483
BAY-JCCP-0220343 – BAY-JCCP-0220350	2008 Reglera Audit
BAY-JCCP-0000110 – BAY-JCCP-0000145 BAY-JCCP-0000601 – BAY-JCCP-0000628 BAY-JCCP-0000629 – BAY-JCCP-0000656 BAY-JCCP-0000657 – BAY-JCCP-0000711 BAY-JCCP-0000712 – BAY-JCCP-0000766 BAY-JCCP-0000436 – BAY-JCCP-0000490 BAY-JCCP-0000491 – BAY-JCCP-0000545 BAY-JCCP-0000546 – BAY-JCCP-0000600 BAY-JCCP-0000161 – BAY-JCCP-0000215 BAY-JCCP-0000216 – BAY-JCCP-0000270 BAY-JCCP-0000271 – BAY-JCCP-0000325 BAY-JCCP-0050368 – BAY-JCCP-0050422 BAY-JCCP-0050423 – BAY-JCCP-0050477 BAY-JCCP-0000326 – BAY-JCCP-0000380 BAY-JCCP-0000381 – BAY-JCCP-0000435 BAY-JCCP-0000146 – BAY-JCCP-0000160 BAY-JCCP-0000943 – BAY-JCCP-0000962 BAY-JCCP-0000963 – BAY-JCCP-0000982 BAY-JCCP-0000983 – BAY-JCCP-0001002 BAY-JCCP-0001003 – BAY-JCCP-0001022 BAY-JCCP-0001023 – BAY-JCCP-0001042	November 19, 2002 IFU September 15, 2004 IFU November 11, 2005 IFU November 15, 2006 IFU June 20, 2007 IFU July 29, 2008 IFU September 9, 2009 IFU October 21, 2010 IFU September 20, 2011 IFU November 16, 2011 IFU March 8, 2012 IFU March 19, 2012 IFU February 27, 2013 IFU July 16, 2013 IFU November 7, 2013 IFU November 22, 2016 IFU May 23, 2003 PIB July 25, 2003 PIB February 26, 2004 PIB July 26, 2004 PIB July 26, 2004 PIB

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BAY-JCCP-0001069 – BAY-JCCP-0001108	March 19, 2012 PIB
BAY-JCCP-0000829 – BAY-JCCP-0000848	August 13, 2012 PIB
BAY-JCCP-0000849 – BAY-JCCP-0000859	September 16, 2013 PIB
BAY-JCCP-0000860 – BAY-JCCP-0000881	January 23, 2014 PIB
BAY-JCCP-0000882 – BAY-JCCP-0000903	February 27, 2014 PIB
BAY-JCCP-0000904 – BAY-JCCP-0000925	September 2015 PIB
BAY-JCCP-0000926 – BAY-JCCP-0000942	January 2017 PIB
	Trending Reports-
BAY-JCCP-0086452 – BAY-JCCP-0086470	Conceptus QA Monthly Project Updates
BAY-JCCP-0086471 – BAY-JCCP-0086488	
BAY-JCCP-0086489 – BAY-JCCP-0086506	
BAY-JCCP-0086507 – BAY-JCCP-0086524	
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BAY-JCCP-0086592 – BAY-JCCP-0086597	
BAY-JCCP-0424151 – BAY-JCCP-0424162	Conceptus Operations Monthly Reports
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BAY-JCCP-0259639 – BAY-JCCP-0259656	
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BAY-JCCP-0085617 – BAY-JCCP-0085626	
BAY-JCCP-0085627 – BAY-JCCP-0085636	Conceptus Monthly PMS Stat Monitoring of Compl
BAY-JCCP-0085637 – BAY-JCCP-0085651	Metrics
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BAY-JCCP-0085760 – BAY-JCCP-0085774	
BAY-JCCP-0085667 – BAY-JCCP-0085671	Essure Monthly PMS PTC Stat Monit of Compl.
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BAY-JCCP-0086042 – BAY-JCCP-0086051	
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BAY-JCCP-0086062 – BAY-JCCP-0086071	
BAY-JCCP-0086167 – BAY-JCCP-0086173	Essure Quarterly PMS for PTCs
BAY-JCCP-0086174 – BAY-JCCP-0086179	
BAY-JCCP-0086604 – BAY-JCCP-0086628	Bayer Quality Global PV Periodic Trend Analysis
BAY-JCCP-0086629 – BAY-JCCP-0086663	Reports
BAY-JCCP-0086664 – BAY-JCCP-0086695	
BAY-JCCP-0086696 – BAY-JCCP-0086737	
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BAY-JCCP-0086873 – BAY-JCCP-0086901	
BAY-JCCP-0086902 – BAY-JCCP-0086934	
BAY-JCCP-0086935 – BAY-JCCP-0086961	

BAY-JCCP-0086992 – BAY-JCCP-0087026	
BAY-JCCP-5523082 BAY-JCCP-5444550 BAY-JCCP-6670784	PowerPoint presentation titled "Current status of Essure Postmarketing Safety Information" Email to Rudge re: Essure triage of legacy cases Guidance for Case Processing and Evaluation
BAY-JCCP-0495227 –BAY-JCCP-0495230 BAY-JCCP-0495231 – BAY-JCCP-0495234 BAY-JCCP-0495235 – BAY-JCCP-0495239 BAY-JCCP-0495250 – BAY-JCCP-0495264 BAY-JCCP-0495265 – BAY-JCCP-0495288 BAY-JCCP-0459019 – BAY-JCCP-0459053	February 7, 2003 Device Defect Report March 28, 2003 Device Defect Report August 1, 2003 Device Defect Report February 8, 2005 Device Defect Report November 2, 2005 Device Defect Report May 31, 2006 Device Defect Report
BAY-JCCP-0547162 – BAY-JCCP-0547163 BAY-JCCP-0187441 – BAY-JCCP-0187452 BAY-JCCP-0546996 – BAY-JCCP-0547001	January 10, 2014 letter to FDA in response to MedWatch inquiry October 5, 2012 letter to FDA in response to MedWatch inquiry September 11, 2013 letter to FDA in response to MedWatch inquiry
BAY-JCCP-0085156 – BAY-JCCP-0085160 BAY-JCCP-0085097 – BAY-JCCP-0085101 BAY-JCCP-0085102 – BAY-JCCP-0085103 BAY-JCCP-0085104 – BAY-JCCP-0085105 BAY-JCCP-0065473 – BAY-JCCP-0065475 BAY-JCCP-0067457 – BAY-JCCP-0067458 BAY-JCCP-0062875 – BAY-JCCP-0062887 BAY-ESSURE-0009017 – BAY-ESSURE-0010756 BAY-JCCP-0085106 – BAY-JCCP-0085116 BAY-JCCP-0062888 – BAY-JCCP-0062898 BAY-JCCP-0062899 – BAY-JCCP-0062908 BAY-JCCP-0062909 – BAY-JCCP-0062920 BAY-JCCP-0062921 – BAY-JCCP-0062932 BAY-JCCP-0062933 – BAY-JCCP-0062945 BAY-JCCP-0062946 – BAY-JCCP-0062958 BAY-JCCP-0062959 – BAY-JCCP-0062970 BAY-JCCP-0062971 – BAY-JCCP-0062985 BAY-JCCP-0062986 – BAY-JCCP-0062999 BAY-JCCP-0063000 – BAY-JCCP-0063014 BAY-JCCP-0063015 – BAY-JCCP-0063029 BAY-JCCP-0063030 – BAY-JCCP-0063044 BAY-JCCP-0063045 – BAY-JCCP-0063059 BAY-JCCP-0063060 – BAY-JCCP-0063078 BAY-JCCP-0063079 – BAY-JCCP-0063099 BAY-JCCP-0063100 – BAY-JCCP-0063120 BAY-JCCP-0063121 – BAY-JCCP-0063141 BAY-JCCP-0063216 – BAY-JCCP-0063221 BAY-JCCP-0063222 – BAY-JCCP-0063235 BAY-JCCP-0063236 – BAY-JCCP-0063240	QAF-2729 Rev A QAF-2729 Rev B QAF-2729 Rev C QAF-2729 Rev D QAF-2729 Rev E QAF-2729 Rev OBS SOP-1630 Rev A SOP-1630 Rev C SOP-1630 Rev E SOP-1630 Rev F SOP-1630 Rev G SOP-1630 Rev H SOP-1630 Rev J SOP-1630 Rev K SOP-1630 Rev L SOP-1630 Rev M SOP-1630 Rev N SOP-1630 Rev P SOP-1630 Rev R SOP-1630 Rev S SOP-1630 Rev T SOP-1630 Rev U SOP-1630 Rev V SOP-1630 Rev W SOP-1630 Rev Y SOP-1630 Rev Z SOP-1630 Rev AA SOP-1630 Rev AB SOP-1630 Rev AC

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BAY-JCCP-0063294 – BAY-JCCP-0063295	SOP-3180 Rev B
BAY-JCCP-0063296 – BAY-JCCP-0063297	SOP-3180 Rev C
BAY-JCCP-0063298 – BAY-JCCP-0063299	SOP-3180 Rev D
BAY-JCCP-0063300 – BAY-JCCP-0063301	SOP-3180 Rev OBS
BAY-JCCP-0062832 – BAY-JCCP-0062841	WI-03304 Rev A
BAY-JCCP-0067643 – BAY-JCCP-0067659	WI-03304 Rev C
BAY-JCCP-0067660 – BAY-JCCP-0067676	WI-03304 Rev D
BAY-JCCP-0067677 – BAY-JCCP-0067693	WI-03304 Rev E
BAY-JCCP-0067694 – BAY-JCCP-0067709	WI-03304 Rev F
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BAY-JCCP-0083564 – BAY-JCCP-0083566 BAY-JCCP-0083523 – BAY-JCCP-0083524 BAY-JCCP-0083535 – BAY-JCCP-0083536 BAY-JCCP-0083556 – BAY-JCCP-0083557 BAY-JCCP-0083572 – BAY-JCCP-0083574 BAY-JCCP-0083581 – BAY-JCCP-0083583 BAY-JCCP-0139720 – BAY-JCCP-0139733 BAY-JCCP-0434994 – BAY-JCCP-0434996 BAY-JCCP-1161281 – BAY-JCCP-1161328 BAY-JCCP-5441171 – BAY-JCCP-5441209 BAY-JCCP-6670784 – BAY-JCCP-6670838 BAY-JCCP-5594548 – BAY-JCCP-5594553 BAY-JCCP-6316660 – BAY-JCCP-6316700 BAY-JCCP-5528841 – BAY-JCCP-5528842 BAY-JCCP-6312269 – BAY-JCCP-6312271 BAY-JCCP-6371986 – BAY-JCCP-6371986 BAY-JCCP-5430314 – BAY-JCCP-5430314 BAY-JCCP-5545443 – BAY-JCCP-5545443 BAY-JCCP-5454018 – BAY-JCCP-5454056 BAY-JCCP-5520519 – BAY-JCCP-5520519 BAY-JCCP-5575092 – BAY-JCCP-5575092 BAY-JCCP-5535402 – BAY-JCCP-5535405 BAY-JCCP-5406193 – BAY-JCCP-5406193 BAY-JCCP-5410030 – BAY-JCCP-5410030 BAY-JCCP-0384347 – BAY-JCCP-0384347 BAY-JCCP-0065619 – BAY-JCCP-0065677 BAY-JCCP-0086471 – BAY-JCCP-0086488 BAY-JCCP-0086489 – BAY-JCCP-0086506 BAY-JCCP-0086507 – BAY-JCCP-0086524 BAY-JCCP-0086525 – BAY-JCCP-0086542 BAY-JCCP-0086543 – BAY-JCCP-0086550 BAY-JCCP-0086551 – BAY-JCCP-0086560 BAY-JCCP-0086561 – BAY-JCCP-0086570 BAY-JCCP-0086581 – BAY-JCCP-0086591 BAY-JCCP-0051922 – BAY-JCCP-0051927 DLSS0000156 DLSS0000265 BAY-JCCP-0052251_R BAY-JCCP-0051899 – BAY-JCCP-0051912 BAY-JCCP-0051964 – BAY-JCCP-0051965 BAY-JCCP-0375067 – BAY-JCCP-0375067 BAY-JCCP-0375081 – BAY-JCCP-0375081 BAY-JCCP-0011212 – BAY-JCCP-0011485 BAY-JCCP-0027221_R BAY-JCCP-0034543 – BAY-JCCP-0034821 BAY-JCCP-0005034 – BAY-JCCP-0005047	

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BAY-JCCP-0087029R_0001	AR Log
BAY-JCCP-7274737	Argus Export
BAY-JCCP-0903905 – BAY-JCCP-0904091	ESS305 Risk Management File RR-03318

BAY-JCCP-0092054 – BAY-JCCP-0092106	Physician Training Manual
BAY-JCCP-0092107 – BAY-JCCP-0092172	Physician Training Manual
BAY-JCCP-0092173 – BAY-JCCP-0092211	Physician Training Manual
BAY-JCCP-0092212 – BAY-JCCP-0092255	Physician Training Manual
BAY-JCCP-0092337 – BAY-JCCP-0092405	Physician Training Manual
BAY-JCCP-0092406 – BAY-JCCP-0092475	Physician Training Manual
BAY-JCCP-0001109	2010/2011 Spreadsheet of Complaints for Auditor
BAY-JCCP-0001110	2010/2011 Spreadsheet of Complaints for Auditor
BAY-JCCP-0001111	2010/2011 Spreadsheet of Complaints for Auditor
BAY-JCCP-0001112	2010/2011 Spreadsheet of Complaints for Auditor
BAY-JCCP-0008300	2013 Spreadsheet of Complaints for Auditor
BAY-JCCP-0008301	2013 Spreadsheet of Complaints for Auditor
BAY-JCCP-0084862 – BAY-JCCP-0084878	Bayer PMS Report
BAY-JCCP-0086091 – BAY-JCCP-0086166	Bayer PMS Report
BAY-JCCP-0086180 – BAY-JCCP-0086282	Bayer PMS Report
BAY-JCCP-0086283 – BAY-JCCP-0086357	Bayer PMS Report
BAY-JCCP-0086358 – BAY-JCCP-0086451	Bayer PMS Report
BAY-JCCP-0086598 – BAY-JCCP-0086603	Bayer PMS Report
BAY-JCCP-0130437 – BAY-JCCP-0130476	Bayer PMS Report
BAY-JCCP-6901071 – BAY-JCCP-6901099	Bayer PMS Report
BAY-JCCP-6901102 – BAY-JCCP-6901129	Bayer PMS Report
BAY-JCCP-6901130 – BAY-JCCP-6901168	Bayer PMS Report
BAY-JCCP-6901203 – BAY-JCCP-6901239	Bayer PMS Report
BAY-JCCP-6901251 – BAY-JCCP-6901279	Bayer PMS Report
BAY-JCCP-6901280 – BAY-JCCP-6901319	Bayer PMS Report
BAY-JCCP-6901320 – BAY-JCCP-6901354	Bayer PMS Report
BAY-JCCP-0086962 – BAY-JCCP-0086991	Bayer PV Report
BAY-JCCP-0696583 – BAY-JCCP-0696611	Bayer PV Report
BAY-JCCP-1323720 – BAY-JCCP-1323751	Bayer PV Report
BAY-JCCP-1323752 – BAY-JCCP-1323784	Bayer PV Report
BAY-JCCP-1323785 – BAY-JCCP-1323819	Bayer PV Report
BAY-JCCP-1437860 – BAY-JCCP-1437889	Bayer PV Report
BAY-JCCP-5476751 – BAY-JCCP-5476785	Bayer PV Report
BAY-JCCP-5551248 – BAY-JCCP-5551274	Bayer PV Report
BAY-JCCP-5563152 – BAY-JCCP-5563176	Bayer PV Report
BAY-JCCP-6038952 – BAY-JCCP-6038993	Bayer PV Report
BAY-JCCP-6194316 – BAY-JCCP-6194347	Bayer PV Report
BAY-JCCP-6194390 – BAY-JCCP-6194418	Bayer PV Report
BAY-JCCP-0084124 – BAY-JCCP-0084143	Conceptus PMS Review Reports
BAY-JCCP-0084144 – BAY-JCCP-0084160	Conceptus PMS Review Reports
BAY-JCCP-0084161 – BAY-JCCP-0084169	Conceptus PMS Review Reports
BAY-JCCP-0084170 – BAY-JCCP-0084186	Conceptus PMS Review Reports
BAY-JCCP-0084187 – BAY-JCCP-0084211	Conceptus PMS Review Reports
BAY-JCCP-0084212 – BAY-JCCP-0084229	Conceptus PMS Review Reports
BAY-JCCP-0084230 – BAY-JCCP-0084245	Conceptus PMS Review Reports
BAY-JCCP-0084246 – BAY-JCCP-0084263	Conceptus PMS Review Reports

BAY-JCCP-0084264 – BAY-JCCP-0084281	Conceptus PMS Review Reports
BAY-JCCP-0084282 – BAY-JCCP-0084300	Conceptus PMS Review Reports
BAY-JCCP-0084301 – BAY-JCCP-0084319	Conceptus PMS Review Reports
BAY-JCCP-0084320 – BAY-JCCP-0084341	Conceptus PMS Review Reports
BAY-JCCP-0084342 – BAY-JCCP-0084363	Conceptus PMS Review Reports
BAY-JCCP-0084364 – BAY-JCCP-0084387	Conceptus PMS Review Reports
BAY-JCCP-0084388 – BAY-JCCP-0084406	Conceptus PMS Review Reports
BAY-JCCP-0084407 – BAY-JCCP-0084428	Conceptus PMS Review Reports
BAY-JCCP-0084429 – BAY-JCCP-0084452	Conceptus PMS Review Reports
BAY-JCCP-0084453 – BAY-JCCP-0084477	Conceptus PMS Review Reports
BAY-JCCP-0084478 – BAY-JCCP-0084506	Conceptus PMS Review Reports
BAY-JCCP-0084507 – BAY-JCCP-0084526	Conceptus PMS Review Reports
BAY-JCCP-0084527 – BAY-JCCP-0084545	Conceptus PMS Review Reports
BAY-JCCP-0084546 – BAY-JCCP-0084557	Conceptus PMS Review Reports
BAY-JCCP-0084558 – BAY-JCCP-0084573	Conceptus PMS Review Reports
BAY-JCCP-0084574 – BAY-JCCP-0084586	Conceptus PMS Review Reports
BAY-JCCP-0084587 – BAY-JCCP-0084598	Conceptus PMS Review Reports
BAY-JCCP-0084599 – BAY-JCCP-0084609	Conceptus PMS Review Reports
BAY-JCCP-0084610 – BAY-JCCP-0084623	Conceptus PMS Review Reports
BAY-JCCP-0084624 – BAY-JCCP-0084642	Conceptus PMS Review Reports
BAY-JCCP-0084643 – BAY-JCCP-0084660	Conceptus PMS Review Reports
BAY-JCCP-0084661 – BAY-JCCP-0084678	Conceptus PMS Review Reports
BAY-JCCP-0084679 – BAY-JCCP-0084697	Conceptus PMS Review Reports
BAY-JCCP-0084698 – BAY-JCCP-0084714	Conceptus PMS Review Reports
BAY-JCCP-0084715 – BAY-JCCP-0084730	Conceptus PMS Review Reports
BAY-JCCP-0084731 – BAY-JCCP-0084746	Conceptus PMS Review Reports
BAY-JCCP-0084747 – BAY-JCCP-0084762	Conceptus PMS Review Reports
BAY-JCCP-0084763 – BAY-JCCP-0084777	Conceptus PMS Review Reports
BAY-JCCP-0084778 – BAY-JCCP-0084793	Conceptus PMS Review Reports
BAY-JCCP-0084794 – BAY-JCCP-0084809	Conceptus PMS Review Reports
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BAY-JCCP-0084826 – BAY-JCCP-0084843	Conceptus PMS Review Reports
BAY-JCCP-0084844 – BAY-JCCP-0084861	Conceptus PMS Review Reports
BAY-JCCP-0086072 – BAY-JCCP-0086090	Conceptus PMS Review Reports
BAY-JCCP-0662352 – BAY-JCCP-0662431	October 3, 2000 CER
BAY-JCCP-0361090 – BAY-JCCP-0361092	November 18, 2008 CER
BAY-JCCP-0662284 – BAY-JCCP-0662327	August 27, 2009 CER
BAY-JCCP-0361093 – BAY-JCCP-0361096	August 27, 2009 CER
BAY-JCCP-0662328 – BAY-JCCP-0662283	August 27, 2010 CER
BAY-JCCP-0360931 – BAY-JCCP-0361089	October 26, 2010 CER
BAY-JCCP-0361097 – BAY-JCCP-0361105	November 12, 2010 CER
BAY-JCCP-0662349 – BAY-JCCP-0062351	January 17, 2011 CER
BAY-JCCP-0361106 – BAY-JCCP-0361113	July 27, 2011 CER
BAY-JCCP-0662477 – BAY-JCCP-0662507	January 16, 2013 CER
BAY-JCCP-0361114 – BAY-JCCP-0361120	January 16, 2013 CER
BAY-JCCP-0662433 – BAY-JCCP-0662454	August 6, 2014 CER

BAY-JCCP-0672939 – BAY-JCCP-0672999	August 6, 2014 CER
BAY-JCCP-0363036 – BAY-JCCP-0363163	August 10, 2015 CER
BAY-JCCP-1121670 – BAY-JCCP-1121792	March 31, 2016 CER
BAY-JCCP-1121624 – BAY-JCCP-1121669	March 31, 2016 CER
BAY-JCCP-0361121 – BAY-JCCP-0363035	November 11, 2016 CER
BAY-JCCP-0661231 – BAY-JCCP-0662283	September 13, 2017 CER
BAY-JCCP-1120549 – BAY-JCCP-1121623	September 28, 2018 CER
BAY-JCCP-0662508 – BAY-JCCP-0662510	Assessment of Essure Breakage Cases
BAY-JCCP-0662511 – BAY-JCCP-0662512	Assessment of Essure Cases Associated with Human Factor (Q4 2015, PMS report)
BAY-JCCP-0662513 – BAY-JCCP-0662514	Assessment of Essure Cases Associated with Procedural Complications (Q4 2015, PMS report)
BAY-JCCP-0662515 – BAY-JCCP-0662518	Assessment of Essure Cases Originated from Spain (Q4 2015, PMS report)
BAY-JCCP-0662519 – BAY-JCCP-0662539	Essure and (simultaneous) endometrial ablation – impact on safety and efficacy
BAY-JCCP-0662540 – BAY-JCCP-0662584	Global Benefit Risk Management Pharmacovigilance Evaluation of Essure Removals (November 7, 2017)
BAY-JCCP-0662585 – BAY-JCCP-0662598	Histological assessment of fallopian tubes from Essure users: Evidence regarding potential allergic-hypersensitivity reactions
BAY-JCCP-0662599 – BAY-JCCP-0662615	Signal Evaluation – Essure and late onset chronic pelvic pain
BAY-JCCP-0662616 – BAY-JCCP-0662642	Product Quality Complaint Analysis Report (June 13, 2016)
BAY-JCCP-0662643 – BAY-JCCP-0662674	Essure and (simultaneous) endometrial ablation – impact on safety and efficacy (February 29, 2016)
BAY-JCCP-0055984 – BAY-JCCP-0055985	Consent Form for Essure Procedure (CC-1670 December 27, 2007)
BAY-JCCP-0050582	Consent Form for Essure Procedure (CC-1670 April 1, 2008)
BAY-JCCP-0057184	Consent Form for Essure Procedure (CC-1670 August 11, 2011)
BAY-JCCP-0813448	Certificate to Foreign Government
BAY-JCCP-0623438 – BAY-JCCP-0623440	Certificate to Foreign Government
BAY-JCCP-0763783 – BAY-JCCP-0763784	Certificate to Foreign Government
BAY-JCCP-0304959	Certificate to Foreign Government
BAY-JCCP-0342514 – BAY-JCCP-0342515	Certificate to Foreign Government
BAY-JCCP-0341594 – BAY-JCCP-0341595	Certificate to Foreign Government
BAY-JCCP-0343529	Certificate to Foreign Government
BAY-JCCP-0342907	Certificate to Foreign Government
BAY-JCCP-1369327	Certificate to Foreign Government
BAY-JCCP-1438313	Certificate to Foreign Government
BAY-JCCP-0861055 – BAY-JCCP-0861708	Summary of Safety and Effectiveness Data
BAY-JCCP-0082841 - BAY-JCCP-0083181	JCCP Production 28:

	Conceptus and Bayer policies and procedures applicable to complaint handling and complaint handling CAPAs as it relates to U.S. FDA medical device reporting for Essure from 2002 through present, A sample set of Essure medical device reports (MDRs) submitted to FDA identified by Plaintiffs' counsel in their November 27, 2017 email to Bayer.
BAY-JCCP-0087030 – BAY-JCCP-0089356	JCCP Production 44: Enclosed Production 44 contains a report of complaints from Master Control from 2011-2013.
BAY-JCCP-0089357 – BAY-JCCP-0091899	JCCP Production 45: Enclosed Production 45 contains the remainder of the 822 complaint files for the following failure modes: Allery, Bleeding, Cramping, Expulsion (all types), Infection, Pain (all types), Perforation (Micro-insert), Perforation (general), Physician Technique, Pregnancy (Ectopic), and Vaso Vagal Response.
BAY-JCCP-00094030 – BAY-JCCP-00096477	JCCP Production 53: Production 53 contains complaint file information responsive to Plaintiffs' Request or Production of Documents Set 8.
BAY-JCCP-0140982 – BAY-JCCP-0144549	JCCP Production 70: Production 70 contains complaint file information maintained in paper form responsive to Plaintiffs' Requests for Production of Documents Sets 8, 10 and 11.
BAY-JCCP-0360931 – BAY-JCCP-0363351	JCCP Production 77: Production 77 contains Conceptus-era complaint files for complaints from social media in response to Plaintiffs' Request for Production of Documents Set 9.
BAY-JCCP-1138728 – BAY-JCCP-1139238	JCCP Production 96: Production 96 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-1268172 – BAY-JCCP-1319889	JCCP Production 105: Production 105 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-1617030 – BAY-JCCP-1617886	JCCP Production 110: Production 110 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-1618388 – BAY-JCCP-1636664	JCCP Production 112: Production 112 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-1759332 – BAY-JCCP-1767258	JCCP Production 116:

	Production 116 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-1767259 – BAY-JCCP-1767436	JCCP Production 117: Production 117 contains complaint files for the AR numbers listed in Appendix A.
BAY-JCCP-2436001 – BAY-JCCP-2456775	JCCP Production 129: Production 129 contains complaint files for the ARGUS case numbers listed in Appendix A.
BAY-JCCP-3930095 – BAY-JCCP-4146848	JCCP Production 153: Production 153 contains complaint files for the ARGUS case numbers and AR numbers listed in Appendix A.
BAY-JCCP-4146876 – BAY-JCCP-4310657	JCCP Production 155: Production 155 contains complaint files for the ARGUS case numbers listed in Appendix A.
BAY-JCCP-4314726 – BAY-JCCP-4810025	JCCP Production 160, JCCP Production 161, JCCP Production 162: Productions 160-162 contain complaint files for the ARGUS case numbers listed in Appendix A.
BAY-JCCP-4810520 – BAY-JCCP-5405050	JCCP Production 166, JCCP Production 167, JCCP Production 168: Productions 166-168 contain complaint files for the ARGUS case numbers listed in Appendix A.
BAY-JCCP-5610420 – BAY-JCCP-5849811	JCCP Production 174 and JCCP Production 175: Productions 174-175 contain complaint files for the ARGUS case numbers and AR Numbers listed in Appendix A.
BAY-JCCP-6422885 – BAY-JCCP-6627901	JCCP Production 188: Production 188 contains complaint files for the ARGUS case numbers listed in Appendix A.
BAY-JCCP-6677413 – BAY-JCCP-6901070	JCCP Production 195 and JCCP Production 196: Productions 195-196 contain complaint files and MDRs for the ARGUS case numbers and AR Numbers listed in Appendix A.
BAY-JCCP-6926552 – BAY-JCCP-7036995	JCCP Production 199: Production 199 contains complaint files and MDRs for the AR Numbers and ARGUS case number listed in Appendix A.
BAY-JCCP-7037195 – BAY-JCCP-7060638	JCCP Production 205: Production 205 contains complaint files for the AR Numbers and ARGUS case numbers from Plaintiffs' Request for Production of Documents Set 35 that are listed in Appendix A.
BAY-JCCP-7171833 – BAY-JCCP-7180395	JCCP Production 217: Production 217 contains complaint files for the ARGUS case numbers listed in Appendix A.

BAY-JCCP-7180396 – BAY-JCCP-7191884	JCCP Production 218: Production 218 contains complaint files and/or MDRs for the ARGUS case numbers and AR Numbers listed in Appendix A.
BAY-JCCP-7191885 – BAY-JCCP-7246745	JCCP Production 219: Production 219 contains underlying materials from Dev@com for the Dev@com numbers listed in Appendix A.
BAY-JCCP-7405924 – BAY-JCCP-7406369	JCCP Production 247: Production 247 contains 115 complaint file documents for the 23 ARGUS case numbers listed in Appendix A.

Literature

Antoun L., The feasibility, safety, and effectiveness of hysteroscopic sterilization compared with laparoscopic sterilization. Am J Obstet Gynecol. 2017 Nov;217(5):570.e1-570

Bouillon K et al, Association of Hysteroscopic vs Laparoscopic Sterilization With Procedural, Gynecological, and Medical Outcomes. JAMA. 2018 Jan 23;319(4):375-387.

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Carney PI, et al., Occurrence of Chronic Pelvic Pain, Abnormal Uterine Bleeding, and Hysterectomy Post-procedure among Women Who Have Undergone Female Sterilization Procedures: A Retrospective Claims Analysis of Commercially Insured Women in the US. J Minim Invasive Gynecol. 2018 May - Jun;25(4):651-660

Conover MM et al., Incidence of opioid-managed pelvic pain after hysteroscopic sterilization versus laparoscopic sterilization, US 2005-2012. Pharmacoepidemiol Drug Saf. 2015 Aug;24(8):875-84. doi: 10.1002/pds.3766. Epub 2015 Mar 31.

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EXHIBIT D

Contains Nonbinding Recommendations

Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization

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Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 31, 2016

The draft of this document was issued on March 4, 2016.

For questions about this document, contact the Division of Reproductive, Gastro-Renal, and Urological Devices at 301-796-7030.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Surveillance and Biometrics

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov . Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2015-D-4803. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1500051 to identify the guidance you are requesting.

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Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance identifies the content and format for certain labeling components for permanent, hysteroscopically-placed tubal implant devices intended for female sterilization. FDA believes this guidance will help to ensure that a woman receives and understands information regarding the benefits and risks of this type of device prior to undergoing implantation.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Female sterilization is an elective procedure that permanently prevents a woman from becoming pregnant by disrupting the fallopian tubes and preventing fertilization of an egg following ovulation. As sterilization is intended to be an irreversible procedure, it is appropriate only for women who are certain that they wish to permanently end their ability to conceive naturally. Female sterilization is one of the most common procedures in the United States, with more than

500,000 performed per year.[1] The procedure may be performed immediately following delivery of an infant (post-partum sterilization) or at a time not associated with a recent pregnancy (interval sterilization). For decades, female sterilization has been performed by surgical bilateral tubal ligation (BTL) through a laparotomy, a mini-laparotomy, a transvaginal approach or at the time of a cesarean delivery, and, more recently, via laparoscopy. During surgical BTL, the fallopian tubes are cut, or various procedures or medical instruments, such as electrosurgical coagulation, implantable clips or rings, are used to physically block or close the fallopian tubes. Surgical BTL is effective immediately, is generally safe, requires little to no patient compliance, and is a highly effective method of permanent sterilization. However, there are certain risks of surgical BTL, including, but not limited to, adverse events related to general anesthesia, possible physical injury to local organs (e.g., bowel), and bleeding. Some of these adverse events, although uncommon, may result in hospitalization and/or re-operation.[2]

In addition to surgical BTL, medical devices have been developed to provide alternative, less-invasive methods of female sterilization through the insertion of permanent implants into a woman's fallopian tubes via a hysteroscopic, non-incisional route. The inserted permanent implants are intended to provide sterilization via physical occlusion and/or the elicitation of a local inflammatory/fibrotic response. This type of device may require a "waiting period" in order to accomplish full occlusion. As the number of hysteroscopic sterilizations with such devices has increased, additional information, including reports of adverse events, has accumulated. This information has included reports of suspected hypersensitivity reactions to the implant materials, persistent pain, irregular vaginal bleeding, fallopian tube or uterine perforation, the identification of inserts in the pelvic cavity, and unintended pregnancy. Some instances of adverse events have resulted in surgical intervention, including device removal.

On September 24, 2015, FDA convened its Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to discuss available data regarding benefits, the aforementioned risks, and potential mitigation strategies to prevent or reduce the frequency/severity of the adverse outcomes reported in association with one such device, the Essure System for Permanent Birth Control.[3]

Based on the 2015 Panel meeting, including comments made during the Open Public Hearing portion of the meeting and comments submitted in the associated public docket,[4] FDA believes that some women are not receiving or understanding information regarding the risks and benefits of permanent, hysteroscopically-placed tubal implants that are intended for sterilization.

This guidance addresses these concerns by identifying labeling components, namely a boxed warning and patient decision checklist, which FDA intends to require as part of the labeling for these devices. FDA believes this will help to ensure a woman receives and understands the benefits

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[1] Chan LM, Westhoff CL. Tubal sterilization trends in the United States. Fertility and Sterility, 2010; 94(1): 1-6.
[2] Jamieson DJ, Hillis SD, Duerr A et al. (2000) Complications of interval laparoscopic tubal sterilization: Findings from the United States Collaborative Review of Sterilization. Obstet & Gynecol 96(6): 997-1002.
[3] For more information and meeting materials, *see* http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm463457.htm.
[4] *See id*.

and risks associated with her contraceptive options so that she can make an informed decision as to whether a permanent hysteroscopically-placed tubal implant intended for sterilization is the right choice for her.

III. Scope

This guidance identifies the content and format of certain labeling components for permanent, hysteroscopically-placed tubal implants that are intended for sterilization. The guidance applies to all devices of this type, regardless of the insert material composition, location of intended implantation, or exact method of delivery. Medical devices used during surgical BTL procedures (e.g., cautery devices, rings, clips) are outside the scope of this guidance.

The guidance is not intended to include a complete listing of all labeling components for permanent, hysteroscopically-placed tubal implants intended for sterilization. Rather, this guidance specifically focuses on inclusion of a boxed warning and patient decision checklist in the product labeling. Accurate product labeling and effective messaging of that labeling is important to make device users and patients aware of the risks associated with permanent, hysteroscopically-placed tubal implants intended for sterilization. FDA believes that a boxed warning and a patient decision checklist as described in this guidance should be included in labeling under sections 502(a), 201(n), and 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA intends to require such labeling as part of a premarket approval application (PMA) for permanent hysteroscopically-placed tubal implants intended for sterilization (or a PMA supplement for already marketed devices). This guidance should be used as a complement to FDA's, "Guidance on Medical Device Patient Labeling" (which describes FDA's current thinking on making medical device patient labeling understandable to and usable by patients), existing regulations, and other relevant guidance documents containing additional labeling recommendations.[5]

IV. Labeling Components

This section contains the content and format FDA believes should be included in a boxed warning and patient decision checklist in the product labeling of permanent, hysteroscopically-placed tubal implants intended for sterilization. The specific examples referenced in the appendices are written to address the currently marketed device of this type.

A. Boxed Warning

[5] We note that a device is misbranded if its labeling is false or misleading in any particular (section 502(a) of the FD&C Act) or, if applicable, its labeling does not provide adequate warnings (section 502(f)(2) of the FD&C Act). Under section 301(a) of the FD&C Act, it is a prohibited act to introduce or deliver for introduction into interstate commerce any device that is misbranded.

FDA believes that a boxed warning should be part of labeling for a permanent, hysteroscopically-placed tubal implant for sterilization and should:

- Note the types of significant and/or common adverse events that may be associated with the device and its insertion, use, and/or removal procedure, including those noted in clinical trials, as well as those reported in other device use experience.
- Include a statement noting that these risks should be conveyed to the patient during the decision-making process.

An example of a boxed warning that follows this guidance is provided in **Appendix A**.

B. Patient Decision Checklist

In addition to the boxed warning, FDA also believes that a patient decision checklist highlighting key risk and benefit information should be included at the end of the document. The checklist is intended to be reviewed and signed by the patient and physician, and should be printed in a fashion where it can be easily separated and marked.

The introduction for the checklist should include a description of the purpose and importance of the checklist, as well as instructions to the patient on how to review and complete the document prior to deciding whether to undergo the permanent implant procedure.

The body of the checklist should include key items related to the device, its use, and its safety and effectiveness. Items that should be addressed include the following:

- Notification of the permanent (and if applicable, irreversible) nature of sterilization in general, and the implant more specifically;
- recognition of available alternative contraceptive modalities and their safety and effectiveness;
- situations in which the device should not be used or implanted (e.g., contraindications);
- steps, if any, that need to be followed before the implant can be relied upon for contraception, and the importance of compliance with those steps;
- information on effectiveness and chances for unintended pregnancy and ectopic pregnancy, including a statement that no contraceptive device is 100% effective;
- significant and/or common adverse events, including patient-reported outcomes, which may occur during or immediately following device placement;
- clinically significant longer-term adverse events or outcomes that have been reported in clinical trials or via other device use experience – including significant events that may persist from the time of implantation and those that may appear for the first time later after implantation;
- a brief discussion of the types of signs, symptoms or events that may represent device-related complications for which the patient should seek prompt evaluation;
- a disclosure of the device materials and any risks that may be associated with them, including allergy/hypersensitivity and Magnetic Resonance Imaging (MRI) safety information, if applicable; and

- information related to device removal and/or reversal (e.g., reasons for removal, techniques, outcomes).

Where applicable, and if known (e.g., based on clinical trial results), probabilities or rates of events should be included within the individual checklist items. The source of the probabilities or rates of events should be identified.

Each topic grouping in the body of the checklist (e.g., items related to birth control options, items related to long-term risks of the device) should be accompanied by a line for the patient to initial her acknowledgment and understanding of that information.

At the end, the checklist should include a section that confirms that the patient has read and understood the material and has had the opportunity to satisfactorily discuss and ask questions of her physician. This should be followed by a signature line for the patient. At the end of the checklist there should also be a section that confirms that the physician discussed the benefits and risks of the device, as set forth in the patient decision checklist, with the patient. This should be followed by a signature line for the physician.

The FDA recommends that a copy of the patient decision checklist be provided to the patient. The FDA also encourages device manufacturers to develop a plan to audit (and if appropriate, institute steps to improve) the distribution and signing of the checklists as a component of the patient decision-making process, and to periodically update the checklist as additional data is collected with post-market experience.

Appendix B provides an example of a Patient Decision Checklist that follows this guidance.

Appendix A: Boxed Warning Example

WARNING: Some patients implanted with the Essure System for Permanent Birth Control have experienced and/or reported adverse events, including perforation of the uterus and/or fallopian tubes, identification of inserts in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions. If the device needs to be removed to address such an adverse event, a surgical procedure will be required. This information should be shared with patients considering sterilization with the Essure System for Permanent Birth Control during discussion of the benefits and risks of the device.

Appendix B: Patient Decision Checklist Example

To the patient considering the Essure System for Permanent Birth Control ("Essure"):
The review and completion of this document is a critical step in helping you decide whether or not to have Essure implanted. You should carefully consider the benefits and risks associated with the device before you make that decision. After reviewing the information in this brochure, please read and discuss the items in this checklist with your doctor. You should not initial or sign the document, and should not undergo the procedure, if you do not understand each of the elements listed below.

Birth Control Options

I understand that Essure is a permanent form of birth control (referred to as "sterilization"). I understand that sterilization must be considered permanent and not reversible.

I was told about other permanent sterilization procedures, such as surgical bilateral tubal ligation ("getting tubes tied"), and their benefits and risks.

I am aware that there are highly effective methods of birth control which are not permanent and which may allow me to become pregnant when stopped.

Patient Initials _____

Requirements for Essure Placement and Reliance
I understand that I am not a candidate for Essure if:

- I am uncertain about ending my fertility.
- I have had a tubal ligation procedure ("tubes tied").
- I cannot have two inserts placed due to my anatomy.
- I am pregnant or suspect that I may be pregnant.
- I have delivered or terminated a pregnancy within the last 6 weeks.
- I have had a pelvic infection within six weeks prior to the date of the scheduled implantation.
- I have a known allergy to contrast dye used during x-ray procedures.

Essure works as intended only when the devices are successfully placed in both fallopian tubes. I understand that if this is not possible in my case, I may need to undergo a repeat attempt at Essure placement or consider a different form of birth control.

I understand that the placement procedure is only the first step in relying on Essure for birth control. After placement I must:

- Use an alternative form of birth control until my doctor tells me I can stop (typically for 3 months).
- Schedule and undergo a confirmation test after three months to determine whether I may rely on Essure. I understand that payment for this test may or may not be covered by my insurance company.

I understand that a satisfactory confirmation test is needed before I can rely on Essure alone. I also understand that after the confirmation test my doctor may inform me that I may not be able to rely on Essure. If this occurs, I will have to use an alternative form of contraception.

I understand that based on clinical studies, approximately 8% of women who undergo attempts at Essure placement are not able to rely on the device for contraception.

Patient Initials _____

Pregnancy Risks

I understand that no form of birth control is 100% effective. Even if my doctor tells me I am able to rely on Essure, there is still a small chance that I may become pregnant. Based on clinical studies, the chance of unintended pregnancy for women who have been told they can rely on Essure is less than 1% at 5 years.

I understand that the risks of Essure on a developing fetus have not been established. If I become pregnant with Essure, there may be an increased risk for the pregnancy to occur outside of the uterus ("ectopic pregnancy"). This may result in serious and even life-threatening complications. I understand that after Essure placement, I should contact my doctor immediately if I think I may be pregnant.

Patient Initials _____

What to Expect During the Procedure and the Days Afterwards

I understand that in clinical studies supporting device approval, the following events were reported to occur during the Essure placement procedure and/or in the hours or days following placement:

- Cramping (Reported in up to 30% of procedures)
- Mild to moderate pain (Up to 9-10%) or moderate pain (Up to 13%)
- Nausea/Vomiting (Up to 11%)
- Dizziness/Lightheadedness (Up to 9%)
- Vaginal bleeding (Up to 7%)

If I experience worsening of any of the events listed above or I continue to have the symptoms 1 week after placement, I understand that I should contact my doctor.

Patient Initials _____

Long-Term Risks

I understand that some women may experience continued pain or develop new pain after Essure placement. I understand that I should contact my doctor if abdominal, pelvic or back pain continues for more than 1 week after placement or if I develop the onset of new pain more than 1 week after placement.

I understand that the Essure implants contain metals including nickel, titanium, iron, chromium, and tin, as well as a material called polyethylene terephthalate (PET). I understand

that some women may develop allergic reactions to the device following implantation and have signs or symptoms such as rash and itching. This may occur even if there is no prior history of sensitivity to those materials. I also understand that there is no reliable test to predict ahead of time who may develop a reaction to the device.

I understand that persistent or new pain, and/or allergic reaction may be a sign of an Essure-related problem which might require further evaluation and treatment, including possibly the need to have the devices removed by surgery.

I recognize that other symptoms have been reported to FDA by women implanted with Essure, although they were not seen in the clinical trials supporting Essure approval. The more common symptoms reported include headache, fatigue, weight changes, hair loss and mood changes such as depression. It is unknown if these symptoms are related to Essure or not.

I understand that because Essure contains metals, I should tell all my doctors that I have the device before getting an MRI.

I understand that there is a small possibility that the device could poke through the wall of the uterus or fallopian tubes ("perforation"), and/or move to other locations in the abdomen or pelvis ("migration"). The rate of perforation in studies has ranged from 1% to 4%. The rate for device migration into the abdomen or pelvis has not been determined but its occurrence is uncommon.

I understand that should one of these events occur, the device may become ineffective in preventing pregnancy and may lead to serious adverse events such as bleeding or bowel damage, which may require surgery to address.

I understand that should my doctor and I decide that Essure should be removed after placement, a surgical procedure will be required. In complicated cases, my doctor may recommend a hysterectomy (removal of the entire uterus). I also understand that device removal may not be covered by my insurance company.

Patient Initials _____

CONFIRMATION OF DISCUSSION OF RISKS

Patient: I acknowledge that I have received and read the Essure Patient Information Brochure, and that I have had time to discuss the items in it and in this document with my doctor. I have had the opportunity to ask questions and understand the benefits and risks of the device and procedure, and understand that alternative methods of birth control are available.

_____
Patient Signature and Date

Physician: I acknowledge that I have discussed with the patient the benefits and risks of Essure as described in the Essure System Patient Information Brochure as well as this document. I have also explained the benefits and risks of other birth control methods. Should device removal become necessary, I may perform the removal myself, or provide a referral to a physician who is willing and able to perform device removals. I have encouraged the patient to ask questions, and I have addressed all questions.

_____
Physician Signature and Date

EXHIBIT E

UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

+ + +

September 24, 2015
8:00 a.m.

FDA White Oak Campus
Building 31 – The Great Room, Room 1503
Silver Spring, Maryland

PANEL MEMBERS:

CHERYL B. IGLESIA, M.D., FACOG	Temporary Chair
DONNA D. BAIRD, Ph.D., M.P.H.	Non-Voting Member
RICHARD J. CHAPPELL, Ph.D.	Non-Voting Member
CHARLES C. CODDINGTON, M.D.	Non-Voting Member
DENISE M. ELSER, M.D., FACOG	Non-Voting Member
GRACE M. JANIK, M.D., FACOG	Non-Voting Member
DAVID F. KATZ, Ph.D.	Non-Voting Member
JOSHUA D. MILNER, M.D.	Non-Voting Member
DEBORAH L. MYERS, M.D.	Non-Voting Member
PETER C. SCHALOCK, M.D.	Non-Voting Member
DAVID B. SEIFER, M.D.	Non-Voting Member
PHILLIP G. STUBBLEFIELD, M.D.	Non-Voting Member
MARSHA WILLS-KARP, Ph.D.	Temporary Non-Voting Member
CYNTHIA CHAUHAN, M.S.W.	Consumer Representative
JO-ELLEN DE LUCA	Patient Representative
JAMES GARDNER, M.D., M.B.A.	Industry Representative
SHANIKA CRAIG, M.B.A., M.H.A.	Designated Federal Officer

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Division of Epidemiology
Office of Surveillance and Biometrics

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MICHAEL REDDICK
Bayer HealthCare

OPEN PUBLIC HEARING SPEAKERS:

LORI RUTTER (Video)
Patient

KRYSTAL DONAHUE
Patient

ELENA MENDEZ, RN
Patient

CHANDRA FARMER
Patient

LISA TATE
Interim Executive Director, Healthy Women

AILEEN GARIEPY, M.D., M.P.H.
Yale School of Medicine

REBECCA HOWELL
Patient

ROXANNE JAMSHIDI, M.D.
American Congress of Obstetricians and Gynecologists (ACOG)

SARAH SORSCHER, J.D., M.P.H.
Public Citizen's Health Research Group

KIM HUDAK
Patient

GABRIELLA AVINA, RN, M.S.N., M.B.A.
Patient

PATRICIA RHODES (Video)
Patient

DIANA ZUCKERMAN, Ph.D.
President, National Center for Health Research
Patient, Consumer, and Public Health Coalition

RAEGAN McDONALD-MOSLEY, M.D.
Planned Parenthood Federation of America

N. EDWARD DOURRON, M.D.
Reproductive Endocrinologist /Robotic Surgeon

VIKKI HUFNAGEL, M.D. (Video)

ANGIE FIRMALINO
Patient
Creator, Essure Problems Facebook Group

AMANDA DYKEMAN
Patient

KIM MYERS
Patient

CARRIE HIRMER
Patient

CECILIA BOGLE
Patient

SHARILYN ERVIN
Patient

JANIE GARCIA
Patient

DAVID BOGLE
Husband of Patient

WAYNE SHIELDS
President/CEO, Association of Reproductive Health Professionals

JULIO NOVOA, M.D.
OB/GYN

CHARLES MONTEITH, M.D.

HOOMAN NOORCHASHM, M.D., Ph.D.
Surgeon/Immunologist

AMY REED, M.D., Ph.D.
Immunologist

RYSZARD ROKICKI
Researcher

MARK BELL
Metallurgical Engineer

AUDREY SHEPPARD
Consultant

LAURA HENZE RUSSELL
Precision Research and Communications

CINDY PEARSON
Executive Director, National Women's Health Network

RUPAL JURAN, M.D.
OB/GYN

TABATHA ROMERO
Patient

AMANDA HOLT
Patient

SHEILA PITT
Patient

AMANDA RUSMISELL
Patient

ALICIA GREAGER
Patient

KIMBERLY HUGHES
Patient

SUSAN SCANLAN
President, Women's Research and Education Institute

CHRISTINE CERVANTES
Patient

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M E E T I N G

(8:04 a.m.)

DR. IGLESIA: Good morning. I would like to call this meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to order.

My name is Dr. Cheryl Iglesia. I am the Chair of this Panel. I am director of the section of female pelvic medicine and reconstructive surgery at MedStar Washington Hospital Center and a Professor of Obstetrics and Gynecology and Urology at Georgetown University School of Medicine.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss the risks and benefits of Bayer HealthCare's Essure system for permanent female sterilization. The system, originally approved in November 2002 under P020014, consists of a delivery system and nickel-containing permanent implants. The implants are placed without a skin incision, through the vagina, within each fallopian tube. They elicit tissue ingrowth, which over time results in tubal occlusion.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'd like to start to my right with Dr. Gardner. And, please, yeah, hit the red button.

DR. GARDNER: Hi, my name is Jim Gardner. I am the Industry Representative on the

Panel. I'm employed by Cook Medical, which is a family of medical device manufacturers based in Bloomington, Indiana, where I serve as medical science officer and director of reimbursement for the organization.

MS. CHAUHAN: Cynthia Chauhan, Consumer Representative.

MS. DE LUCA: Jo-Ellen De Luca, Patient Representative.

DR. SEIFER: David Seifer, OHSU, reproductive endocrinology.

DR. JANIK: Grace Janik, Reproductive Specialty Center, Milwaukee, reproductive endocrinology and fertility and minimally invasive surgery.

DR. CODDINGTON: Charles Coddington from the Mayo Clinic, Department of Obstetrics and Gynecology, where I am a gynecologic surgeon and reproductive endocrinologist.

DR. CHAPPELL: Rick Chappell, Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison.

DR. MYERS: Dr. Deborah Myers, Professor of OB/GYN at Brown Medical School, Providence, Rhode Island. Expertise is female pelvic medicine and reconstructive surgery.

DR. ELSER: Dr. Denise Elser, female pelvic medicine and reconstructive surgery in the Chicago area.

MS. CRAIG: Shanika Craig, designated federal official.

DR. MILNER: Dr. Josh Milner, Senior Investigator in the National Institute of Allergy and Infectious Diseases; allergy and immunology.

DR. STUBBLEFIELD: Phillip Stubblefield, obstetrician/gynecologist at Beth Israel Deaconess Hospital in Boston, and practice in the division of family planning.

DR. KATZ: David Katz, Duke University. I am a Professor of Biomedical Engineering and a Professor of Obstetrics and Gynecology.

DR. SCHALOCK: Peter Schalock, Harvard Medical School, Mass General Hospital, Associate Professor of Dermatology.

DR. BAIRD: Donna Baird. I'm with the National Institute of Environmental Health Sciences, a reproductive epidemiologist and adjunct professor at the University of North Carolina.

DR. WILLS-KARP: Dr. Marsha Wills-Karp. I'm at the Johns Hopkins School of Public Health. I am a professor in the Department of Environmental Health Sciences, and my area of expertise is allergy and immunology.

DR. YUSTEIN: Ron Yustein. I am the Clinical Deputy Director in the Office of Surveillance and Biometrics at the Center for Devices and Radiological Health here at FDA.

DR. FISHER: Ben Fisher. I'm the Division Director for the Division of Reproductive, Gastro-Renal, and Urological Devices in the Office of Device Evaluation here in the Center for Devices. I am a developmental toxicologist with a focus on developmental genetics.

DR. IGLESIA: Thank you very much. And if you could all just turn off your mikes when you're not speaking and just turn them on when you are, because this is being recorded, for the background noise.

So, for topics being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak

into the record only if recognized by the Chairperson. We look forward to a productive meeting.

Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of the meeting room.

And Ms. Shanika Craig, the Designated Federal Officer for the Obstetrics and Gynecology Devices Panel, will now make some introductory remarks.

MS. CRAIG: I will now read the FDA Conflict of Interest Disclosure Statement, Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee, September 24th, 2015.

The Food and Drug Administration is convening today's meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at U.S. Code 18 Section 208 are being provided to participants today in today's meeting and to the public.

FDA has determined that the members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under U.S. Code 18

Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of U.S. Code 18 Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss the risks and benefits of Bayer HealthCare's Essure system for permanent female sterilization. This system, approved in November 2002, consists of a delivery system and nickel-containing permanent implants. The implants are placed without a skin incision, through the vagina, within each fallopian tube. They elicit tissue ingrowth, which over time results in tubal occlusion.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and the consultants, no conflict of interest waivers have been issued in accordance of U.S. Code 18 Section 208.

Dr. James Gardner is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Cook, Incorporated.

We would like to remind members and consultants that if the discussion involves any

other products or firms not already on the agenda for which FDA participants have a personal or imputed financial interest, that participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as a part of the meeting official transcript.

For the duration of the Obstetrics and Gynecology Devices Panel meeting on September 24th, 2015, Ms. Jo-Ellen De Luca has been appointed to serve as a Temporary Non-Voting Patient Representative, and Dr. Marsha Wills-Karp has been appointed to serve as a Temporary Non-Voting Member. For the record, Ms. De Luca serves as a consultant to the Gastrointestinal Drugs Advisory Committee in the Center for Drug Evaluation and Research, and Dr. Wills-Karp serves as a consultant to the Allergenic Products Advisory Committee in the Center for Biologics Evaluation and Research. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

These appointments were authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on September 22nd, 2015.

Before I return the meeting back over to Dr. Iglesia, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside of the meeting room.

The FDA press contact for today's meeting is Deborah Kotz.

All written comments received were provided to the Panel for their review prior to today's meeting. The link to the docket, which contains the written comments, is available at the registration table.

I would like to remind everyone that the members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, or it has changed, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you.

Dr. Iglesia.

DR. IGLESIA: Thank you, Ms. Craig.

We will begin today's meeting with introductory remarks from the Assistant Commissioner for Women's Health, Marsha Henderson.

MS. HENDERSON: Good morning. I am Marsha Henderson, Assistant Commissioner

for Women's Health. The Office of Women's Health is responsible for protecting and advancing the health of women through policy, science, and outreach.

Thank you for coming to the FDA to participate in this important public Advisory Committee meeting. All FDA Advisory Committee meetings are centered in science, and this one will be as well. But the FDA also called this meeting because we value your point of view, and we want to hear your very personal and professional perspectives. We are committed to being transparent and sharing information with the public. We know that it is critical to listen to the voices of patients, advocates, health professionals, and companies throughout the lifespan of the products we regulate. The Agency's primary concern is the safety and well-being of patients.

FDA's product review centers carefully monitor all reports of potential harms. They review a variety of sources to get as full a picture as possible of how devices work in the real world after approval. This means examining adverse reports submitted, reviewing the scientific data that manufacturers submit to FDA annually, reading the scientific literature, speaking to the clinicians who are using our regulated devices, and reviewing the public comments on the dockets for meetings like this one. Although the Office of Women's Health has no direct regulatory authority, we support these efforts. And we know that as the science evolves, so will the Agency's science-based decisions, as we carefully weigh each product's benefits and risks.

Over the years FDA's human product centers, like the Center for Devices and Radiological Health, have placed greater emphasis on the health needs of women and greater emphasis on the collection of data on women who participate in clinical trials.

These efforts have resulted in the development of new guidance and regulations for industry, advances in women's health research, outreach to communicate risk information to women, more detailed information on product safety and effectiveness when used on women, and of course, the approval of many lifesaving products.

I want to end by saying that I applaud the effort CDRH has made in preparation for this public meeting. It offers patients, members of the public, and healthcare providers with an opportunity to present their positions and for us to hear their concerns. We are listening.

Again, thank you for coming today to share your --

(Microphone off.)

DR. IGLESIA: Thank you, Assistant Commissioner Henderson.

At this time we will hear a presentation by Bayer HealthCare. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Bayer HealthCare, you may begin.

DR. ZAMPAGLIONE: Thank you, Madam Chairperson, members of the Committee, FDA, and members of the public. We are grateful for this opportunity to work with the Committee to review the benefits and risks of Essure.

Good morning, everyone. My name is Dr. Edio Zampaglione. I am the Vice President for U.S. Medical Affairs for Women's Healthcare and Neurology. Prior to joining the pharmaceutical industry, I was a private practitioner OB/GYN. I cared for many patients like the women here today who are to speak and tell their story. I learned a lot about what they

go through, their concerns, and how important it is that they are listened to and that their concerns are properly addressed. Our number one priority at Bayer is ensuring patient safety through the appropriate use of our products. We welcome the opportunity for an ongoing and open dialogue on permanent birth control and look forward to working closely with the FDA on any next steps that are discussed at this meeting.

So our presentation this morning will have several sections. I will present the clinical need for permanent birth control options, followed by a brief overview of Essure, the clinical development program and the physician training program. I will then conclude my portion of the presentation with a review of the topics of interest as identified by the FDA. Dr. Cindy Basinski, a private practitioner in Indiana with extensive experience in the placement and the management of Essure, will describe the need for permanent birth control as well as her experience as an Essure provider. Dr. Patricia Carney, Director of U.S. Medical Affairs for Women's Health at Bayer, will finish up the presentation with a review of the benefit-risk summary for Essure.

So data from the 2011 to 2013 National Survey of Family Growth has demonstrated that about 45% of women age 25 to 44 years old, who have completed childbearing, use permanent birth control as their method of contraception. That equates to about 650,000 procedures a year. About half of them are done as what's known as interval procedures, which means they are performed at a time that's distant from childbirth.

Now, prior to the approval of Essure, women had only one option, and that was a laparoscopic bilateral tubal ligation or a tubal ligation done through an open incision called a laparotomy. Now, while these procedures are common and relatively simple to perform,

they are not without risks, and some of them can have serious consequences. So it was recognized that there was a need for an alternative approach to permanent birth control. Approval of the Essure system in 2002 made an alternative approach to permanent birth control possible by providing women with an important option so that they can achieve their personal reproductive objectives.

The Essure system is a Class III PMA device. It was approved by the FDA on November 4th, 2002, following the PMA review pathway. Now, this pathway is the most stringent FDA review process for devices prior to marketing.

Essure is commercially available in the United States, Canada, a number of European countries, Australia, and several Latin American and Asian Pacific countries. Since its approval, approximately 1 million Essure systems have been distributed worldwide.

The Essure system is indicated for women who desire permanent birth control by bilateral tubal occlusion of the fallopian tubes. The inserts are small and flexible. They're approximately 4 cm in length and expand up to about 2 mm when released from the delivery catheter. The device is only to be used by physicians who are knowledgeable hysteroscopists and have successfully completed the mandatory training program.

So let's watch an animation of a placement. As you can see, the inserts are fed into the fallopian tubes through a delivery catheter. They are released from the delivery catheter on both sides. Once placed, occlusion takes about 3 months to occur. During this 3-month period, the patient must use an alternate method of contraception until the required 3-month confirmation test documents appropriate location and occlusion. If the inserts are found to be in the proper location, there's a very high likelihood, approximately

99%, that occlusion will have occurred. Initially, the only confirmation test in the United States was the hysterosalpingogram or a modified hysterosalpingogram. Bayer recently received approval for the use of transvaginal ultrasound as a first-line option for the confirmation test if certain criteria during the procedure were met. If the confirmation test is satisfactory, she is told she can rely on Essure and is no longer required to use an alternate method of contraception.

I will now give a brief overview of the Essure clinical development program just to demonstrate how rigorously the Essure device has been and continues to be studied.

The original insert was called the STOP device, and this was used in the registration studies. The feasibility studies were conducted in women who were scheduled to undergo a hysterectomy for benign reasons. The objective of these studies was to demonstrate the feasibility and safety of the Essure placement procedure and to provide support for the mechanism of action.

The Phase II and pivotal studies were multi-center international studies determining the safety and efficacy of Essure. These studies are the basis for the safety and efficacy data that appear in the instructions for use and met all requirements for a Class III device. In fact, since it was a first-of-a-kind device, the FDA referred the PMA to an outside Panel of experts on July 22nd, 2002. The Panel reviewed and discussed the safety, efficacy, labeling, training, and post-approval requirements. Eight of the nine experts agreed that Essure should be approved, with one abstaining due to personal reasons. As with any medical device, research and development continues to look at incremental refinements to improve safety and performance.

This slide demonstrates the refinements of the Essure system over the course of the development program. The feasibility, Phase II, and pivotal studies used the STOP insert and delivery catheter. The first U.S. launch of the device was the ESS205, which refined the delivery system for the same STOP insert, as shown on the top.

Through direct feedback gathered from physicians, a more user-friendly delivery catheter was developed. This is the currently available Essure system called the ESS305. For this model, minor changes were made to the proximal end of the insert to accommodate changes made to the delivery catheter. You can see that on the left side of the two photos of the inserts. These refinements did not affect the critical design aspects of Essure or the safety and efficacy of the device as demonstrated in the post-approval clinical trials.

The top portion of this slide shows two post-approval studies that continue to evaluate the safety and efficacy of Essure as well as assess the learning curve for physicians. The first study evaluated the minor changes to the delivery catheter from the STOP to the ESS205. The second study evaluated the change of the delivery catheter from the ESS205 to the 305. Both studies evaluated bilateral placement rates with the design changes made to the delivery system, as well as the bilateral placement rate of newly trained Essure physicians versus physicians who were experienced. Placement rate data from the 305 is reflected in the current instructions for use.

These next two studies that are shown are currently ongoing. The transvaginal ultrasound study was conducted to support the use of TVU as a first-line confirmation test in the United States and is currently in the long-term extension phase where patients will

be followed up to 10 years. What is particularly valuable about the TVU study is that the current version of the ESS305 was used. The study demonstrated a safety and efficacy profile that is consistent with the original pivotal study.

The purpose of the last study on this slide is to evaluate the effectiveness and safety of the Essure system when a NovaSure endometrial ablation procedure is performed following a successful Essure confirmation test. This study is expected to be completed in the next few years.

The body of knowledge about the safety and efficacy of Essure continues to grow, and a lot of data also comes from outside of the United States. A large study in France called SUCCES II is currently ongoing with 2,600 women enrolled and being followed long term. SUCCES II is a prospective, non-interventional, multi-center observational study. Recruitment started in 2008, and the primary objective of the study is the assessment of patient satisfaction at 5 years. Secondary objectives include assessment of complications.

Because this is an observational study, there is no systematic collection of safety endpoints, with the exception of the 3-month post-procedure time point. Patients at this time point were specifically asked if they experienced bleeding and/or pain or cramping post-procedure. After the 3-month post-procedure time point, safety data was collected at 1-, 2-, and 5-year contacts where patients were asked if they experienced any adverse events.

This table shows the results focusing on bleeding and pain or cramping reported at the 3-month time point and the interim 2-year assessment. As expected, given the specific questions on post-procedural pain and cramping and bleeding at the 3-month follow-up,

relatively high rates of these symptoms were reported. At subsequent contacts, rates of bleeding and pain were consistent with rates found in other studies. Five pregnancies have been reported, resulting in a contraceptive efficacy rate of approximately 99.6%. And the adverse events reported in the interim analysis as of July 2015 in SUCCES II are similar to the type and frequency to those already identified in the pivotal study.

So data about Essure continues to accrue in clinical trials that further characterize the experience and risks with this device.

So, to summarize the clinical data, a total of 2,676 women have been studied, with 557 completing 5 years of follow-up. And the TVU study follow-up will continue to follow an additional 493 women for 10 years. In addition, SUCCES II has added another 2,600 with 5 years of planned follow-up in an observational study.

As shown, a relatively large number of women are being studied out to 5 and even 10 years, and a consistent efficacy and safety profile has been observed with the clinical data and long-term follow-up. We use this data and experience as part of the Essure physician training program known as the Clinical Pathway.

Now, this program is to train physicians that we have and is regularly updated. The training has been mandatory since the PMA approval in 2002. A physician must successfully complete the Clinical Pathway certification before being able to independently order and perform the Essure procedure.

The Clinical Pathway program has three steps. Step 1 is the didactic portion that provides an overview on Essure, including appropriate patient selection, counseling, indications, contraindications, warnings, precautions, the placement steps and the

confirmation test, and all the clinical trial data available. This basically follows the instructions for use. The physicians also receive a comprehensive training manual as well as a demonstration video of the Essure procedure. Once they complete this first step, they move on to a hands-on training that involves the use of computer simulators and/or silicone uterine models. The final step involves placing Essure in patients under direct supervision and demonstration of proper technique and at least five procedures. Once the Clinical Pathway is completed, the physician receives a certificate of completion.

Now, our commitment to training doesn't stop with the Clinical Pathway. It also includes a physician's office staff such as nurses and other appropriate staff members. The key counseling points are reviewed, and the importance of a patient following all of the necessary steps through the confirmation test are stressed. They also learn where they can find all the resources on the Essure website, and these resources can be downloaded to support patient care.

Several additional physician programs have also been developed over the years. We offer this advanced workshop that is conducted in collaboration with the major endoscopic equipment company and Essure experts. It emphasizes office-based procedures, placement of the Essure inserts in challenging cases, and interpretation of the confirmation test.

Radiologists also play a very important role in the Essure procedure, as they are most often the ones performing the confirmation tests. A training program was implemented to provide radiologists with the information they need to interpret the confirmation test. All three programs I've discussed so far are tailored to the practicing professionals.

Residents are the future practicing physicians, and therefore it is important to provide them the skills to effectively offer Essure to their patients. A program specific for residents was implemented and has been adopted in the majority of OB/GYN residency programs in the United States. The program is led and managed by the residency director or any attending staff that's intimately involved with resident education. In addition to the structured training, we offer a number of individualized support services to address any specific need a physician may have.

The proctor program. This facilitates peer-to-peer placement training with experienced physicians. We have a national consultancy network which consists of physicians with extensive experience in the management of Essure patients. Case-specific questions to Bayer's medical information center are triaged to these consultants.

Physician inquiry requests, or PIRs, are managed by our medical information department and encompass a variety of questions ranging from providing data to triaging guidance on specific issues. These PIRs are recorded, and they're tracked. This gives us the ability to monitor and determine the types of questions physicians are asking. And this then allows us to cross-reference our training curriculum and look for areas that may need to be addressed.

So before I go into the topics of interest and share the data available, I would like to briefly review additional sources of data and information that inform these topics. In our own review document for this meeting, we draw on clinical trial data, external literature, and postmarketing monitoring data to address all of the topics of interest identified for this Advisory Panel meeting.

Regarding the external literature, we have focused on independently conducted and funded studies that appear in peer review journals in order to minimize biases.

And, regarding the postmarketing monitoring, the number of adverse event reports has increased over time, which is reflective of the increased exposure to Essure, as based on the number of kits sold. However, there has been a noticeable increase in case reports since the third quarter of 2013 and a disproportionate increase in non-medically confirmed cases. This increase coincides with the acquisition of Conceptus. And there's also been a recent increase in social media as well as traditional media. But Bayer has responded to these trends with activities that facilitate reporting, such as active listening and subsequent outreach programs to try to obtain as much information as possible and better understand these cases.

As the FDA stated in their review document for this meeting, there are many limitations to postmarketing adverse event reporting. But, despite these limitations, we consider it important to closely analyze the reports and types of adverse events received.

I will now present data on the topics of interest as identified by the FDA. In the interest of time, I will present data on seven of the topics, but all the topics are addressed in our Executive Summary that the Panel has received. The topics I will present today are efficacy; unsatisfactory location; pain, specifically persistent and chronic pain; allergic reaction and hypersensitivity to nickel; device removal; death; and pregnancy outcomes. Whenever possible we will present clinical trial data followed by the literature and postmarketing data. So let's begin with efficacy.

Now, we all know no method of contraception is 100% effective. And, since

approval, the instructions for use and all patient materials have clearly stated that fact. While no pregnancies were reported in the Phase II or pivotal trials, all labeled materials have always stated that pregnancies can occur with Essure in place and have been reported in the commercial setting. In the most recent study supporting the use of transvaginal ultrasound as a first-line confirmation test in the United States, four pregnancies out of 547 subjects were reported. Of the four pregnancies that occurred in the TVU study, two were due to perforations and two were due to unsatisfactory device location.

Several published studies in the United States look at Essure efficacy. Shown here are independently performed and independently funded studies. On this graph, the vertical line represents 99.2% contraceptive efficacy, the overall rate noted from these studies. Overall, a consistent picture of efficacy is seen. Independently performed studies in other countries report the same efficacy rate. The postmarketing reporting frequency of pregnancy is 0.21%, which includes pregnancies occurring before the confirmation test.

So, in conclusion, pregnancies with Essure in place have been reported in the commercial setting and in the literature.

Patient compliance with the 3-month alternate contraception as well as obtaining the confirmation test are important factors to prevent unintended pregnancies.

The findings are consistent across all data points and demonstrate an efficacy of greater than 99% when the Essure device is confirmed to be in the proper place and location.

I will now discuss unsatisfactory location of Essure inserts. Placing the inserts in a proper location is important for efficacy, as I've stated. A properly placed insert spans the

interstitial segment of the fallopian tube. The ultimate location of the tube -- in the tube, I'm sorry, is primarily determined by the position of the insert at the time of deployment in the placement procedure.

Unsatisfactory locations can be divided into three groups. One is when the insert is deployed too proximally or not sufficiently far in the tube, with most of it lying in the uterine cavity. These can be expelled into the uterus or vagina and even out through the body and can be associated with bleeding and/or cramping.

The second unsatisfactory location is when the insert was advanced too far into the tube and is distal from its ideal location.

The third unsatisfactory location is where the insert perforates the tube or uterus, and these perforations can be associated with significant pain or discomfort.

Distally placed inserts or perforations are more likely to migrate or get expelled into the pelvis or abdomen. Migration may occur between the hysteroscopic placement and the confirmation test. But migration of a satisfactorily located insert, as determined by the confirmation test, is unlikely to occur as tissue ingrowth around the device stabilizes its position.

This is the data on the reasons for unsatisfactory locations reported from the clinical trials and the Phase II, pivotal, and the most recent TVU study. The reported ranges for total unsatisfactory location ranged from 2% to 6.5%, as seen in the last column on the right. The range for perforation was 0.3% to 3.4%. The literature contains only a few studies analyzing the rates of unsatisfactory location. They focus primarily on perforation. A review of these studies and cases show that abdominal pain was the most common

symptom reported with perforation, though most are asymptomatic. Perforation and migration rates ranged from 0.02% up to 3.6%. The majority of cases in our postmarketing database are medically confirmed, and the reporting frequency noted for all types of unsatisfactory locations is approximately 0.4%.

In conclusion, unsatisfactory location of an insert is a known complication of the Essure procedure. The warnings and risks regarding an unsatisfactorily located insert are clearly stated in the instructions for use and patient information booklet.

An examination of peer-reviewed published literature and an analysis of all data available reveal that incidence of unsatisfactory location inserts are low.

As an unrecognized unsatisfactorily located insert can have serious consequences, the physician training program emphasizes identification through either the patient symptoms or the confirmation imaging as well as the appropriate management of these cases.

The next topic of interest is persistent and chronic pain. Chronic pelvic pain is a common gynecologic problem with an estimated prevalence between 5.7% and 26.6%. Some transient pain or discomfort is expected with the Essure placement procedure. However, as with any procedure we do in medicine, any patient with unexpected or prolonged pain must be evaluated.

This graph represents the reported incidence of pain during the pivotal trial and 5-year follow-up. Overall, the rates of pain are consistently low and continue to decrease with time.

This slide shows the rates of recurrent and persistent pelvic pain during the pivotal

study and 5-year follow-up. Recurrent pain was defined as pain that was reported at least twice during the follow-up period. Persistent pain is defined as pain that was reported at every prior follow-up visit.

A retrospective study of 458 women found that chronic pain, defined as pain lasting more than 3 months after the procedure, occurred in about 4.2% of women. In a large database review of almost 27,000 patients, 0.88% of women who chose hysteroscopic sterilization and 0.93% of women who chose laparoscopic tubal ligation had a diagnosis of chronic pain post-procedure. Formal testing proved that there was no statistical difference between the two groups. From our postmarketing monitoring, the reporting frequency for abdominal, pelvic, and back pain is 0.3%. Reports on pain from healthcare professionals are frequently reported in the context of unsatisfactory device location.

So, in conclusion, short-term pain or discomfort after the Essure procedure is expected and is reflected in the instructions for use and patient information booklet.

The only comparative study between bilateral tubal ligation and hysteroscopic sterilization reported no difference in pain rates post-procedure.

Analysis of the data reveal that improperly placed Essure inserts have been identified as a potential factor for persistent or chronic pain.

So let's turn to allergic reaction. The development of nickel hypersensitivity and/or allergic reaction is a consideration with a nickel-containing device in situ. However, as with all medical devices, the materials used in Essure are of medical-grade quality as opposed to the nickel contained in everyday items such as jewelry. Essure inserts are made of a super-elastic nitinol outer coil and a stainless steel inner coil wrapped in PET fibers. Since the

mid-'80s, nitinol has reliably been used for medical and dental applications, products such as vascular stents, heart valves, orthodontic archwires, all common nitinol applications. The nickel ions in nitinol are tightly bonded to titanium. The entire alloy surface is covered with a protective layer of titanium oxide. Both the bonding and the protective layer minimize nickel ion release.

In vitro testing of the Essure inserts found that the maximum leaching rate is approximately 0.14 µg/day. Now, this is far less than what is noted from other approved nitinol implantable devices, which can range from 0.42 to 8.4 µg/day. And all of these pale in comparison to the normal daily exposure from food and water, which can be up to 300 µg/day. Furthermore, all biocompatibility testing requirements were met.

Now, allergic reactions to nitinol are rare. Only 3 in more than 5,000 women in company-sponsored studies reported symptoms consistent with an allergic reaction. The peer-reviewed published literature contains few reports on nitinol allergic reactions in general or specifically regarding Essure. A large retrospective study in Spain of over 4,300 women revealed only two cases of allergic reaction to Essure, with a reported rate of 0.05%. And studies have also demonstrated that there's no correlation between skin-testing results and allergic reactions to Essure.

Postmarketing monitoring reports a reporting frequency of suspected allergies. It's approximately 0.06%. Fifteen percent of the reported cases in our database were test or specialist confirmed allergies.

In conclusion, the amount of nickel released from Essure is minimal, hypersensitivity is rare, and clinical trial and published literature support a rate of less than 0.1%.

Skin patch testing is not a reliable predictor of clinically significant reactions to nickel-containing implantable devices. But appropriate counseling is very important prior to implanting inserts.

Let's turn now to device removal. The Essure inserts are intended to be left in place. The instructions for use, however, has always provided guidance about when removal is appropriate and how to attempt removal. As with any device, the instructions for use are periodically updated. And recently more guidance on how removals should be performed was added based on published literature and case studies. Prospective clinical trials of removal techniques have not been done. Ultimately, it's the clinical judgment and surgical expertise that must be used by the -- must be used to guide physicians as the best approach for each unique or different patient situation.

This table is showing the data for removals for the Phase II, pivotal, which was up to 5-year follow-up, and the most recent TVU study. Removals were done via a number of techniques: laparoscopic salpingectomy, cornual resection, and hysterectomy. Most of the hysterectomies, however, were not related to Essure itself but done for other reasons such as bleeding or pain from other gynecologic pathologies or sources.

Most published literature on removal focuses on individual case reports, which correct the misperception that hysterectomy is the only effective way to remove Essure. The case reports show that the inserts can be successfully removed via hysteroscope if the removal is attempted up to 7 weeks post-placement. Cases also report successful removals via linear salpingostomy or salpingectomy either through the laparoscope or laparotomy. Laparoscopic salpingectomy has been described from 10 weeks up to 4 years post-

placement. Now, cornual resection can also be used to perform -- can also be performed, but the patient should be counseled about an increased risk of hysterectomy with this particular procedure. It's also important that the location of the insert is confirmed prior to any removal procedure in order to minimize the need for future surgical interventions.

From our postmarketing monitoring database, the principal reason for removal is unsatisfactory location. Bleeding disturbances and pain are also cited. And the reporting frequency is 0.11%.

So, in conclusion, data from clinical studies, literature, and postmarketing monitoring show that the need for Essure removal is infrequent. The method of removal will be different for each patient and will depend on the location of the insert, her symptoms, as well as any other pathologies such as fibroids, endometriosis, or adenomyosis.

Now, while the literature is somewhat limited on removal techniques and methods, it is clear that removals can be successfully accomplished without the need for hysterectomy in the majority of cases.

The specific technique and the instruments to be used must be guided by general gynecologic and surgical principles that gynecologists are expected to have. It is important that the physician involve the patient in the decision on what specific technique and what method is best for her, given her symptoms and other possible gynecologic pathologies.

It is well accepted that all medical procedures carry the risk of serious adverse events, including death. It is devastating for the family and devastating for the physician when this occurs. And we have a few deaths associated with the use of Essure through

reports since 1998.

Here is what is known about death in association with Essure. From the clinical trials, two deaths were reported. Both were unrelated to Essure. One was due to leukemia, and the other was due to a myocardial infarction post-bypass surgery. In the literature there are no reports associated of death with Essure placement.

In the postmarketing monitoring there are seven cases of death; however, none were directly caused by the inserts. There were three anesthetic complications, which included a case of a suspected air embolism during the placement procedure. There was one case each of cardiac arrest, sleep apnea, Group A strep, and a pulmonary embolism that occurred during a hysterectomy.

So, in conclusion, deaths specifically due to the inserts have not been reported, and the risk associated with the Essure procedure is low and is in line with laparoscopic tubal ligation fatality risks.

Pregnancy outcomes is the final topic of interest we will address this morning. Essure is effective and only a small number of pregnancies occur in these patients. There were four luteal phase pregnancies in the pivotal study, and this means that these pregnancies occurred or had begun before the Essure procedure was done. None of the pregnancies were continued. One woman who had a successful bilateral placement later decided to undergo in vitro fertilization with the Essure inserts in situ. The result was a healthy baby. There were also four pregnancies in the recent transvaginal ultrasound study. Two were terminated, and two had an early miscarriage.

There is limited reporting in the literature on the outcomes of unintended

pregnancies. Postmarketing analysis of the available data and information on pregnancy outcome reports that the reporting frequency of pre-term events, such as stillbirth and fetal anomalies, are within the expected ranges for women of the same average age group as Essure users.

But it may be more informative to look at outcomes of desired pregnancies with Essure in place, when it is used off label for the treatment of hydrosalpinx in a woman prior to an in vitro fertilization procedure. Because these are desired pregnancies, they are closely followed, and the outcomes are well documented.

We examined the published systematic review that identified 11 studies of 115 women using Essure before IVF for hydrosalpinx. There were 54 pregnancies. The pregnancy rate was 39% per embryo transfer. The live birth rate per embryo transfer was 29%. In a separate study, comparisons to salpingectomies in the same setting have shown comparable pregnancy rates and outcomes.

So, in conclusion, the data suggests no evidence that Essure increases the risk of adverse fetal outcomes.

So Essure research spans over a decade. We have data on over 10,000 women. That data affirms that the safety and efficacy of Essure is consistent across all data points, clinical trials, independent literature, and postmarketing surveillance. In addition, ongoing studies continue to follow over 3,000 women.

So, now to continue our presentation, Dr. Cindy Basinski will be speaking today about her and her patients' real-world experiences with Essure.

Dr. Basinski.

DR. BASINSKI: Madam Chair and Advisory Committee members, I would like to thank you for giving me the opportunity to speak today about my and my patients' real-world experiences with Essure.

For background information, I graduated from Purdue University with a biomedical engineering degree and obtained my medical degree from Indiana University. I completed a general surgery internship and completed an OB/GYN residency with a focus in urogynecology under the guidance of Drs. Tom Benson and Doug Hale. I am board certified in female pelvic medicine and reconstructive surgery. I have published articles in the fields of general surgery, urogynecology, and in-office gynecologic procedures.

I wish to disclose that I have been involved with consulting work for Bayer, in education and training of physicians, with a focus in the area of patient counseling. I have been compensated for my time and travel for this meeting, but I have no financial interest in Bayer.

A little bit about myself. I am a private practice physician practicing in a small community in Indiana since 1999. My community is built around manufacturers such as Toyota, Alcoa, GE, and Bristol-Myers, by whom many of my patients are employed and insured. I spend half of my time practicing urogynecology, caring for conditions such as incontinence and prolapse, and the other half of my time in minimally invasive gynecologic surgery, with a focus on in-office gynecologic services. I have been performing in-office procedures since 2006, including operative hysteroscopy, cystoscopy, endometrial ablation, and Essure. In the past 9 years, I have performed over 1100 Essure procedures. In 2006 there were very few physicians performing in-office procedural -- offering in-office

procedural options. With my gaining experience, it was the first time -- it was at that time that I was asked to share my personal knowledge about patient counseling, safe in-office pain control protocols, and procedural setup with other physicians, allied health personnel such as nurses and administrators, as well as residents and students.

In 2009 I was involved with the American Medical Association and the Centers for Medicare and Medicaid with coding and payment for in-office gynecologic procedures, as I believe these are important avenues for care of patients.

Since that time I have become deeply interested in clinical research. I have been involved in several pre- and postmarket FDA trials for in-office technologies. I am also an advocate for physicians creating personal databases with patient outcomes for the various procedures and treatments they provide. I also try to find time to report data in the literature to share personal experiences and patient outcomes when the data seems relevant.

In 2013, when I began hearing more concerns with Essure, I wanted to create a database of my first 1,024 patients and review outcomes with these patients. Some of the interesting data that was found in that review was that we had 1,732 women-years of follow-up, with an average follow-up of 1.7 years in a range of 0 to 8 years. We found a 94.4% intent-to-treat reliance right in our population. Nine patients experienced perforation, which represented 1.2% of my population, and that rate is consistent with the 1.8% rate seen in the clinical trials. We also noted that patients with a perforation -- no patient with a perforation requested removal or reported pain. There were six expulsions, which represented a 0.8% rate, which is also consistent with the clinical trial rate of 2.2%. I

had one patient request device removal due to pain. Her devices were removed at 3 weeks after placement with a laparoscopic procedure, and her pain resolved. No reports were documented of any allergic reactions or autoimmune symptoms in this population. We had two luteal phase pregnancies despite negative pregnancy test at the time of their procedures. Both patients resolved their pregnancies and went on to rely on Essure for the contraception.

Based on the data review in my practice, Essure outcomes were consistent with the data that was seen in the clinical trials and provided a good contraceptive option for my patients.

We need contraceptive options for our patients. Based on data from the CDC National Survey of Family Growth in 2010, 36% of women who did not want any more children were using temporary methods to prevent pregnancy, and astonishingly, 8% were using nothing at all. I was made acutely aware of this issue once I began offering Essure to my patients as an option.

I thought I was actually doing a pretty darn good job of talking to my patients about contraceptive care, and once I started talking to them, I realized many of them were not using anything, and I began to ask them why they weren't using anything. A lot of them said that they did not want to use hormonal products because those products cause them headaches, decreased sex drive, weight gain, and other reasons. And some women couldn't use hormonal medications because they had health problems that prohibited them from doing so. They knew tubal ligation was an option; they just didn't want it. They didn't want to have surgery; they didn't want to miss time away from their families. And so there was

no good option for them at that time.

So I began to talk to them about the Essure procedure, and many of my patients were very interested in this option. The idea that they could have a procedure in the office without anesthesia, incisions, or hormones and return to work the next day was ideal for a lot of my patients.

Since I've been performing Essure procedures for over 9 years with high patient success, I'm often asked what I feel contributes to optimal patient outcomes. When it comes to real-world use of the Essure devices, three components are essential for optimal patient outcomes. First is that physicians must be skilled to perform hysteroscopic procedures. Second, physicians must be knowledgeable about available data concerning Essure and its proper usage. Finally, physicians must be able to translate that knowledge to their patients to properly educate them about the Essure product.

But the most important overriding issue for optimal patient outcome is choice. And, in the case of permanent contraception, there are only two choices available right now. It is important to remember that while both laparoscopic and hysteroscopic procedures are considered overall safe and effective, there are very large differences between these approaches for permanent contraception that are meaningful to women.

Laparoscopy inherently involves specific risks that are often avoided with a hysteroscopic approach. When approaching a tubal ligation laparoscopically, incisions are required to be made in the abdominal wall, instruments inserted into the abdominal cavity, directly exposing internal abdominal content such as bowel, blood vessels, liver, and spleen to surgical instruments 100% of the time. In addition, all tubal ligation procedures

necessarily involve the destruction of the fallopian tubes, often with electrical energy sources that cannot only heat the fallopian tubes, but risk transfer of energy to surrounding organs. If electrical energy is not used, suture, metal clamps, or silastic bands can be used to clamp the tube, leaving foreign material in the abdomen. Furthermore, a laparoscopic procedure necessarily requires general anesthesia and an operating room.

A hysteroscopic approach uses the natural pathway of the vagina and cervix to enter into the uterine cavity, seldomly exposing instruments to the internal abdominal cavity. No energy is used when inserting the Essure devices, and no destruction of the fallopian tube is undertaken. An advantage of hysteroscopy is that it can be performed in a physician's office with no general anesthesia.

It is important to recognize that all tubal ligation procedures result in scarring of the fallopian tubes to create blockage and prevent pregnancy, whether it is laparoscopic or hysteroscopic. And foreign material such as suture, metal, or silicone can be left in the body even with laparoscopic procedures or other surgical procedures in medicine.

But we must keep in mind that optimal patient outcomes with either laparoscopic or hysteroscopic permanent contraception is premised on the underlying skills of the physician, and the value of good hysteroscopic skills is an important aspect of the Essure procedure.

Overall, hysteroscopic abilities are related to (1) basic hysteroscopic skills acquired in residency or other physician-to-physician training program; (2) how often operative hysteroscopic techniques are applied on a day-to-day basis in a physician's practice is significant, as we know that the more a physician uses a skill, the more likely they are to be

good at that skill and less likely they are to have complications; and if the physician seeks additional training to improve or increase operative skills.

In an effort to increase and improve operative hysteroscopic skills for physicians, many avenues of education have been created since the introduction of the Essure device in 2002. Tremendous effort has been focused on making Essure an integral part of residency education and procedural training for residents. In addition, if one partner of a group of physicians demonstrates sufficient hysteroscopic skills, often that physician will take the lead in helping his or her partners in better performing the hysteroscopic procedures.

Governing organizations within OB/GYN, like ACOG, AAGL, or SLS, have advanced hysteroscopic skills by offering workshops with hands-on training with known expert hysteroscopists. However, multiple private industry organizations have also partnered with each other and with governing organizations, like ACOG, to create additional learning opportunities.

Seminars have been offered by Conceptus, and now Bayer, in conjunction with hysteroscopy companies to provide educational programs. These programs offer physicians, who desire to learn more about hysteroscopy and the Essure procedure, the chance to work one-on-one with a very experienced hysteroscopic physician. Once a physician feels they have good hysteroscopic skills, they may choose to enter into the Bayer Clinical Pathway to perform the Essure procedure.

However, once a physician has gone through the Clinical Pathway, the opportunity for further education is provided. Peer-to-peer opportunities are available to physicians who seek additional proctor or consultative information. And I'm involved in the Bayer

consultancy network, and this is a new program that was developed over the past 6 months. Any physician who has a question in the United States regarding the Essure product can place a request to speak with a consultant like me. Once I receive the request, I will make contact with the physician within 24 hours. Some of the situations I may assist physicians to solve is offering advice on device removal or interpretation of HSG results or management of patients with complications.

The proctoring program offers physicians the opportunity to have a physician present for a procedure to receive hysteroscopic or Essure-related training to improve technique or patient outcomes. I personally have been involved with proctoring programs in which physicians, nurses, and office managers have actually come to my practice to learn about appropriate safety and relevant procedural-related issues to have a safe Essure procedure in the office.

I also use the proctoring program as an opportunity to educate physicians about patient counseling, for which I have a very strong belief is one of the most important aspects of patient care. I absolutely believe that physicians should not be telling patients what they need to do, but rather giving them accurate and up-to-date information about options available to them.

Once patients have good information, they can decide what is right for them. Contraception is a quality-of-life issue that is about choice. Whenever it comes to contraception, we should understand whether patients desire reversible options for which birth control pills, IUDs, injectables, or implantables may be most appropriate, or if they're interested in permanent options, for only which two options are available. That's

abdominal or laparoscopic approach or hysteroscopic approach.

If a patient chooses a hysteroscopic approach, it is very important, as a physician, that I provide them with reliable and accurate data. Many types of clinical information are available to physicians and patients that include prospective, retrospective, case report, and anecdotal evidence. It is important to be aware of all of these types of information, but clearly we know that scientific collection of information is important, and that when women make decisions, physicians need to present good scientific information to our patients.

In the case of Essure, there is this very good scientific data about the high efficacy and positive safety range of the procedure. The use of the FDA pre- and postmarket clinical trial data has been reviewed by experts in the FDA, stringently monitored by national organizations and risks properly adjudicated, and is the most important source of counseling that I use to help patients understand risks and benefits of the Essure procedure. However, there are hundreds of additional publications in the literature with over 10,000 patients in support of the FDA clinical trial experience.

The likelihood of a successful bilateral placement is 97%. But patients should be made aware that there is a 3% chance their procedure will not be completed. The need for confirmation testing is an important aspect of the procedure, and a patient must understand and agree to this. Risk and complications such as device perforation, expulsion, or patient patency should be explained. In fact, this is a time where I can reinforce the need of the confirmation test to make sure that they know this is the only time we can identify those types of events.

If a woman is using a hormonal medication to suppress pelvic pain or heavy

bleeding, women should be aware that cessation of these medications after any sterilization procedure may result in a recurrence or exacerbation of pain or bleeding once they stop their medication. Each patient has a very unique medical history, and physicians must be cognizant of factors that may make one approach suitable over another.

I also like to make sure that patients have an opportunity to actually touch an Essure device. I want them to put it in their hand, I want them to feel it, I want them to understand what's going into their body, and I want them to ask me questions. And I also talk to them about the other places that devices like this are used in the cardiac field and the orthopedic field and dental field so that they can ask questions about that, too.

True informed consent is a very active process for both physician and patients. I try to explain procedures using multiple modalities. I want to speak to you in words that you understand and make sure that you're hearing what I'm saying to you. I also want to make sure that I give you written information that's available so that you can understand the procedures that you're having. And I also draw pictures. I want you to see on a picture where an Essure device sits and what a perforation may look like if that would happen. And, finally, I want my patients to know that if a complication should happen, how I am going to help you take care of that.

While gynecologists understand the great difference in benefits and risks with laparoscopic and hysteroscopic approaches to permanent sterilization, the need for continued responsibility of industry, oversight agencies such as the FDA, and organized medicine to continually obtain data is recognized to be important by all of us in the healthcare community. Physicians should be vigilant to look for good and bad outcomes in

their patients. However, we still have to rely on good scientific data and information to counsel our patients and guide their decisions.

I certainly appreciate that not all women can have a good outcome with Essure, as is the case with any surgery or procedure. Proper and conscientious discussion of benefits and risks must be performed. However, for the over 1,000 patients in my practice relying on Essure, Essure has proven to be a valuable and desired contraceptive option.

Thank you.

DR. CARNEY: Madam Chair, members of the Committee, and guests, thank you for this opportunity to speak. My name is Dr. Patricia Carney, and I'm the Director of U.S. Medical Affairs, Women's Health, with Bayer HealthCare.

Prior to joining Bayer, I spent 17 years as a private practitioner and then as an academic physician. For several years I served as a residency program director, educating our future OB/GYN residents. And I had the honor of serving as an oral board examiner for the American Board of Obstetrics and Gynecology. One of my most important jobs as a physician, however, was patient counseling. Every procedure, device, drug, and decision in medicine carries both benefits and risks. Helping put this information in the proper context for patients is a vital part of the informed consent process.

When I was in practice and I needed to counsel a patient about a risk of a particular procedure, I would, of course, say the risk of something is one in however many. What I always told her, however, is that if she was the one, the risk was 100%. We know that an adverse outcome for an individual patient can be devastating, and this should never be minimized. Still, when looking at benefit-risk, we do need to understand the profile for all

women.

According to the ACOG practice bulletin on benefits and risks of sterilization, counseling should be comprehensive and include a discussion of technique, efficacy, safety, potential complications, and the alternatives to female sterilization. Benefit-risk must take into account not only the specific procedure under discussion, but also all alternative options to that procedure.

It is important to make sure patients understand the limitations of different data sources. Only after an appropriate discussion of benefit-risk, in context with alternative procedures, as well as the baseline risk for specific outcomes in the general population, can a patient make a truly informed decision. In addition to this overall analysis, the discussion should also include how particular risks can be mitigated should they occur.

Women should be counseled to utilize the most effective method of contraception they're willing to use. For women who are sure that they have completed their childbearing, this includes permanent birth control options. The decision not to use any contraception at all also carries risk, since pregnancy itself can be accompanied by serious and sometimes fatal outcomes. In addition, no method of contraception is 100% effective, and this includes permanent birth control methods.

Once a patient decides she's interested in a permanent birth control option, the specific procedure needs to be selected. There are many factors that may influence her choice. For Essure, the instructions for use outlines the requirements for this counseling process, part of which is shown here on the slide. As pointed out, the decision to undergo treatment is at patient discretion following physician counseling and informed consent.

Essure has a number of benefits. As Dr. Zampaglione described, both clinical trials and independently performed studies demonstrate high efficacy when Essure is placed properly and there is a satisfactory confirmation test. The procedure does not require general anesthesia. It can be performed in the office setting and does not require entry into the peritoneal cavity.

Patients also need to be aware that due to variations in anatomy or other issues such as difficulty with visualization of the tubal ostia, Essure may not be successfully placed in a small percentage of cases. Data from the clinical trials indicate that this occurs in approximately 3% to 4% of cases.

The Essure inserts contain nickel with a potential for allergic reaction. This information has always been in the instructions for use.

It is crucial that patients are made aware that compliance with 3 months of alternate contraception and the Essure confirmation test are essential for success of the procedure.

Patients also need to be aware that after the confirmation test, a small number of women, approximately 3%, will be told that Essure is not in the proper location and that they will not be able to rely on it for contraception. A plan needs to be in place as to what is the next step in assuring effective contraception for this woman.

Specific adverse events such as pain, perforation or other unsatisfactory location, menstrual changes may occur in a small number of women.

While highly effective, no method of contraception is 100%, and pregnancies have occurred in women with Essure.

As an alternative to Essure, laparoscopic tubal ligation is a safe and effective method

of permanent birth control.

While there are no head-to-head prospective clinical trials of Essure versus tubal ligation, extensive data exists for both procedures, including some comparative studies.

Once a bilateral tubal ligation is performed, the method is immediately effective, and there's no need for additional patient compliance. Occasionally, however, it is not technically possible to actually complete the surgical procedure, and an alternative method of contraception then needs to be used in this patient.

Laparoscopic tubal ligation, however, is not without risks, some of which can be very serious. Risks of laparoscopic tubal ligation include bowel injury, particularly at the time of Veress needle or trocar insertion. A recent systematic review by Llarena et al. in 2015 estimated that the risk of bowel injury specific to laparoscopic tubal ligation is 1 in 3,333 cases. Injury to the major blood vessels of the pelvis is rare but a potentially fatal event, with an estimated risk of approximately 1 in every 5,000 laparoscopic procedures.

While tubal ligation is very effective, the overall 5-year risk of pregnancy is 13 per 1,000, or 1.3%, when all types of laparoscopic sterilization methods are considered. Should pregnancy occur, the risk of ectopic pregnancy may be as high as 65% with some methods of tubal ligation, such as bipolar cautery. In addition, the procedure requires the use of general anesthesia, and complications with general anesthesia can occur.

Laparoscopic tubal ligation can be performed in a variety of ways. The Filshie Clip and Falope-Ring are two commonly used devices. The instructions for use for the Filshie Clip includes the information shown on the slide. As you can see, placement of these devices laparoscopically can result in pelvic pain, musculoskeletal pain, clip migration or

expulsion, and misapplication of the device.

Similar AEs are seen with Essure. In this table we see adverse events from the day of the placement procedure.

This table reflects the adverse events experienced by women during the first year of reliance, based on the pivotal trial.

Both of these tables are presented in the instructions for use for Essure.

In conclusion, all permanent birth control procedures carry risk. It is important to balance these risks with the benefits of the option under discussion, in addition to the risks and benefits of alternate procedures.

The efficacy and safety profile of Essure is well characterized and compares favorably to the benefit-risk profile of bilateral tubal ligation.

We at Bayer continue to work to mitigate the risks associated with Essure. This includes information in the instructions for use and the patient information booklet, educational materials such as patient and physician websites, well-constructed and updated physician training, patient counseling materials, and programs to support the needs of physicians and their patients.

Women deserve safe and effective options when it comes to permanent birth control. For the properly counseled patient, for the patient who meets the criteria outlined in the instructions for use, Essure is a good option. Hundreds of thousands of women have benefited from the availability of Essure. Our assessment concludes that the overall benefit-risk profile of Essure remains positive.

Thank you.

DR. IGLESIA: Thank you very much. I'd like to thank Bayer HealthCare for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during our Panel deliberation session this afternoon.

Introduce yourself.

DR. ELSER: Denise Elser.

My question is, based on your rates of long-term follow-up as far as perforation or other complications, is there any demarcation between the different forms of the device after changes were made?

DR. ZAMPAGLIONE: No, the pivotal and the Phase II studies used the STOP, the initial coil, and then the ESS205 was studied and then the 305. And what was seen really from the transvaginal ultrasound, there really is not a significant difference in the safety and efficacy that was noted. Those changes were very minor to the coils.

DR. IGLESIA: I actually do have a question. In terms of intent to treat, I just notice on your 1-year follow-up on the pivotal trial, your *n* initially was 558, and the 1-year follow-up was 441, and I was just wondering what attempts were made for the retention and any kind of follow-up on the 110 patients or so that were lost.

And then my second question is what comparison studies do we have right now, head to head, on permanent sterilization options, laparoscopic abdominal versus hysteroscopic?

DR. ZAMPAGLIONE: Sure. Let me answer the second part first. We do not have any

head-to-head or direct head-to-head studies with bilateral tubal ligation with a laparoscopic or laparotomy. There were some comparative studies that were shown during the presentation, but not true prospective head-to-head studies.

For the first part of your question, I'd like to call up Dr. Kimberly Rosen. She's our clinical development lead for Essure and will be able to answer that question.

MS. CHAUHAN: Cynthia Chauhan.

DR. IGLESIA: Let them answer this one.

MS. CHAUHAN: Oh, I'm sorry, I thought he was finished.

DR. ROSEN: Good morning. Kimberly Rosen, Bayer HealthCare. Thank you for the question.

Just to clarify, in the initial pivotal study, there were initially 518 women enrolled in the intent-to-treat population; 507 of those women had device placement attempts, and a total of 464 women had bilateral placement, I believe, is the number. So we would only have followed women who had at least one insert in place after the placement procedure was accomplished. Regardless of whether or not women were instructed to rely on their inserts for birth control, they were followed for safety in that study if they had at least one insert in place.

DR. IGLESIA: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Thank you.

When you were talking about unsatisfactory location, the percentage differences in Spain and Canada were quite significant, I thought. Can you comment on that?

DR. ZAMPAGLIONE: It is hard to comment on that one because these are outside of the U.S. and, you know, the training programs are essentially the same. There are, of course, going to be some country differences. The materials, everything used are the same. But it is very challenging to start trying to compare different countries just due to different practice patterns. But the same device, the same system is used worldwide.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

I have one question. Of your perforations, what percentage of the devices fractured versus intact in these situations?

DR. ZAMPAGLIONE: So let me bring up Dr. Kimberly Rosen again from our clinical development. She's in the best position to answer that question.

DR. ROSEN: Thank you.

So, in the pivotal and the Phase II study, we do have one report of a device being fractured during attempted removal hysteroscopically. The device was placed and then attempted to be removed through the hysteroscope, and that device fractured. The only other reports of device fracturing that were -- that come from those two studies are during surgery either for hysterectomy or device -- or completion of a sterilization procedure in women with a perforated or unsatisfactorily located device, where the device was transected during the surgery. During the TVU study, which is currently ongoing, we do not have any reports of the insert breaking.

DR. IGLESIA: Okay, we will now take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members

inside or outside of the audience. We will resume at -- Shanika?

MS. CRAIG: 9:41.

DR. IGLESIA: 9:41. Thank you.

(Off the record at 9:32 a.m.)

(On the record at 9:50 a.m.)

DR. IGLESIA: Okay, if everyone can please be seated, we'd like to get started. At this time you will hear a presentation by the FDA.

I'll remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA, you may begin.

DR. CORRADO: Good morning, Panel members and guests. Thank you for participating in this public meeting to discuss the Essure system for permanent birth control that was approved by FDA in 2002. I'm Julia Corrado, a medical officer and clinical reviewer from the Office of Device Evaluation, which reviews medical device submissions prior to marketing.

We have just heard from Bayer HealthCare, the Sponsor of Essure, and later today we will hear the experience of members of the public. At this time you will be hearing three publications from the FDA. I will present some milestones in female sterilization, a snapshot of premarket review and PMA approval of Essure, and an overview of the current clinical landscape for female sterilization --

DR. IGLESIA: We need microphone assistance.

(Pause.)

DR. CORRADO: Dr. Ron Yustein, Deputy Director of the Center for Devices and Radiological Health's Office of Surveillance and Biometrics, our postmarket review office, will provide a comprehensive review of safety outcomes data on Essure. Next, Allison O'Neill will present the epidemiology review of effectiveness data on Essure. We hope the FDA presentations will provide clarity and transparency regarding the FDA review processes for Essure. Later today, FDA will be posing multiple questions for the Panel members to discuss. We're looking forward to hearing your discussion and recommendations based on what you have heard today.

As discussed in the background section of FDA's Executive Summary for this meeting, we believe the first publication on tubal ligation appeared in 1881. After this date and prior to 1930, multiple authors contributed to literature on this topic, but we think that it is appropriate to highlight the first report describing Ralph Pomeroy's technique of tying off with resorbable suture and resecting a loop of fallopian tube. That appeared in 1930.

The early to mid-20th century was a period of technical innovation in laparoscopic surgery. What may be the first published account of minimally invasive laparoscopic tubal sterilization appeared in a Swiss journal in 1936; however, the actual technique is unclear. A more recent but still earlier report describing electrosurgical laparoscopic sterilization using unipolar current appeared in a French language journal in 1962. Bipolar current was introduced in the 1970s to prevent thermal injuries with unipolar current. Also in the 1970s and early 1980s, occlusive tubal implants were introduced. The Essure system was the first of two hysteroscopic sterilization systems that made it possible to achieve incision-free

female sterilization and without general anesthesia. Essure was approved in 2002. The availability of hysteroscopic sterilization in 2002 also transitioned female sterilization from the operating room to an office setting.

In summary, tubal ligation was largely a laparotomy procedure from the late 1800s until the 1960s, when innovation in laparoscopic instrumentation led to adoption of minimally invasive, that is laparoscopic, sterilization. Female sterilization was still confined to the OR for another 30 to 40 years before further innovation led to office-based hysteroscopic sterilization after 2002.

This slide, the title of which is Sterilization Utilization in U.S., is intended to provide again a high-level overview of numbers of sterilization procedures. Female sterilization is among the most commonly performed surgeries in the U.S. Our estimate of annual incidence on this slide is based on several references using data from the 2002 National Survey of Family Growth and ranged from approximately 640,000 to 700,000 annual procedures.

FDA does not regulate sterilization; however, FDA does have regulatory authority over medical devices used to perform these procedures. As I will discuss on the next slide, this authority is most relevant as it relates to devices used in radiofrequency electrosurgical sterilization, laparoscopic occlusive devices such as Hulka clips, Filshie Clips and bands, and Essure.

Regarding postpartum sterilizations that comprise about half of the 600,000 to 700,000 annual sterilizations, surgeons typically use manual surgical instruments such as scalpels, which are Class I devices. These instruments are not specifically indicated for

female sterilization; therefore, FDA does not regulate them for such intended uses. Manufacturers of these devices are required to register with FDA and declare their products conform to general controls, including manufacturing quality and labeling.

In contrast, FDA does review premarket submissions for Class II laparoscopic instruments and electrosurgical accessories under Class II. These devices require premarket notification through the 510(k) pathway in order for FDA to determine whether they are substantially equivalent to other legally marketed devices.

Class III devices such as laparoscopically placed clips and bands that are specifically indicated for tubal sterilization and hysteroscopic tubal occlusion systems require premarket approval through the PMA process. This means that sponsors of these devices cannot claim substantial equivalence to another device. Rather, the sponsors must provide reasonable assurance that the device is safe and effective for its intended use. The level of evidence to support PMA typically includes a pivotal clinical trial.

In the next several slides, I'm going to provide just a snapshot of the evidence for FDA's approval of the Essure PMA in 2002.

Both the Phase II and pivotal clinical trials were prospective, multi-center, international single-arm studies. The landmark CREST study provided a historical control against which to compare the effectiveness of Essure against multiple methods of surgical tubal ligation. The Essure pivotal trial enrolled subjects in such a way as to age-match Essure and CREST participants. Follow-up to at least 5 years following sterilization procedure was available for both the Essure and CREST studies.

Availability of CREST outcomes data led FDA to conclude that a concurrent control of

surgical tubal ligation was unnecessary to obtain "reasonable assurance of safety and effectiveness" of Essure as required under Section 513(a) of the Federal Food, Drug and Cosmetics Act. And I would note that a representative from the CDC made a presentation on the CREST study to the FDA Advisory Panel in 2002.

Outcomes from the Phase II and pivotal trials were pooled to provide contraceptive effectiveness data on 632 women at 1 year and 197 women at 2 years when the Sponsor and FDA presented the PMA to the Advisory Panel in 2002. A slightly higher number of subjects contributed to the safety outcomes review. This group included women, as we've heard earlier today, who had received at least one Essure insert but who were not relying on Essure for pregnancy prevention.

This slide is a summary of the safety data presented to the 2002 Advisory Panel. Additional data was also provided, but this slide does appear in the summary of safety and effectiveness for Essure. It can also be found in the appendix to the Executive Summary for today's meeting.

Included in this table are pain, headache, and change in bleeding. That will be discussed in detail along with other adverse events in Dr. Yustein's presentation. I'd like to add that at the time of the Essure Panel meeting in 2002, data on device perforation and expulsions that prevented reliance on Essure were also discussed.

As the Sponsor has already discussed, Essure is a sterilization method. Unlike tubal ligation, Essure is not a one-time procedure. There are three mandatory steps that must be completed before a patient may rely on Essure. These are insert placement, use of alternate contraception, and presenting for the Essure confirmation test. FDA's analysis of

Essure's effectiveness is based on the clinical trial participants who completed the three-step method. The prospective IDE study protocol for the pivotal trial specified that any pregnancy that occurred prior to completing all three steps would not be counted as Essure method failures. All product labeling, including patient labeling, is explicit regarding adherence to the three-step procedure.

This slide presents the number of participants in the Phase II and pivotal trials combined. Please note that the first number in these boxes refers to the Phase II study, and the second refers to the pivotal study. As you can see, 227 participants from the Phase II and 518 from the pivotal study underwent attempted bilateral insert placement. There were 81 participants who did not -- who were placement failures; 664 had successful bilateral placement. Of these, 643 underwent the confirmation test and were advised to rely on Essure; and of the 643, there were 1-year follow-up outcomes data on 632.

Reasons for the inability to rely on Essure included perforation, expulsion, and tubal patency. Table 4 in the Executive Summary provides numbers of study subjects who at least initially could not rely for the above reasons, although some subsequently may have been able to rely.

This slide provides the pregnancy outcomes, in the pink boxes off to the right, for the combined Phase II and pivotal trials. As the Sponsor noted, there were four pregnancies determined to have been conceived prior to the insert placement procedure based on early first trimester sonogram. There were no pregnancies at the 1-year anniversary of reliance on Essure. Two-year outcomes data at the time of the 2002 Panel meeting were available for 197 participants. There were no pregnancies among the subset of trial participants.

Based on the safety and effectiveness outcomes from the Phase II and pivotal trials, the result of the 2002 Panel meeting was as follows:

- The Panel found a favorable benefit-risk profile for Essure;
- They voted to recommend approval by a vote of eight recommending approval, zero recommending disapproval, and one abstention;
- Conditions of the approval, however, included continuation of the clinical trials out to 5-year follow-up following reliance on the device and a new study to evaluate placement rates in newly trained physicians.

In my last two slides I'm going to turn to the topic of the broader clinical landscape in which a patient considering permanent sterilization might find herself. To start with this slide, I'd like to present a high-level comparison of hysteroscopic sterilization with tubal ligation. Regarding adverse events, Dr. Yustein will be providing detailed outcomes data on Essure's safety after my presentation.

We presented the summary of safety outcomes following tubal sterilization in the Executive Summary, and we relied for that on an analysis by Jamieson et al. of approximately 9,500 participants in the CREST study. Six categories of outcomes were evaluated by Jamieson et al.

1. Unintended major surgery
2. Transfusion
3. Febrile morbidity
4. Life-threatening event
5. Rehospitalization

6. Death

No deaths were reported in this group.

The rate of women who experienced any of the above events -- and again, we're talking about tubal sterilization -- was 153 out of 9,475, or 1.6%. Independent predictors of any complication were diabetes mellitus, general anesthesia, prior abdominal or pelvic surgery, and obesity.

Regarding the other outcomes in this list, the comparative pregnancy risk at 1 and 5 years, as presented in the Essure patient brochure, is listed here, and FDA reviewed those numbers. The timing of effectiveness is a minimum of 3 months for Essure compared to immediate effectiveness of tubal ligation, again, the point being that these numbers reflect women who successfully completed the method, the three-step method, and were told to rely. The need for patient compliance is high for Essure relative to tubal ligation.

Regarding the actual procedure, Essure requires neither a skin incision nor general anesthesia and can be performed in the office as opposed to the operating room. Interval tubal ligation does require a skin incision and is performed under general anesthesia in the OR.

Here I'm departing somewhat from the narrow discussion of sterilization to include a comparison of Essure and long-acting reversible contraception, or LARC. As you know, LARC includes both non-hormonal (for example, the ParaGard copper IUD) and hormone released in products (for example, levonorgestrel-releasing intrauterine systems as well as etonogestrel-releasing subdermal implant). All are indicated for prevention of pregnancy, and one has an additional indication for treatment of heavy menstrual bleeding for women

who choose to use intrauterine contraception as their method of contraception. These LARCs provide pregnancy protection for 3 to 10 years.

The reason for including this slide is to acknowledge one of the findings from the CREST study, which was that cumulative risk of sterilization regret within 14 years following sterilization was 20% for women 30 years or younger versus 6% for women who were older than 30 at the time of sterilization. Women who are even slightly uncertain about their desire for sterilization may be offered LARC products. As with Essure, there are risks associated with LARC products, which are described in detail in approved labeling, that is, the prescribing information for these products.

The most commonly reported adverse events in the clinical trials of all four of the hormone-releasing products are acne, headache/migraine, abdominal discomfort or pain, and breast tenderness or pain. Abnormal bleeding is listed under the most commonly reported adverse events category for three of the four hormone-releasing LARC products.

Device expulsion or migration is listed as an adverse event in the labeling for all LARC products; however, this event is not listed among the most commonly reported adverse events for those products.

As you can see, pregnancy risk is similarly low for hysteroscopic and LARC methods. There are important contrasts between these types of contraception regarding the timing of effectiveness, the need for patient compliance, and the need for a skin incision.

To conclude, for women contemplating permanent birth control, the clinical landscape is complex. FDA attempts to address this complexity by providing detailed safety information in physician and patient labeling. It is impossible, however, to include every

single type of adverse event reported in clinical trials and device labeling.

As part of our total product lifecycle approach to medical device review, we are constantly reviewing new safety and effectiveness information and require revised labeling when it is warranted. For PMA products, we can require the sponsor to have FDA review every change they make to labeling, and FDA frequently proactively requests such changes.

We are looking forward to your deliberations this afternoon. I'll turn the podium over to Ron Yustein, who will discuss both premarket and postmarket safety outcomes data for Essure. And thank you for your attention.

DR. YUSTEIN: Good morning. Again, my name is Ron Yustein, and I will be presenting our safety review for the Essure device, and then Ms. O'Neill will present effectiveness results after that.

Before starting, I wanted to describe the sources of information considered in our review, which are shown here, as well as the topics we focused on. One source of data was the 5-year follow-up of the cohort from the PMA Phase II and pivotal studies, which Dr. Corrado just described. The follow-up was ordered as a condition of approval and both conducted as post-approval studies. Both were completed by the end of 2007.

This table provides the number and percentage of patients providing data at each follow-up in those studies, with the percentage based on the number of subjects who had received at least one implant. Both studies had slightly over 80% of subjects available at the 5-year follow-up.

In slides I will show related to these studies, for events of pain and bleeding, a rate at a given follow-up represents the percentage of patients who experienced that event

since the previous follow-up. As these do not provide information related to persistent symptoms, the Sponsor, for the pivotal cohort, also provided recurrent rates, which represent the percentage of subjects reporting the event at more than one visit, and persistent rates, which represent the percentage of subjects reporting the event at all visits through that follow-up.

The ESS305, Study 16974, which I will refer to as the transvaginal ultrasound or TVU study, is a prospective, single-arm, multi-center study being conducted under IDE regulations. The Sponsor designed this to support approval for a change to the confirmation protocol. The study is ongoing, and the most recent annual report includes 2- and up to 3-year data on subjects. In their report, the Sponsor cited rates of events based on the 597 women who underwent Essure placement procedures. However, as of the last annual report, 493 subjects remain enrolled and are being followed. I will provide results for this study alongside Phase II and pivotal study results, as they were all three IDE studies.

A review of the literature was performed through June 2015 using the search criteria noted on the slide. In addition, case reports and abstracts were also reviewed for the specified adverse outcomes discussed today. There were significant limitations to the literature, and these will be discussed during our presentation.

The Sponsor already described their SUCCES II study. Although this is a large prospective study, it is being conducted entirely outside the United States and is not under IDE. In addition, it is worth noting, as the Sponsor noted, that although interim data are available on over 2,200 patients at 3 months and 1,200 patients at 2 years, beyond the 3-month visit, the follow-up questionnaire did not include any systematic data collection for

safety endpoints. Rather, unsolicited adverse events were captured in a free field section of the case report form.

We also reviewed the medical device reports submitted to FDA through May 2015. Although MDRs are a valuable source of information to monitor a device's performance under real-world use conditions, they represent a passive surveillance system and, as such, have important limitations. Numbers can be difficult to interpret as events may be underreported, or their numbers can be impacted by a change in the number of uses of the device, a recent regulatory action, or public attention. Unfortunately, MDRs often lack critical or complete information related to the patient, event, or outcomes. They cannot be used to calculate rates of events and often cannot be used to prove the device caused or worsened an event.

This graph depicts the number of Essure MDRs by year. A spike began in late 2013, and the majority of those were voluntary, seen in green, not manufacturer reports. It is important to note that the year listed is that in which the report was received, not the year of the event. Many reports submitted since late 2013 describe events that occurred in earlier years.

FDA also has received information related to the device from other sources, including communications with patient groups, pilot evaluations of social media sites, inspections of manufacturing sites, and information from global regulatory partners. Some of these are included in more detail in our memo but, because of the amount of data to present, will not specifically be presented this morning.

I also wanted to introduce the specific safety topics that are included in our review.

Taking a step back, this table was produced based on events listed by Essure patients on websites or in MDRs. We are not suggesting causality with the device in each of these. We are simply presenting the types of events publicly cited or within MDR reports.

FDA primarily reviewed events which were most commonly discussed, which appear to have significant impact on a patient's well-being and for which scientific data was likely available. This is not to downplay any of the other events reported, but we recognized a need to focus our review on a subset of those issues noted on the previous slide.

We tailored our safety review to chronic or persistent abdominal pain or cramping, bleeding irregularities, headache, metal allergy, perforation, migration, and device removal. Pregnancy issues will be discussed by Ms. O'Neill a little later. Many of these events are known complications and are already included in Essure labeling. Due to time constraints this morning and the amount of information to be provided, our presentation will provide overviews, and we refer you to our memo for more details.

All right. I will start off with post-procedural abdominal and pelvic pain or cramps. Although procedural pain is a well-known event, it typically resolves within hours or days. However, reports suggest that some patients experience more persistent pain events. One difficulty in assessing abdominal pain is the fact that it is a common symptom and, although may be due to the device, may also be the result of unrelated processes involving the digestive, genitourinary, reproductive, musculoskeletal, and/or nervous systems.

This slide presents data from the IDE studies. The results from the time of PMA approval are on top. The bottom represents data from their 5-year follow-up as well as the ongoing TVU study. The percentage of patients noting pain at the latest follow-up generally

ranges from 1% to 5%, consistent with the data at the time of approval. However, for the Phase II and pivotal studies, these are rates at the 5-year visit and only capture events occurring since that previous visit. They do not speak to rates at prior visits or the chronicity of symptoms for a given subject.

The graphs on the next several slides depict the rates of pain events in the pivotal cohort at each follow-up. This first graph represents general pelvic pain, suggesting rates of 3% to 6% at each visit during the first 18 months and lower subsequently. For dysmenorrhea, rates at each follow-up point also generally remained in the 3% to 5% range after the initial 3 months, and for dyspareunia, again, generally less than 3% to 4% at each visit following the 3-month follow-up.

The Sponsor presented this data which shows that, per their definitions, approximately 4% to 6% of pivotal trial subjects experienced recurrent pain during follow-up, and only one subject reported persistent pelvic pain, which lasted through 2 years. Again, the percentage of subjects providing data at each visit should be taken into account when evaluating the rates for pain, as persistent pain may have been a reason for patients exiting from the study with time.

Next, turning to the literature. Post-procedural chronic or persistent pain has not been a common outcome reported in the literature, and this slide captures the publications from our memo. Since they are described more there, I wanted to just make a few points.

The Sponsor noted the Conover paper in their presentation. However, the rates, although low, may be difficult to interpret. In addition to potential issues related to coding, women with only on pelvic pain diagnosis or women who had prescribed non-opioids or no

medications for their pain would not have been captured. On the other hand, the study assumes that opioids were for pelvic pain, and some women may have been included incorrectly. Furthermore, the hysteroscopic group included patients who had undergone the Adiana procedure as well as the Essure procedure.

The Yunker publication, which was a retrospective review, noted a 4.2% rate for chronic pain, which was defined as pain persisting for more than 3 months after insertion. The authors also identified preexisting chronic pain conditions as a risk factor for chronic abdominal or pelvic pain after Essure. This is particularly notable because the IDE studies, which we already discussed, and possibly others excluded such patients.

The two large cohort studies by Arjona-Berral and Povedano cite low rates of persistent pain; however, both represent retrospective reviews from the same institution. In addition, Arjona-Berral reported on patients who did not respond to standard analgesics and who underwent device removal. We do not know how many others in their cohort had persistent pain that did respond to analgesics and/or did not undergo device removal.

Sakinci cited a zero rate at a mean of 83 months. But this was a small study and relied on telephone interviews years later.

Sinha and Duffy reported higher rates. However, both studies were relatively small and only reported findings out to 3 months. In both, it is difficult to determine whether the pain reported was persistent pain and/or whether procedural pain was included. Furthermore, the Duffy study had follow-up data on only 35 of 48 implanted subjects.

With respect to the high rate in the SUCCES II trial at 3 months, this represents all possible pain events and does not speak to the type, timing, or duration of the pain.

This next slide is busy but is intended just to present a higher-level picture of certain aspects of the study designs with respect to prospective or retrospective, single site or multi-site, and length of follow-up (more or less than 3 months). The IDE studies are on top and separated from the literature and SUCCES II studies by a double line. Outside of the IDE studies, there are a limited number of prospective studies, and they are mainly small, single center, and with limited 3-month follow-up.

Interpreting data related to persistent pain within the literature is made more difficult by other uncertainties or inconsistencies, including the definitions of chronic or persistent in terms of duration, the timing of onset of the pain, how and when the pain was assessed and using what scales, and what types of pain were included or not. For example, some reports may have included procedural pain in the rates and others may not. Some may have included cyclical or intermittent pain such as cramping, dysmenorrhea, or dyspareunia in their definition and others may not have. Many times, the studies did not provide that level of information.

FDA referenced several case reports in our memo which note persistent pain following Essure placement. Although many cited onset of pain at the time of the procedure, there were reports where the patient was asymptomatic following placement and developed pain weeks or even months later. Their duration of pain varied as patients sought attention at various times. Some authors noted difficulties during or immediately after insertion, including malposition or perforation, but others did not.

The case reports frequently noted device removal due in part to the pain. This was done either hysteroscopically or by laparoscopic salpingectomy and sometimes out several

years after insertion. When outcomes for pain following removal were provided, many noted improvement or resolution, sometimes within a short period of time. However, other cases noted only partial resolution, unchanged symptoms, or even worsening of pain.

In the MDRs, pain is the most commonly reported symptom. Over 3,500 reports are coded with at least one item related to pain. Like the case reports, specific details were limited and, when provided, showed considerable variability in terms of onset, duration, and patterns, including whether the pain was constant or intermittent; 341 of the 452 MDRs we have, which note women undergoing device removal, cite at least one pain-related complaint, although it is difficult to know whether the pain was the primary reason for removal. Of those 341 subjects, 135 reported resolution of pain after removal. However, many of the other reports did not provide sufficient information either way, and the actual number may be higher.

In summary, abdominal or pelvic pain, including cramping, were the most common events reported in MDRs. Various types of pain generally appeared at rates of 2% to 5% at follow-up points in the IDE studies. In the pivotal study, recurrent pain occurred in approximately 5%, whereas persistent pain, at least by the Sponsor's definition, was noted in one patient. It is important to keep in mind that patients with chronic pain syndromes, a potential risk factor for post-placement pain, were excluded from enrollment in the IDE studies.

There is limited literature regarding persistent pain following Essure. Several publications reported rates of less than 1%, although one quoted a rate of 4.2%. Many of these studies were retrospective. Limited data were often available in these studies

regarding pain characteristics and associated findings or causes. In addition, issues related to case definitions add to the difficulty in interpreting the data. Multiple individual case reports and reports submitted to FDA suggest persistent pain sometimes lasting months or years and, when the information was provided, often resolving with device removal. However, information from case reports and MDRs cannot be used to calculate rates.

I'd now like to move on to a discussion of vaginal bleeding following Essure placement. In the original PMA, women were asked to assess bleeding patterns compared to usual menses, and changes were reported in 1% to 2% of subjects. At the 5-year follow-up, particularly in the pivotal cohort, higher rates were reported. However, higher rates included heavier flow as well as lighter flow. Rates in the TVU study had been lower. However, no data is being systematically collected asking women to compare bleeding patterns to their usual menses in that study. For all three IDE studies, no control cohorts were included, and as such, it is not possible to gauge what changes may have been part of natural history. In addition, we do not have information related to the use or discontinuation of use of hormonal therapy, which might impact bleeding characteristics.

The graph on this slide shows the rates provided by the manufacturer for several bleeding patterns at each follow-up in the pivotal study. At each visit, approximately 20% of women noted heavier flow when compared to usual menses, 10% to 15% noted lighter flow, 5% to 10% irregular menses, and 5% to 10%, intermenstrual bleeding.

The Sponsor provided information from the pivotal study related to recurrent and persistent symptoms. Between 15% and 38% of subjects experienced recurrent irregular bleeding symptoms, but again, this included lighter as well as heavier flow. And 1.5% of the

pivotal study subjects reported persistent heavier flow at 1 year, and that percentage declined over the study. In addition, less than 1% of subjects had persistent irregular bleeding and/or intermenstrual bleeding throughout the study.

This slide captures our references. And, again, I'm just going to raise a couple of points. The Chudnoff paper represents the 5-year pivotal study, which we discussed on previous slides. Several other studies show similar event rates and also show increases in lighter bleeding.

Mino reported no changes in 857 women who were surveyed. The method of survey was not clear, but it appears to have been done at 3 months. And some, if not many, patients may have still been taking contraceptives at that time.

The citation for Levie is an abstract describing a retrospective cohort of 193 women with Essure and 139 who underwent surgical tubal ligation over a 7-year period at one U.S. site. Although details on this study, including length of follow-up, were not provided, irregular cycles were reported in 30% of Essure patients and 28% of tubal ligation subjects. And menorrhagia was reported in 36% and 46%, respectively.

In the SUCCES II trial, the percentage represents all possible bleeding events and does not speak to the timing, duration, or characteristics of the event.

Here I am again presenting a similar chart as before for pain. And, again, studies on bleeding outside of the IDE cohorts, which includes the Chudnoff paper, tended to either be retrospective single-site reports or short-term, relatively small prospective studies.

Symptoms related to vaginal bleeding were reported in almost 1,600 MDRs and included prolonged, frequent, and/or heavy menstrual bleeding, irregular bleeding,

intermenstrual bleeding or spotting, less frequent or severe bleeding, as well as amenorrhea. However, heavier menses were noted in about half of the MDRs. The reports tended not to provide information related to past bleeding patterns or hormonal therapy use, although some specifically note being placed on hormonal therapy by their physician to address the symptoms. Some others also noted undergoing endometrial ablation or even hysterectomy to resolve or address their symptoms.

Summing up. Although rates of reported bleeding changes were relatively low in the Phase II and pivotal studies at the time of initial PMA submission and in the TVU study, follow-up of the pivotal cohort showed higher rates with time and about one-third of subjects reporting recurrent symptoms.

Few publications have specifically addressed the issue of changes in bleeding patterns, although those that did reported rates similar to the 5-year pivotal cohort.

The lack of control groups in the IDE and literature studies makes the assessment of cause and effect more difficult.

Numerous MDRs describe varying bleeding symptoms, with slightly over half describing heavier flow.

Most of the data reviewed, regardless of source, did not provide information on hormonal therapy use or menopausal status.

Turning now to headaches, which was one of the more commonly reported symptoms in MDRs, like abdominal pain, this is particularly difficult to assess as headaches are a very common symptom in the general population and in women in particular. As seen in this slide, headaches which were deemed to be possibly associated with the device or

procedure have been reported in about 1% to 5% of subjects in the IDE studies, although the criteria used to make that distinction is not known. However, without a control group for such a common symptom, it is difficult to know whether the rate of headaches is higher than in patients without the device.

Literature related to headaches is limited. Yunker's publication found that women with previous diagnoses of chronic pain, including headaches, were at increased risk for persistent abdominal pain but did not report on the rates of headaches postoperatively. Others were essentially case reports at early time points.

Approximately 1,400 MDRs list the presence of headache, including migraines, as a symptom. However, as headaches were often one of several symptoms noted in a given report, additional details were often limited. When information was provided, their frequency of headaches varied considerably from constant every day to monthly or just occasionally. Reports did not typically provide information related to prior headache history or information regarding evaluation and treatment specific to the headache, although a handful of reports did note improvement in headache symptoms after device removal.

I'm going to switch now to allergic or hypersensitivity reactions reported in association with the Essure device. This is a topic which has emerged in the patient community because portions of the Essure inserts are made of a nickel-titanium alloy called nitinol, a material with significant history of use in implantable medical devices, including endovascular implants. As noted in our memo and summarized in the table on this slide, the Essure device itself has been evaluated in terms of nickel leaching, and the release rate

has been found to be comparable to or lower than that of selected cardiovascular nitinol devices.

It is important to point out that cutaneous nickel allergy is common, and up to 25% of women may be affected. We traditionally associate this with a contact dermatitis after skin exposure. However, a systemic contact dermatitis after exposure through other routes may also occur, and some authors have described systemic signs and symptoms, including chest pain, migraines, and respiratory issues, among others. These very potential clinical manifestations make the assessment of a reaction challenging as they can be common symptoms with a variety of causes. The exact mechanism of hypersensitivity reaction to implanted metal devices is not known, and there's no reliable method to identify individuals at risk, although patch testing is sometimes cited in the literature. But since nickel allergy is so common and nickel is present in many products and foods, a positive patch test may be difficult to interpret.

No cases of nickel allergy were specifically diagnosed in the pivotal and Phase II trials, although several dermatological events were reported. In the TVU study, there has been one patient with a metal allergy, although it was mild and resolved without treatment. Several other patients had dermatological events, although no formal diagnosis of an allergic reaction was made.

This slide summarizes literature related to metal reactions. The first two listed were actually reviews of other data sources, including MDRs. However, for both, it is unclear what criteria or set of symptoms each author used to define a hypersensitivity reaction. The remaining two studies, also both reporting very low rates, were both single-site,

retrospective reviews, and again, we are uncertain as to how the diagnosis of allergic reaction was sought or made. In the SUCCES II trial, two subjects have experienced allergic reaction to date.

This table lists four case reports from the literature which describe women who developed dermatological signs from 3 days to 3 months following Essure insertion, three site-positive nickel patch testing after the onset of symptoms, and three note that the patient was at least partly unresponsive to steroids. All four reports note that the patient had the devices removed, with resolution of dermatological symptoms sometimes as soon as 36 hours after removal.

Turning to MDRs, as I noted before, the signs and symptoms which are presumed to constitute an allergic reaction may vary by author or reporter. This makes the classification of MDRs for this event difficult.

For our review, all reports which specifically stated that the patient had an allergic or hypersensitivity reaction with reference to a metal were included, as were reports that mentioned skin manifestations. This is regardless of what symptoms were considered by the reporter to represent the reaction and regardless of any formal evaluation or diagnosis. This resulted in a total of 878 MDRs.

Again, as this was usually one of several issues being noted in a given report, details were often limited. When cited, there was variability in time to onset of symptoms, although some stated it began within hours of insertion. Few provided information regarding formal evaluations, how events were managed clinically, and whether they responded to medical therapy.

The clinical symptoms presumed related to an allergic reaction varied considerably in the reports. And although dermatological signs such as rash or itching were present in some reports, many instead describe systemic symptoms, including pain, headaches, and bleeding. Of the 878 MDRs, 212 describe device removal, although it is not possible to know what degree the allergic symptoms played in that decision. The status of symptoms following removal was provided in 117 of those reports, and all of them noted symptom improvement or resolution following removal.

So with respect to allergic and hypersensitivity reactions, although cutaneous nickel allergy is known to affect a substantial percentage of women, what constitutes a reaction to a metallic medical implant and how to diagnose or predict it is not well defined. Keeping this in mind, the prospective IDE studies have reported few specific metal allergy reactions. Few studies in the peer review literature have addressed this symptom complex, and although they typically cited rates of less than 1%, the data was obtained from retrospective reviews at single sites or was based on MDR or complaint numbers. It is also not clear how an allergic reaction was defined.

A handful of case reports have noted individuals with dermatological manifestations, positive patch testing, and resolution with device removal, suggesting a device-related reaction in those cases. Numerous MDRs cite allergic reactions to the device, including some noting resolution of symptoms with device removal. However, the limited information provided and the variety of symptoms reported to represent the reaction in many can make their interpretation related to cause and effect challenging.

Moving on to insert uterine or fallopian tube perforation during or after Essure

placement, this is a known but potentially significant complication and therefore included in our review.

In the 5-year reports for the Phase II and pivotal studies, uterine or fallopian tube perforation was reported at rates of 3.4% and 1.1%, respectively, with all but one having been noted at the time of the original PMA submission. In the Phase II study, which had the higher rate, five of seven perforations were associated with the use of a support catheter, which is no longer part of the Essure system. In the TVU study, three perforation events have been reported in two subjects to date, both presenting following an unintended pregnancy approximately 1 to 1.5 years after placement.

Due to the number of citations, this slide is busy, but again, the IDE studies appear above the double line, and our cited publications in our memo are below the double line. Many of the literature studies cited rates of perforation at or below 1%. This included several prospective cohorts, although they tended to be single-site experience and often had limited 3-month follow-up. It is also not known if and how perforations were systematically sought in these studies. The highest reported rate of 3.6% was from one of the retrospective studies. To date, in the SUCCES II studies, 30 events have been reported in the combined migration and perforation category, but at this time we can't specifically cite the number of perforations.

FDA cited several case reports or series describing perforations in our memo. The diagnosis of a perforation may have been made any time during or after insertion, with some being made years after the procedure. In some of these cases, patients may have been asymptomatic during some or all of that time. Multiple reports note perforation even

after a prior uncomplicated procedure or even after a confirmation test showing successful placement and occlusion.

Patient presentation at diagnosis usually manifested in one of a few ways, new or persistent abdominal or pelvic pain, asymptomatic women but found after -- a perforation found after evaluation for patent tubes during confirmation, or evaluation of patent tubes following an unintended pregnancy. Some of the cases were associated with intraperitoneal migration or bowel injury, which I will discuss in subsequent sections.

Approximately 300 MDRs describe Essure perforation events, with 90% being diagnosed after the insert procedure. Perforations were diagnosed based on similar presentations noted for the case reports. Although the majority involved perforation of the uterus or fallopian tubes, several described perforation of other organs. This includes five reports in which the reporter alleges that an insert may have perforated the amniotic sac of a pregnant woman, and 12 MDRs which describe bowel perforation, which again I'll comment on in a minute.

In summary, although the Phase II study noted a perforation rate of 3.4%, the pivotal and TVU studies have seen rates of 1% or less. A mix of studies in the literature also cite rates less than 4% and generally closer to 1%.

Numerous case reports and MDRs describe perforations, some diagnosed at insertion but many diagnosed later. Some perforations have been noted in women despite an uneventful insert procedure and even after successful bilateral occlusion assessment. Although some women with perforation present with abdominal or pelvic pain, others are diagnosed only after evaluation of a patent tube, typically when asymptomatic at

confirmation testing or after an unintended pregnancy.

An important set of points to keep in mind is that pain is not always indicative of a perforation. Some perforations may be asymptomatic, and some patients, symptomatic or not, may not undergo laparoscopic evaluation. As such, it may be difficult to detect or confirm a perforation on clinical grounds, and this may, in turn, affect the reporting and calculation of event rates.

I'm going to move to intraperitoneal insert migration, which we attempted to define and evaluate as an issue distinct from proximal tube migration or from expulsion into the uterine cavity, which is a well-described event following the Essure procedure.

In the Phase II study, six cases were reported where at least a portion of the insert was found to be intraperitoneal. However, in only three of these cases were the inserts located entirely within the peritoneal space. In the TVU study, two events of insert migration into the peritoneal cavity have been noted to date.

This next slide summarizes our literature citations with respect to intraperitoneal migration. As with perforations, studies generally reported rates near or below 1%. However, it was not always possible to know whether the definition of migration included cases of proximal tubal migration or vaginal expulsion in addition to intraperitoneal migration. In many of these studies, the migration was noted during confirmation testing, and at least one was associated with unintended pregnancy. The exact location of insert migration was not typically provided.

Most of the publications cited in our review were retrospective single-site cohorts, and prospective studies outside the IDE trials were generally limited to 3 months of follow-

up. Several individual case reports note intraperitoneal migration of an insert or insert fragment. Migration tended to be noted in asymptomatic patients at the time of the confirmation test, although some were also associated with bowel injury and GI symptoms. Although migration is largely felt to be a follow-on to insert perforation, in some cases authors specifically noted that no perforation was present at laparoscopic evaluation, raising the possibility, among others, that the device may have migrated distally.

A few of the reports described local complications or findings at the time of laparoscopy, including bowel perforation or obstruction, adhesions, and inflammation, although the relationship to the device was not always clear. In many reports, the inserts were removed laparoscopically without complications, although in some, intraoperative fluoroscopy was required to locate the insert or fragment. Some surgeons, however, elected to leave the inserts in place if the patient was asymptomatic.

In terms of MDRs, FDA has received 227 reports related to insert migration. About half simply note the abdominal or pelvic cavity as the location, and 25% report migration to or around parts of the bowel. It is possible that some of the remaining reports that describe migration may actually represent expulsion. In cases where the device migrated to or around the bowel, the patient may have presented with signs or symptoms of bowel perforation or bowel obstruction, although this was not in the majority. At least one report noted a surgical ileocecectomy because of a bowel perforation. This case may overlap with one of the literature case reports.

It should also be noted that MDR requirements do not mandate the reporting of an insert migration in which the patient is asymptomatic. Hence, the manufacturer may have

additional reports of migration which are not in the MDR database.

Summarizing intraperitoneal migration, limited numbers of cases have been reported in IDE studies in the literature. However, many of the literature publications were retrospective data collections not necessarily focused on migrations. On the other hand, some may have included cases of proximal migration or expulsion in their definition.

Case reports suggest that intraperitoneal migrations are often asymptomatic and found at routine imaging or during evaluation of suspected patent fallopian tubes. Many describe laparoscopic procedures to remove the migrated device with or without fluoroscopy, although some authors elected to leave asymptomatic migrations alone.

Two hundred and twenty-seven cases of migration have been seen in the MDRs, although it is not certain that all represent intraperitoneal migration. Information regarding these MDR cases were similar in nature to the case reports.

Although migrated inserts may be easier to detect on routine imaging studies than a perforated insert, since they may be asymptomatic, the diagnosis of the event may be delayed or perhaps missed, similar to perforation events.

I wanted to briefly summarize the information regarding reports of bowel injury related to Essure perforation and/or migration. There are three recent case reports which cite small bowel obstruction, perforation, or both, as shown on this slide. All three were diagnosed within a month of placement, and all presented with pain, nausea, and vomiting. Two patients required bowel resection. In addition, FDA has received 12 MDRs citing bowel perforation in association with the Essure device, two of which also report obstruction. Two of the 12 reports describe the need for ileocecectomy, but many represent -- but may

represent the same event reported by two different sources and may overlap with the case reports.

Moving on to device removal, although Essure is intended to be a permanently implanted device, we have seen and heard multiple reports of women seeking or undergoing surgical procedures in order to have the devices removed. As such, we thought this was an important topic to include, and one of our questions to the Panel later today specifically focuses on insert removal.

During the premarket studies, there were five cases of insert removal, as shown on this slide. At the 5-year follow-up, 5.8% of women in the Phase II and 4.2% of women in the pivotal trial had undergone device removal. Our number for the Phase II is different than that presented by the Sponsor earlier as we also included one case of hysteroscopic removal. Removals were largely performed laparoscopically or by hysterectomy, and pain or bleeding were the common issues noted. In the TVU study, 2% of women have had their devices removed to date. Again, pain and bleeding had been the most common clinical scenarios. And for over 63% of the subjects, symptoms resolved after removal.

In terms of literature regarding device removal, the recent Chudnoff report provided additional details on the 15 women who underwent hysterectomy in the 5-year pivotal cohort. The principal reasons included menorrhagia, pain, and dysmenorrhea, although the author stated that only two hysterectomies were due to the Essure device. How that determination was made is not provided.

As we mentioned previously, the Arjona-Berral paper focused on women who sought removal for persistent pain. It did not specifically mention whether additional women in

their cohort had removals for other reasons. But this study did note improvement in symptoms in the seven subjects who were included.

In the SUCCES II study, to date, at least 56 subjects have undergone removal by hysterectomy or laparoscopic tubal surgery to date.

Multiple case reports note insert removal, which we have alluded to in prior sections. Many of these describe laparoscopic removal, including procedures more than 4 years after implantation. Several others noted successful hysteroscopic removal even out beyond 3 months. The more commonly cited reasons for removal were persistent pain and abnormal bleeding, although inserts were also removed following diagnoses of perforation or migration and also at the time of surgical tubal ligation. When outcomes were cited, many noted improvement or resolution of the main complaints. Although many of the reports note no complications associated with the removal procedure, others have noted device fragmentation or difficulty in locating inserts or insert fragments without the use of fluoroscopy.

As I mentioned earlier, FDA has received 452 MDRs describing Essure device removal. These include hysteroscopic and laparoscopic removal, but almost 60% report hysterectomy. Reasons for removal are similar to those mentioned in previous slides but also include presumed allergic reaction, adenomyosis, and prolapse. Only 196 of the 452 MDRs provide additional information on the outcome of symptoms following removal. Of those, about 90% state that the symptoms attributed to Essure either resolved or significantly improved, many times soon after surgery. This includes reports of multiple symptoms resolving, including pain, headache, fatigue, rate changes, and many others.

Conversely, 20 of the 452 reports specifically noted that the pain -- the symptoms did not improve or resolve. Most of those 20 still reported pain.

Summing up device removals, follow-up of subjects in the IDE cohort show rates of approximately 2% to 6%. In the IDE studies as well as case reports and MDRs, common clinical scenarios associated with device removal were abdominal or pelvic pain, vaginal bleeding, perforation, and/or migration. However, in all sources of data, some women underwent removal, and particularly by hysterectomy, for reasons which also included endometriosis, adenomyosis, prolapse, and fibroids, which certainly may have been unrelated to the device. Literature reports tended to note removal via hysteroscopy or laparoscopy, whereas MDRs tended to report removal by hysterectomy.

Regardless of the methodology and the source of information, when symptoms outcomes were reported following removal, many reported significant improvement or resolution.

Finally, I'm going to describe the deaths which have been reported in association with or following Essure placement. As the Sponsor mentioned, two deaths have been reported for subjects in the IDE studies, and they described those. Prior to June 1st, 2015, FDA had received 11 MDRs which described a patient death, although limited information in these makes an assessment of causality difficult in some.

Five reports describe fetal death, which the reporter presumed was due to Essure coils perforating the amniotic sac. We are uncertain if there is duplicative reporting among these cases, and no additional clinical information was provided to assist in the determination of cause and effect.

The remaining six reports describe four unique events: one woman with Group A streptococcal infection 2 days following implant; one woman experiencing cardiopulmonary arrest during insertion, whose autopsy revealed a probable paradoxical air embolism and patent foramen ovale; a woman who died from a pulmonary embolism 13 days after hysterectomy to remove the implants; and one woman who committed suicide, although no additional data was provided.

With that, I would like to introduce Ms. Allison O'Neill from the Office of Surveillance and Biometrics, Division of Epidemiology, who will be presenting some of the effectiveness data that was included in our review memo.

MS. O'NEILL: Good morning. My name is Allison O'Neill. I am an epidemiologist in the Office of Surveillance and Biometrics.

Today I'm going to present a brief summary of the results of FDA's literature review and MDR analysis regarding effectiveness and procedural outcomes. First, I will talk briefly about the Essure procedure in terms of timing and follow-up. Second, I will present a summary of the literature on Essure placement rates. Third, I will present literature and MDR results regarding unintended pregnancy after Essure placement. Fourth, I will present a summary of the literature on patient satisfaction with the Essure device and procedure. And, finally, I will summarize the strengths and limitations of the reviewed literature.

Before I present the results of the FDA literature review, I'd like to highlight a point previously made by Dr. Corrado. Essure is unlike bilateral tubal ligation in that it is a multiple-step method requiring patient compliance with a confirmation test 3 months post-placement. During the 3-month period, the patient is counseled to use alternate

contraception. Therefore, there are three types of unintended pregnancies that may occur after Essure placement. Luteal phase pregnancies refer to pregnancies that have already occurred but are unrecognized at the time of placement. The second type is a pregnancy that occurs either during the 3-month period before confirmation or occurs in a patient who is not compliant with receiving the confirmation test. However, these two types generally do not represent a method failure. The third type is an unintended pregnancy that occurs after an apparently successful confirmation test. This illustrates why reported effectiveness rates may vary by patient compliance and timing of the pregnancies reported.

The effectiveness of the Essure system depends on successful bilateral insert placement. Bilateral placement rates were generally high in the studies reviewed. The overall successful bilateral placement rate, including multiple attempts in studies with more than 50 subjects, ranged from 85.8% to 100%, with most studies reporting rates higher than 90%. Multiple authors reported more than one attempt was sometimes needed to successfully place the inserts.

Factors contributing to unsuccessful placement included:

- Poor visualization of ostia
- Tubal stenosis
- Tubal spasm
- Previous tubal occlusion
- Anatomical irregularities
- Patient discomfort

To increase likelihood of successful placement, some authors have suggested

premedication with NSAIDs and placement during the follicular phase of the menstrual cycle to improve visualization of the tubal ostia as well as decrease the chance of luteal phase pregnancies.

Previous systematic literature reviews have stated that unintended pregnancy is rare following a confirmation test, successful confirmation test, and that the failure rate is comparable to that of other contraceptive methods such as tubal ligation. Many pregnancies after Essure are associated with patient or physician noncompliance or misinterpreted confirmation test results. Failure rates are likely to vary by perfect use versus typical use, meaning that higher failure rates are likely for women who do not receive proper device placement or a confirmation test.

In the literature, confirmation test compliance rates ranged from 28.8% to 100% for different study populations. However, 28.8 was a bit of an outlier from a study of a clinic population in Detroit, and the authors stated that health insurance coverage was a barrier to confirmation testing for many of their patients. All other studies reviewed reported rates of 53% compliance or higher. Health insurance coverage was one of the most important determining factors for patient compliance. For a more detailed discussion of compliance rates and placement rates, please refer to Appendix A of the FDA review memo.

FDA conducted a literature review of the effectiveness of Essure in 2009 as part of ongoing postmarket monitoring and became aware of unintended pregnancies that had occurred in the commercial setting. As a result, a subsequent change to the physician and patient labeling was made in order to include information on these pregnancies.

This is Table 7 from the physician and patient labeling, which is presented in

Appendices B and C in FDA's review memo. The table shows 748 pregnancy reports received directly from the Sponsor, recorded in the FDA MAUDE database, and reported in the scientific literature. The time range is 2001 through end of 2010. Since this labeling change, FDA has continued to monitor potential effectiveness and safety signals as identified by medical device reports, published literature, and other sources as part of regular ongoing postmarket monitoring.

For the recent literature review regarding the effectiveness of Essure, FDA reviewed the peer-reviewed literature from 2002 to 2015, focusing on data from clinical trials and prospective and retrospective cohort studies. In order to better assess effectiveness rate over time after the 3-month confirmation test, articles were assessed regarding sample size and length of follow-up.

This is an abbreviated version of Table 13 from the FDA review memo that includes only studies of more than 500 patients and follow-up of at least 1 year. There were three prospective studies and four retrospective studies, as shown in the third and fourth columns. Each study reported an unintended pregnancy rate between 0.2% and 0.9%. However, many of these pregnancies occurred within the 3-month period before confirmation testing.

Chudnoff et al. described the results of the 5-year follow-up for the Phase II and pivotal trials. As previously noted, there were four luteal phase pregnancies that occurred before device placement and no unintended pregnancies occurring after the confirmation test. However, this study suffered from about a 30% loss to follow-up of the intent-to-treat population.

Two articles reported four pregnancies each that occurred after confirmation testing. Povedano et al. described one pregnancy that occurred 32 months after the Essure procedure. After delivery, laparoscopy showed a unilateral tubal perforation. Details were not given for the other three pregnancies. Veersema et al. described four pregnancies that were each associated with either device expulsion, misinterpreted transvaginal ultrasound, and/or a protocol violation.

Additionally, Fernandez et al. used retrospective French hospital discharge data for more than 39,000 women who received Essure and reported a rate of unintended pregnancy of 0.36% compared to 0.46% observed in those undergoing tubal ligation. However, this and other retrospective data are limited to pregnancies that were associated with the hospital procedure, and thus some pregnancies may have been missed.

In summary, in the highest quality data available, the rates of unintended pregnancy after Essure were low (less than 1%), and more than half of observed pregnancies occurred before the 3-month confirmation testing.

FDA has received a number of medical device reports citing unintended pregnancy. However, due to limitations of the reporting system that have previously been discussed, these reports cannot be used to calculate the total number or rate of unintended pregnancies that have occurred in a commercial setting.

Since device approval in 2002 through June 1st, 2015, FDA has received 337 medical device reports related to unintended pregnancy associated with Essure use. This includes 21 reports that cite more than one pregnancy in a given patient and 69 involving ectopic pregnancy.

Of the 127 MDRs which provided a fetal outcome, there were 76 reported live births, 32 reported miscarriages, and 19 reported elective terminations.

Regarding the outcome of patient satisfaction, satisfaction with the device and/or procedure was generally measured with one or two of the following questions, whether the patient is satisfied with the device or procedure on a scale from 1 to 5 or a Likert scale, and whether the patient would recommend the procedure to a friend.

In the literature reviewed, patients' satisfaction ranged from 89.2% to 100% in six studies with less than 1 year of follow-up. The Chudnoff article, describing the long-term follow-up of the Phase II and pivotal trials, reported that 98% of those not lost to follow-up were somewhat or very satisfied at 5 years. One small Turkish study reported 100% satisfaction at 8 years.

However, the measurement of patient satisfaction has some limitations. First, patients who require device removal due to dissatisfaction or who become pregnant are likely to be lost to follow-up, possibly causing inflated satisfaction rates at the final follow-up visit. For example, in the Turkish study, a patient who experienced an unintended pregnancy during the study did not contribute satisfaction data at 8-year follow-up. Second, satisfaction rating scales varied by study.

The reviewed literature has some limitations as follows. Our presentation has focused on data from prospective, well-controlled studies such as the pivotal and Phase II studies which were used to support the PMA application and supplements. However, many other studies in the literature were retrospective in nature, with variable length of follow-up which may be more vulnerable to study bias. Detailed information about pregnancies,

such as length of time after procedure and occurrence of device migration or perforation, was missing in some articles

Study investigators used different confirmation tests, including HSG, TVU, and/or pelvic X-ray, especially in studies conducted outside the U.S., which may limit comparison between studies. Only one study included a comparison group, and this study was retrospective. And, finally, the measurement of patient satisfaction had limitations, as previously discussed.

The strengths of the available peer-reviewed literature include data from clinical trials as well as real-world use, multiple studies with sample sizes of 100 or more women, and international data including women from North America, Europe, and Australia.

This concludes the section on effectiveness and procedural outcomes.

In summary, Essure has been approved for marketing within the United States and many other nations for over 10 years. Two prospective clinical trials were performed by the Sponsor and reviewed by FDA and its Obstetrics and Gynecology Devices Advisory Panel in support of the approval decision in 2002.

Over the past 2 years, FDA has seen an increase in the number of voluntary adverse event reports related to the Essure system, many coming from women implanted with the device.

In performing our current review of safety and effectiveness data for Essure, which is represented in our review memo and in our talk today, we focused on a number of the more commonly reported issues or concerns and included data and information from a variety of different sources, all of which have their own strengths and limitations.

Later today, the Committee will be asked to review and discuss this data along with other information provided by the device manufacturer and members of the clinical and patient communities. You will be asked to discuss specific safety events, such as the ones presented, and provide recommendations on what risk mitigation steps, if any, might be warranted.

We will also ask the Panel whether any of the issues discussed should be further evaluated through the collection of additional preclinical and/or clinical data.

Finally, you will be asked to consider the current safety data in relation to the device's effectiveness and to provide us with your overall assessment of the risk-benefit profile of the device.

We appreciate your time in helping us review and interpret the current data related to the Essure system and look forward to your discussion and recommendations later this afternoon.

This concludes FDA's presentation. Thank you.

DR. IGLESIA: I would like to thank the FDA for their presentation.

Does anyone on the Panel have a brief clarifying question for the FDA? And please remember that the Panel may also ask the FDA questions during the Panel deliberation session this afternoon.

I'll start with Dr. Stubblefield.

DR. STUBBLEFIELD: A comment on the first FDA presentation comparing LARC methods to hysteroscopy. I'm very fond of LARC methods, but I have to point out that the expulsion rate for both IUDs is more or less 5% per year, and that goes on year after year.

Also removal for pain and bleeding is comparable and again goes on for year after year. The etonogestrel implant has about a 20% removal for excess bleeding in the first year. So if you're comparing the methods, there is -- it's kind of hard to keep people on the LARC methods for 5 or 10 years. It takes a lot of love and care and repeat procedures and so on.

DR. IGLESIA: Thank you.

Dr. Coddington.

DR. CODDINGTON: Thank you very much. And I'll thank the FDA for their review, complete review of the different aspects of the device.

For all of them, the question comes up on the MDRs, that there is not specific data available to allow us to get some insight into the process. And as Dr. O'Neill said, there was 53% compliance and then 30% lost to follow-up. So my concern is, is that there's a lot of information in that dataset. It was not clear to me whether they had the opportunity to look over the data from the manufacturer, stating why there were dropouts or why there was lack of compliance. And so I think some of that may give us a better insight, particularly when Dr. Yustein related to the fact that there was bowel injury, for instance, that occurred within a month of the placement of the device. Your thoughts from the FDA group?

DR. IGLESIA: Dr. Yustein.

DR. YUSTEIN: So I'm sorry, can you rephrase? Is there a specific question that you'd like us to try to address?

DR. CODDINGTON: Well, I guess the question is, is do you have access to any of the -- I'll call it raw data from the industry that allows insight into some of these dropouts or

information, you know, so that you might have a better explanation or understanding of our process? I mean I know the MDR process has its limitations. I appreciate that. But I guess the simple thing is do you have any access to the raw data from industry?

DR. YUSTEIN: So I guess I just want to clarify. So the raw data in terms of the MDR events or the raw data from the clinical trials that they conducted or both?

DR. CODDINGTON: Let's just say both, and I'll let you take from there.

DR. YUSTEIN: Okay. So I mean, it's two different topics here. So in terms of medical device reports, the majority of time -- Essure being an exception, the majority of time the reports we get mainly come from manufacturers. We typically say that about 95% or over 90% of our MDRs come from manufacturers. With Essure it's a little different. As you saw in one of the graphs I showed, we have a much higher percentage of voluntary reports. The manufacturer reports that come in, they are expected to do an evaluation of the event and include that information in the MDR that they send in.

They also have the ability to send in what we call supplements to the MDRs as they learn additional information, because manufacturers are supposed to send in an MDR within 30 days of learning of the event. So that doesn't always give them the opportunity to know everything that happened within 30 days. So it's not uncommon for them to then submit additional information as an MDR supplement for that event. Within the MDR there are different sections of an MDR document, and there are sections for narratives or conclusions that the manufacturer based their evaluation. So they do give that information. Do we have all the information that they did in terms of their investigation? That would be in their files.

In terms of the -- I'll defer to the ODE folks. So your other question is in terms of why patients may have dropped out of clinical studies. Does anybody want to handle that one? Can we kind of discuss that after lunch maybe? Is that okay?

DR. CODDINGTON: That would be great. Thank you for the clarification, really, for all of us.

DR. IGLESIA: Thank you.

Dr. Seifer.

DR. SEIFER: Partially as a follow-up on that, in terms of -- it's been presented by multiple people that this is a three-step mandatory process and that when Bayer presented their information about pregnancies occurring, they said all of them occurred before the 3-month confirmation test. And I think Ms. O'Neill was talking about half of the pregnancies occurring before the confirmation test, and she also stated this broad range of compliance rates between 28% and 100% in the literature. So can we get some more information about why that range is so broad? She mentions health insurance was an important factor. Can you give us some information about that?

DR. YUSTEIN: Give us one second.

(Pause.)

DR. YUSTEIN: We have a backup slide, and we'll try to pull that up.

DR. IGLESIA: Would it be easier to do this after -- for the afternoon session?

DR. YUSTEIN: We can do it after lunch if you just want to give us some questions that you'd like us to --

DR. IGLESIA: That way we'll -- but I'll remember it.

Dr. Myers. We'll take two more questions from Dr. Myers and Dr. Milner.

DR. MYERS: Yeah, I just wanted some clarification about the adverse event of pain. And I believe I heard a statement made that patients with preexisting pelvic pain were excluded from the IDE studies. Was that correct? So therefore everything presented in what we've been seeing is post-procedure pain, not preexisting and recurrent.

DR. YUSTEIN: Right. What we presented -- what was that?

(Off microphone comment.)

DR. YUSTEIN: Right. For the IDE studies, patients -- one of the exclusion criteria was chronic pain. Right.

DR. MYERS: Thank you.

DR. YUSTEIN: Right.

DR. MYERS: Thank you.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Just sort of a general question that derives from a specific point that was made, which is that in the Phase II and pivotal studies, with respect to metal allergy and hypersensitivity, it says there were no allergic reactions, and then it says there were four reports of itching, hives, rash, or eczema. And so I guess my question, first of all, is what is that if it's not allergy?

And then the second question is what are the specific standards that are used to define what allergy and hypersensitivity is, and were the same standards applied for these studies? Is there a specific standard that is common to all trials like this?

DR. YUSTEIN: So thank you very much for that question, Dr. Milner, and I think that's

one of my questions to you guys as well. When we were presenting our data, we tried to be very careful in terms of how things were coded. So certainly one of the reasons why I listed those dermatological events was because, even though they were not specifically listed under the MedDRA coding or a coding as an allergic reaction, certainly some may interpret it as an allergic reaction.

So I was just trying to give that data, and the interpretation is certainly up to you. I think one of the things I tried to point out during my presentation is that reading through a lot of the literature, it is very unclear in terms of how people defined what is an allergic reaction or a hypersensitivity reaction, and I don't think it's possible to know in a lot of literature how they defined it. They would just come out and say the rate of allergic reaction was 0.04%, but I don't know how they sought it.

DR. MILNER: I guess my question is, in an IDE --

DR. YUSTEIN: Okay.

DR. MILNER: -- is there a standard for reporting? When you get a symptom, is there a standard for what -- specifically with respect to allergy and hypersensitivity or if you see that symptom it gets listed under there and that's --

DR. YUSTEIN: And I think every IDE -- and I'll let the ODE folks talk to this. Every IDE study and protocol probably has distinct -- you know, there's no standard definition, I think, that we use across every IDE study. And I can't tell you, in this particular one -- maybe we can look that up -- if and what that definition was. But oftentimes the individual study may define it for that particular study, but we can try to find out for you if and how it was described in this particular one.

DR. IGLESIA: Okay, thank you very much.

We will now take a 10-minute break, but I encourage all Panel members to write down any questions that we may have so we can discuss them in the afternoon. And, Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience.

And, Ms. Craig, we will resume at?

MS. CRAIG: 11:26.

DR. IGLESIA: 11:26.

(Off the record at 11:16 a.m.)

(On the record at 11:42 a.m.)

DR. IGLESIA: Would everyone please take a seat? Thank you. We will now proceed with the first portion of the Open Public Hearing. For the record, all Panel members have been provided written comments received prior to the meeting for their consideration. During the Open Public Hearing, public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing Disclosure Process Statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that

you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. IGLESIA: The FDA and this Panel place great importance in the Open Public Hearing process. The insights and comments provided can help the Agency and this Panel in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of the goals today is for this Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

Now, each registered speaker will be given 3 minutes to address the Panel. We ask that each presenter speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

Will Speaker No. 1 please step up to one of the two floor microphones on the floor? Or if you are unable to do so, a microphone can be passed to you. Please state your name and any organization you are representing for the record. Thank you. Correction, the first speaker is the first video.

(Video played.)

MS. RUTTER: My name is Lori Rutter. I was diagnosed with MS late in '97. Essure was implanted December of '03. There was no nickel test. I was told it was no risk. It was a good option for me with no surgery. I had trouble within a few months with severe pain and heavy bleeding, et cetera. The doctor moved out of the state soon after. Over the next year, my disease progressed. I stopped driving in a week. I had to use a wheelchair. And then in 2011, I needed to use a power chair 24/7. Now I struggle to stand for 15 seconds. Many have MS in my area, many not in wheelchairs, and virtually none who have been on an MS drug since the beginning like me. I thought my body responded inevitably to this device being implanted. Now I understand completely.

After further research, I learned of something called FBR, or foreign body response. The immune system is intended to be our protector. When the immune system finds a foreign body, it destroys and eliminates it from the body. However, in autoimmune diseases, it actually attacks itself rather than the foreign substance, thus creating a perfect storm to wreak havoc in your body, like it did with me. Having an underlying autoimmune disease is a counterdiction for mesh, according to some mesh manufacturers to the doctors.

Cancer researchers know there are links between chronic inflammation and development of cancer. Autoimmune researchers know there are links between autoimmune diseases and the chronic inflammation. Some surgeons know there are links between implants and autoimmune disease. Degradation and products of PET are considered toxic. Substantial testing was not done. PET has been identified to make cancer cells multiply. Inflammation can become chronic. Cell mutation can result and create an

environment that is conducive to new development of cancer. So much more, but bottom line, this is an inflammatory device that is worsening and creating autoimmune disease and cancer at the expense of women and families everywhere, not to mention all of the other issues. I was not given the proper information to make an informed decision. PET fibers in Essure causes chronic inflammation, which in turn caused my body to react. Long-term nickel exposure is toxic.

I urge you to recall this device. Not everyone will get cancer and develop autoimmune disease, but there are certainly those of us who do and deserve the right to know. My desire to avoid surgery could have killed me with malignant cervical cancer. It did change my MS. I was a functioning adult living life with a chronic illness until Essure. All medicine stopped working and the disease changed course. I have not been a mother or wife for a long time, and because of this fact, I cannot live without assistance. Essure was the worst decision I ever made.

Thank you.

DR. IGLESIA: Will Speaker No. 2 please come up to the microphone? State your name and affiliation. Krystal Donahue, come on up.

MS. DONAHUE: Currently there are over 7,000 Essure adverse events filed with the FDA. A study I co-authored was recently published in *Pharmaceutical Medicine*. It analyzed adverse event submissions from 1,349 women received via the MedWatcher app over a 7-month period. One of the major findings was that 77% of these women reported serious events, including hospitalization, disability, and permanent damage after implantation. One patient reported three times before an investigation was completed. One's directly to

Conceptus, one's through MedWatcher app updating to report surgeries and a diagnosis of cancer, and the third time her doctor filed a report. The result of the third complaint was their concluding that since no product was returned, we were unable to perform an investigation.

As a voluntary reporter, I am not an extreme case. I did not get pregnant, develop life-threatening complications, or get cancer. My coils did not migrate or perforate. I did, however, endure physical pain and mental anguish for 2 years after being implanted with Essure. My major complications were abdominal pain, painful sex, extreme fatigue, joint pain, rashes, and abdominal swelling. I visited a doctor more than 20 times in the 2 years wearing Essure. I had multiple blood tests, four ultrasounds, a CT scan, pelvic X-ray, a month of physical therapy, a cortisone injection, exploratory laparoscopy, and Lupron to rule out endometriosis. My primary care doctor finally told me that if I could not convince an OB/GYN to remove them, he would refer me to a general surgeon who would.

I was finally able to find a doctor at a small practice who would discuss Essure removal. After an internal exam where I convulsed off the table in pain, he agreed that they needed to come out right away. I had a hysterectomy on my 37th birthday. I thank Dr. Lacher, Dr. Adashek, and GBMC for freeing me from the pain Essure caused. I wish I could thank the FDA, ACOG, or Bayer for helping, but they are simply failing us. Focus on profits.

Despite the thousands of women harmed and despite all the data presented here today, Bayer and the FDA have difficulty seeing the causal relationship between Essure and our health due to limited data. Adequate studies should be required before marketing a

device that is meant to be worn for life. This is totally unacceptable. It is my opinion that premarket approval should be revoked on this product due to continued patient harm from the procedure and wearing the device over our lifetime.

Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 4, please step up to the microphone. State your name and affiliation. Elena. Elena Mendez.

MS. MENDEZ: My name is Elena Mendez. I am from -- I'm sorry. Hi, my name is Elena Mendez, affiliated with Essure problems. I would like to start by thanking you for giving me this opportunity to speak. I felt it was important for me to be here and travel from New York to share my experience I had with Essure.

I was implanted with Essure in February 2008. My doctor highly recommended it to me. He felt I needed permanent birth control due to the fact I previously had, 3 weeks prior, NovaSure ablations. It was described to me as soft, flexible inserts, no hormonal side effects. And the biggest selling point to me at that time was no down time. I was working as an ER nurse, I had two small children, and this was an optimal situation for me. I was told that my sensitivity to nickel and my previous piercings that rejected multiple times were not an issue for me because Essure was not made of the same nickel that was in costume jewelry. I was informed that I would need an HSG or a sonogram within a few months. When I called the facility to schedule my HSG, I was informed that I could not have the HSG because I had a NovaSure procedure done prior. I tried for several months. I tried several facilities to no avail, and no one would do this HSG for me.

Multiple sonograms were done over the years due to my complaints of pelvic pain, bladder pain, pressure, and painful intercourse. The sonograms were performed in my doctor's office and led by my doctor, and I was informed that Essure coils were within normal limits and no other pathology was noted. Well, I was told repeatedly that Essure had no side effects, they don't move, and there's nothing wrong with me. I lived in constant pain. My quality of life was severely diminished. Chronic pain became my norm every day. I could not have sexual intercourse with my husband as the pain was excruciating. This negatively impacted my marriage. I could not be a mother to my children that they deserved or the mother I was before Essure was implanted. I couldn't even be the ER nurse I was before Essure. Most nights I was at work taking care of patients, holding my own pelvic area, appearing as if I myself was in need of emergency medical services.

Every aspect of my life was affected and altered in so many ways. After years of enduring pain, another doctor ordered a pelvic-abdominal CAT scan. My Essure coils were not in the correct location. Upon laparoscopy and hysteroscopic, my right Essure coil was found totally covered in scar tissue and buried in my endometrial cavity. The left coil was barely in my fallopian tube. And while Essure and my fallopian tubes have parted ways with me, I am left with adrenal and kidney issues and memories of the woman, mother, and nurse I was before I had Essure implanted. I count too, and I am real.

(Applause.)

DR. IGLESIA: Thank you.

Speaker No. 5, please state your name and affiliation.

MS. FARMER: My name is Chandra Farmer. I have no financial conflict of interest

with Bayer or Essure.

I chose Essure for birth control when my last child was born in 2012. Three weeks after implanting, I experienced heart palpitations, weight gain, hot flashes, migraines, insulin resistance, nickel and chemical allergies, psoriasis of my hands and my vagina, interstitial cystitis, and 37 other symptoms. Soon I became so tired I was sleeping 18 hours a day. My neurological team was stumped. I had all the symptoms of narcolepsy. I even tested positive for the narcolepsy genotype but never once tested positive for narcolepsy in multiple sleep studies. Their last words to me were go home, get a good night's sleep, and see a psychiatrist. Those words devastated me. They were the specialists. They were supposed to help. HLA genotyping should have been part of the clinical studies.

Each of my narcolepsy symptoms were scary in their own right, but the narcolepsy symptom cataplexy was debilitating. Cataplexy is defined as loss of muscle tone upon emotions while being completely conscious. My cataplexy was mostly full-body attacks. I would fall to the ground completely paralyzed and lay there for up to 8 minutes at a time, and I could do this 20 times a day. Living with cataplexy was a daily struggle. I had to stop driving, be mindful of my surroundings because of falling, and even then found myself in the ER with concussions. I became depressed because I literally had to stop feeling. I was captive in my own body.

I remember a terrifying instance where I had swung too far forward, and I thought I was going to die of suffocation, and all I could do was scream inside my own head for help. After 1 year of having cataplexy, it became normal for my very young children to tell strangers, it's okay, my mom does that sometimes. There is nothing more heartbreaking in

this entire world than having your babies have to be your caretaker or your advocate.

I found Essure problems online. I took the information to my new OB, and he agreed to a hysterectomy on August 29th of last year. It has been 1 full year since surgery, and I have not fallen down with cataplexy since. Not once. All of my other symptoms have vanished. The only thing that lingers are my new autoimmune problems.

There are many, many more women out there with neurological problems like me. I have personally talked to dozens who have said they have the same symptoms and just didn't know what to call it. They are out there, and they are real. I had the most horrific experience with Essure. I had the coils removed during a surgery I was terrified to have. But now I'm living instead of existing. You all can call it what you want, but we call it Essure.

Thank you for your time.

(Applause.)

DR. IGLESIA: Thank you.

Speaker No. 6, please state your name and affiliation.

MS. TATE: Good morning. I'm Lisa Tate, Interim Executive Director of Healthy Women, the nation's leading online women's health resource. We are a nonprofit organization that receives funding from a wide range of sources. I understand that we have received funding from Bayer in the past. I have no personal financial interest.

Prior to joining Healthy Women, I was CEO for a long time for a national patient organization for women with heart disease. During my tenure there, I saw the development of the vast array of online options for women to educate themselves about their health.

The Internet and sites like Healthy Women have provided unparalleled opportunity to empower patients and consumers. For example, today, when we go to our physician, we often walk in with a list of questions that we've gotten from research on the Internet. This absolutely does result in better care.

But along with these positives there are also negatives, particularly with the explosion of social media. My organization had a 15,000-member patient community. However, even though the community had policies against giving medical advice, it was uncommon for women to follow this. One example was women who had experienced very serious side effects from cholesterol medication and advised women not to take that, even though this is literally life threatening for a woman with heart disease. And there are many options to reduce the side effects, like taking -- and these decisions should be made with a woman in consultation with her doctor.

Today we're talking about birth control, which is an important choice and one of many very important life decisions that women have to make along their personal healthcare journey. Yet, not every woman needs the same type of birth control. Birth control is not one-size-fits-all, and all women need scientifically sound information to guide them in their decision making. Having access to birth control options that fit a woman's individual needs is important, particularly if she has completed her family and is looking for a permanent solution for family planning. This is a big decision in a woman's life. The cornerstone of this level of decision making starts with a conversation between the patient and the healthcare provider. Women need to know what questions to ask, and healthcare providers need to be at the ready with the answers.

As an educational source for the more than 5 million women who annually visit healthywomen.org, we understand the importance of availability of reliable, medically sound scientific health information. We advocate that women should have access to the full array of contraceptive options approved by the FDA and that a woman's choice of birth control method, or any other major healthcare decision, should be made in collaboration with her healthcare provider. This hearing today will provide important information for both women and their healthcare providers.

Thank you.

DR. IGLESIA: Thank you.

Speaker No. 7. Please state your name and affiliation.

DR. GARIEPY: Good morning. My name is Dr. Aileen Gariepy from Yale School of Medicine, Department of OB/GYN.

Next slide, please.

I am a trainer for the Nexplanon reversible contraceptive.

Next slide, please.

Today I'd like to focus on effectiveness. The introduction of Essure in 2002 was very exciting for women and doctors. Essure was publicized in popular women's magazines and focused on office procedures and avoiding anesthesia.

Click. Can I get a click? Can you advance? Thank you. Natural barriers -- and click -- and superior effectiveness. Click, please.

I was excited to be a doctor offering Essure, until I found that the clinical reality did not reflect the published data. Click. Click. So I looked more closely at the published data.

The major disadvantage of Essure is that it's a multi-step procedure, which means there are multiple opportunities for a problem. I found that Essure publications and advertisements focused on the best-case scenarios of effectiveness -- click; click, please -- if everything went perfectly. And it excluded women with unsuccessful steps. If you could click the next field. And also excluded women who got pregnant at each step. If you can click again. Unfortunately, as we know, few things in life are perfect, and women and doctors want to know realistic chances of each step being successful. So that was the analysis that I did. Click.

My colleagues and I performed an intention-to-treat analysis incorporating all available published data in the peer-reviewed literature, which mostly -- which more closely reflects real-life experience. Click. And what that showed is that 85% of women attempting Essure were sterilized at 3 months. Is 85% good enough? That depends. With laparoscopic sterilization, 99% of women who attempt the procedure are sterilized. And this doesn't even take into account the risk of pregnancy.

So I performed a second intention-to-treat analysis. Click. Again, based on all the published data in the literature at the time that it was published, there was -- sorry, click -- a 10-times-higher risk of pregnancy with Essure at 1 year than there was compared to the CREST data for laparoscopic sterilization. Click, please.

When we talk about contraception, we typically report on perfect and typical failure rates at 1 year, but currently we do not report that for female sterilization. Click. We can and should differentiate -- please click -- and advertise what the perfect versus typical rate is for Essure. Please click.

The good news is, is that Essure may still have promise. It's still not incisional. It can be performed in an office. Laparoscopy can be avoided and maybe even general anesthesia. However, we are missing key pieces of data, and more data is needed. Click. We need transparent reporting of the data that we currently have -- click -- including mandatory pregnancy reporting of all pregnancies to a national, impartial data and safety monitoring board. Please click. We should be talking about typical failure rates, not perfect failure rates. Please click. And I do believe it's time for CREST 2.0 and update a national multi-site collaborative review of sterilization. Our CREST data is now 30 years old. We need a prospective cohort that directly compares Essure and laparoscopic sterilization, measuring all clinically meaningful outcomes, including side effects and repeat surgery. We need an intention-to-treat analysis, prompt publication of data, and then we can know how sure Essure is.

DR. IGLESIA: Thank you.

DR. GARIEPY: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 8, please state your name and affiliation.

MS. HOWELL: Good morning. My name is Rebecca Howell, and I have no ties to Bayer. Thank you for taking the time to hear our case.

After my third child was born, heart complications required either my husband or I to become sterilized. We saw Essure advertised as a perfect product for a new mom scared to conceive again. I was implanted with Essure in August 2011, and in November 2011, I was told I had been made sterile and the placement was perfect. This perfect placement

was also confirmed by several CT scans, X-rays, and ultrasounds over the course of the 2½ years I had Essure in my body. This placement did not prevent the long list of symptoms that appeared immediately after placement and the months and years after: back pain, joint pain, increased migraines, weight gain, struggle to lose weight, bloating to the point I looked pregnant, chronic fatigue, food sensitivities, heavy painful periods, urinary tract infections, monthly yeast infections, painful intercourse, hair loss, elevated CRP and sed rate, and nickel sensitivities. I had to stop wearing my wedding bands because of the nickel content in the white gold.

These symptoms got so severe I had to educate my home-schooled children from my bed. There were days when I would not get up out of the bed except to crawl to the bathroom in tears. I felt less like a woman, less of a human. I became depressed. It was only my faith in God and my loving family that kept me from ending it all.

After finding a group of women with similar issues, I began my struggle to find a doctor who would listen to me. The doctor who implanted my Essure device refused to see me. Emergency room doctors thought I was a drug addict. University of Florida OB/GYN attendings had no idea what to do with me. It wasn't until I had proved that I had developed a Level 2 nickel allergy on a scale of 0 to 3 after having the implants put in that I had a doctor listen to me.

On December 20th, 2013, my cervix, uterus, and fallopian tubes were removed. My coils were handed over to me intact. They had not migrated out of my tubes or broken. My symptoms improved after removal. Yet, there are side effects of Essure and hysterectomy that may never go away. My story is simple and by far not the worst story you're likely to

hear today. Yet, in my eyes, it proves that even with perfect placement and no complications of breakage or migration, that Essure wreaks havoc on the lives of women. Had I opted for a simple tubal ligation, I would not have gone through this. My children and husband wouldn't have to watch me in misery. I would have an intact body and not deal with the ramifications of a hysterectomy at 30 years old.

The only, only acceptable solution for the women suffering, the women and children who have died, the families torn apart, and the physical, mental, emotional, spiritual, and socioeconomic stress on our lives is for Essure's premarket approval to be revoked, Essure to be permanently recalled, and for the Bayer company to be held responsible for the damage caused by their faulty product.

Thank you for your time.

DR. IGLESIA: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 9, please state your name and affiliation.

DR. JAMSHIDI: Good morning. My name is Roxanne Jamshidi. I'm an OB/GYN. I'm an Associate Professor of Obstetrics and Gynecology at George Washington University. I'm also the director of the division of general OB/GYN there, but today I'm actually here on behalf of the American College of Obstetrics and Gynecology. I have no financial conflicts of interest to disclose.

ACOG is a national medical organization representing nearly 59,000 OB/GYNs and partners in women's health. On behalf of ACOG, I thank the FDA for its attention to the safety of hysteroscopic sterilization with Essure as the health and safety of patients is of

utmost importance.

Contraception is an essential part of women's health. The majority of women will use birth control at some point in their lives. Female permanent contraception or tubal occlusion, commonly referred to as sterilization, is one of the most popular methods for women. Six hundred thousand tubal ligations are performed each year in the United States.

ACOG considers it essential that less invasive tubal occlusion options, like Essure, be made available to women because it is critical that women have a choice when it comes to contraception.

As you know, female permanent contraception can be performed through two different routes, abdominal or transcervical. At this point Essure is the only technology available to perform a less invasive transcervical tubal occlusion which does not require general anesthesia and can be performed in a physician's office rather than the general operating room. All medical procedures carry risks and benefits, and no single approach is right for everyone. However, a woman's coexisting medical conditions, including obesity, cardiac or pulmonary disease, may make a less invasive approach a safer sterilization option. Additionally, because the hysteroscopic approach does not require entry into the abdominal cavity, major morbidity associated with general anesthesia and abdominal surgery can be avoided.

In order to improve the use of hysteroscopic tubal occlusion in the future, we ask the FDA to take steps toward obtaining more high-quality data on both its safety and efficacy. We know that there are tools available to the FDA and the medical community to better track and understand Essure use. Postmarket surveys and studies, comprehensive patient

registries, and unique device identifiers will allow us to evaluate not just a patient's insertion experience but also her long-term response and wellness, including the potential side effects and incidence of those side effects.

We know that permanent contraception is of life-long importance to women and their families. We want to understand the positive and negative impacts of this choice. This involves improving the data available to women, to physicians, and to the FDA itself.

Moving forward, ACOG would be happy to continue to advise the FDA on the importance of contraceptive choice and on the information that will help us make appropriate decisions in the future.

Thank you.

DR. IGLESIA: Thank you very much.

Speaker No. 10. Michelle Garcia. Ms. Garcia.

(No response.)

DR. IGLESIA: Okay, we're going to skip on down, then, to Speaker No. 12. Sarah. And please state your full name and affiliation.

MS. SORSCHER: Before I begin my presentation, I'd like to ask permission from the Chair to present at the podium where I can have access to a remote to move my PowerPoint through.

DR. IGLESIA: Can you move over to the microphone on the -- to your right? Oh, I'm sorry, your left, my right. So we do have an advancer on that microphone.

MS. SORSCHER: Okay. And I'd also like my full 3 minutes restored, if that's possible. I'm not seeing my presentation up yet. And now I'm trying to get this clicker to work.

There's no -- over there?

UNIDENTIFIED SPEAKER: Here it is.

MS. SORSCHER: Okay. This is going to be challenging. Well, if there's no alternative, I'm going to ask to verbally move the slides forward. Okay.

Good morning. My name is Sarah Sorscher. I am a researcher with Public Citizen's Health Research Group. I have no conflicts of interest.

Slide, please. Oh, go back, please.

Today's meeting was called in response to a large increase in adverse event reporting driven largely by patients. I won't dwell on these reports because so many of those patients are here today.

Slide, please.

Instead, I will focus on safety issues in the two premarket trials conducted by Conceptus, Essure's prior manufacturer.

Slide, please.

The total number of patients experiencing an adverse event related to pain in these trials was not reported, and pain severity was also not reported systematically. And even these results show that nearly 1 in 10 women experienced back pain in the first year, and severe pelvic pain and cramping occurred in at least a small but notable minority of women.

Slide, please.

Strikingly, removal rates in the premarket trials were over 4%, and the main reasons for removal involved safety issues, including bleeding and pain.

Slide, please.

The 5-year follow-up reported apparently glowing patient satisfaction and lack of persistent pain.

Slide, please.

Yet, this extension study had many flaws, and points involving comfort and satisfaction with the device were vague and subject to biased interpretation. Again, severity of pain was not reported. And in the follow-up, pain outside the pelvis, including low back pain and abdominal pain, were also not reported, although they were collected by Bayer -- by Conceptus. Finally, the definition of persistent pain or pain recorded at every visit was too rigid, resulting in exclusion of patients with chronic recurring pain.

Slide, please.

To illustrate some of these problems, I have data from a subject enrolled in the pivotal trial, Kim Hudak. She is testifying today and has given permission to use her name.

Slide, please.

Kim experienced long-term debilitating pain and other symptoms that began soon after receiving the Essure implant and largely resolved after the device was removed via hysterectomy after the trial. Kim reported this pain, yet her physicians insisted that it was unrelated to the device, and her forms were consistently marked with ratings of excellent and very satisfied.

Slide, please.

Here's the summary. Her comfort and satisfaction appeared uniformly high in spite of reports of severe pain. And because pain was not recorded at every visit, her long-term pain would not have been considered persistent. Pain severity and other symptoms, such

as 80 pounds of weight fluctuation, were not reported at all in the published results.

Slide, please. And slide, please.

The patient testimony today makes clear that Kim's experience is not an isolated one. But even if such stories were rare, and we do not believe they are, a device that causes this level of debilitating long-term pain should not remain on the market. Essure's benefits do not outweigh its risks, and it should be withdrawn.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 13. And please state your name and affiliation as well.

MS. HUDAK: Hi, my name is Kim Hudak, and I have no affiliations.

I was part of clinical trials for Essure. In 2000 when I signed up for this, I was really excited to be a part of this revolutionary product. It's something that I wanted for all women. It was my understanding that clinical trials for a new product were designed to test the safety and efficacy of a new product in a controlled environment where all possible side effects would be recorded. Within a few weeks of the procedure, I was experiencing a constant sharp pain in my left hip. I was also suffering from debilitating fatigue and severe PMS symptoms. By my 3-month follow-up, I was in nearly constant pain and suffering from extreme migraines.

When I spoke to the clinical trial nurse and my doctor about these symptoms, they made it clear that they did not think that the symptoms were related to the device. They recommended that I seek help from outside doctors, my primary gynecologist and other specialists. When I would mention my procedure to these other specialists, they didn't

know how to help me. I was terrified, and my health was rapidly declining, and no one had any answers for me.

The clinical trial questionnaire didn't allow for accurate reporting of all symptoms. The questions were presented in a very leading way. For instance, the question, rate your comfort of wearing the device, I was told specifically that if I can't definitely feel that coil inside of me, I should rate it as excellent. And another question was rate your satisfaction with the device. For this question I was told that because the product did exactly as promised and I did not become pregnant, I should also rate that as excellent.

With each passing month, my symptoms became more severe. With each clinical trial follow-up, I was told, I'm sorry, your symptoms are just not related to this device. Within 12 months of placement, I developed pain throughout my entire body, odd rashes, constant infections, and minor neurological issues. By the time I had a hysterectomy in 2013, I had cognitive problems, slurred speech, widespread pain and swelling. I couldn't work and can barely function as a mother.

I have slides and, you know, I just feel that -- they're not here. There we go.

As you can see by my medical records, many of my answers regarding pain were crossed out and replaced with answers showing I was satisfied. It's unclear what was actually reported back to the FDA, but what is clear is the severity and diversity of my symptoms were not reported.

Since removal in 2013 and another surgery to remove a remaining piece of the coil in 2014, most of my health issues have improved or are completely gone. That's a small consolation to the almost 15 years that I lost. Please don't let this happen to other women.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 14. And then just state your name and affiliation.

MS. AVINA: My name is Gabriella Avina, and I have no affiliation with Bayer. I want to thank you for this opportunity to be heard for a second time.

In July 2002 I stood before you in Washington, D.C. to express my support for Conceptus and the Essure device. I was on the panel to request FDA approval for this new, revolutionary device. I am here today, almost 13-plus years later, to say I was wrong. So please listen carefully to me and to these women with me today. Time has changed my thoughts, my beliefs, and most importantly my health.

I am a registered nurse with a master's of science degree in women's health nursing and an M.B.A. I was involved in the clinical trial at both a professional and personal level. I became a part of a clinical trial after my third child was born with an IUD and my husband's vasectomy grew back. I assisted in the placement of the devices in the operating room with Dr. Don Galen, and I became a clinical trial participant in October 2000. Because of my experiences both as a clinician and a patient, I was asked by Conceptus to speak at the annual AAGL convention in San Francisco and share these experiences. This began a professional relationship as a spokesperson for Conceptus that lasted through 2008.

I traveled the country speaking to large groups of doctors, nurses, patients, and Conceptus employees. I managed the link on the Essure website known as Ask Gabby, where I answered thousands of questions regarding the product, adverse events, fears, concerns, and general information. All of that information was recorded, tabulated, and

returned back to Conceptus. As I became the face of Essure women, my health was in a grave tailspin, and I had failed to connect the dots.

In April 2001, not 6 months following placement, I was diagnosed with Hashimoto's thyroid disease, whereby the body attacks the thyroid believing it to be foreign. The only foreign objects in my body were the Essure coils. In 2003 I was hospitalized with an acute onset of immunologic thrombocytopenic purpura with a platelet count of 4,000. I was hospitalized for nearly 2 weeks with several transfusions, treatments, and tests. My children were not allowed to hug me for fear of causing a bleed. One year later, after several hospitalizations and complications, I was started on chemotherapy to suppress the bone marrow production of these bad antibodies. I finally reached a safe zone and remission in late 2005. But during this time, I lost my job due to my illness.

In 2007 I was diagnosed with another autoimmune disease, celiac disease, a gastrointestinal disease where the lining of the bowel is broken down when exposed to gluten. The result is pain and malnutrition among other discomforts. At this point I had not realized the root cause of my problems, but as disease progressed, it was becoming glaringly obvious.

In 2008 I was finally able to go back to work when all my blood work and labs returned to normal. I was starting to feel like I was getting my life and body back when I was diagnosed with a fourth and fifth disease, the worst being myasthenia gravis. As the disease progressed, I began to lose control over my ability to chew and swallow. I was scheduled for a thymectomy in February 2010. If myasthenia gravis progresses, the lungs can become too weak to work, resulting in death by myasthenia crisis. I went through a

short remission that lasted until 2013 but spent 2014 in chemotherapy again.

I felt hopeless and feared realizing that I had no control over my own health. These Essure women found me on Facebook and asked me one question: How is your health? I was intrigued, and there began a relationship. I had been praying and hoping for remission, but now I knew there was only one way to assure the possibility of a healthy future. I needed to rid my body of Essure coils. And I spoke with all of my doctors, all of which were supportive and felt this was probably not a coincidence. Even Dr. Galen, when I tracked him down in retirement, could not argue the fact.

DR. IGLESIA: Please summarize. Thank you.

MS. AVINA: Again, I ask you to listen to this group of women who all have a story. Their lives were changed by a device that was not adequately monitored during clinical trials by physicians who were not adequately trained and by a company that has not adequately listened to their patients.

Thank you.

(Applause.)

DR. IGLESIA: Can we please play video 15? Patricia Rhodes.

(Video played.)

MS. RHODES: My name is Patricia Rhodes. I joined the STOP 2000 clinical trial at the Arizona Women's Health Research clinic in Phoenix, Arizona, because my ex forced me to get sterilized. After I joined, I was never given the opportunity I was told I would have to see the implants, to see the packaging they came in, and feel what was going to be implanted in my body. Had I been given the opportunity to feel the devices and see the

packaging, I never would have allowed them to be implanted in my body as I would have known within seconds of touching them that I was allergic to them.

In the beginning I asked at least a half a dozen times what they were made out of because I have metal allergies, before being told they were 100% surgical stainless steel with a coating to promote scar tissue growth. They made them sound so innocent and harmless. If I had known then what I learned at the end of last year, I never would have allowed them to be put in my body.

I suffered the effects of nickel allergy all over my body for 14 years, 5 months, and 2 days, until having them removed by hysterectomy in March of this year. After the procedure, I experienced pain, cramping, and bleeding. It took several months for the bleeding to stop, which they blamed on my having been on Depo-Provera, despite the fact that I had been off of it and regulated before getting the implants. If you look at my records, you'll see complaints and visits for pain and recurrent yeast and urinary tract infections I started experiencing over and over after getting Essure.

I know I'm not the only one in Phoenix who complained of the same issues. There's at least one other that I talked to in the waiting room while waiting for a follow-up appointment that had the same problems. Apparently we weren't allowed to discuss our experiences for some reason as they separated us as soon as they overheard us discussing our problems.

During the study, my paperwork was altered and/or filled out for me, instead of reflecting my true experiences. The first time I sat in the office filling out the questionnaire, I only completed part of it before the doctor took it and helped me finish it. After the first

one, I do not recall ever seeing any of the others that were filled out for me. At the end of 2008, I experienced my first pregnancy with Essure in place, because it ended in miscarriage, and they delayed getting me into the office for testing or falsified the result. They denied that I was ever pregnant, saying that there had been no pregnancies with Essure, which I since learned after finding Essure problems on Facebook last year was a lie. I had two more early term miscarriages with Essure since 2008 but didn't bother to report them to the clinic as they probably would have only denied them as well. Essure is nothing more than a torture device that causes pain, suffering, and agony for thousands of women.

The chemicals and materials in the coils cause autoimmune problems, weight gain, and very possibly cancer. They do not prevent pregnancies as much as they claimed they do. If they do not prevent pregnancy, cause thousands of women, some as young as 20, to have major surgery to try to undo the damage they've caused, what good are they doing? I've lost everything but my left ovary to Essure, and I'm still suffering from probably permanent debilitating issues they caused. Essure needs to be pulled off the market now before any more unsuspecting women end up suffering and going through needless surgeries to correct the mistake of getting them.

(Applause.)

DR. IGLESIA: Speaker No. 16. And please state your name and affiliation.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research, and I'm speaking on behalf of our center and also on behalf of members of the Patient, Consumer, and Public Health Coalition. We're all nonprofit organizations, and we do not have financial ties to any product. Because I'm speaking on behalf of two groups,

I have 6 minutes, but I've only been given 3 on my thing, so please change that. I appreciate it. Thank you.

Just to give you my perspective, I'm trained in epidemiology and public health at Yale Medical School, and I've been working on issues of safety and effectiveness of medical products for, I'm sorry to say, more than 30 years.

Next, please.

Our center conducted a study of women who had problems with Essure. So this is not a random sample; it's a study of women with problems. And you can see that 86% of the women with problems reported problems with pain, mostly pelvic pain but not entirely, but generally in that area. Bleeding was reported by 34%, and this was often very excessive bleeding. Some women told us they didn't stop bleeding. Basically, they were bleeding every day of every month. Fatigue reported by 22%. And this is where we get into some autoimmune responses. Fatigue 22%, hair loss 16%, and depression, which can be autoimmune also in nature, 12%. You can see that 12% of the women had hysterectomies; 7% had allergy symptoms. And I'm not reporting the less common symptoms. Again, of the women who reported problems, these are the kinds of problems they reported, and you can see a very clear pattern that's somewhat similar to other ones, such as the ones that have been reported to the FDA directly.

Next, please.

This is a photograph of two Essure devices that had been taken out of a woman. You can see they look quite different from what they look like when they're inside. And they are in pieces as well. And some of the pieces of these devices were still in the woman who had

them taken out and still causing her pain after her Essure was removed. I think what's really important to talk about this, is that also in our study, almost -- approximately half the women -- no, I'm sorry, about a third of the women had had their Essure taken out, and about half of those women said that they had had a complete loss of all the problems they had had. So their symptoms disappeared for about half the women, and only 5% of the women said they had had no improvement after Essure was removed. So, to me, that suggests that these problems were related to their device for the vast majority of the women, even though sometimes these symptoms obviously build on each other.

Next, please.

This is from the chart that you were given by the FDA. I just looked at the most common types of pain that were reported. And there's red ink. It's a little hard to see, but I tried to show the fact that even though these numbers vary from year to year and they tend to get lower as the years go by, but if you look at the sample size and the lost to follow-up, you can see that the numbers of women correspond with the lost to follow-up. Because so many women are dropping out of the study and so many of the women dropping out are women who've had severe pain and other complications, you're losing track of them, so you can't really see them. But, even so, if you add across these pains and these are -- it was still 8% of the women at 4 years.

Next, please.

Here's another. This was Table 8 from the material you were given. And, again, looking across the pain, at total recurrent pain, it totals to 18%. Now, I assume that some of these women had pain in more than one area, so we don't know exactly how many

women based on the data that we're provided. But just to give you a sense that women are having pain in a lot of different places, and that if it does total up, it's very high, again, if you at look baseline, you look at 3 months, you look at what's happening later, the numbers of women are dropping in the study as well as the numbers reporting pain.

Next, please.

And here we combine Tables 9 and 10 to look at irregularities and bleeding, and you can see again that these numbers are quite impressive at 5 years and during that time. And, again, in talking to the women, it's clear that these are very serious problems.

Next, please.

This you've seen where things were crossed out.

Next, please.

Again, more things crossed out. So the question is, can you believe what the data are showing, or do you believe what the women are telling us? And what the women are telling us, for example, is that they were thrown out of the studies when they were having pain. When they were reporting that they wanted their Essure removed, they were thrown out of the studies, and yet it wasn't reported that they had had the pain. You've lost those women to follow-up.

Next, please.

These are the main issues for you to be considering. The safety and effectiveness compared to what? Why weren't those studies required to have a comparison group, using other kinds of birth control? A good question.

The accuracy of the data. Were the women being told to say they were satisfied

when they weren't, to say they were satisfied when they were in excruciating pain?

The next question: How do you safely remove the product? We don't know the answer to that one either.

DR. IGLESIA: Thank you.

DR. ZUCKERMAN: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 17.

DR. McDONALD-MOSLEY: Hello, my name is Dr. Raegan McDonald-Mosley. I'm here on behalf of Planned Parenthood Federation of America, and I have no financial relationship with Bayer HealthCare or conflicts of interest.

I thank the FDA staff and members of this Essure Advisory Panel for allowing me to make comments today on behalf of Planned Parenthood. We consist of a national office and 59 affiliates. Our affiliates serve more than 2.7 million patients a year. In fact, one in five American women report having received care at a Planned Parenthood health center at some point.

At Planned Parenthood, the health and safety of our patients is our top priority, and we work every day to ensure that our patients have a positive experience. With input from medical experts, we update our standards of care on a regular basis according to available medical evidence. Therefore, when Essure was approved, we recognized the potential benefits for women interested in a safe non-incisional form of permanent birth control that could be performed in an ambulatory setting without the additional risks of general anesthesia.

Planned Parenthood has always recognized the importance of a wide array of contraceptive options, and our role as a provider is to inform a woman about her options, with the inherent risks, benefits, and alternatives of each. With this information, a woman may then decide which method is best for her to accomplish her reproductive life plan and overall goal. Additionally, we recognize that many women choose permanent birth control once they've reached their desired family size.

Planned Parenthood has provided support and training for affiliates who have decided to offer this service. For the first set of affiliates that implemented Essure services, we devised a system of inter-affiliate training such that experienced Essure providers trained newer providers. And in 2011 we subsequently developed a handbook that provided clinical and operational information as well as program requirements for our affiliates.

Moreover, our affiliate risk management and quality improvement programs require affiliates to report and analyze complications related to Essure. Affiliates providing Essure have experienced low rates of accepter dissatisfaction and procedure complications; 23 affiliates provided Essure in 2013, and 24 affiliates provided this service in 2014. In this time frame, failed procedure rates reported ranged from 2.4% to 8.3% as compared to the failure rates in the pivotal clinical trial. In 2014 adverse events such as recurrent or constant pain after their procedure ranged from 1.3% to 7.1%.

Based on published literature and our experience, we continue to offer Essure as an important option. However, since many women have reported problems after Essure, we feel that further study across longer periods of time is prudent, including the establishment

and maintenance of a registry in order to determine adverse event frequencies among Essure accepters.

In summary, Planned Parenthood believes that women should have the option of undergoing an Essure procedure after adequate counseling and education about the risks and alternatives. However, we support the efforts to glean additional epidemiological information in order to further analyze the risks and side effects related to Essure.

I thank you very much for your time and consideration of our experience with Essure at Planned Parenthood.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Now, before the Panel breaks for lunch, I'd like to ask Panel members if there are any brief clarifying questions that you have for this first portion of the Open Public Hearing.

Dr. Elser.

DR. ELSER: This question is for Dr. Zuckerman. It looked like you had some categories of pain, such as dyspareunia, dysmenorrhea, and other pain, which may not be mutually exclusive. And were you adding those up across the columns?

DR. ZUCKERMAN: Yes. And that's from the chart that was in the material that FDA provided to you. So that's not the chart from our data. That's the chart from the Conceptus study. So I wasn't sure, you know -- as I said, we didn't know whether you could add them up or how much overlap there was, and I don't know the answer to that question.

DR. ELSER: Okay. So you added it up, but the chart does not add them up. So we

don't know if one patient had -- she was the one in the dysmenorrhea column and the dyspareunia column.

DR. ZUCKERMAN: That is correct. But there were other kinds of pain, I believe, that were not on that chart that were reported. So, you know, we missed those data.

DR. ELSER: Thank you.

DR. IGLESIA: Any other question?

(No response.)

DR. IGLESIA: Okay. So we will now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room at exactly 1:30 p.m. to resume the Open Public Hearing. And I will ask that all Panel members please return at that time.

(Whereupon, at 12:43 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:44 p.m.)

DR. IGLESIA: Would everyone please take a seat so we can get started? So we will now proceed with the second portion of the Open Public Hearing. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will again read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

DR. IGLESIA: Thank you.

And we have the questions, and we'll discuss those questions during the open

forum, but at this point I'd like to call on Speaker No. 11 to go back, and if you could please introduce yourself and state your affiliation.

DR. DOURRON: Thank you, Madam Chairperson and panelists, for allowing me to present what I do. My name is Dr. N. Edward Dourron. I am a reproductive endocrinologist and robotic surgeon in Atlanta, Georgia, and I have no financial disclosures.

Next slide, please.

So my position is that I've always been out as an advocate to save patients' uteruses. I've been doing robotic myomectomies for 10 years, and that's where I preserve the uterus by removing the fibroids and allowing women to continue to have functional uteruses. So when I had patients coming to me and saying that they've only been given the alternative of a hysterectomy -- can we go to the video, please -- for removing the Essure device, it was logical for me to do what I do best, which is to work at trying to preserve the uterus.

So here I'm presenting a patient that I performed surgery on 2 -- actually, 4 weeks ago. And you can see the rigid Essure device protruding from the left fallopian tube here. With robotic surgery, you have seven points of articulation and actually four robotic arms that you can control simultaneously. What this does is it allows very precise dissection and removal of the Essure device with the uterus that's scarred around it, as well as the fallopian tube. The visualization that you have is three dimensional, high definition, magnified.

As you can see, during the sewing of the uterus, all the instruments allow precise suture placement, and with the injection of the patress (ph.), and the entire surgery can be accomplished in under 2 hours with less than 25 cc of blood loss. The advantages of robotic

surgery open -- compared to an open laparotomy procedure are that all the patients are able to go home the same day, recovery takes 2 to 3 days, the risk of infection is less, patients have one-third the blood loss, and they're able to resume normal activities much more quickly than with an open incision.

Here's the left side, and it shows the metal sticking out at the proximal portion of the tube. By looking more closely you are able to move in the camera, zoom, and actually see a small fragment of the nickel coil and remove that separately.

At the end of the surgery, the patients recover very quickly. What I do is once all the sewing is complete, I place a thin mesh over the uterus, called Interceed, that dissolves over time. But you can see how deep the suture placement can be. And I've had women that have asked to have their Essure removed in order to have additional pregnancy. So it is possible to even do a segmental resection of part of the tube and re-implant the fallopian tube so that fertility can actually be restored in patients that wish that.

It's important to remove the remaining portion of the fallopian tube because there have been reports that that could contribute to future ovarian cancer, so that it makes sense that if you're going to remove part of it, remove the entire fallopian tube. And here you can see it leaving the patient through a small belly button incision.

DR. IGLESIA: Thank you very much.

Our next presenter is -- we're going to go back to Video No. 2.

(Video played.)

DR. HUFNAGEL: In 1995, as Slide 1 shows, is that I testified against morcellation as an oncological fellow and stated that the device was defective and would spread cancer and

other diseases and it would kill women. I also discussed the problems with Ovabloc and asked for a recall many times, and that device was not recalled. It does need to be recalled.

At this time, there's a mythic concept that if we destroy the uterus or the fallopian tubes, that we're going to cause no harm, and that's literally insane thinking. These products all cause problems of fraud, battery, mayhem, and in the case of morcellation, attempted homicide and negligent homicide. Female victims are very difficult to help, but they're looking to seek healing through legal means, and they have anatomical, physiological, and psychological issues which need to be healed, and they are not getting this help. We need to look at sterilization methodology and the understanding that destructive aspects of hurting female organs is not a means of proper device creation.

All of the chemicals and cofactors made by the fallopian tube are destroyed. What do you get? Well, an example you'll get is that you'll get more rheumatoid disease in these women because you're destroying the factors made by the fallopian tube to reduce rheumatoid disease in women. Lack of ethics, lack of science, and no hormone studies. How could we create devices and not see how they affect female hormones? That is another issue of insanity in looking at this from a point of view of ethics and medical science.

I am requesting all of my documents from the FDA. I have sent a demand notice to the FBI for investigation and prosecution for all of the wrongdoings by corporations or any individuals involved. I am filing my own international legal action against these companies and against their products for mayhem and negligent homicide and other serious charges. I want to remind everyone that poor women in developing countries are used as guinea pigs.

My future work. I will be asking to work to review the MedWatch program and publicate on that. I'm here to work with everyone who wants to bring about positive change.

Thank you.

DR. IGLESIA: I'd like to invite Speaker No. 18 to come up. This speaker will have 6 minutes. Please introduce yourself and state your affiliations.

MS. FIRMALINO: I also have a PowerPoint that's supposed to automatically play for the 6 minutes.

My name is Angie Firmalino. I have no financial conflicts of interest to disclose. What you are viewing are images and posts from women suffering from Essure.

I was implanted with Essure in 2009, 3 months after the birth of my son, Elijah. I started the Essure Problems Facebook group in 2011 after finding out my coils expelled and were embedded in my uterus. After the ultrasound that revealed this, I felt very betrayed and misled, not only by my doctor but by the manufacturer. I honestly had no idea that these devices could expel from our fallopian tubes and perforate organs or embed in other areas of the body. That is just not made clear to patients at all. Even though I now know that migration and perforation are currently listed adverse events, the reality of what that means and what one faces if that happens is ruthlessly downplayed.

After creating the group to warn my female friends and family members, many women that I did not know started joining and posting similar stories of their problems with Essure. After more than 4½ years now and approaching 21,000 members in the group, I have probably read a quarter of a million posts, day after day, week after week, month after

month, posts from women in debilitating pain, women suffering, having no one who will believe them that Essure may be the cause, let alone help them. If this were men complaining of pain, bleeding, or sexual dysfunction after having a medical device implanted in their testicles, no doctor would question the cause or hesitate to remove the implant. It's just not the same for women.

I only have time to share a very small fraction of what we see in our group on a daily basis, but I will do my very best to represent these women who have put their faith in me to come here today.

The clinical trial information that Conceptus, now Bayer, presented to the FDA in 2002 is not what is happening in the real world. There is no one in this room who has more experience with what is going on in the real world with Essure problems than me and my team of administrators and the women who have lived through this nightmare. There will no doubt be women here today to tell you how happy they are with their Essure procedure. We understand and expect that. I just hope that they can understand that because of the life-altering damage this device can do to some, we believe it is not fair to sacrifice one more woman, one more mother.

Is it not advancing?

UNIDENTIFIED SPEAKER: Just say click.

MS. FIRMALINO: Click. We've watched mothers have to bury their babies after Essure coils perforated the infant's amniotic sac. We've had to mourn the loss of women in our group. We've seen suicides and we've seen death during or after Essure-related surgeries. We watch surgery after surgery every single day in our group. In fact, there's 11

surgeries going on today. The complications that come with them can be extreme. We've seen the coils in the spine, in the colon, in the kidney, in the cervix. Husbands are walking out on families because women can no longer have sex with them due to the excruciating pain. We've watched mothers cry in despair because they cannot take care of their children anymore. We watch women lose their careers, all because of problems from Essure.

There are patterns of autoimmune disease, cancer, pelvic adhesive disorder, PID, and other recurrent infections that will just not go away. These side effects are extreme. This is not just period-type cramping. The allergies some are experiencing are not just simple dermatitis. These are life-altering side effects that stop you from functioning as a person.

At the time Essure was presented to the FDA for approval in 2002, there were 281 women who had been followed for 18 months, 149 for 24 months, and 5 who had relied on Essure for 36 months. One of those five women is in our group, and so are 17 others of the clinical trial participants. They are finding us, one by one, looking for answers to their failing health and looking for help. You have heard from three of them today. At the last FDA meeting that we had regarding Essure, I invited every single person in that room to please join our group and see what is going on. Look at the reality of what is going on in the real world. No one made that effort.

Epidemico recently wrote and published a paper called "An Analysis of Adverse Event Reporting for the Essure Device in the U.S." Working with our admin team and our Facebook group, we jointly educated women on how to file an event report using the MedWatcher app. They recently presented their findings at a conference in Boston. The

Epidemico employees who had to read and enter the Essure reports told our admins they were absolutely horrified at what they were reading every day.

DR. IGLESIA: Please summarize.

MS. FIRMALINO: The fate of Essure ultimately lies in the hands of the Panel members and the FDA today. Bayer has no intention of issuing a recall or stopping any of this. It's time to take a good, hard look at this. It's time to put people before profits. Either the FDA acts in the best interest of the people or they don't. It is unlawful and inhumane to sacrifice a group of unsuspecting women for the benefit of the majority, especially over birth control.

DR. IGLESIA: Thank you very much.

MS. FIRMALINO: So my slides didn't play?

(Applause.)

DR. IGLESIA: We invite Speaker No. 19. Please state your name and affiliation.

MS. DYKEMAN: Hello, my name is Amanda Dykeman. I have been an administrator on the Essure problems page since 2012, and I have no financial conflicts to report.

Nonsurgical female sterilization, the holy grail of all birth control. For decades, researchers have tried to develop a device to occlude the fallopian tubes without surgery, but they have failed due to migration and serious side effects. In recent years there has been an increase in pressure from governments internationally to put more resources into family planning. In fact, Dr. John Kerin, a lead Australian investigator for Essure, cited this pressure in the early stages of Essure's development in a medical journal, titled "New Methods for Transcervical Cannulation of the Fallopian Tube."

"The pressure in governments and international agencies to place more resources into the population control may facilitate the accelerated development, application, and cost containment of these new devices and delivery system."

That makes it no surprise that Conceptus then appointed someone like Dr. Charles Carignan as an advisor in 1995. Dr. Carignan's work is in the introduction of new contraceptive technologies for government and international agencies such as Planned Parenthood Federation of America.

So I think it's important that someone points out the obvious. Essure was granted accelerated approval in order to provide women with low -- in the low-income population an option for permanent birth control. It was developed and intended to be pushed out in clinics, such as Planned Parenthood, to avoid unwanted pregnancies. The problem with that is that there is not enough long-term evidence to support Essure as a reliable and safe option for use, and women are becoming pregnant.

In a sworn affidavit provided to the FDA in a recent petition, clinical trial participants provided evidence of alterations made to their medical records. These alterations were made by the lead American investigator of Essure, who also held equity positions with the company, providing serious financial conflicts of interest.

When problems persist for women that have been provided free sterilization from the clinics like Planned Parenthood, they have no recourse when things go wrong. Planned Parenthood cannot assist them in emergency surgical situations, and oftentimes these women do not have insurance and cannot afford to pay out of pocket to be seen elsewhere.

Bayer can stand here today and tell you they have years of data and follow-up with

thousands of women supporting the safety and efficacy of Essure. But the truth is none of it supports Essure as safe and effective because we have seen how patients' concerns have been ignored during the clinical trials and passed off as not related to the device. The FDA must revoke Essure's PMA in order to maintain the integrity of data submitted for premarket approval.

Dr. Seifer, you asked, during the original meeting to approve Essure, what the FDA would do in 5, 10 years if we were seeing problems with Essure. Well, the fact is history has indeed been repeated with a failed nonsurgical sterilization device, and we are here to say Essure has failed, and we are all real.

DR. IGLESIA: Thank you.

I'd like to invite Speaker No. 20. And please state your name and affiliation. Thank you.

MS. MYERS: Hello, my name is Kim Myers. I am a victim of the Essure and an administrator for the Essure Problems group.

A big problem we see with Essure are all the "ifs." During the clinical trials with expert doctors and carefully screened women, they failed to place one or both devices in one out of eight women. Many women will go through this procedure, and in reality, Essure won't work for them. There are so many conditions that have to be met for Essure to work. We call them the "ifs" of Essure.

- If they can even place the devices.
- If they are properly placed.
- If they stay in place.

- If the fallopian tubes occlude.
- If you have problems finding a doctor who has enough experience to remove them, can be a problem. Then there is
- If they can even get the devices out without leaving pieces or fragments that may be hard to find and remove.

My experience with Essure included having two devices removed, two devices removed shortly after placement but then spending the next 3 years with chronic pelvic pain, which I would describe as labor-like cramps. I had several CT scans and numerous transvaginal ultrasounds, which were all deemed normal. I finally insisted on a hysterectomy.

The photo of the uterus. That's what was found, a device embedded on the outside of my uterus, during surgery. In the instructions for use manual, it states that the outer device may be visualized. This means that it often is not. This is a huge problem when the devices migrate, break, or fragment and are scattered throughout the body.

As a group, we are not anti-birth control. We are for safe, effective birth control. Essure is not safe and just has a lot of potential for things to go wrong.

I don't have enough time to express what Essure has done to me personally and what I have found it has done to other women over the years. Even if I was given more time, I don't know if I could convey the physical and emotional pain that I and other women have suffered due to these devices, the sense of utter betrayal we have felt from the medical community, who I feel has been manipulated by Bayer into placing these devices in women for profit, which has left most of us fearful for ourselves and our families' future

healthcare needs. Obviously, I feel betrayed by Bayer for putting products before patients, but one might expect that from a for-profit corporation.

But the biggest sense of betrayal is by the people who I thought were supposed to protect us and who I thought operated over and outside the money and the politics. FDA holds all the cards on our health and well-being, and I want it known how the FDA treats the consumer who they are charged with protecting. Let's remember that Essure went through the FDA's most rigorous approval process. The FDA has given Bayer an enormous amount of time over the years to present information claiming Essure is safe. The FDA gave me 3 minutes.

DR. IGLESIA: Thank you.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 21. And please state your name and affiliation.

MS. HIRMER: Hi, my name is Carrie Hirmer. I have no financial conflict of interest with Essure or Bayer. I'm an admin for the Essure Problems Facebook group and also help admin several of our subgroups.

I had Essure done in 2013. At the time, I was running my own consulting business and working on my master's degree in public policy. Within 2 weeks of Essure insertion, I developed an abscess in my left fallopian tube that resulted in a 4-day hospital stay. Two weeks later, I had a hysterectomy. My doctor told me that when he opened me up, the abscess was the size of a softball and was leaking infection into my abdomen. I have survived two brain aneurysms. They're totally unrelated to Essure. But I've survived two

brain aneurysms, and I almost died; I could have died for birth control. Due to all the problems Essure caused, the hospital stays, recovery time, I had to drop out of the graduate program I was in.

My dream had always been to get my master's degree and then go on to get my doctorate. Because of the side effects I'm left with, I am now permanently disabled. Essure took that dream from me. I went from running a successful business and being in grad school to becoming permanently disabled in less than a year.

And I'm not the only one. There are many, many more women just like me, women who lost their careers, their incomes, their financial security, their independence, their peace, their partners, their lives as they once knew it. All for birth control. There are children who no longer have the mothers they once knew. There are husbands and partners who no longer have the life partners they knew. There are families who've lost their homes, cars, farms, businesses, and so much more. All for birth control. There are women who live in constant pain, constant agony, and who will never, ever be the same. There are women who are in so much pain, they were in such despair that they took their own lives. Not one, as said earlier, but two. We have two women in our group who committed suicide. All of this for birth control.

In September of last year, I've seen a lot of women come back reporting really serious health conditions after Essure removal. We started subgroups specifically for them. That group has grown immensely and includes women with autoimmune conditions, neurological problems, spine and joint disorders, cognitive function issues, and more. We recently surveyed those women. Over 77% of them said their doctors don't know what kind

of illness or condition they have. Essure has created something in us that is outside the realm of normal diagnoses. They don't even know what to do to help us get better. Of course, had real long-term studies been done, this would have been known.

In that same survey, over 50% of them said they suffer from things like chronic fatigue, chronic headaches, overall muscle weakness, joint pain, lumbar spine pain, and have bulging discs. The women whose doctors have been able to diagnose them have been handed diagnoses like MS, myasthenia gravis, lupus, fibromyalgia, Parkinson's disease, spine and joint disorders, cognitive disorders. And the list goes on and on and on.

I won't even pretend to understand the science behind how Essure has caused all of these problems. But I do know this: When you have a group of previously healthy women with similar health conditions and one common denominator, there is definitely a problem for us; that is, Essure. We have each been given a lifelong sentence. We agreed to birth control. We did not agree to live in agony and financial ruin while the lives we once knew crumbled around us. We did not agree to watch our children live in fear of us dying. And it doesn't matter what percentage that you claim we make up of the women with Essure, because every -- no matter what the numbers say, every woman matters, every life matters --

DR. IGLESIA: Thank you.

MS. HIRMER: -- every family matters.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 22. And please state your name and

affiliation.

MS. BOGLE: My name is Cecilia Bogle, and I'm with the Essure Problems group.

Essure is supposed to be safe and effective. That has proven to be false for me and many others. Since being implanted, I've become pregnant, had multiple surgeries, and I still have fragments. I've had a hard time finding doctors that can help. In the Essure Problems group, I track and support the women who have become pregnant. These events are devastating for us as the ones who have gone through it. According to what has been reported in our group, women are miscarrying at a higher rate than average. A recent Yale study shows that chances of becoming pregnant are higher than in tubal ligation. Also the risks to the child and the mother are unknown and understudied. In our group alone, we have had 650 reported pregnancies to our group; 273 of those have been reported to miscarry. That's approximately 42%.

There have been eight babies reported to have not survived past the 24th week. Any loss of life is unacceptable. While some babies are born healthy, other babies born after Essure fails suffer from physical disabilities, underdeveloped lungs, asthma, autism, blindness, mental delays, allergies, and much more. These risks are far too high for birth control, and these need to be studied. The babies, that is.

Many families have to go through the grief and loss of a child that Essure should have prevented. After these pregnancies, these coils are left behind to continue to damage our bodies and wreak havoc. Having made the decision to not have any more children and then to find out I was pregnant and having a child was very hard for me. I was very scared, and I was very sick during that pregnancy, and I did not know what to expect. Of course,

now she is the biggest blessing ever, but there are so many things that could have gone wrong. It was a miracle for her to be as healthy as she is.

This product should've never been allowed on the market with such short-term studies for birth control that is supposed to be permanent in the human body, with such minimal study groups. The FDA needs to take action immediately to get Essure off the market, revoke the PMA, ban and prevent further harm to the public. It is unlawful and inhumane to sacrifice a group of unsuspecting women for the benefit of the majority. Our lives matter too.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 23. And please state your name and affiliation, please.

MS. ERVIN: I'm Sharilyn Ervin, part of the Essure patients. I have no affiliation with anyone.

I got my Essure on Halloween as a treat to myself. As soon as I got it, problems started happening. I had migraines, bleeding, cramping. You'd go to the ER; they would have no clue what Essure is. They have to call up somebody, they have to do this. So you're waiting and waiting. It got to the point where I lost all bowel control. My 12-year-old was my caretaker. She had no life at 12. She changed my diapers. She took me to the potty. She bathed me. She had no childhood. She would not leave my side for fear of death.

I was hospitalized for 17 weeks. No one knew what was wrong, neurologists, gynecologists, oncologists, general specialists. They were calling in people from everywhere trying to figure out what could be wrong. What is wrong is these devices that are in me,

taking away my life, taking away my kids, to be a mother to my four kids. They will never know their mother because I cannot be a mother because when I try to -- I have 10 minutes of energy, and then I'm back in the bed because of pain and the suffering. For me, it is too much.

And so all of you that have children, I would like you to think about that. You may be able to go to the park with your kids or you may be able to go to their school function. My kids, I don't even see them enough. They don't know. They think my mom is my mom. Because why? I had to move in with my mom because I lost my job. I can't qualify for anything because I don't have a diagnosis. So I have no disabilities. So at 37 I live with my mother. My four kids live with my mother. My husband lives with my mother.

How much of a burden do we have to continue to put on these women? We've been tricked. My Halloween treat for myself is no longer a treat. It's a trick, Bayer and FDA. And you need to look at this and get it off the market.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Due to the technical glitch for Speaker No. 18 with the slides, we would like you to come back up, if possible, and finish that remainder of your presentation for the slides that were not shown. So do we mind pulling those slides up? And just let us know which one you'd like to resume from because there was -- it was not scrolling during your presentation. So just let us know.

MS. FIRMALINO: Okay. I mean, you can just start it there. I only have four

paragraphs.

DR. IGLESIA: No problem.

MS. FIRMALINO: Epidemico recently wrote and published a paper, "An Analysis of Adverse Event Reporting for the Essure Device in the U.S." Working with our admin team and our Facebook group, we jointly educated women on how to file an event report using the MedWatcher app. They recently presented their findings at a conference in Boston. The Epidemico employees who had to read and enter the Essure reports told our admins that they were absolutely horrified at what they were reading every day.

You see, once you spend a few weeks or even days watching what is going on out here, you cannot help but wonder why this device is still on the market. This is not a lifesaving device. This is just birth control. There are safer and more effective options out there, like tubal ligation and vasectomy.

While we understand the desire of the Population Council and the World Health Organization and the decades of research and trials to try to find a way to sterilize women in an office setting, we are here to tell you Essure is not the answer. The fate of Essure ultimately lies in the hands of the Panel members and the FDA today. Bayer has no intention of issuing a recall or stopping any of this. They just invested millions in a new manufacturing plant in Costa Rica for Essure, and they just got approval from the FDA to replace the follow-up HSG with transvaginal ultrasound. One of the women from that clinical study just gave birth. She got pregnant after her confirmed ultrasound. And even though her clinical trial paperwork said that she would be compensated a whopping $800 if she became pregnant, she has yet to see that money.

You see, not only do we have trial participants from the original studies, we have them from a slew of postmarket studies as well. And just like in the case of Conceptus, Bayer seems to cut ties with anyone who has a problem with their device in the trial, and it's time to take a good, hard look at that. It's time to put people before profits. Either the FDA acts in the best interest of the people or they don't.

DR. IGLESIA: Thank you very much.

MS. FIRMALINO: Thank you.

(Applause.)

DR. IGLESIA: I'd like to call up Speaker No. 24. And please state your name and affiliation.

MS. GARCIA: Hello, my name is Janie Garcia, and I have no financial interest or conflict. Thank you for giving me the opportunity to come here before you and speak about the wide range of concerns and dangers regarding Essure, with emphasis on removal of these devices.

As co-administrator of two Facebook pages relating to Essure issues, I see thousands of women seeking direction and answers to their concerns. The Texas page has over 900 women, and the Essure problems multinational main page has over 21,000 members. Women who are considering Essure often join the group to ask questions, but most of the women in our group already have Essure and are seeking answers to their questions they have about the deterioration in their overall health. These women are frightened and desperate for help. On a daily basis, I see comments from thousands of women expressing a regret of having this procedure done. Women in this group consider themselves lucky to

have a removal and/or hysterectomy. Imagine looking forward to a major surgery. The fortunate women only require one surgery to remove these devices. Other women like myself have not been so lucky.

Since the manufacturer has only one protocol for removal, many doctors are removing these devices improperly, causing breakage of the device. And fragments are left behind, resulting in multiple surgeries and many other complications. This concern is the cause for one of our doctors in our group who has helped many women with removal to begin his study in hopes of developing an appropriate removal protocol. This protocol should have been in place upon approval of the device.

It would seem the women facing surgery to remove devices are a part of a separate clinical trial, one with no control or standards. My first surgery was removal of my fallopian tubes and Essure, as well as a DNC and a NovaSure ablation. I continue to have pain and excessive bleeding. So 5½ weeks later I had a hysterectomy, yet another surgery to remove my uterus, cervix, along with the fragment and clip left behind from my first surgery. Three weeks later I was fighting for my life against an infection and underwent a third surgery to drain the abscess that I had developed. And I had to wear a drain bag at home for a week to drain the abscess.

After this, for 4 months, I continued to have pain and underwent my fourth surgery to remove my left ovary, which had adhered to scar tissue throughout my pelvic area and my bowel due to the inflammatory response caused by the PET fibers found in Essure. These surgeries caused so much pain and every emotion you could possibly think of, not just for me but my entire family. This is not often acknowledged but a very real side effect.

This put the strain on relationships, finances, and quality of life.

Doctors must have a standard for removing these devices safely and completely. Had this been in place, it's likely that I would've only had one surgery. Hindsight is always 20/20. However, knowing all that I know now and have learned in this process, it seems logical to assume that the permanent sterilization being a foreign body was not a good thing or that if it did not work for someone --

DR. IGLESIA: Thank you very much. Thank you.

(Applause.)

DR. IGLESIA: Before we go on with Speaker No. 25, I'd just like to remind the audience that flash photography is not allowed.

Would Speaker No. 25 please make it up to the podium? Mr. Myers. William Myers.

(No response.)

DR. IGLESIA: Okay. How about Speaker No. 26, Mr. David Bogle.

MR. BOGLE: And I am here because my wife had got pregnant after Essure and now has fragments that are unable to be removed. And I have no financial conflict of interest.

As a husband, it is hard to see your wife in pain. I am sure that it's heart wrenching and stressful for any husband that has been put in this position. Having to watch my wife go through multiple surgeries and the risks involved, it is extremely stressful and downright scary. Our wives that have been victims of this dangerous device are not the only victims. Watching my wife in pain and unable to do the things she used to be able to do has taken a toll on my entire family. There are children with injured mothers and husbands that have to cope with the complications from Essure. The stress upon our relationship and intimacy,

though not talked about a lot, is a big factor when this implant fails our wives due to where Essure is located. I can live with the failure to prevent pregnancy, and I love our daughter regardless, but the failure to be safe in the human body is unacceptable.

I believe action needs to be taken to assure these injuries do not get ignored or continue to happen to unsuspecting women everywhere. More studies are not going to make this product any safer. I believe what is happening right now with women that already have this device speaks for itself. I feel a vasectomy or a tubal ligation is already safer and more effective than Essure. There is no need for this product to be put in another woman's body.

Thank you.

(Applause.)

DR. IGLESIA: Thank you very much.

Speaker No. 27. Please state your name and affiliation.

MR. SHIELDS: Good afternoon. My name is Wayne Shields. I'm President and CEO of the Association of Reproductive Health Professionals. I haven't received any financial support to be here today, and I'm here to represent my organization's 14,000 healthcare provider members, who are physicians and nurse practitioners, physician assistants, nurse midwives, and counselors. ARHP has in the past received grant support from Bayer.

I wanted to thank the Panel today for basically how well you handle these types of inquiries, and ARHP's members and leaders really respect the thoughtful process that you take and appreciate your continued reliance on the best available science to inform your decision making. But I also want to, on behalf of my organization, respect and acknowledge

the experiences of the women you've heard in this room today. They're very real, and it's important that we hear them and important that the providers hear them as well, my people.

ARHP believes that more comprehensive provider education is part of the solution, and we do believe and support continued availability of transcervical sterilization, like Essure. We just advocate for more effective, comprehensive provider education as part of the solution.

To describe the people I work with, they're actually a lot like you on the Panel. A lot of folks are researchers, health researchers and professionals who also practice healthcare, and that's who my folks are. But we're an accredited group who focuses on sexual and reproductive health specifically. So this is an issue that's key to my folks. And really they do need to be -- do the best possible evidence-based, patient-centered care when it comes to this method and any contraceptive method. So as I said, we advocate for that as a solution.

ARHP really supports evidence-based education and policy as well, and we look to the literature and expert consensus to guide provider education. When the literature isn't full enough, we rely on guidance from other groups, like ACOG, and we rely on consensus of experts in order to develop our education. And we have a huge emphasis on what's called client-centered care. That is kind of a fancy way of saying it's not up to the healthcare provider to make decisions for every individual. It's up to that individual, especially because everybody's unique. So we really want the availability of as many safe and effective choices as possible. The alternative to a pregnancy that's not prevented is there are issues,

including -- up to and including continuing with a pregnancy that has many health risks. So we can't avoid that as part of the conversation either.

We do take the position that transcervical sterilization is an important option to women, especially for those who no longer want children but prefer to avoid the more invasive process of tubal ligation or the health risks of pregnancy.

As an organization, we spend a lot of time and energy at educating providers about options counseling and in particular about educating about risk and benefits.

DR. IGLESIA: Thank you very much.

MR. SHIELDS: Thank you.

DR. IGLESIA: Thank you.

I'd like to invite Speaker No. 28 to come up. And please introduce yourself and state your affiliation.

DR. NOVOA: Hello, my name is Dr. Julio Novoa. I am a practicing OB/GYN from El Paso, Texas. I've been in private practice since 1999 and have managed over 15,000 patient cases, including 5,000 deliveries, and have performed over 1,000 in-office, awake surgical procedures and over 1,000 laparoscopic tubal ligations. I am the main commentator for the Essure Problems forum on Facebook, representing over 20,000 women from the United States, Canada, the U.K., Ireland, Australia, the Netherlands, Spain, Finland, and New Zealand. I would like to say, for the record, that I have no conflicts of interests to declare, and I am not being paid by anyone to be here, or any organization for my testimony.

Essure problems patient surveys and Essure MAUDE data analysis have shown exceptionally high complication numbers, including pelvic pain, abnormal bleeding,

improper placement, implant migration, and device failure leading to pregnancy. These percentages represent thousands of real people and are in stark contrast to what is quoted in the company-sponsored trials. The FDA's reliance on company-sponsored clinical data is by its very nature flawed. Published data suggesting a high level of efficiency and safety regarding the Essure is based on experienced clinicians representing ideal and not real-case scenarios. Relying so heavily on such small group sampling factors out time and procedural errors, learning curve errors, and malpractice errors caused by the novice hysteroscopic surgeon or, most commonly, the inadequately trained and inexperienced gynecologist placing the Essures.

The Essure MAUDE data is also limited. It does not include the 16,000 adverse reports file turned over to the FDA by Bayer. And more importantly, the vast majority of patients are completely unaware that the MAUDE data reporting system even exists. Therefore, the actual number of adverse reports appears to be grossly underreported and well above 25,000 adverse cases. Data collection from Essure problem surveys lists over 500 unintended pregnancies with ectopic pregnancies, and Essure-induced abortion rates as high as 40%. Further, Essure-related salpingostomies, salpingectomies, and/or hysterectomies now average over 100 cases per month, with 11 cases being done just today.

The FDA is also guilty of complacency by continuing to allow Bayer to advertise the placement of the Essure as a nonsurgical procedure, which this is on the website, in the literature, and in the clinical manual as nonsurgical. The placement of the Essure is absolutely and unequivocally a surgical procedure. Medical state board regulations,

hospitals, surgical privileges, CPT coding, as well as insurance company preauthorizations list the Essure operative hysteroscopic procedure as a surgical procedure. Advertising the Essure as nonsurgical is not only misleading but unethical and potentially criminally deceptive. Allowing this to continue compromises the trust and welfare of the U.S. consumer and must stop immediately. Before the close of this meeting, the FDA should order Bayer to stop advertising the Essure as nonsurgical. They'd do anything less --

DR. IGLESIA: Thank you very much. Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 29. And please do state your name and affiliation.

DR. MONTEITH: I was told I had 6 minutes, so I'm not sure --

DR. IGLESIA: You do indeed, sir.

DR. MONTEITH: Okay. My name is Dr. Charles Monteith, and the only conflict of interest I have is with myself, because I am here to speak out against the Essure device, but I also make my living based on treating Essure-related complications.

As a former medical director of Planned Parenthood of Central North Carolina, over a 4-year period I did over 60 Essure insertion procedures. Currently I practice -- my practice is devoted to female sterilization reversal, and I have performed, over the last 6 years, 233 surgeries to remove Essure devices, both for women who wish to become pregnant and for women who are having side effects from the device.

Sterilization procedures should be as safe to use as fire extinguishers. They should be easy to use, highly reliable, and should not cause harm to the user. I would like the Panel to consider a fire extinguisher that my company has designed. We have found that, in

our pivotal trial, it discharges propellant 88% of the time with the first time used. If it doesn't work the first time, that's okay. You turn it upside down, you shake it, you wait 10 minutes, and an additional 4% of the time it will work. We feel that this is acceptable because it will put those fires out. Only 8% of the time did the extinguisher not work, and in this case we recommend a more traditional, older method like running and calling 911. We had four adverse events. The extinguisher exploded and embedded propellant into the hand of the user, but that was corrected with surgical debridement. My question is, would any of us approve this fire extinguisher for general public use? Would any of us feel comfortable with this less than perfect fire extinguisher in our home?

One of the biggest problems I had with inserting Essure is that I never knew if it was going to work when I sat down to insert it. I was never sure if I was going to be able to get the device in bilaterally. And if I did, I was never sure if I was going to see the patient back for the confirmation test. In the pivotal trial, basically about 1 out 10 times you couldn't insert it successfully the first time. So if I asked everyone to fly on an airplane with me and the landing gear would not retract 1 out of 10 times, how many of you would want to fly with me? It's okay, we can take the plane back around again and try a second time, and a lot of the times it will work the second time. But if not, we can abort and just do a soft water landing. Essentially, that's what we're dealing with when we're talking about Essure sterilization. When you're going into a sterilization procedure, you may only have one time to get it right.

In regards to Essure complications, unlike hormonal treatment, Essure can't just be stopped. Unlike intrauterine contraception, there's just no string to pull on to remove the

device. Essure can only be removed with surgery under general anesthesia. The recommended treatment has been cornual resection, although most gynecologic surgeons have limited experience with cornual resection. Attempting to remove the device with traction can oftentimes result in fracture of the device. Women who have Essure complications are having hysterectomy procedures because this is a surgical procedure that most gynecological surgeons are familiar with.

We have just conducted a 14-year, non-randomized, uncontrolled trial on the effects of Essure on American women, the complications of which have been reported by self-reporting, which we know notoriously underestimates complications. The complications have come from small trials and some international trials. Guys, we know where we are with this. We have reached this fork in the road. And as the late Yogi Berra said, when you get to the fork in the road, you got to take it. It is time for a randomized controlled trial on Essure versus other methods of sterilization.

I would like to challenge Bayer that if you truly care about the health of American women, that you would fund such a study and have this study look at patient-centered outcomes, and have a third party who's not affiliated monitor and oversee this study. I would like to commend Bayer on improving the physician educational materials. Those materials were far better than anything I ever had when I was with Conceptus, when I inserted the device and Conceptus was the manufacturer. But you can also look at the device and see how -- or that educational handout and see how difficult it is. It's not always an easy procedure to do.

In conclusion, sterilization procedures should have the same safety standards as do

fire extinguishers. A fire extinguisher that requires many steps, does not work 12% of the time, harms its users, requires major surgical treatment for those injured by the device would not be considered acceptable for public safety. I don't see why we would consider the Essure sterilization method any differently.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 30 to the podium. Let's make way. Please state your name and affiliation.

DR. NOORCHASHM: Good afternoon. My name is Hooman Noorchashm. I am a surgeon and a Ph.D. immunologist in Philadelphia.

I've had the very unfortunate privilege of being in this very room before a similar panel advocating for patient safety, for women's health, for medical ethics. And I have to tell you that without a clear understanding of medical ethical principles, which there's very scarce discussion of here, practice will be turning into unforgivable harm. And first I want to remind every federal agent and federal officer here that you are guardians of the public and of an agency that's charged with protecting every American life. You're not here to protect Bayer's interests or the gynecological community's interests. You are here to protect the interests of people, of the public.

It's very ironic to me that we're sitting back here, the advocates and the patients, and Bayer is sitting on that side with FDA and with the expert Panel. Very ironic and surprising.

Ladies and gentlemen, you've heard a lot about Essure. It's a nickel-based coil. It's

placed in the fallopian tubes in otherwise young and healthy women. Okay. This device is not designed to cure an incurable disease. It's designed to irreversibly prevent pregnancy, and there is a lot of doubt as to whether or not it's effective here, okay? It's designed to create an inflammatory response in the mucosal surface, which is poorly understood and really was not part of the PMA process, the study of basic immunology. I think if you tapped Dr. Milner's expertise here, you'll find out that the study of the mucosal immune response to nickel was never part of the original PMA process. This inflammatory process goes rogue, and what you're seeing here is a group of women -- and I'm going to ask you folks to stand up and remain standing until I'm done so everyone sees you clearly.

So it appears that Bayer here and the gynecological industry are having us accept this concept that majority benefit justifies avoidable harm to minority subsets of people. And, you know, I ask you to consider what failed societies of the past have done that. You know, we're talking about something that's avoidable. It's a medical device that's completely avoidable. And what I want to know from this Panel is what percent harm are you going to accept, 0.1%, 1%, 5%, 10%? And how are you going to justify that? Preventable, avoidable device, avoidable harm, this minority subset of women.

You know, we're at a crossroad here in American medicine and in particular, it appears, in women's health and at the Center for Devices and Radiological Health, okay, because it appears that the preservation of choice, the preservation of convenience, the preservation of majority benefit are overriding the sound principles of medical ethics, okay? And that's okay as long as it's a minority subset of lives. I ask you, is that acceptable? I ask industry, is that acceptable? I ask the expert Panel, is that acceptable? I ask the FDA, is

that acceptable?

You see these folks who are standing up here? They can't even take their case to court because the Supreme Court of the United States has taken away their right to seek justice in the court system --

DR. IGLESIA: Thank you.

DR. NOORCHASHM: -- because this device is a PMA-approved device.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 31 to the podium. And please state your name and affiliation as well.

DR. REED: My name is Amy Reed. I don't have anything to claim. I have my M.D. and Ph.D. in immunology, and I'm here to support all of these women who have been harmed by these Essure coils. And I'm here to talk to you about why it might be easy and convenient to do it in an office or an outpatient setting, and it might have great efficacy or maybe not. But the fundamental basis for the Essure coil is immunologically flawed, as any immunologist would say and my husband referred to.

How Essure coils work. The basis for which they work and the problems that they cause and the inability to quickly fix them, that makes them an unsafe device. And I'm sorry if this wasn't studied appropriately, and that's what I'm hearing beforehand. The Essure coils, the nickel, and then the metal, and then they cause scarring. And I've heard that some people dumb this down and say, oh, well, we use similar metal in stents. But that's not a mucosal surface. That's like someone saying I need contact solution, and I say, oh, I

have some nail polish remover. It's safe. It's apples and oranges; it's wrong marketing, and it's lying to an entire group of women.

Regardless, this inflammation goes completely out of whack, as you have here. Women are presenting just like you would see in a rheumatologist's office, hair loss, rashes, joint pain, tired, all of these diffused kind of, well, we really can't pin it down and it doesn't happen all the time. These are classic symptoms of immune symptoms run awry. And these poor, otherwise healthy women are subjected to these horrific, big abdominal repeated operations to try and fix this. But you can't stop this runaway train. In a lot of cases, you can't reverse an immune system that's gone crazy just by an operation. And I'm sure these women, too, have experience with this.

So what recourse do these women have that have been subject to this deliberate inflammation? And like my husband alluded to, it's because you all put this stamp of approval on it. The Supreme Court said the PMA process says this is a perfect device. You don't have recourse to seek out damages in a civil court. Sorry, the FDA says it works and the federal government says it works. But, importantly, what kind of onus of responsibility does that put back onto the company if they have 0% liability exposure? A bunch of women with a few symptoms comes to them. The federal government says they're protected. None. They have no incentive to seek out what's going on here.

So I ask you, the members of the Panel, the FDA, we don't need registries, we don't need to hurt any more women. There are plenty of them here.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 32. Speaker No. 32. And just please state your name and affiliation.

MR. ROKICKI: My name is Ryszard Rokicki. I'm independent researcher in metal finishing field, specializing in biochemical compatibility improvement of medical device made of nitinol, stainless steel, and cobalt formulary. My credentials can be found from ResearchGate webpage. I report no conflict of interest.

After denied my citizen petition and restricted from public view my open letter to FDA Commissioner and most recently my comments concerning safety of Essure, FDA should be well aware what's causing the Essure-made problems and how to fix it.

In my opinion, there are only two ways to resolve the sometimes severe medical problems connected to Essure: totally ban it or make it safe. To make it safe, the faulty nitinol material outer coil of device with surface intermetallic inclusions should be detected and discarded before device is assembled. The only way to achieve this is to use very simple, cheap, 100% reliable chemical test for detection of nitinol surface intermetallic inclusions.

The uniform nickel leaching from properly finished nitinol without surface intermetallic inclusions, even if galvanically coupled to another metal, as in case of Essure, is of negligible importance. However, nitinol surface inclusions of adjusted matrices are source of catastrophic nickel leaching to surrounding tissue after implantation.

Somebody can ask, why don't we hear a similar complaint of people implanted with other kinds of nitinol medical device such as stent, heart valves? The answer is place of

implantation. Stents, heart valves are vascular devices permanently exposed to blood flow, and therefore nickel leached from them to surrounding blood is carried away and eventually leaves human organism with urine. However, we have totally different situation with Essure, which is permanently embedded in tissue of fallopian tube. In this case, leached nickel from surface inclusion or adjacent matrix stay and accumulate in tissue which is in direct contact with leakage.

At present, checking nitinol medical device for surface intermetallic inclusion is governed by ASTM F206 test, which is performed visually by inspecting nitinol samples. This test was the reason given by FDA for denying my citizen petition, which demanded the introduction of more reliable, 100% pure sodium hypochlorite test procedure. The FDA stated that visually inspected samples of nitinol lots per present test will protect public health while not overburdening manufacturer of nitinol. This is an important statement. However --

DR. IGLESIA: Can you please summarize?

MR. ROKICKI: Yes, thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Our next speaker is Speaker No. 33. And this speaker will have 9 minutes.

MR. BELL: Good afternoon. I'm Mark Bell. I am a licensed registered metallurgical engineer, and I wanted to talk about the Essure failures. I don't have an interest in Bayer. As a consultant, people hire me to give an unbiased, factual engineering opinion. And so

that's what this presentation is going to be. So it's just the facts. I try not to be an advocate, but as an engineer, I can present the facts. But it's hard, it's difficult not to get emotionally involved because I've got daughters-in-laws, I've got a wife, I've got nieces, and this really speaks to -- everybody can identify or empathize with this problem.

So my analysis. I think that just the physical way the Essure is being made is -- the ones that I've seen, there's latent manufacturing processing defects. These didn't come from being in situ in service inside the ladies. It's actually preexisting, so I call it latent.

Next, please.

I've introduced myself. I have 40 years of experience. I do failure analysis. I've done probably 1,000 of them. Different types of machinery, different types of metals. Some pharmaceutical, some biomedical, but a lot of it is food processing, oil, energy, and just metals.

It's my expert opinion, based on the studies I've done, is that Essure is not a safe product, especially compared to what I've seen industry be willing to scrap, walk away from if it's a defective material, not to continue to process it, not to put money into it, not to sell it, and not to have it in the field. And once they find out there's something wrong with it, my experience with industry is they pull it. It's good business, it's moral, and it's a good engineering decision not to let it stay in service.

Mid-level engineers have the power, if they see something defective in a Fortune 500 company -- if I've seen something wrong with a big expensive compressor, I write a stop order. Manufacturing stops until the problem gets addressed. And that's the same way I have done my analysis with Essure, is to evaluate this on a factual engineering decision.

So next, please. Please.

We talk about risk analysis. I'm sure most of you all have seen charts like this. The idea is you've got severity, and you've got likelihood. What you want to do is avoid the scenarios where you get a high likelihood and a high severity. In that red up there, that's unacceptable. You want to avoid situations like that.

Next slide.

Terrible. Sorry about the lighting. It repeats what I just said, avoid combinations of high severity and high likelihood. And what I've seen on Essure manufacturing, you've got a high likelihood of a failure. And the rest of the day has been spent on how severe it is when these things do fail.

Next slide.

So here's an Essure that I've looked at in my lab.

Next slide.

I can tell when -- this is a stainless steel wire from Essure. Now, this is the end that's probably been cut from manufacturing. It's fine, but the point I show you is, is you can distinguish between something that's failed in service and something that is cut. This probably is acceptable.

Go ahead.

See, it's just a close-up. That's a very thin stainless steel wire that's been cut.

Go ahead.

That's the marker that shows you how far you should pull the Essure out. It's stainless steel, but you can see how it's expanded. You can see the desiccated body tissues

on it. It's a good way to analyze these products.

Next slide.

See the ribbon? There's a blue arrow on there.

Let's go to the next slide.

That blue arrow pointed to the tip of this ribbon. Now, this ribbon is probably three-tenths of a millimeter wide, and it's very thin, and I have no idea what the loading is on a human body in the fallopian tubes, but apparently it migrates, it moves. There are stresses on it. And let's look at some of the flaws in the metal that might accentuate the loading of the body stresses.

Next slide.

And these are latent material defects, is what we're talking about. They existed before it was even inserted.

Next slide. Boy, if those overhead lights could be dimmed. This is a good slide. It's from an electron microscope. Is anybody going to do that? Dim the overhead lights because that slide is washed out. If you could, please.

What this is showing is probably some cracks in the edge of that ribbon. How do you make a part like that? You can't machine it; you can't grind it. You have to be very careful as you draw it and bring it through the tooling. I think there are some cracks on this, and these cracks are parallel with the edge of the ribbon.

Next slide, please.

This is the same thing. There's an edge. There are some cracks in there, or there are some surface defects, and as the ribbon is bent and flexes, these defects will act as stress

concentrations and make it very likely that the ribbon will fail and break in service.

Next slide, please. Go ahead, next slide. Yeah. Next slide.

See, I've got some arrows pointing to where these surface defects are. Are they cracked? They could be. We need to do some more analysis, but I think it's good calling it a defect, and this could initiate the fracture of the ribbon.

Next slide, please.

This is just the surface finish. It's not polished; it's just rolled. And this is the nickel-titanium ribbon alloy. Fairly rough. I would be very surprised if that's acceptable to be in a medical implant. Usually I see things that are electropolished and very, very clean surfaces.

Next slide, please.

So I would consider even this to be a latent defect. And you can see the horizontal lines from the rolling and the handling of the ribbon.

Next slide, please.

Some things you can just look at. The tip of the insert, do you see where the red arrow is?

Next slide.

That's that melted tip of stainless steel, and even that gets damaged from packaging, from handling, or from removal.

Next slide, please.

Just a close-up of that. That's not a defect. That's probably not going to cause a failure, but it's easy to find things like that.

Next slide, please.

These are the stainless steel wires. Very clean, very good. They're not nickel-titanium.

Next slide.

The edge. The crimped nickel-titanium is that sheet that's crimped over the wire. I think it might have failed there.

DR. IGLESIA: Please summarize.

MR. BELL: Next slide, please.

My recommendation is that a stop order -- these Essure products should be stopped from being put on the market until more work has been done to show that there are preexisting latent defects.

DR. IGLESIA: Thank you very much.

MR. BELL: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 34. And please introduce yourself and state your affiliation.

MS. SHEPPARD: My name is Audrey Sheppard. I have no financial relationship with any organization affected by the topic of this meeting. Professionally, I consult to organizations seeking to see that safe, effective products are available to fulfill women's unmet needs.

In late 1994, I joined FDA's new Office of Women's Health. As a layperson, neither a scientist nor a health practitioner, during my 5-year stint at the office, 4 years as its director, my emphasis was making sure that science was faithfully followed and also taking

a pro-consumer approach to women's health questions and issues. I have the highest regard for women consumers as they champion their own health needs and consult their healthcare providers about what makes the most sense for them. And I take most seriously the testimony of the patients sitting around me that we're hearing from today.

My now 25-year history in women's health led me to my decision to speak today because I think that your review is critically important. With a one-of-a-kind product in the category of permanent contraception, there may be a strong need for action to further protect the future female consumer. But what are those actions? I've rewritten this a lot.

We all know that women, nationwide, use and depend on various FDA-approved methods. Ninety-nine percent of American women ages 15 to 44 have used at least one contraceptive method during their lives, and permanent birth control is the second-most common form of contraception employed by American women. Like any product the FDA approves, this one must pass scientific hurdles and continue to pass them. We can only imagine that there are tens of thousands of women who have the product who are doing well, appreciate the benefit of not having to have surgery, to take hormones, who are going about their lives today. As advisors to this Panel, you have your work cut out for you because weighing the need versus the problems is really, really tough.

I can't necessarily follow all of this. Okay, I am optimistic that patients, advocates, clinicians, the company, with a careful review of all available data, that you, the advisors, and you, the FDA and the division, will find the right answer. This is not an easy one, and I don't envy you.

Thank you for your time.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 35 to the microphone. And please state your name and your affiliation.

DR. JURAN: I have slides, too. My slides?

DR. IGLESIA: Got those slides up? Do we want to work on that and go to Speaker No. 36? Let's do that. I apologize. If you would just work with the people on the side and we'll move to Speaker No. 36.

MS. HENZE RUSSELL: I have slides.

(Laughter.)

DR. IGLESIA: And we have them. Please state your name and your affiliation.

MS. HENZE RUSSELL: Thank you. I am Laura Henze Russell, the principal of Precision Research and Communications. I have no conflicts to disclose. I'm here to present and call for a framework for precision devices to look at whether a device such as Essure is right for you, for the individual patient.

Next slide, please.

So patients are on a bell curve. The lucky ones that are not in this room are in the fat and happy parts of the bell curve. The people who are here and the 20,000 that they represent are on the tail ends of the bell curve, what I call the bell curse. So 1% to 3% we currently have identified as being in the bell curse. Unfortunately, it tends to grow over time. Here's an early warning signal. A number of women are losing fillings and teeth at early ages, which shows the impact of bioaccumulation for people with genetic methylation

defects when there's the synergistic impacts of metals, perhaps in your fillings, of galvanism, and so forth.

Next slide, please. Next slide.

This slide presents 12 gene variants that are associated with methylation defects that have been identified with heavy metals toxicity. The primary route for nickel toxicity is depletion of glutathione. That's essential for many processes in the body, and as we've heard, inflammation is the root of many chronic disease processes.

Next slide, please.

OB/GYNs help women bear and then care for children, the next generation of Americans. We ask you, throughout the process from approval to postmarket surveillance, to use the highest standards for safety.

Clinical trials need larger numbers, longer duration, basket studies. There are pretests that can be done to determine blood reactivity to device materials that can be used in advance, in addition to patch tests for allergies. You've heard, though, it's not just about allergies; it's immune reactivity. So we should screen patients for exclusion factors based on them. We need informed consent for health and cost impacts. The cost impacts are off the charts. Postmarket surveillance. And I would like to see all panels have a toxicologist and a geneticist on them.

Next slide, please. Next slide.

The outcomes will be better health and lower healthcare costs for all stakeholders. It will help women's lives and reduce ugly surprises.

The last slide, please.

In conclusion, Essure is easy in, high risk for too many, and hard and costly to remove. It should not be used. It should be recalled. There are lower-risk, safer alternatives. We ask you to join a call for medical and dental device safety urgent reform. If you have any questions, please contact me or other women in this room.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Okay, we're going to still move on to Speaker No. 37, please. And please state your name and affiliation.

MS. PEARSON: Hi, I'm Cindy Pearson. I'm the Executive Director of the National Women's Health Network. We don't accept any financial support from pharmaceutical companies or medical device manufacturers.

In 2002 we spoke before this Committee advocating for the approval of Essure. At that time we commented on the importance of providing information on the risks, benefits, and potential consequences of Essure to prospective users. In light of recent developments and the new evidence brought forth in the form of women's personal accounts, the network now believes that the FDA should require Bayer to significantly revise the patient information guide and to sponsor a national registry. These steps, which are within the authority of the FDA, would go a long way towards meeting women's needs for full, accurate, and objective information about Essure.

The personal and brave testimony of the women speaking here today should not be dismissed by the Panel simply because it did not result from a clinical trial. Women's

reports of pelvic pain and autoimmune disorders should be taken seriously, and these experiences should be easily available to other women considering Essure. Women who are considering using this device deserve to know this information. No woman should learn after the fact that more information was available which could have affected her decision to take a particular drug or use a certain medical device.

So today we ask the Panel to recommend that the FDA change the labeling and patient information guide for Essure. A paragraph should be added explaining that women have experienced an array of adverse health effects after receiving Essure, and this section should explain that while these effects were not reported during the clinical trials or not reported in significant numbers, the information is being added in order to be transparent about women's experiences with this product.

We also ask the Panel to recommend that the FDA take patient labeling one step further and require that women receive written information about the device prior to implantation. The FDA should use all of its resources to make this knowledge sharing of women's experiences real.

And, finally, today we call for the creation of a national registry to serve as a central database for women who have received Essure. This registry should be funded by Bayer and administered by a third-party vendor. The purpose would be to make sure that all women with Essure are followed and that data collection and analysis is not controlled by the Sponsor. Requiring a registry is within the authority of the FDA, and we urge the Panel to recommend this important step.

Ignoring the voices of women standing before you today leaves out women's

experiences that do not fit the narrative that serves the purposes of the Sponsor. The physical and emotional effects these women have suffered are real. Their stories and voices deserve to be heard and respected.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: We're ready for Speaker No. 35. Thank you for your patience. And when you come up to the microphone, just state your name and your affiliation.

DR. JURAN: My name is Rupal Juran, and I am a board certified OB/GYN. I'm also fellowship trained in minimally invasive GYN surgery.

Next slide, please.

I have no financial disclosures, and I have no financial relationship with Bayer.

Next slide.

As a gynecologist, I talk to women about health issues every day, and I feel that symptoms reported as being related to Essure unfortunately affect the entire population of women at pretty high rates, as this slide shows. And I wanted to demonstrate with this slide the frequency of many of these health issues that women and I, myself, as a woman, have faced throughout our lives. As a gynecologist, I've seen these issues in women who have gotten tubals, whose partners have gotten vasectomies, and who are using no birth control at all. I also want to point out, the lifetime hysterectomy rate among American women is 45%, and these numbers are all from peer-reviewed papers published in scientific journals.

Next slide, please.

This slide demonstrates the lifetime prevalence of other medical issues that we, as women, may face throughout our lives. Unfortunately, many of these are pretty common too.

Next slide, please.

All that being said, first, I want to say that the medical and health issues faced by all the women who came here today are very real. And, you know, if a patient came to me saying she wasn't comfortable with her coils and she really wanted to get them out, I would say this is your body, let's get them out. But I am concerned that women in a vulnerable position, who already are not feeling well, are being told they must have more surgery or being told that simply removing their Essure coils is going to resolve their health issues, or being told that they need to have a hysterectomy to remove the coils, which may not be true. The health issues that women face after Essure may or may not be related to their devices, but I'm concerned that women are being told that they need to have more surgery to cure them.

Next slide, please.

On a different tack, when a patient requests sterilization for herself, we have two options. And this has been discussed already, but one option is tubal ligation, which does require general anesthesia and abdominal incisions, and the failure rate can be as high as 3%, and the complications can include perforation of bowel, bladder, or uterus at a rate of 0.4% to 1%, and 4 in 100,000 result in death. And I'm sad to say that I've seen some of these complications after tubals.

Next slide, please.

By contrast, the only other option for female sterilization is Essure, with the nickel-titanium coils placed in fallopian tubes usually without having to access the abdomen. The risks of perforation and expulsion are part of the counseling, as seen here on this slide. And then the risk of hysteroscopy include the small risk of perforation and hemorrhage.

Next slide, please.

So I want to point out that I feel that Essure should remain an option for women. And while no method is 100% effective or 100% complication free -- and complications from all sterilization types are rare. But, overall, the complications from Essure do tend to be minor compared to the complications that we see after tubals, and Essure has been shown to be more effective. And I am looking forward to more data in that regard as well.

And the next slide shows my references. I also want to, on a personal note, say that in our practice we've done over 1,300 Essures, and I personally have done about 200, and I feel very -- I'm so glad that my patients could have that experience. We have no pregnancies. We have no damage to bowel, bladder, or vasculature with our Essure procedures. We have a very high patient -- rate of patient satisfaction. I'm very glad we were able --

DR. IGLESIA: Thank you.

DR. JURAN: -- to offer that to our patients instead of abdominal surgery.

DR. IGLESIA: Thank you very much.

I'd like to invite Speaker No. 38. Speaker No. 38. And when you make your way up to the microphone, then just please state your name and affiliation.

MS. ROMERO: Good afternoon. My name is Tabatha Romero, and I have no affiliation with Bayer.

On June 4th, 2012, I was implanted -- oh, I'm sorry. Excuse me, I have some slides. And where is the little monitor that I can -- oh, okay. Perfect.

DR. IGLESIA: Do we have her slides before I start the timer? Is that it?

MS. ROMERO: That is it.

DR. IGLESIA: Great.

MS. ROMERO: Okay. On June 4th, 2012, I was implanted with two different versions of the Essure device, ESS305 and ESS305-R1.

You can switch the slide.

It has been the worst mistake of my life. I currently suffer from 18 side effects since implantation. The most noticeable and life-altering side effects are severe daily pain, extreme fatigue, noticeable hair loss, severe cramping and debilitating menses, continual yeast infection, brain fog, painful intercourse, and depression. After 2 years of receiving zero help from my physicians with my pain, dissatisfaction of comfortability with the implants, and many other symptoms, I went out in search of what could be done to remove Essure.

I got a hold of my implanting report, HSG images -- you may click the slide -- and radiology report. It was then that I discovered -- the next one -- several discrepancies in the operative report -- the next one -- and radiology reporting, and an even greater finding. Both right and left coils were positioned incorrectly, in which you consider a grade 3 position, too distal into the fallopian tubes.

In months to follow -- next slides -- I would encounter woman after woman joining the group who were also suffering from incorrectly placed devices, all the while being told by their physicians that everything was normal or that we were the very rare cases of Essure. But not so fast. Because your Panel was fully aware of many flaws, one that I would like to bring the attention to is the failure rate of 12% in the clinical trials. And that failure rate was among expert hysteroscopists. In fact, your Panel spoke in great detail that the probability of the failure rate of 12% would increase when introduced to practicing 35,000 GYNs who are not experts.

Dr. Noller, who was on the Panel, basically screamed from the rooftops about the failure rate, and I quote him in regards to the failure rate. "I expect it's going to be 20% among people who don't do this very often. So even with the 12% rate, if women are told up front, unless there is a fallback plan like laparoscopy at the same time, I don't know why they would accept this." He went on to add, "It just doesn't say now that there is a one in eight chance that this won't work. And I think every women deserves to be told up front, in big letters in a box, you know, this isn't perfect."

Your Panel knew and acknowledged this device wasn't perfect. Yet, you approved it with a preemption status as though it were, and that is criminal. I want to know why physicians who implant Essure are not trained to remove it. The product labeling clearly states that we can demand it be removed. However, implanting physicians claim it cannot be done or that it can only be done by hysterectomy. I did not sign up at the age of 33, now 36, to have my female reproductive organs removed. A hysterectomy is unacceptable to me and my family. My wishes about what happens to my body deserves to be respected. I

am a wife, a mother, daughter, sister, aunt, friend, and business professional who just wants her life back.

DR. IGLESIA: Thank you.

MS. ROMERO: This product has altered my life and has killed my spirit, and it needs to be recalled.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 39 to the microphone. And please state your name as well as your affiliation.

MS. RUSMISELL: Before I start, we're going to -- she's going to stand over there and click my slides for me because the technology is not --

DR. IGLESIA: No problem.

MS. RUSMISELL: -- provided the same for the public as it was the FDA and Bayer.

DR. IGLESIA: Do we have her slides? Okay, I'm going to ask you to come over to the side and just check on your slides for a second, and we'll come right back to you.

We invite Speaker No. 40 to the microphone.

MS. CERVANTES: I have slides also.

DR. IGLESIA: And let's check on her slides as well. And we do not have your slides. Okay, would you like to step to the side as well?

Speaker No. 41. And please state your name and affiliation. Thank you for your patience.

MS. HOLT: My name is Amanda Holt, and I have no financial affiliations to disclose.

I am a wife to Chris, I am a mother to Carter, Cameron, and Cailyn, and I'm also an Essure victim. I'll begin by saying that I don't believe that the FDA will force Bayer to recall Essure. Unfortunately 20,000 similar voices will simply never be statistically relevant enough. I'm here to beg for information, data, and education. Move information gathering outside of the pivotal groups, update labeling on true failure rates, on true side effects, and inform women on what can happen when this device fails. These side effects are real, and our experiences are real. I know this because I was implanted with Essure in January of 2008. I was fully occluded; I was deemed a success. And 4 months later I started getting my period every 10 days.

Three months after that, I found out I was pregnant by an at-home test in my bathroom in the middle of the night. Because I had no idea what was going on, I went to the emergency room. The emergency room had never heard of Essure, and my doctor had never had anyone become pregnant. Four months after that, during a routine ultrasound, we found shadows on my uterus. Unfortunately, at that point, I couldn't go through any other further testing. I was pregnant. But we did guess that the coils had either moved or migrated or were expelling. The tech was baffled.

Early 2009 I experienced my high-risk pregnancy, getting monitored every 10 days, ensuring that my baby was growing. I did deliver a healthy baby girl in July of 2009, but unfortunately, in the first 2 years of her life, she developed a blood disorder.

From 2009 to 2011 my health quickly declined. I had migraines for the first time in my adult life. I had psoriasis covering my head and my shoulders, my fingernails and my toenails. I had hives and rashes. The autoimmune responses that I was going through, not

one doctor could figure out how to help me. I spent 3 months with the Mayo Clinic trying to understand a hemifacial spasm. The Mayo Clinic sent me home and said I was stressed. They had no idea what to do.

On October 11th, 2012, we found a softball-sized tumor in the center of my chest, and I was diagnosed with Hodgkin's lymphoma. For years I was sick. Specialists, doctors, the best of the best could not tell me what was going on, and I simply called an allergist. I found out that I was allergic to nickel. And in March of 2013, while I took out a portacath for cancer treatment, I had a hysterectomy to remove Essure.

It was the FDA's job to protect us and to inform us and to ensure we knew what we were getting ourselves into. That didn't happen, and I would like to know why.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Can we have Speaker No. 42? And then we'll go back up after that. But as you work your way up, just let us know your name and your affiliation.

MS. PITT: My name is Sheila Pitt. I'm here on my own, with no financial assistance. I am a private citizen. I'm here today as a wife, as a mom, a face to an adverse report, and as a woman who thought I would have Essure permanent birth control in me permanently, but I had it for just over 9 years.

My story is pretty simple. I got Essure in 2004, and I had it removed in 2013 after seeking help for unexplained issues similar to those described by the others today. I'm sorry, I'm very nervous. Within the first few days after my major surgery for removal, I felt

better than I had in years. At the time I didn't really know and understand what happened. Even my sense of smell returned. I had lost it in 2011, with no explanation. I am not a medical professional. I ask the Panel, when considering all the questions, that everything that you talk about today and any information changes be given to people that currently have Essure, not just those who are considering Essure. It seems to me that adverse effects of pain, migration, and even developing metal sensitivity have been added to the list of Essure side effects on different websites.

Although I no longer have Essure, my question and concern is for those that I know personally, and here today, who know so many other people. My concern is will any recommendations made today be communicated to women who have had Essure for years? How about the adverse events that have been talked about today? How are women going to know if they have an adverse effect? They don't even know what they are. I think information needs to be given to current Essure patients and, as we've discussed already today or heard, information to be given to patients considering Essure.

The Panel has seen, in my opinion, that little info on identifying side effects in women that have Essure for years, like over 5, 10 years -- I'm saying that I don't think there's much that exists. For something that is meant to be inside for 50 years, I feel that current, not just future, patients need information. As many women may not return to their implanting doctor for various reasons, I think that all medical professionals need to know about Essure side effects discussed today, and ways for removal.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: We're going to go back to Speaker No. 39, please. And I think those slides are ready now. So I'd like you to also state your name and your affiliation.

MS. RUSMISELL: Can the technology people just let Carrie know where she needs to point the clicker so that it works?

My name is Amanda Rusmisell. I'm from Charlotte, North Carolina. I have no financial conflict of interest.

I had Essure implanted in December 2008 during the most painful procedure I've ever endured. After this, my life was altered by pain and debilitating periods until I had a total hysterectomy because of Essure. The 20,000 members of our Essure Problems group have been impacted in many ways. I am here to discuss how Essure economically impacted us. Specifically, we're going to look at the out-of-pocket expenses that our members reported on a survey that covered the time from implantation to removal.

First slide, please.

This is implantation. We had 229 women participate in the survey. Essure is sold as a low-cost procedure. Only 30% of our survey had out-of-pocket expenses.

Our next slide is confirmation tests. We had 164 women have some type of confirmation test. Some did not have the test because it was not covered by insurance. Out of the 164, we see that 34% had out-of-pocket expenses. Essure is costing the patient more.

Our next slide is doctors' appointments due to complications. Two hundred and fourteen women from our survey had doctors' appointments. This looks at all primary care

and specialist appointments. Now we see the jump; 67% had out-of-pocket expenses.

Our next slide is emergency department visits. One hundred and thirty-three surveyed had emergency department visits, emergency visits for things like extreme pain and heavy bleeding; 57% had to pay out-of-pocket expenses.

Our next slide is tests to diagnose complications. One hundred and eighty-two women from the survey had diagnostic tests. Some examples are blood tests, ultrasounds, radiology imaging, and allergy testing; 52% had out-of-pocket expenses.

The last slide is Essure removal. From this survey group, 113 women have had Essure removed; 64% of them had out-of-pocket expenses for removal. Remember, this is up from only 30% having out-of-pocket expenses with implantation.

This is just a small peek into the financial impact of Essure. We were told that Essure was low cost. These statements demonstrate that Essure was anything but low cost. Essure cost us financially, physically, and emotionally. Every woman should have the right to a safe, effective, and affordable birth control. This is not the case with Essure. The FDA failed us, and the FDA failed our families.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 40 to the microphone. And I think those slides are ready. They're not. Okay, pardon me.

We will then move on to Speaker No. 43 while we resolve that issue. Speaker No. 43. There you go.

(Off microphone comment.)

DR. IGLESIA: Take your time. Just state your name and your affiliation.

MS. GREAGER: Hi. Good afternoon. My name is Alicia Greager. I am not here with anybody or affiliated with anybody, and absolutely nobody gave me any money, nor will they when I get out of here.

What Bayer has said, I was the perfect candidate for Essure. In June of 2008, I went to the gynecologist. I chose to have permanent sterilization. With the recommendation from my doctor, I fully consented and thought I understood everything, and I really and honestly thought that Essure was a perfect solution for me.

Within a few weeks I went back. The surgery was okay. I was asleep, though, I believe, because my insurance paid for it. And a few weeks later I went back, I had a couple follow-ups, I was bleeding a lot. She said, oh, you know, that's going to take a while, that will take a while, that will take a while. I said okay. It took a while. Well, it's 2015. I bleed every 12 days, every 12 days, with massive cramping, clotting. I now have rectal bleeding too, which is fun. I have hair loss, which my grandchildren lovingly crawl right through and wrap themselves in. I lost four teeth, literally popped out of my mouth. Don't know why. I have no clue.

I have excessive sweating, which is lovely, lovely, lovely. Walking around and people randomly walk up to you and say, ma'am, are you okay? I'm fine. My heart rate is at resting, and when I say resting, I mean when I wake up in the morning, 90 beats per minute. Hasn't changed. I've been hospitalized, and they thought I had a stroke. My daughter had to come to the hospital, and she was in the Marine Corps at the time. She runs down to the hospital, and she comes to me thinking I'm dying. They can't find anything besides the

stroke symptoms, but no signs of an actual stroke.

I have a medical record, which I didn't bring with me today only because it's a public hearing, that will show you, without a doubt, a clear path from my history, which I have all the way from when I was a child to now. It is the Essure, whether I have an allergy to it, which that's another fun thing. I have nice skin itching. That's great. And little boils that pop up everywhere. I have problems with pain every day. Twitching. That's another fun one. And one of the worse things about the whole thing is I have to smile and be happy and move on. And it's really hard. I had to adapt to that. I had to adapt to all of those things. And now, today, I want to tell you how important it is that I'm here. Right now, at this very moment, my daughter is in Washington where I came home from, I live in Pennsylvania, and she's in labor with my third grandchild. And I'm here because my whole family supports me to do this.

I believe you should recall it. Bayer, I 100% believe you should set up some kind of fund for us and please take them out of here. You know, the Panel, I think that you should tell the FDA -- I trust them, I do. They stamp my meat, I love meat, and I think you should advise them to do something for it.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 44 to the podium. And please state your name and affiliation.

MS. HUGHES: My name is Kimberly Hughes, and I have no financial conflicts of

interest to report.

My Essure procedure was done in 2009 in a hospital, with anesthesia, and I wasn't asked about metal allergies because if I had, I would have refused the procedure. The years that followed brought pain, confusion, doctors without answers, and two major surgeries. My side effects included constant pelvic pain, dizziness, ovarian cysts, heavy and painful periods, periods lasting half the month, anemia, vitamin D and B12 deficiencies, weight gain, abdominal swelling, and eczema on my hands, all problems that didn't exist prior to getting the Essure procedure done.

In late 2011, after more complaints of pelvic pain, a CT scan and ultrasounds revealed a 10 cm cyst on my right ovary. So I had surgery to remove the cyst and the ovary, but the pain continued. Dizziness led to two falls down flights of stairs. The fall in 2011 resulted in injury to my coccyx and lower back, making it painful to sit or stand for any length of time. The fall in 2013 resulted in a concussion. Post-concussion syndrome has left me with frequent migraines, memory problems, difficulty with word recall, multitasking, and concentration, as well as light sensitivity, confusion, difficulty remembering new information, noise sensitivity, mental fatigue, sensory processing problems, brain fog, and one pupil larger than the other.

More than 10 doctors and dozens of tests later, I still didn't have any answers. None of them put the pieces together. But the simple names of the side effects and problems don't even begin to illustrate the occupational, social, financial, and psychological impact they have on a person's life. And that's the true impact of Essure. It wasn't until I found a group of thousands of other women who have been suffering from the effects of Essure

that the struggles I had been going through for the past 6 years began to make sense. I found this group of women when I was searching for answers when my period began one day and just never stopped. I was very anemic and weak, and I didn't know what was happening.

I had to have a hysterectomy in June of this year. The pathology report showed that there was extensive endometriosis and adenomyosis. A hysterectomy was my only option by the time I put the pieces together. I may have been able to get rid of the constant pain and bleeding and some of the allergic reactions; however, I'll have to live with the life-altering effects of chronic back pain and post-concussion syndrome.

The simple procedure that Essure was billed to be turned out to be the most devastating mistake I have ever made. I have no doubt there are thousands more women suffering that have no idea that Essure is the cause, because their doctors are not connecting the dots or taking the complaints seriously. Other victims of Essure are the only hope for them right now because the FDA has failed to warn and protect them properly.

This device needs to be taken off the market now before more women are harmed, and Bayer needs to be held accountable to all the women who have suffered with Essure.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 45 to the microphone. And if you could state your name and affiliation.

MS. SCANLAN: Good afternoon. My name is Susan Scanlan. I'm President of the Women's Research and Education Institute, or WREI, which has provided timely nonpartisan

policy analysis to the women in Congress since 1977. For 9 years, from 2004 to 2013, I served as chair of the National Council of Women's Organizations, a coalition of 240 progressive women's groups representing 12 million American women. Women's health and reproductive rights were at the top of the National Council's agenda.

I have accepted no payment to speak here today and have no financial relationship with Bayer. It's my job this afternoon to tell you how critically important it is for women in the United States and around the world to have access to safe, effective, and affordable permanent birth control, birth control that Essure provides to so many.

Essure represents a vital and growing reproductive option that has been successfully performed on more than 800,000 patients over the past 13 years. A recent practice bulletin issued by the American College of Obstetricians and Gynecologists recognizes that hysteroscopy tubal occlusion for sterilization has high efficacy and low procedure-related risk, cost, and resource requirements.

Of course, all of us are concerned about possible side effects that are being raised today. We're not just concerned; we're heartsick. We do not discount any individual's personal claims or suffering, but no form of birth control is without risk or should be considered appropriate for every woman. It is important that female patients discuss all risks and benefits with their physicians and adhere to all medical protocols. It seems to me that a lot of them have gone in uninformed, and that is not right.

It is equally important that data about possible side effects be collected and analyzed in a careful and irrefutable way. Such scientific fact finding has not occurred in the case of Essure, and a fearful message is being sent to people who might most benefit from

it. My concern is that access to this proven medical device could be limited or even denied to women who want and need it. The market shows that American women are looking for permanent birth control that is simple, reasonably priced, and does not require a lot of recovery time, that can be performed in their doctor's office, that does not require surgery or exposure to its potential risks, and that does not contain any hormones. Essure does answer every one of these requirements. American women have the right to make an informed decision to use it.

I thank you for listening to me today. You have a set of tough decisions ahead of you, but I'm confident you'll find a way to balance majority needs against the compelling, tragic stories that these brave women have told us today.

DR. IGLESIA: Thank you very much.

And, finally, I'd like to go back to Speaker No. 40. And I think those slides are ready, and this is our final speaker. And if you could just state your name and affiliation. Thank you very much.

MS. CERVANTES: My name is Christine Cervantes, and I have no financial conflict of interest. I traveled from Lake City, Texas to be here to speak today.

I was a 39-year-old mother of four when I talked to my gynecologist about becoming sterilized. I requested a tubal ligation, but my doctor was quick to recommend Essure as a safer, nonsurgical option. I told my doctor that my only concern, since she had assured me of its safety, was of migration. My younger sister had had Mirena, and it had migrated into her abdomen and had to be surgically removed. I did not want to have a similar experience as my sister. My doctor assured me that migration couldn't happen due to the scar tissue

forming around the implant and holding it in place. She said the migration warning on the pamphlet was standard because it was a medical implant.

At the time of my HSG test, it was confirmed that my left implant was in place and my fallopian tube had occluded. My right implant was shown to have migrated and, per my report, was in my abdominal cavity. I immediately contacted my gynecologist, very upset. Her initial response was to repeat the procedure, putting another implant into my open fallopian tube. By this time I had started noticing changes throughout my body, side effects, if you will. And not only did I not want another Essure device put in my body, I wanted the two existing Essure implants taken out.

My gynecologist then contacted Bayer to find the proper protocol to remove Essure and was informed that there was no protocol for removal once migration had occurred. She informed me that she was no longer willing to perform the surgery and forced me to become my own advocate. After calling numerous doctors, I found a gynecological oncologist that would take my case, even though I did not have cancer, because she was experienced with complicated surgeries.

During my LAVH-BS, it was discovered that in fact both of my Essure implants had migrated, and both were protruding through my uterus. You see, there is a complete disconnect between doctors and patients when it comes to their response to migrations, complications, failures, and side effects. If doctors are not being trained to handle the complications that can and will arise, then they have no business implanting women with these medical devices.

As a victim of Essure, I'm here to say enough. Women deserve and demand better

than what these devices are doing to our bodies and to our lives. I'm asking Bayer and the FDA to remove Essure from the market.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I apologize, but there were two speakers that were absent. I'm going to just give them one last chance, if they're present, to come up to the podium. One was Speaker No. 10, Michelle Garcia. And the second was Speaker No. 25, William Myers.

MS. MYERS: Williams Myers is my husband, and we couldn't afford to pay for him to come.

DR. IGLESIA: Thank you.

(Off microphone comment.)

DR. IGLESIA: Okay. Well, thank you then.

At this time, if we could get the lights back on, I'd like to ask our Panel members if there are any Open Public Hearing speakers -- that they have any questions at this time. Yes.

DR. CHAPPELL: Brief questions or brief clarification?

DR. IGLESIA: Correct.

DR. CHAPPELL: I have one for Mark Bell, if he is still here. And I'm supposed to announce my name, right? Rick Chappell. Yeah.

(Off microphone comment.)

DR. IGLESIA: Okay. Yes, this will be the only opportunity before we reconvene as a

Panel. Are there any other Panel members that may have brief clarifying questions for our speakers this afternoon? The public speakers.

Deb.

DR. MYERS: Deb Myers.

Speaker Laura Russell, Medsurge, if still here. In your presentation you talked about blood tests for screening patients. I was hoping you could give additional information on that.

MS. HENZE RUSSELL: I will follow up in writing with more detailed information on the screening for medical devices. I'm familiar with similar screening tests for tolerance versus toxicity for dental materials, because I had that a blood test can tell you which materials you are highly, moderately, and least reactive to. And I know this because I was sick for 20 years from mercury from dental amalgam, which is how I got introduced to metal toxicity issues with devices. I've been trying to track that down because I've been told by people who have done orthopedic procedures that there are tests that can be done. Are there any physicians in the audience who could address that?

(Off microphone comment.)

MS. HENZE RUSSELL: Orthopedic Analysis does specific Essure testing. And I believe that there are tests that can be done for basically any or all medical devices, and I think that's something we should all learn more about and recommend, if not require, before devices are installed on a non-emergency basis.

DR. IGLESIA: Thank you very much.

DR. MYERS: Thank you.

DR. IGLESIA: Dr. Chappell.

DR. CHAPPELL: Yes, thank you.

I have a question for Mark Bell. Could you please clarify -- and I'm sorry if you already said this -- whether the photo micrographs of Essure that you presented were new products or post-implant or a combination.

MR. BELL: Everything was post-implant.

DR. CHAPPELL: Thank you.

DR. ELSER: Denise Elser.

This is for -- I think it was Ms. Reed who is an immunologist, is that right?

UNIDENTIFIED SPEAKER: Dr. Reed.

DR. ELSER: Dr. Reed? Sorry. Because we hear a lot of symptoms that may be related to some type of -- are you saying it's like having a rheumatology office? These are likely autoimmune diseases that we're seeing, or symptoms. Is there any testing to link a correlation or any others outside of these symptoms and the timing of the procedure?

DR. REED: So one of the things that makes it very difficult to prove cause and effect -- and even if you look at diseases that we have a much better handle on, like lupus and rheumatoid arthritis, people really can present with a spectrum of symptoms, and there's no one symptom that you say aha. Even with rheumatoid arthritis, some people get joint pain, some people have high levels of rheumatoid factors, some don't. In a case like this where, like we said, that the mucosal immune response is not well understood in animals much less in this sort of setting, that there's no -- I can't think of a single -- I mean, you could look for inflammatory markers, and I bet you'd be high in every one of these women,

but that doesn't really tell us anything prognostically.

DR. IGLESIA: Thank you very much.

Okay, there being no further questions, I want to take a moment to acknowledge and thank all of those who came to speak at our public hearing. The Panel realizes how difficult it is for you to travel here at your own expense and to share your personal stories with us about your experiences with Essure.

I now pronounce the Open Public Hearing to be officially closed. We will now proceed with today's agenda, and during that deliberation, at the request -- at my request, we may be able to take some further questions from the presenters.

But at this time we will take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience. We will resume at 3:59.

(Off the record at 3:49 p.m.)

(On the record at 4:10 p.m.)

DR. IGLESIA: If everyone could take your seats, we will begin the Panel deliberation session now. So we will now begin the Panel deliberations. I want to open the floor to the experts around the table to begin deliberating on any thoughts that you may have with any information you have heard today or the material that you have read in your Panel packets.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair.

Now, first, do any of the Panel members have any questions or comments for FDA or Bayer HealthCare before moving on? I know that there were two. And please be reminded

that during this time, persons may only approach the podium when directed by the Chair.

So I know that Ms. De Luca had a question, and Dr. Seifer had a question specifically to the FDA. So we'll start with you, Ms. De Luca.

MS. DE LUCA: Jo-Ellen De Luca, Patient Representative.

I was wondering if the women that have problems generally, if they go to the same physician. So if they are going through the Essure process with a physician, do they keep that same physician? It seems to me it would be a bad move to then go to physician Y and then Z to prevent the problems from happening in the first place and keeping track of anything wrong.

DR. IGLESIA: So does the FDA have any information, Dr. Yustein et al., on lost to follow-up where a patient is an index case and may have a problem but does not see the same implanting surgeon?

DR. YUSTEIN: I don't think that's information that we normally collect. It might be worth asking some of the audience members who have presented today their experiences.

MS. DE LUCA: I guess I'm looking if some of the poor performers are people who neglected to go to their physician in the correct follow-up manner.

DR. IGLESIA: I know that that was mentioned --

DR. YUSTEIN: Right.

DR. IGLESIA: -- on the -- in the public hearing portion.

DR. FISHER: May I? Real quick. Actually, there were a couple questions that were asked before lunch that we have prepared answers to, and I believe that one of those --

DR. IGLESIA: Was Dr. Seifer's.

DR. FISHER: One of our responses kind of addresses that question, and it has to do with the lack of follow-up. So maybe if we -- before we get into additional questions, maybe if we had a chance to respond to the questions that we had.

MS. DE LUCA: I'm looking for follow-up in an explicit way, not just go to Dr. Smith and then go to Dr. Somebody Else, get another answer, and never probably getting their original problem seen and followed.

DR. FISHER: So I understand your question. That is not information that we have. But, once again, I think that some of these patients, from what I've heard, it sounds like they have gone to multiple doctors, but that's not information that we have.

DR. IGLESIA: But I do recall that Dr. Seifer was the one who had the initial question about some of the complications. Is that what you had to prepare?

DR. FISHER: Well, there were three questions, and if you don't mind, can I go ahead and --

DR. IGLESIA: Please address.

DR. FISHER: -- try to address those?

DR. IGLESIA: Please.

DR. FISHER: Okay. So there were three basic questions. I want to start with Dr. Coddington, and it had to do with lost to follow-up. And lost to follow-up can be interpreted a couple different ways. True lost to follow-up -- I think your question to FDA was, do you get additional information on patients? Can you get additional information from the company on lost to follow-up? And we can request additional information, but usually lost to follow-up is lost to follow-up, and there's not a lot of information that comes

with those patients. Now, I will say that going back and looking at the IDE studies, true lost to follow-up, there were only three patients that were lost to follow-up, okay? But I would like to make a distinction here because there's also something that has to do with patient discontinuation.

And if you look at the Executive Summary, Table 4 is on page 16, and it talks about events that delay and prevent the reliance on the Essure device for contraception, and it lists a couple different reasons why a patient may not continue on in the study. They would still be followed, but it has to do with perforation, expulsion, maybe they got a unilateral implant, I think. And I can ask the company if they would like to clarify this. Probably the only patient that they wouldn't follow would be one where they couldn't get an insert in at all, okay? So that's where there's a little bit of difference there between loss of follow-up and discontinuation with patients.

Now, when we talked briefly, there was also the question kind of like lost to follow-up. What happens with a patient during that compliance period where you lose them? This is a method, so they have to come back for that confirmation test. And one of the things that we had presented, we had presented ranges of patient confirmation, and it ranged from 28% to 100%. Now, the information that we have is from the scientific literature, and I'm going to ask Allison O'Neill to come up, and she can put the slide up to show you where we're getting these numbers, okay, because these were not part of the IDE. These are non-sponsor -- non-company sponsored studies. And in addition to that, I think she has some information as to some of the reasons behind why patients failed to come back for that confirmation test.

MS. O'NEILL: So I believe it's the next slide, please. Yes. So this is a slide that shows some of the compliance rates that we found in the available literature. This represents studies from both the U.S. and outside the U.S., so it's not exclusively HSG. But this is where we got those ranges that we presented.

The first two references with the lowest compliance rates, both represent clinic populations where a majority of the patients had public insurance. And in reviewing those two references, we found a couple of reasons that patients may not be compliant with HSG, including health insurance coverage or lack of. Second, the patient may be responsible for scheduling their own HSG with a radiology unit, especially when there's a lack of patient tracking or follow-up by a staff member. And another reason could be scheduling difficulties between -- coordinating between the gynecology and radiology unit and possible inconvenience related to that. So this is just a quick snapshot of kind of a spectrum of compliance rates, and a little bit more detail can be found in Appendix A of our review memo.

DR. SEIFER: Do you have any estimation about the lack of insurance coverage for the HSG? In other words, was it more than half of the noncompliance that could be explained by that?

MS. O'NEILL: I believe in the first study it wasn't half, but it was the first -- it was the most common reason.

DR. FISHER: Okay. And then I think that there was -- thank you, Allison. I think that there was a third question that Dr. Milner had, and it was in regards to metal allergy or allergic reactions and how it was defined during the IDE studies. And we went back, and we

looked at that, and there was no solid definition of reporting an allergic reaction. But I would like to bring Dr. Corrado up, if I could, please, to provide some insight as to when we started looking at this issue of some of these other symptoms and considering could it be an allergic reaction and some of the things that we did.

So, Dr. Corrado, could you come up?

DR. CORRADO: So I'm just going to very briefly say that it's our recollection that we were not explicitly advised of nickel allergies in the Phase II and pivotal studies at the time of the premarket review. However, in approximately 2011, in one of the PMA supplements, we were discussing labeling around potential nickel allergy, and the Sponsor at the time, Conceptus, informed us of the following:

Records of over 650 women in the Phase II and pivotal trials were reviewed for adverse events potentially related to nickel allergy. The women were followed for up to 5 years after being implanted with Essure micro-inserts. There were no chronic reports of skin rash or itching. Four reports of itchiness, hives, rash, or eczema occurred that were not attributed to another cause. All were of short duration and resolved with medication. Micro-insert removal was not required for any of those reports.

So that was the information as it evolved from the premarket review to postmarket.

DR. MILNER: So just so I understand, so they were thought perhaps to be related to the insert; is that correct?

DR. CORRADO: Basically by default. They could not be attributed to anything else.

DR. MILNER: Okay.

DR. CORRADO: And so what the Sponsor was trying to do at the time was say we

didn't identify anything as an allergy per se. However, we went back on records, and we found these four symptoms, essentially signs or symptoms, and we're telling FDA -- we're telling you about that because they could be evidence of nickel sensitivity.

DR. MILNER: Okay. But then what was the criteria that was used to decide what is an allergy?

DR. CORRADO: That is a question I am unable to answer. I'm sorry. Maybe the company would like to take a crack at that one.

DR. IGLESIA: Would you like to address that?

DR. MILNER: If there's an answer, yeah, sure.

DR. IGLESIA: Would Bayer like to respond about the allergy issue? And just please state your name.

DR. ZAMPAGLIONE: Sure. Great, thanks. Edio Zampaglione, Bayer HealthCare, U.S. Medical Affairs.

No, there was no criteria per se in the studies to identify or to say this is an allergic reaction. So we also do not have that.

DR. MILNER: So how is it that you can declare that there's no allergy if you don't have a criteria for whether there's an allergy or not?

(Applause.)

DR. ZAMPAGLIONE: So the symptoms that are with these allergic reactions, they're broad. There are so many different etiologies. We're exposed to so many different types of chemicals, of foods, et cetera. It comes down to clinical understanding and clinical judgment with these and trying to determine is this due to the inserts or potentially due to

something else? And it seems to us that it ends up being an exclusion at the end of the day, that you just rule out what it is and what might be the cause, and then you're left with, you know, in the cases that I'm hearing, possibly that it's the insert. But it still is very rare from all the data that we have seen and looking at the literature.

DR. IGLESIA: Dr. Schalock.

DR. SCHALOCK: Peter Schalock.

My question is this, how can Bayer and the FDA have no knowledge of nickel allergies when the original package insert prior to 2011 -- at least my quote from my own talks state that a contraindication is a known hypersensitivity to nickel confirmed by skin test. How do we not have data on this?

DR. IGLESIA: Is that a question for Bayer or for the FDA?

DR. SCHALOCK: It was a question for anybody who will answer it. How do we not have data on nickel allergy when we have a device that's 55% nickel, and 20% of women -- approximate numbers -- are known to be nickel allergic? Why is there no data? How can you put this in your package insert and then have no clue?

DR. IGLESIA: I just want to remind everybody, even when you come back to the mike -- and I'm Dr. Iglesia -- that we have to state our name each time for the transcriptionist.

And I'm going to invite Dr. Zampaglione or anybody else from Bayer, if you have an answer to that question from Dr. Schalock.

DR. ZAMPAGLIONE: So Edio Zampaglione, Bayer.

The skin test, the requirement for that has shown that there's no correlation. From the studies that were done by Dr. Zurawin in 2011 that was published, there was no

correlation. You know, you're talking about dermatologic reactions as compared to something that's inside the body. But let me bring up one of our allergy specialists who can help shed some light on this as this is not my extreme area of expertise.

Could I have Dr. Hamilton, please?

DR. HAMILTON: Hi. Robert Hamilton, Johns Hopkins University School of Medicine. I am a Professor of Medicine, and I oversee a diagnostic allergy laboratory.

Allergy, for me, is immediate-type hypersensitivity. So the definition really has to be clearly defined. And when we're talking about T-cells, we're talking about slightly different. So for those that are not immunologists, there are four types of hypersensitivity, and three of them involve antibody. Today we're talking really about T-cell responses or Type IV hypersensitivity. So I take a quote from Dr. Schalock's nice review where he said, basically, that either cutaneous or systemic reactions can occur from implants, even though they're very rare.

And so if I could have the first slide, please.

So we've been already told, both by Bayer and by the FDA, that nickel released from the Essure device is actually very minimal, and compared to levels that are released from other devices and also from environmental exposure, they're very, very insignificant.

So if I could have Slide No. 2, please.

So if we can define nickel allergy as an exaggerated immune response that only occurs in genetically predisposed individuals when exposed to nickel, the key here is high exposure and genetic predisposition. It occurs most commonly after skin contact to nickel, and the most common exposure we have in the environment is to nickel jewelry, where we

get a contact dermatitis. In fact, I have a Type IV hypersensitivity to nickel due to a ring I bought. Another example of contact dermatitis is poison ivy, which involves the contact of urushiol from the actual plant itself.

And nickel allergy is mediated by the white blood cells, called T-cells for those of you that are not immunologists, and classified immunologically, as we mentioned, as a Type IV hypersensitivity. And there are four classic symptoms of a Type IV inflammation associated with Type IV hypersensitivity, and those are swelling, redness, heat, and pain. And I believe these are the four symptoms that have been used to select the criteria for trying to define whether the observed symptoms were in fact "latex allergy," which I would like to suggest now we talk about as -- I mean nickel allergy. I suggest we talk about it as nickel sensitivity or hypersensitivity at this point.

DR. IGLESIA: I'd like to ask if Dr. Wills-Karp has a question, and then we'll get back to you, Dr. Schalock.

DR. WILLS-KARP: I think your --

DR. IGLESIA: And just introduce yourself again.

DR. WILLS-KARP: Marsha Wills-Karp.

I think your points are well taken, and as you pointed out, the nickel sensitivity is lower, although in my reading of it, it's increasing with increasing exposure of the population by piercing and earrings and other things. The incidence of nickel sensitivity is increasing. But, in the population of the studies you did, you might not have picked it up or had the power to detect it because it is a very small population, but it does seem that listening to today's conversation, that it's worth going back and revisiting this and taking a

look at it, so that if some of these side effects are really attributed to that, that could be put as a contraindication to the use of this device. It's not clear at this point whether all the symptoms that were being reported are due to that, but it's possible and it's unknown. So I think there needs to be some further analysis of the data.

So I don't know if I can do this, but how many people in the audience actually know they're allergic to the nickel?

DR. IGLESIA: I have to ask the questions.

DR. WILLS-KARP: Oh, I'm sorry.

(Laughter.)

DR. WILLS-KARP: That's why I said I didn't know if I could do it.

DR. IGLESIA: Yeah, that's okay. I'm going to go with Dr. Schalock here for a second, just to finish up the conversation.

DR. SCHALOCK: I'm going to reiterate the same question I asked before. You -- well, Conceptus, maybe not Bayer -- listed initially to consider testing for nickel in patients pre-implant. I may be paraphrasing too broadly. Where is your data? Where did you test these people? How did you test these people? What did you test them with? And what in the world happened to that information, or does it not exist?

DR. IGLESIA: So, to paraphrase, you're asking about what kind of screening was done prior to implantation, if any, on instructions for use?

DR. SCHALOCK: Well, considering that they listed it as a contraindication themselves. At least from my understanding, if they're listing it, are we just making this up just for fun, or is there data? Do we have data? That's what I want to know.

DR. IGLESIA: And does Bayer have any information about the screening for such, since it was listed as a potential relative contraindication?

DR. ZAMPAGLIONE: Sure. Edio Zampaglione.

Let me call up Dr. Kimberly Rosen. She's head of our clinical development group for Essure, and she will hopefully be able to answer that.

DR. ROSEN: Thank you. Kimberly Rosen, global development.

So I don't think I can exactly answer your question, but I can at least explain how the initial protocols were worded with respect to metal or nickel allergy, which is there were no contraindications and there was no screening in advance of entry into the Phase II or pivotal studies for nickel allergy. We were not, as a sponsor, involved at the time of the initial PMA approval with discussions in terms of what was included in the initial contraindications, but there were no in- or exclusion criteria related to nickel allergy for the pivotal and Phase II studies.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Josh Milner.

I just wanted to get back again to the question about allergy. Certainly, from an allergist's point of view, we do like to be very, very careful about what we call an allergy versus a Type IV hypersensitivity, which is not mediated by IgE, which is not necessarily mediated by mast cells, and it does cause a tremendous amount of confusion to patients. For them, it's all the same thing. And I agree that those do need to be separated. But, either way, the patient needs to know about both things. So they need to know about if there is a Type I hypersensitivity and there are clear criteria for that, and if there is a Type

IV hypersensitivity and there ought to be clear criteria for that, which would be laid out a priori in any instance of contact to something like that. And I think that's -- otherwise you get a zero, which is not true.

(Off microphone comment.)

DR. IGLESIA: Dr. Myers.

DR. MYERS: Deb Myers.

A question. Are we aware of any animal models or any sort of basic science models that involved nickel? Not skin contact, but within the body cavity. A general question.

DR. IGLESIA: And that's a question for Bayer or FDA or other?

DR. MYERS: Other.

DR. IGLESIA: Dr. Corrado or Ben? Because you mentioned the 2012, the four cases that potentially could have had some relationship to the implantation device, did that spawn any more basic science research in this area?

DR. FISHER: So I know that there was traditional biocompatibility testing done for -- with the PMA. Most of the biocompatibility testing came back negative. The one that came back positive had to do with -- I believe it was the muscle implantation, but I have a gentleman behind that will correct me if I'm wrong. But it had to do with, I believe, the PET fibers actually being able to initiate that ingrowth. So it wasn't something that was surprising to us.

DR. IGLESIA: So the PET is the polyethylene terephthalate coating.

DR. FISHER: That's right.

DR. IGLESIA: So would that person like to address that topic right now?

DR. FISHER: Ron, do you have anything that you can add to that?

(Off microphone response.)

DR. IGLESIA: Would you like to come to the microphone?

DR. FISHER: No, I don't think that he has -- well, I shouldn't speak for him.

(Off microphone comment.)

DR. IGLESIA: You have to come to the microphone and introduce yourself.

DR. BROWN: Ron Brown, toxicologist, CDRH.

Actually, Dr. Fisher, I hadn't had the opportunity to see those data. And so my efforts on this device are really focused on the potential risk of adverse effects occurring from the nickel exposed to the device. So I haven't had a chance to look at those data.

DR. FISHER: Okay. Thank you, Ron.

So I don't know that any of the biocompatibility testing or any of the animal testing specifically addressed an allergic response, and I am not the person to say what an appropriate model for something like that would be.

DR. CHAPPELL: May I follow up?

DR. IGLESIA: Let's just go down the line. I know that Cynthia --

DR. CHAPPELL: It's similar.

DR. IGLESIA: Okay. If we're on the same topic, I'll let you go, Dr. Chappell. And introduce yourself.

DR. CHAPPELL: Rick Chappell.

On the same topic of sensitivities to polyethylene terephthalate, besides reactions to the organic compounds in it, there is a metalloid element, antimony, which is used as a

catalyst in its production. And I know of that because there is what many countries consider excessive levels in juices and other liquids that are used. They're used for beverage containers, which makes me a bit worried about having it contact with -- constant contact with an internal organ.

(Applause.)

DR. CHAPPELL: Will that worry may be justified? I don't know. But I would be interested in data to see if there is any evidence of antimony leaching, and that can be determined from blood samples or other kinds of very direct and relatively cheap measurements. So the question is whether that has been done or contemplated, and it's directed to the FDA and Bayer.

DR. FISHER: And I would say that that was not part of the information that was provided with the PMA.

DR. IGLESIA: And Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

My question sort of follows Dr. Chappell's. I'm wondering about the percentage of nickel to other metals in the device. I'm wondering if there has been any looking at the interaction of those metals with each other that may cause something to happen. And putting this metal device in a soft tissue organ seems to me to possibly be different. They brought up other implants, but this is different from those others, I think. So I'd like to hear from the -- no. Immunologists? Allergists -- about these things. Or the toxicologists. I just think there should probably have been more pre-human studies and --

DR. IGLESIA: And would you like to start with the FDA or with Bayer?

MS. CHAUHAN: I'm open.

DR. IGLESIA: Okay.

MS. CHAUHAN: Whoever would like to start.

DR. IGLESIA: Well, let's start with Bayer, for the allergists and/or immunologists, the gentleman from Johns Hopkins perhaps. And the specific question is the metal on metal and direct contact with mucosal surfaces.

MS. CHAUHAN: Metal on metal, percentage of metal to metal, for direct contact with an organ in the body as opposed to a bone implant or something like that.

DR. HAMILTON: Okay. Dr. Hamilton, Johns Hopkins University.

When metal ions are released, they're actually targeted to proteins that contain sulfhydryl groups. So we know that they attach to proteins, and as such, they could come from haptens to actually intact proteins that can be viewed as foreign by the immune system.

In terms of metal on metal, we don't have any -- I don't have any data that really speaks to that issue. But we do know that when metal ions are released, they target to proteins that contain sulfhydryl groups. And therefore you can argue that a metal ion released from a device and a metal ion that is ingested in food could very well form the same interactions with proteins, and therefore, they might very well represent similar exposures. Does that address your question?

MS. CHAUHAN: It addresses it. It doesn't completely answer it. It just seems to me that more testing should be done. I don't know if the FDA has something they want --

DR. IGLESIA: Dr. Fisher.

DR. FISHER: Yes. Before you sit down, could I ask a clarifying question? I'm sorry. Then I promise that I'll bring the FDA guys up. But speaking to metal allergies, is there a level of nickel that if you go over is safe, and if you go under you're not going to have a problem?

DR. HAMILTON: Well, I believe that the Academy of Sciences has defined 35 µg/day as safe. And we do know that levels released from devices, both the Essure and also the cardiovascular devices, are well below that, which may reflect why we don't see a lot of obvious allergy. I'm not talking about IgE antibodies, but more like T-cell related responses that are very obvious. And, in fact, I know that when I got nickel allergy, it was because I had high-dose exposure from the nickel jewelry that I used. It far exceeded what I actually was consuming for many years in my food as an environmental exposure, 300 µg/day.

DR. FISHER: Okay, thank you.

And yes, I would like to call Ron Brown up to address the issue for FDA. Thank you.

DR. BROWN: Ron Brown, toxicologist, FDA.

I think you raise a very good point in general about the potential for metals to cause toxicological interactions. In the case of this device, we know that the primary metals are nickel and titanium. So titanium for the most part is biologically inert and, when combined with nickel as in nitinol, has a long history of safe use in many types of medical devices, including cardiovascular devices. So although I think it's true in general that we have to be concerned about potential toxicological interactions of metal, here's an example of an alloy that's very well characterized and has been used for many years for a number of clinical applications.

I do just want to make one clarifying point. And our colleague from Bayer mentioned a tolerable intake of 35 µg/day as being safe. I have to take either partial credit or blame for coming up with that number. And I just wanted to point out that when we derived that number, we purposely excluded hypersensitivity reactions as the basis for that value. So we believe that 35 µg/day -- and I should point out, that's a provisional value because that hasn't been published by FDA at this point. It was just derived in response to a workshop that was held 3 years ago, actually in this room, to look at the safety of nickel leached from nitinol in cardiovascular devices. So even though it's a provisional value, we were very clear that it was not intended to be protective for hypersensitivity ranges.

DR. IGLESIA: So may I ask a clarifying question for that? So if somebody does have a hypersensitivity, then that level of exposure could be much, much less. This is akin to like latex allergy. If someone is really, really allergic, I mean, just opening a pack of gloves can cause a major antiepileptic reaction similarly.

DR. BROWN: It is. And, in fact, that's a good analogy. So we recognize that there are some individuals in the population that are uniquely sensitive to certain allergens, and we don't feel that that colorful intake value is appropriately protective for those individuals.

DR. IGLESIA: Now Dr. Katz and then Dr. Baird. Thank you.

DR. KATZ: David Katz.

I had a compound question, and part of it was answered. But while you're here, is there anything unique about the epithelium in the tube, in making quantitative inferences about how much is too much, compared to the other sites where such testing has been done with other types of implanted devices?

DR. BROWN: That's a very important question for implanted devices. How does the local environment that surrounds the local tissues that surround that device, will they play a role in any toxic effects that might be manifested? I think that's best addressed by the biocompatibility testing that Dr. Fisher was mentioning. So if the device is tested in a clinically relevant environment, then if adverse effects were likely to be seen, we would hope that the biocompatibility tests would pick them up.

DR. IGLESIA: Does that answer your question, Dr. Katz? You said it was compound, so I assume there was another question, Dr. Katz?

DR. KATZ: The first part of it was already answered by the prior question.

DR. IGLESIA: Dr. Baird.

DR. BAIRD: So if this is a hypersensitivity reaction, are there ways to test for that?

DR. BROWN: Actually, since that's beyond my scope of expertise, I'm going to defer to my colleagues who are immunologists and allergists.

DR. IGLESIA: Yes, Dr. Milner, would you like to comment? Or Dr. Schalock?

DR. MILNER: Well, certainly, I'll just say from one point of view, which is sort of bets are off when it's inside the body. So you really can't say much of anything in terms of a test. There's not going to be a test that you could definitively say it's because we just don't know enough about that. One could end up finding out that a skin test has some sort of predictability, but we don't know that now. So I think that would be the most straightforward question.

(Off microphone comment.)

DR. IGLESIA: Microphone. And your name.

DR. BAIRD: Donna Baird.

It sounds like it isn't very predictive from what's already known.

DR. IGLESIA: Dr. Schalock and then Dr. Fisher.

DR. SCHALOCK: Just briefly. Peter Schalock.

Yes, I think the patch test, which is at least a skin test for nickel -- and I hope we can maybe define our terms a little bit better here. We're falling back into the term allergy. What type of allergy are we talking about? Are we talking Type I, Type IV, something else? Because they're very different things, and there are different tests for both of them. There are different cell lines involved. So I think we need to define our terms on what in the heck we're talking about. So as far as my end of things, the patch test is a good skin test for Type IV allergy, but it may not be relevant for mucosal findings, and it's kind of -- the data we have so far basically show that a positive patch test doesn't necessarily predict you're going to have a reaction when you have a device placed.

DR. IGLESIA: Dr. Fisher and then Dr. Milner.

DR. FISHER: I was just going to say, these are the issues that we're going to ask the Panel to deliberate. So, you know, if there are clarifying questions that you have for either FDA or Bayer, we'd be happy, but what the Panel is talking about right now are the exact same questions that we're going to be asking you to deliberate and discuss.

DR. IGLESIA: We'll let you get a comment, and then we'll maybe redirect specifically to FDA and Bayer.

DR. MILNER: No, it's a question, and the question is about biocompatibility studies and the question is (a) how reliable would nickel hypersensitivity be in the biocompatibility

studies that were performed in those models? And then duration as well, as it compares to the duration that we're talking about in the patients who have been reporting.

And just one last question is, whenever anyone has reported this, has pathology -- we heard one person mention pathology in the uterus, but I would be most interested in knowing what the pathology directly surrounding the device looked like upon removal in someone who removed it by choice because they wanted to get pregnant versus someone who was having adverse effects and did it correlated to their adverse effects. So I'm sorry for the three questions.

DR. BROWN: So with regard to the first question -- this is Ron Brown, FDA -- since I didn't have the opportunity to review the biocompatibility studies for this specific device, I can't answer it specifically. But, in general, we evaluate the potential for allergic reactions to occur, Type IV allergic reactions to occur, using two animal tests. One is a guinea pig maximization test, and one is a local lymph node test in mice. There are concerns about using either of these for metals, in terms of their accuracy. So I can't speak specifically about the ability of these tests to pick up a potential nickel hypersensitivity reaction.

And with regard to the second question, I think I'd have to defer to people who had seen the submission and can answer that directly. The histopathology.

DR. FISHER: So this is Ben Fisher, FDA.

So the testing, the biocompatibility was done according to ISO 10993, what was ever in place back in 2000 -- excuse me -- yeah, 2000 or when these studies were being conducted. So some of the biocompatibility testing has been changed, but I would say that actual devices were not tested for the biocompatibility testing, especially sensitization.

These were extraction studies that were done and tested in animal models. We can bring up some backup slides if you would like to see specifically what was done. It looks like you're about to get them anyway.

DR. IGLESIA: Okay, go for it. While we're putting it up, I actually do have a question, and maybe I would like to bring Bayer back in because, you know, one of the reasons why maybe they didn't screen was because they thought that the background rate of nickel allergy was so low. But my question is what rate were you going at as being so low? And also what is the potential of developing one de novo? You know, because now you're being exposed on an epithelial surface. So those are questions that I'd like answered. We will have FDA bring this up, though, first.

DR. FISHER: We could. This is just a summary slide of the biocompatibility testing that was performed for the PMA. It shows the different tests that were done. I can probably get more information if it was done on mouse or rabbit. I just want to, you know, let everyone know that these are not -- these are in vivo tests, but they're done in animal models. And I would like to say that from what I recall from reviewing the data, all the tests, the biocompatibility testing was negative, with the exception of the one test.

DR. IGLESIA: Yes, Doctor. And introduce yourself.

DR. WILLS-KARP: Marsha Wills-Karp.

Can I ask you if these studies were done in backgrounds of animals that were known to be susceptible to these type of responses?

DR. FISHER: Okay. So these studies would have been done under GLP, okay? So they are done -- usually they're done in rabbit or mice. Most of the tests were done in

mice. They're standard inbred strains. The rabbit, I'm not quite sure which actual strain was used. But most of these tests are done by a contract research organization or done in-house according to GLP. So the protocols are set for both strains and exposure conditions.

DR. WILLS-KARP: So do you have a positive control?

DR. FISHER: I cannot say if positive controls were done in these studies. Some of these -- I think some -- well, do you know if any of these require a positive control?

DR. IGLESIA: There's the mike, Dr. Brown.

DR. BROWN: Some of the test methods do require positive controls, and others don't. Generally, the in vitro ones are ones that positive controls are used in.

DR. IGLESIA: Dr. Milner, was your question completely answered on this pathology question? And then I'm going to revisit the question that I had with Bayer.

DR. MILNER: No, I just -- and the question again was either to Bayer or to the FDA, as to whether actual pathology of the surrounding tissue of removed implants was examined in both cases of suspected inflammation and where there's no suspected inflammation.

DR. IGLESIA: And, quite honestly, that question would maybe help address the de novo development of nickel allergy.

DR. FISHER: So just a quick response. Was pathology done? Yes. Pathology would have been done for the chronic and the subacute systemic -- oh, I'm sorry.

DR. MILNER: Josh Milner.

I'm talking about the patients.

DR. FISHER: Oh, patients. Right, I was -- okay.

DR. IGLESIA: So please introduce yourself again.

DR. ZAMPAGLIONE: Sure. Edio Zampaglione, Bayer.

Yeah. In the preclinical trials, the women who were pre-hysterectomized, they got Essure, and then there were sections that were done. Let me bring Dr. Mario Caturegli up here, who can explain and give some information on these. And we do have some slides also that will show this.

DR. CATUREGLI: Good afternoon. My name is Patrizio Caturegli. I am originally from Italy, as you can tell. I trained as endocrinologist, and then I trained as a pathologist at Johns Hopkins University, where I am an associate professor, and I am also the director of the Autoimmune Disease Research Center.

I reviewed the study that was published by Valle, about 51 patients that were predicted to go to hysterectomy and had the Essure implant device. So I reviewed those images. You're going to get the slide, but I reviewed the images, and the images show evidence of inflammation, which is what you would predict to see in a patient that received an implant.

So this slide shows an example. On the left side is a cross-section of a fallopian tube. You can see the lumen in the center line by the mucosa, and they are basically around the inflammatory cells that infiltrated the mucosa.

And then the middle section is an example of a woman that is -- the utero was sticking out 1 week after the implant. You can see that around the device there is an accumulation of inflammatory cells. This magnification is difficult to see, but the cells are

represented by -- mainly by polymorphonuclear cells. So it's an indication of acute inflammation.

And on the slide on the right you can see, about 3 months after the implantation, the acute inflammatory cells are gone, and what predominates the architecture is the position of collagen fiber, which is basically a scar. So it's a fibrotic reaction that is the attempt of the body to wall off and form a barrier around the device.

DR. MILNER: Josh Milner.

I guess the question was -- this is exactly what you would expect to happen when you implant it. The question was when they were removed for pathological reasons when inflammation was going on, compared to when they were removed not for pathological reasons.

DR. CATUREGLI: Yes, this is a very good question. We discussed it, and nobody has the data. If the data can be acquired, we'd love to look at those slides.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: My question is on FDA protocol. Can I ask that now?

DR. IGLESIA: Actually, can I ask one question about -- Bayer, about what you quoted or thought is your rare background rate of nickel allergy, for the reason not doing a screening for it? How did you define rare?

DR. ZAMPAGLIONE: So Edio Zampaglione.

Are you referring to from the original PMA and getting into the label?

DR. IGLESIA: Correct.

DR. ZAMPAGLIONE: We don't have that information now. We can try to look and

see if we can get it for you, and if we can, we will. But at this time we don't have it.

DR. IGLESIA: Sorry, Ms. Chauhan. Go ahead.

MS. CHAUHAN: No, that's okay. Cynthia Chauhan.

If approval is continued, does the FDA have the authority to have a company cease and desist any consumer advertising as part of the approval?

DR. FISHER: As part of the approval?

MS. CHAUHAN: Yeah. You know, you can keep this device --

DR. FISHER: So we would review -- right, we would --

MS. CHAUHAN: -- but not advertise directly to consumers. Can you do that?

DR. FISHER: So this was -- okay. So this was reviewed under a PMA, which is -- this was reviewed under a PMA. Oh, okay. Ms. Wolf will answer that question, from the Office of Compliance.

MS. WOLF: I'm Deborah Wolf. I'm regulatory counsel in CDRH's Office of Compliance, and I deal primarily with promotion and advertising issues.

The Agency doesn't have the authority to tell a company not to advertise, and we don't -- generally, we're very different from the Center for Drug's authority. If anybody is familiar with Drug's authority, Devices' authority is very different. We don't pre-review or review, as CDER does, simultaneously look at promotional launch of materials. So the only advertising authority that we have for restricted devices, which this is because it's a Class III device, is to require that advertising include a statement of the product's intended use and any relevant risk information that's related to that, to the use.

DR. IGLESIA: So we have about 15 more minutes left on this deliberation. I know

that Dr. Stubblefield had a question way back, if you still remember it. And I will also go around the table for anybody who has not spoken.

Dr. Stubblefield.

DR. STUBBLEFIELD: Phil Stubblefield.

This is a completely different topic. We were shown today, by more than one of the speakers from the public, copies of research forms that had been crossed out and new information put in, and we were also told that in some cases the investigators just filled out the forms for the patients and the patients didn't see them. Can someone speak to this?

DR. IGLESIA: The FDA and Bayer.

DR. FISHER: What's that?

DR. IGLESIA: The FDA and Bayer, for their pivotal trial.

DR. FISHER: Sure. So yes, I would like to point you to page 19 in the Executive Summary from FDA, and it says that "The FDA is aware of allegations from women who participated in the original Essure clinical trials that the feedback they provided about the comfort wearing the device was not recorded accurately by clinical staff." At the time of the issuance of the PMA, there are inspections that take place during that time. And I think the concluding statement there is that "These inspections audited data provided in support of the PMA, as well as sponsor activities during the studies, and did not report findings concerning the case report forms or patient comfort/satisfaction data submitted in support of the PMA."

Now, the one thing that I cannot do right now is comment, I can't acknowledge, I can't give updates on any compliance actions that might be under way.

DR. IGLESIA: May I ask Bayer to comment as well?

DR. FISHER: Sure.

DR. IGLESIA: Would you have additional comments? And state your name.

DR. ZAMPAGLIONE: Sure. Edio Zampaglione.

So, first of all, no one has alleged that anyone at Bayer has changed these records, okay? These allegations are part of a telephone interview from 2002 that was initially completed by a research assistant and then updated by the lead investigator. What was shown on the screen before was totally good clinical practice followed. Changes were made that were crossed out, initialed, and dated. And when you actually look at the entirety of the forms, you'll see some areas where there was a yes, adverse event, then crossed out to no. But if you look later on towards the end of it, you will see a no that was crossed out and then a yes put in. So we can only speculate, and I can't comment any further than that, but all I can say is good clinical practices were followed, all the rules were followed. It just seemed like things were being moved around a bit.

DR. YUSTEIN: Dr. Iglesia, Dr. Corrado wanted to add a couple of statements regarding that issue.

DR. IGLESIA: Please. Dr Corrado.

DR. CORRADO: So when FDA became aware of this issue at the time of the meeting we had with some patients who had had bad experiences with the product, we took it very seriously, and we looked into whether it was possible to audit all of the case report forms from the Phase II and pivotal studies, and we were told that these forms are not required to be maintained beyond a few years. So that was not possible for us to do. What we did do

is we were in the process of reviewing the -- a later IDE study for the transvaginal ultrasound protocol, and that study enrolled approximately 600 women. And as part of our review, when we became aware of this and saw the evidence that the patients brought us, we thought that we should do everything that we could to determine whether there was a pattern and whether similar events were happening in subsequent IDE studies and whether there was a pattern that this was happening across many women.

So I will tell you what we did, and that is that we asked the company to look at specific case report forms for that study on which adverse events were collected. There were Case Report Form 7, 8, 12, and 13, at which time information on adverse events was collected. Case Report Form 16 was a form that collected data on unscheduled visits or study contact. So we asked the company to identify where any -- on any of these case report forms someone reported pain or another adverse event and whether if on that case report form there was also information on comfort wearing the device, because we wanted to know if there was discordance between reporting of pain or an adverse event and, at the same day, excellent or very comfort wearing the device. And the company provided extensive records following an audit of all of those case report forms.

And what I will share with you, and I'm hoping it's okay with the company, is that it appears that there were approximately six cases of the approximately 500 or 600 patients where it was possible that there was a discordance. Although not having been there, we can't say that, you know, somebody intentionally misrepresented someone's level of comfort wearing the device. But, because of that very small number, six out of a very -- approximately 600 patients, we concluded that there was not a pattern of discordant

reporting. So that is how we handled that. Put it to the Panel to discuss.

DR. IGLESIA: Was that just one particular site where this was a problem or just --

DR. CORRADO: No.

DR. IGLESIA: Okay.

DR. CORRADO: No, no. So these were sporadic case report forms across multiple sites.

DR. IGLESIA: Yeah. Thank you very much.

Does that answer your question, Dr. Stubblefield?

DR. STUBBLEFIELD: I guess that's the best we could get.

DR. IGLESIA: I'm going to move down the line here.

Dr. Elser.

DR. ELSER: This is Dr. Denise Elser.

This is for either the FDA or for Bayer. In the reports coming in now through MDR, does there seem to be any geographic pattern? Are these clustered or all over the place?

DR. IGLESIA: Would you like to answer?

DR. YUSTEIN: Yeah, sorry. Ron Yustein from FDA.

In our analysis, we did not break it down by geographic location within the United States. Most of the reports are from within the United States. We also do get some reports outside -- from outside the United States, but most of them are U.S. But we don't have it broken down by geographic region. Sorry.

DR. IGLESIA: Bayer, would you like to respond as well?

DR. ZAMPAGLIONE: Sure. So Edio Zampaglione.

I'd like to call up Dr. Andrea Machlitt, our global pharmacovigilance lead for Essure.

DR. MACHLITT: Andrea Machlitt, Bayer HealthCare, Global Pharmacovigilance.

We do collect adverse event information from postmarketing sources worldwide, and we pay attention to the geographic location. Regarding Essure adverse event reporting from postmarketing, we have to state that the large majority of cases are reported from the United States. That can in part be explained by also over 60% of the devices having been sold in the United States, but it is also emphasized in postmarketing reporting in general.

If you would bring up Slide 1, please.

Our global safety database contains about 17,563 adverse event reports in total. So this is all cases regardless of the causality or of the source of information, and as you can see, United States accounts for about 15,000 of these reports. Other countries that present with a larger number of case reports are France, Netherlands, Spain. And that is also representative of the market share Essure has in other countries than the United States.

DR. IGLESIA: Thank you very much. We'll just go down the line.

Deb, do you have any questions? Dr. Myers?

DR. MYERS: Deb Myers.

A question about post-procedure time period. Probably this is directed to Bayer. It sounds like you have resources for physicians to call when they have a complicated patient and need some guidance. Are there patient hotlines or resources as well for patients who are having problems and need expertise?

DR. ZAMPAGLIONE: Edio Zampaglione.

Yes, there are. We have a dedicated phone number for patients, and there's also

one that could be used to call the medical information line. But there is a specific line that's dedicated for Essure that women can call.

DR. IGLESIA: Dr. Chappell, anything?

DR. CHAPPELL: No further comments or questions.

DR. IGLESIA: Thank you.

Dr. Coddington.

DR. CODDINGTON: One following up on Dr. Elser's comment. Do you have it divided, as far as the comments, by size of practice? In the other countries that were listed, it's very commonly done at the center, knowing where the expertise is. In the United States, there would be a greater chance that it might be done more in a private practice setting or whatever. There is a learning curve on anything. Is there a way to have this -- and probably Bayer might have it more than FDA -- where it would be broken down by practice size or by number of procedures done? We heard individuals stating about how many they had done.

DR. IGLESIA: So, for clarifying, you're trying to figure out whether or not there are outliers who have higher than expected complications rates based on technique, learning curve. I mean, Doctor, they did explain how there are modules and simulation models and then the proctoring of a minimum of five cases before actually implanting. But the question is, where is the due diligence on sort of the outliers who may have greater than expected complications?

DR. CODDINGTON: Right.

DR. ZAMPAGLIONE: Thank you. So Edio Zampaglione again. Excuse me one second.

So I just want to make sure I understand the question. So your questions pertain to are we looking at outliers to see those clinicians or offices who have had higher rates of adverse events?

(Off microphone response.)

DR. ZAMPAGLIONE: Okay. It's very difficult to track, and we're not able to. What we do track or are starting to look at a little bit more closely, really, is the replacements that are coming in for various reasons. And if we do see -- in the cut-up, it was around four or five replaced for bent tips, let's say. That could potentially indicate a technique issue where we then have our Essure specialists go and find out what's going on. Is there a need for retraining? Is there a need for a proctor to go in? Is there a need for anything else to be done to try to find out what is going on? So that's the best that we're doing right now.

DR. IGLESIA: Does that answer your question, Dr. Coddington?

DR. CODDINGTON: Not ideally, but it's an answer.

DR. IGLESIA: Grace Janik, do you have any questions? You might want to follow up on your fragmentation question from the first session.

DR. JANIK: I have thoughts about things. The fragmentation. Why I was concerned about that is removal, and the long-term consequences for patients are much more profound if it's gathered through the abdomen, if you can't remove it completely. And then I question, with removal in general, what type of resources are available to patients, of who's capable of removing, what kind of outcome they have, how can you direct patients, and how do you know what those outcomes will be? It seems like that's a very important source of information, is these people that are being removed both from a pathological

evaluation perspective, evaluating what symptoms brought them there and then their follow-up after. So what's done with this resource?

DR. IGLESIA: Would you like to take that question? I mean, you talk about the bent tips. And do you have a recommendation of who to go to for complicated removals?

DR. ZAMPAGLIONE: Sure. So Edio Zampaglione again.

Yeah, there is a physician locator on the website that a woman could put in her zip code and whatever radius she wants to or is willing to travel. We also again, with the toll-free number, between -- from patients or even if it's a physician who has an Essure patient and is not sure, they contact us. They contact us through our medical information group, and we have a network of consultants. These are very highly expert Essure physicians, a lot of experience with the placement, but not only with the placement, the management and even removals. So we do offer as much guidance and especially peer to peer.

I mean, that's the most important thing, is to have that peer-to-peer guidance. Each patient is going to be different. Each case is going to be different. Each removal is going to be different. So it's really us trying to facilitate a physician who has that question, to connect them with somebody with a tremendous amount of experience to help guide them through.

DR. JANIK: If you have experience with placement, that really doesn't mean you have experience with removal. It's a completely different skill set, isn't it?

DR. ZAMPAGLIONE: Correct.

(Applause.)

DR. JANIK: Oh, my name is Grace Janik.

So I question how you really vet those people and what kind of outcomes you see, and with this, what percentage of them are fragmenting when they are removed, and how much follow-up of those removal experiences do you have?

DR. ZAMPAGLIONE: Okay. So it's a very good comment because you're absolutely right; placing it does not mean you're an expert at removing it. And that is again a couple of things. Number one, the instructions for use recently was updated with some more guidance, some more information about removals. We are incorporating a little bit more removal information into our training programs to try to -- to cover this, to try to give as much guidance as possible.

The experts that we have, these are well known in the minimally invasive world. They just have a tremendous amount of experience. We consult with them all the time, we interact with them all the time, learning from them, getting guidance, getting advice. That's how we vet them through, and these are the ones that we are utilizing. In fact, Dr. Basinski is one of them and really again has -- this resource has been proven to be very invaluable for the physicians out there. And we're working towards more -- providing more information and training on removal. There was more to the question. It was about fragments. I apologize, I didn't get the whole thing.

DR. IGLESIA: Tracking of fragments.

DR. JANIK: When they are removed, what percentage have fragmentation? Is the path evaluated, and is any history evaluated with removals?

DR. ZAMPAGLIONE: Okay, let me bring up again Dr. Machlitt from our global pharmacovigilance group to help answer that question.

DR. MACHLITT: Andrea Machlitt with Bayer.

So, in preparation of this meeting, we attempted to analyze all the information we have on women who undergo surgical procedures subsequent to the Essure procedures, including salpingotomies, salpingectomies, hysterectomies, and hysteroscopies, and many of them are in relationship with removal. Even so, that is not always reported verbatim.

I have a slide. Excuse me. Can we bring up Slide No. 1, please? Regarding complications of the device removals, I have a slide here that lists the total number of events we could identify, and that is 1127 reports of subsequent surgery, as I described beforehand. And what you can see here on that slide is a breakdown of cases with reported removal complications, and that accounts for 4.8% of the cases, and 95.2% were reportedly without complications. And you can see here that fragmentation is among the possible complications. But we also found that sometimes it's reported that the removal procedure could not be completed or the physician was unable to locate a device. Other complications such as postoperative infection or even more severe outcomes like embolism due to the conducted hysterectomy are very rare.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: Given what we've heard about migration and perforation, it seems like placement of these coils may be fundamental to that. Can someone just review for us what the actual proctoring is of these five or more than five cases that are done? Can you go into detail about -- are those five cases, where there's bilateral placement, consecutively or is this five cases -- can we hear the details about that? What effort has been made to -- you know, this started 13 years ago. Is it the same instruction and the same training that went

on 13 years ago that's going on today? Have you modified it over time?

DR. ZAMPAGLIONE: Okay. So Edio Zampaglione.

I think I understand your question. What you were asking again is how is the training done? Is one case truly one case or just one attempt? Is that what you were asking?

DR. SEIFER: Can you give us some detail about the -- I know they read the manual, they go through the course, the proctoring process --

DR. ZAMPAGLIONE: Sure, okay.

DR. SEIFER: -- and how you sign off on saying somebody knows how to do proper placement.

DR. ZAMPAGLIONE: Sure. So basically, again, as you had said, they go through the didactic, they get all the clinical information. They then do the simulator, whether it be the uterine model or the electronic simulator that very well simulates these cases. They then go on to live cases. That is done whether in the physician's office or an operating room by our Essure specialists. They are there to make sure the physician understands the appropriate steps following the delivery catheter, going to the specific markers on the delivery catheter, being able to release it appropriately, and that they have the proper amount of trailing coil, such as between three to eight is what is the ideal number of trailing coils that are left inside the uterus.

Though most of the time it is able to be done in one setting, sometimes it's not. If there's a tubal spasm going, that's really one of the major things to stop, do not keep trying to force. That's where you really increase the risk of perforation, but that is not considered

one case. If they have to go back and make a second attempt then and it's completed, that would be considered the one case. After that fifth case, then there's the sign-off case where again, if they're able to demonstrate that they know the procedure, they're able to place it properly or successful bilateral placement, they then get their certificate of completion.

DR. SEIFER: And that's pretty much the end of the training process. They're signed off, and then is there any other surveillance after that?

DR. ZAMPAGLIONE: The physicians themselves, no, they no longer followed a proctor intentionally. If they ask, if they say, you know, I would like another case to be supervised, that's where -- or if they even request another physician to come in, that's the proctor program that we have that is peer to peer. But once they get the sign-off case and they get their certificate of completion, they are done.

DR. IGLESIA: Thank you.

Ms. De Luca.

MS. DE LUCA: Looking at the other end of the spectrum, I live in a small community now, and it's a lot of poverty in our community, and unfortunately most of the people have no insurance, and if they can't go to the free clinic or the family clinic nearby, or the man that has the roving wagon that does free physicals, they're probably not going to seek anything. They're just going to stay at home and suffer because they just have no other options, and that's pretty much a large part of the deep southern population. So I'm just bringing that up. It's not always just Bayer's fault or the doctor's fault or following people. It's just a matter that people don't seem to have a choice, a path that they know that they

could follow.

DR. IGLESIA: Or lack of access.

Ms. Chauhan.

MS. CHAUHAN: This is a question for Bayer. You've been asked to specify geographical distribution of adverse events, and you always go to international, where the distribution shows that the United States has more. I would like to see if you have information on the distribution within the United States geographically.

Also I'd like to know, are all the devices manufactured in the same place and subject to uniform quality control? If they're not manufactured in the same place, have the problems come from one site more than others?

(Applause.)

DR. ZAMPAGLIONE: Okay, Edio Zampaglione.

So, breaking down geographically in the United States, that was your first question. That we do not have. I don't know if we're going to be able to get that. I mean, it's not something we'd be able to get right at this point in time.

But the other question -- I apologize. What was the second part of your question?

MS. CHAUHAN: The second part was about manufacturing sites. Are they all manufactured in the same place? Are they all subject to the same quality control? If they're not manufactured in the same place, have you noticed that one manufacturing site may have more problems than others?

DR. ZAMPAGLIONE: Got you. Great. I'd like to bring up Michael Reddick for that question. He's in our quality assurance department.

MR. REDDICK: Michael Reddick, with QA product technical complaints.

So all of the product that is being distributed is all manufactured in one facility, and so they're all contained within the same quality system. Does that answer your question? So there is one quality system that controls the entire process.

MS. CHAUHAN: Have you noticed any timeline difference in the ones that cause problems?

MR. REDDICK: Timeline difference. No. We do a very rigorous postmarket surveillance review of our data, and we have taken a look at that data to see if it correlates with any type of timeline or any certain lots, and we have not seen a correlation with that.

DR. IGLESIA: Dr. Gardner. And then I'll come back to this side. I think there were two questions here.

DR. GARDNER: Jim Gardner.

And this is a little bit of a piggyback on Cynthia's question. We talked about complaint rates in the U.S. and outside the U.S. We talked about the fact that you really can't use those well to establish actual rates. Having said that, probably a lot of us sit here and try to do the math in our head and understand, well, what might the rates be? Can you share with us again what are -- how many devices have been placed since the inception and how many of those have been in the U.S. and how many of those have been outside the U.S.?

(Applause.)

DR. ZAMPAGLIONE: So Edio Zampaglione.

Since approval, approximately 1 million units or kits have been distributed

worldwide. We are not able to track each individual patient or how it gets to, because of the distribution process that incurs. And this is just standard with these type of devices in the industry. Most of the sales are in the U.S., as I think Dr. Machlitt had shown. Essure is distributed in 23 different countries. The U.S. has the biggest portion of the sales or distribution. I don't have a percentage off hand at this point. I'm sorry, I just got it. It's 60% are in the United States. The other 40% are in the other 22 different countries worldwide.

DR. IGLESIA: Dr. Katz, did you have another question?

DR. KATZ: Two questions back on that question. So we're trying to understand the distribution of complications and adverse events, and we're trying to understand what the denominator is and the way we think about it, as well as the details of the provider. Now, does Bayer have -- you showed a chart in which you looked at the prevalence of AE reporting, and I think the number was something like 87% was in the states, and the other 13% were in about 20 countries. Can you take that chart and at least normalize each number by the sales to that country? Because the impression is that the incidence of these reports is much higher in the states and that, in fact, it may not be simply -- and I think one of the key questions is, is it because more devices are in the states, or is it the way the devices are being provided in the states?

DR. ZAMPAGLIONE: I'm going to bring up Dr. Machlitt to help with that one. Yeah, Dr. Machlitt.

DR. MACHLITT: Thank you. We can certainly break down the numbers of the per sales in a certain country, but let me point out one aspect, and that is we are talking about

postmarketing reporting, which is acknowledged to have a factor of underreporting. Typically that degree of underreporting is fluctuating. What we have seen in recent years is strong input from the side of the consumers with a lot of consumer reporting. We believe that the social media plays an important role in that aspect. So what we currently see is stimulated reporting, many reports that also date back to previous years, as you also heard today. And that all has an impact also on the distribution of the adverse events generally. When we try to understand the safety profile of a device, we look on the global data, and we currently base it on an estimated 1 million devices sold overall and the related number of women who are potentially exposed to the device.

DR. KATZ: And then part two. On quality control, what is the quality control?

(Applause.)

MR. REDDICK: Michael Reddick, with QA technical complaints.

So we have one quality system that governs the process from the very beginning to the very end. Our oversight of quality begins at our suppliers. We provide our suppliers with specifications that have to be met for the raw materials and subcomponents that we use. Once those materials get into our process, we have an incoming inspection process that there's defined procedures and things that we look for, things we inspect for.

Once we inspect those materials and they pass, they get into the production process. As with any device manufacturer, there are multiple steps in a manufacturing process. So with every one of those steps, we have very clearly defined and established work instructions, procedures, specifications that have to be met by the product at every single step. Once the product gets all the way through the process, there is a testing that occurs

at the end. So every production lot that's made, we pull samples from that lot. We do destructive testing on the samples. We do functional testing. After we confirm that the device works as intended, we then tear apart the device and test the individual components to make sure that those components meet our specifications. After all that testing is done, we then send the product to a sterilization process. After the sterilization process, we then do additional sampling from the same lot. So we sample again, and we do functional testing again. And then we do visual inspection throughout the entire process. So we feel that we have very, very good, tight controls over our manufacturing process to make sure that we get the best product out to our customers.

DR. KATZ: Some of that testing is, of course, going to be in accordance with standards organizations, like the materials that you receive, focusing upon the completed devices. Now, has any of that testing been created specifically for -- to be suited to the performance of Essure? Is there anything unique to the testing of the Essure device?

MR. REDDICK: We have a couple different types of testing that we do. Some of it is just like tension testing, making sure that bonds are to a certain strength, testing materials to make sure that they have the strength required. We do have a functional test that we've developed, which basically simulates the actual uterine cavity and how the device actually moves. And so we do have a functional test that we use, and we also have standard testing.

DR. KATZ: So that's a mechanical test simulating the in situ environment. Is there any testing done where you simulate the in vivo environment? It's like accelerated aging, but you take the final device and you look at it under those conditions to see what it's like at high temperature, for example, to look at what it's like months later, for example.

MR. REDDICK: That's not part of our normal production process.

DR. IGLESIA: Okay, I think we have two final questions before the break. Dr. Baird and Dr. Wills-Karp.

DR. BAIRD: Dr. Baird.

I wondered about the people who don't have success on the first time, and there has to be another trial to get a bilateral implant. And do you know how many of those -- how does that work? Do they have to pay double, then, or what happens with the costs? And who provides the extra? And can you estimate how many of your million implants that have gone out actual are not actually placed? And does that vary by country?

(Applause.)

DR. ZAMPAGLIONE: I'm sorry, I couldn't hear the second part of the question.

DR. BAIRD: And does that vary by country?

DR. ZAMPAGLIONE: Is it by country? Okay, there is no extra cost to the patient. Okay. So if there has to be a replacement, that's taken care of. Let me see who would have the other part of the question, that if we have -- do we have anything on the number, you know -- and you're talking postmarketing, of course, right? You're not talking from the clinical trials.

DR. BAIRD: Right.

DR. ZAMPAGLIONE: Correct.

DR. BAIRD: Correct.

DR. ZAMPAGLIONE: Yeah, we'd have to look into -- yeah, we'd have to look into that one because that's postmarketing information. Yeah. We have it for the clinical trials.

Would that be helpful?

DR. BAIRD: No, I'd really like it for postmarketing.

DR. ZAMPAGLIONE: Sure, sure. Yeah. We'll try to get that for you.

DR. IGLESIA: Okay. And then maybe before the next question session. Last question before the break.

Dr. Wills-Karp.

DR. WILLS-KARP: Marsha Wills-Karp.

In listening to the speakers this afternoon, it seemed like there were a lot of complaints of autoimmune-type responses. So I'm wondering if any family history of autoimmunity or any data was collected. You may not have known that a priori obviously in the clinical trials. But do you have any information suggesting also that perhaps that information should be collected at some point?

DR. ZAMPAGLIONE: Sure.

DR. IGLESIA: Right, somebody mentioned HLA type.

DR. ZAMPAGLIONE: So Edio Zampaglione again.

No. For the clinical trials, that information was not collected or asked ahead of time.

DR. IGLESIA: Okay, we will now take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience. We will resume at 5:42. Thank you.

(Off the record at 5:32 p.m.)

(On the record at 5:50 p.m.)

DR. IGLESIA: At this time let us focus our discussion on the FDA questions. Copies of

the questions are in our folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the Executive Summary, the presentations we heard today, and the expertise around the table. With this said, I would ask each Panel member to identify him or herself each time he or she speaks to facilitate transcription.

FDA, please read the first question.

MS. BLYSKUN: This is Elaine Blyskun, Branch Chief for OB/GYN devices at FDA.

Based on available information, the following events have been reported to occur in association with use of the Essure device (Note: This list is not intended to be a complete listing of all adverse events reported to have occurred in association with Essure):

a. Procedural pain that is persistent, or new pain that arises at a later point
b. Perforation of the uterus and/or fallopian tubes by the Essure insert
c. Intra-abdominal or pelvic device migration
d. Post-implantation bleeding irregularities
e. Metal (nickel, nitinol) allergy or hypersensitivity reaction
f. Pregnancy (e.g., ectopic pregnancy)
g. Other

Please discuss each item and comment on the following:

a. The degree of association of the item with use of the Essure device
b. The reasons for this conclusion
c. The level of your concern for the item, if any, and the level of evidence to support the concern

DR. IGLESIA: Okay, I'd like to lead off the discussion actually with our Patient Representative and to see if you have any other concerns or any other information and your general impression on this particular question.

MS. DE LUCA: All right. Jo-Ellen De Luca, Patient Representative.

I feel that the answer, from the patient point of view, is still out there. I think that this has been a great opportunity to find some possible answers, but I think there's still some great unknown. I lead a very large support group, and I know a lot of patients will be, knowing I'm here today, but will be concerned around the country, knowing -- looking for answers when this comes out. And I think that we have plenty of patients that have been here that don't have their questions answered, and I feel that will continue.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: In thinking about these, I've been thinking about the large number -- oh, Cynthia Chauhan. I'm sorry.

DR. IGLESIA: No problem.

MS. CHAUHAN: Cynthia Chauhan, Consumer Rep.

In thinking about these, I've been thinking about the large number of women who have identified themselves as having problems and a kind of consistency of the problems. It made me wonder if there's a role for genomic variants testing in this, where I think a real issue if this drug -- I'm sorry -- if this device stays on the market is, going forward, how do you find people for whom this is an appropriate device, who will not be subject to these? And I think, looking at this cohort that's existing and planning from that and considering genomic variants may be useful.

DR. IGLESIA: Thank you very much.

Would anyone like to lead off the discussion regarding these listed complications and the degree of association of the Essure device? Let's start with pain.

Dr. Stubblefield.

DR. STUBBLEFIELD: Procedural pain that is persistent seems to me to be highly likely to be associated with the device. Pain, a new pain, less clearly associated. Could be, could be something else. So many different structures that can cause pain in the pelvis.

DR. IGLESIA: May I ask, is that -- you're saying that it's going to persist because you're off, you've changed the modality of contraception from something that may have also addressed the pain, i.e., continuous birth control pills, to something else or -- or what led you to that conclusion?

DR. STUBBLEFIELD: Well, I think you're absolutely right. I wasn't actually thinking of that at the time.

DR. IGLESIA: Oh.

DR. STUBBLEFIELD: I was thinking of it as related to the surgery --

DR. IGLESIA: Okay.

DR. STUBBLEFIELD: -- or to the procedure. But that's an important consideration --

DR. IGLESIA: Okay.

DR. STUBBLEFIELD: -- as we've already discussed. Abandoning the previous hormonal contraception.

DR. IGLESIA: Dr. Coddington, then Dr. Janik.

DR. CODDINGTON: Dr. Charles Coddington.

I agree with Phil, and I think the practical point is that probably 1-2% of the fallopian tubes are not just straight shots in the sense that they're very tortuous, and the development of the female genital tract has aspects of that, as a woman develops her cervix, also may be very tortuous. So I think the point is, is that there are going to be some anatomic variations, so it would not be inappropriate for there to be some implant that would be more painful or certainly less comfortable. There will be some, if you will, that it will just drop right in and there won't be a problem at all.

So I think that just kind of looking at separating potentially these two things out where there is procedural pain, and then we can talk about how to evaluate for that and that sort of thing from the other in the sense that, yeah, the device could migrate out the tube causing a similar type of pain, true, but I think one of the things that I think has broken down here, no pun intended, is the fact that the physician/patient bond has been broken in the sense that many of the young ladies we heard from today did not have the confidence and good interaction with their physician, that they could come back with a problem and get a reasonable evaluation and answer. And I think that is a concern that I have of some of the things that I've heard, so I think we need to try and figure things out as close to the point of service as we can so that people do not suffer for a month or whatever before something is done and evaluation carried out.

DR. IGLESIA: Dr. Janik. Thank you.

DR. JANIK: Grace Janik.

I look at the pain as different, too. If you look at some of the literature, most of the pain that's procedural pain is resolved by 99% by 7 days, so if you have pain that started at

the procedure and it's still persistent at a week, you probably have a problem and maybe you should intervene and it shouldn't be --

(Applause.)

DR. JANIK: -- many, many months to years before it's addressed. So I think there's an opportunity for early intervention analysis of a placement issue.

And then there's the second, of pain that develops later and -- which could (1) coming off of OCPs or whatever was the previous birth control method, or is there delayed pain that could be device related, and I think that the only way to really know that is more study. I don't think you can really answer that with the data that we have available. But I do wonder how much support that physicians and patients have gotten for that early phase when they call and what should I do, and maybe early intervention before we risk bowel obstruction as the thing has migrated through should be a change in protocol thought rather than wait it out and see what happens.

DR. IGLESIA: So your level of concern seems rather high?

DR. JANIK: I think it's high. It reminds me of endometriosis --

DR. IGLESIA: Um-hum.

DR. JANIK: -- patients which wait 7-8 years before they have a diagnosis and three or four surgeries before it's corrected.

DR. IGLESIA: Um-hum.

DR. JANIK: So it has that same feel to it.

DR. IGLESIA: Um-hum. And so -- and maybe you might recommend some imaging earlier rather than just general --

DR. JANIK: I would suggest imaging if, you know, if you're not resolved definitely by a week. You do some imaging, 3-D ultrasound, you probably can see if you have migration, perforation. You can see if you have a problem early.

DR. IGLESIA: Other discussion on this topic of pain?

Dr. Myers.

DR. MYERS: One thought as we've been listening today is some sort of -- like some sort of protocol change. Maybe there's a post-procedure ultrasound that's done to confirm placement in the tube, is it already perfed through the tube, you know, something a little bit more timely than 3 months --

DR. JANIK: And I think that would be wonderful, too, if you have problems at a week or ideal would be if you do the procedure and you do 3-D ultrasound --

DR. MYERS: Right then and there.

DR. JANIK: -- right after the procedure, you're done. It's like part of the procedural package.

DR. MYERS: Exactly, yes.

DR. IGLESIA: Other comments on pain? Yes, and then we'll move on.

MS. CHAUHAN: Cynthia Chauhan.

My question is to Dr. Coddington and Dr. -- I'm sorry, I can't - - Janik. Would there be any usefulness, given your comments about the physiology and your comments about the length of pain, to pre-procedural imaging to check the tubes to see that they can handle this?

DR. JANIK: Grace Janik.

No, because you can't see it. It's all just -- and it's all soft tissue, it's all angled, it's all how you manipulate things, and there's not imaging that would really help you with that.

DR. IGLESIA: I actually do think that this is a nice -- this conversation is a nice segue to 1b and 1c, you know, because of the anatomic variations and the possibility of whether or not, when you put it there initially, is it in the right spot for a perforation and/or is it in the right spot and then -- or is it out of the right spot and has already migrated. And so that then leads to this question of intraoperative evaluation or early procedural intervention for imaging. Is there discussion on that?

DR. JANIK: I agree with everything you said. Grace Janik.

So I think immediate ultrasound or very early ultrasound -- complications to -- for documentation.

DR. IGLESIA: Yeah.

DR. JANIK: Rather than waiting to discover.

DR. IGLESIA: Rather than waiting up to 3 months for just occlusion because you're --

DR. JANIK: Because there's two things you want. You want, one is --

DR. IGLESIA: Confirmatory.

DR. JANIK: -- placement damage, and then the second is occlusion. It's two different topics. So separating the two answers could be beneficial for the patient.

DR. IGLESIA: Quite frankly, I do think that there is an issue, it seems maybe 2-3%, I'm trying to figure that out, where it's not working, whether it be tubal spasm, the anatomical variant of the tube. I'm saying if this is not going smoothly, we need a Plan B. I mean, the patients need to be saying, okay, we can't get this in. You want permanent sterilization, we

have permission to go ahead and proceed with the tubal ligation or whatever you end up deciding to do. I'm not necessarily sure that that conversation is happening.

Dr. Coddington.

DR. CODDINGTON: I think a lot of them, there were a few young ladies that had had the procedure done under anesthesia, and that would be a very reasonable Plan B. But many of them have them done in an office with maybe a paracervical, if that.

DR. IGLESIA: Yeah.

DR. CODDINGTON: And so I don't know if you could reasonably do that, but it's a great thought.

DR. IGLESIA: Oh, I'm not saying on the same day, but you'll say --

DR. CODDINGTON: Oh, yeah. Yeah.

DR. IGLESIA: -- oh, we're aborting this, this is not going smoothly. We, you know, need to schedule it.

DR. CODDINGTON: Right, yeah.

DR. IGLESIA: Absolutely.

Dr. Wills-Karp.

DR. WILLS-KARP: So Marsha Wills-Karp.

I agree. I also think that if you decided early on that it wasn't working for some reason for that individual, removal at that time would be a lot less complicated --

DR. IGLESIA: Yeah.

DR. WILLS-KARP: -- than waiting until it's embedded and causing other problems.

DR. IGLESIA: Yeah. It didn't go in smoothly, you have more coils, you know, no more

coils are left, and so you know that this thing is probably in too deep or there's too many coils and the whole thing, so it's going to expose because you're not in far enough. Abort. Abort and go get a Plan B.

Dr. Elser.

DR. ELSER: Denise Elser.

Several of the articles in the literature comment on that perforations and complications were more likely when they went back and asked the clinicians if they had difficulty with the procedure. So, again, there may be more guidance on if it's not going smoothly, you can wait for spasms, spasms should alleve, and then it goes in smoothly again. But if you're still putting pressure, putting pressure, and the device does not go in the tube smoothly, maybe -- you know, we don't want to force it in, and there could be stronger guidelines.

DR. IGLESIA: Is that good discussion? I think we can move on to the bleeding irregularities, then. I will summarize, so we'll have more time, opportunity for discussion. And I know 1e is going to be one that's going to require probably a longer discussion. But the post-implantation bleeding irregularities, would someone like to lead this off?

Denise.

DR. ELSER: Well, I think this one is actually --

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

I think this one's actually hardest -- because unless we know how many women came off of hormonal contraception at the time of their Essure, and are they developing bleeding

abnormalities related somehow to the implant, or is it their own physiology that they are having bleeding abnormalities because of their age, their hormonal status. And I think we heard some comments, too, about people developing pain and found to have adenomyosis, endometriosis, and we can't comment if that's device related at all because that's a common finding in women who are not on hormone contraception.

DR. IGLESIA: Other questions, I mean comments on this, for the bleeding?

(No response.)

DR. IGLESIA: Okay.

Dr. Stubblefield.

DR. STUBBLEFIELD: On that question, I think that I understood, from reading the presentations, that part of the time the bleeding could be associated with perforation, and if that's the case, then maybe bleeding warrants at least an ultrasound to look for that and not just assume that's just endometrium.

DR. IGLESIA: That's a good point. Maybe one of the early intervention protocol to add that to the list, the checklist.

Dr. Coddington.

DR. CODDINGTON: I think in -- I mean, your point is well taken. In looking at this, we deal with abnormal uterine bleeding. And if you've increased the menstrual flow, then we kick over into a paradigm of working out the bleeding. I mean, heaven forbid she could have a polyp or other things like that that are intervening, or a myoma. All of those things are possible. They could -- you know, I can't necessarily relate them to the device in that sense, but what I'm saying is, is that we then address the problem of the bleeding and go

about that aspect so --

DR. IGLESIA: And clearly there were some case reports about pretty significant infections and abscesses and endometritis, and I think, you know, developing a uterine infection is also in there and is a cause for bleeding.

So let's tackle 1e, on the nickel allergy. I think we might start with Dr. Wills-Karp or Dr. Milner on this. Is that okay?

DR. WILLS-KARP: Yes. Well, first of all, I think we need more data, and I don't think, in the literature, that there's sufficient data to predict how nickel exposure in the reproductive organs, actually, how you respond to them. And is that different than skin or other sites? So I think we definitely need to understand that better. But I think in the context of the study, it would be worth collecting information about nickel sensitivity in people who have these devices and see if that is, with the larger sample size now, to see if it is connected with some of the symptoms. It may or may not be, but it seems like it's worth pursuing. I think on the same -- and I'm going to group it in here with the sensitivity because I think there may be some other altered immune phenotypes associated, and this -- hypersensitivity in general. It may not be to nickel alone, it could be to other aspects of the device or just the foreign body response by itself. So also to clear up --

DR. IGLESIA: Can I ask about your degree -- your thoughts on the degree of association of that with Essure and your level of concern? Just in terms of do you think that that would be an absolute contraindication or relative contraindication even right now as a recommendation?

DR. WILLS-KARP: Well, I agree with Peter, who I had also found that they had had

that as a contraindication early on and seem to have been lost somewhere along the way. I think it would be worth including at this point, but more data would probably be good because it may not be simply nickel; there may be some other aspects that need to be explored. I wouldn't want to just say it was nickel and then it would be something broader than that.

DR. IGLESIA: Dr. --

DR. SCHALOCK: I think --

DR. IGLESIA: Your name.

DR. SCHALOCK: Sorry. Peter Schalock.

If we want more data, we need to find what we're looking for, assuming a Type IV allergy, a delayed hypersensitivity. So, first of all, we need to define what test we're going to do to define what this allergy is, so we need to decide are we going to be doing a patch test for this, which, in general, even though it's not a perfect test and certainly data has shown it's not conclusive, does it predict anything? But at least it gives us some data: Is the patient nickel allergic or not?

The other option, which I think was brought up, I forget whose question it was, is there a blood test? There is a blood test that's available through, I believe it's Orthopedic Analysis, as well as some other companies out there, which is not FDA approved and not standardized, called the lymphocyte transformation test. Or the MELISA is, I think, a little variant of that. I would be a little hesitant to recommend something until it is a little bit more standardized and approved, but that test is out there, and some people believe that it's useful. So maybe that's something that needs to be explored, is doing a simple blood

test going to be enough to give us nickel data or -- as well as the other stainless steel components.

And my concern on this, I just feel like there's a disconnect between the number of women who are nickel allergic versus the information from the study, the Zurawin study, where they found essentially nobody had nickel problems, just -- I don't know. I just feel like if there's no data, that's -- I don't necessarily say the study is wrong, but on the other hand we don't have data, we don't know who is allergic, are they allergic, how often is it relevant. And maybe with a big enough sample size, we can actually do statistical analysis and figure out maybe there is a link. So I would be in favor of collecting this data somehow.

DR. IGLESIA: Dr. Milner.

DR. MILNER: So I think, first of all, we need to sort of separate out what we're talking about, as was discussed with Dr. Hamilton, and it's more likely that it's -- quite likely that it's more than one hypersensitivity. Whether it's a Type I and a Type IV, it's probably even something else. And, in particular, as it relates -- and with respect to the numbers that are coming up, being nickel sensitized and having a reaction are going to be two very different things. And then developing nickel sensitization once it's embedded are also separate things, and I think we've been confusing all three of those.

DR. IGLESIA: Right.

(Applause.)

DR. MILNER: So a point that I think is sort of bringing together what a lot of folks have mentioned during the public comment with respect to this auto-immune constellation or inflammatory constellation, so point No. 1 on that is, is that it would be great if we could

actually capture the inflammation, which is why I was so focused on what the biopsies of these specimens from people who had it removed -- and we've captured everything.

We know whether they've resolved, we know what they've been complaining about when they did, so getting a biopsy and looking to see what's going on seems to be an extraordinarily obvious thing to do to really get a sense of is there inflammation, because you can point to that, you can see it, and if it correlates with the complaint, then you have a pretty good sense that there's something that's happening, we don't know what, but something is happening.

Another point, though, that I think is important to make is that the constellation that a lot of folks have described, and in particular the downward slope of one thing and the next thing and the next thing and the next thing. So we actually -- it's important just to point out that especially in allergy, where we get brought lots of stuff where people don't know what's going on, we actually see that in many, many different scenarios well before Essure ever existed and well before -- in a variety of different settings.

Very often it is a major event. It could be trauma, it could be stress, it could be surgery or anything like that, and very often we see patients come in after such an event and begin to develop a series of complaints very, very similar to those which were brought up here. I have to be very clear. That doesn't mean that the response to this device is not one of the ways that this happens directly related to the device and not directly related to a trauma, but it just has to be pointed out that in addition to that, if -- to the extent that there is a direct correlation there, there does exist, even with autoimmune phenomenon, the emergence of antibodies, the emergence of specific complaints, and also in terms of

non-directly measurable things, which are unfortunately put together as functional complaints like bellyaches with no pathology or headaches with no pathology. Those are often unfortunately all thrown together, but they are very often seen in an allergy setting where it's completely unclear where it's coming from. And I just think it's important that it be out there that that's there, but not to sit and blame that possible thing which very often people say it's in your head, not to ever dare to do a thing like that, but just to be aware that it exists in both places.

(Applause.)

DR. IGLESIA: Okay. We'll go down the line, one, two, three. Sorry.

DR. CHAPPELL: Rick Chappell.

I would like to expand upon Dr. Wills-Karp's and Dr. Schalock's comments. More specifically, they asked that we get more information about allergies or sensitivities not only to nickel, but also perhaps stainless steel. And there's a third component, which is PET or its trace contaminants, which may well have undesirable inflammatory responses, because as far as I could tell, and I'm not the expert in this, but from reading Bayer's own material, it has a desirable inflammatory response, and that's how it implants. If it doesn't have an inflammatory response, it won't be effective. And therefore -- well, so that's a good -- it's intentional, right? And these patients should all know this if they were educated. But then it could perhaps not stop at the desirable level and keep going.

(Applause.)

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: That was exactly what I was going to say, is not forget the PET, I

mean, because that --

DR. IGLESIA: And Dr. Seifer.

DR. SEIFER: David Seifer.

So this issue about the systemic reaction to mercury is just one example of many issues that we're concerned about in terms of collecting more data. Even the numerator/denominator incidents of these complications, pregnancy, blah, blah, blah, and what's been suggested by more than one person from the floor is the idea of a registry going forward so we can have an accurate assessment of the frequency of what's going on, whether it be this reaction or the other five or six issues that we're discussing.

DR. IGLESIA: Great. I think we have had a good discussion on the hypersensitivity/allergy. I'd like to move on to the pregnancy, if that's okay, issue and would anyone like to lead that discussion? I know that some Panel members talked about CREST 2.0 and -- Grace.

DR. JANIK: Grace Janik.

So it seems like the data when -- uses -- with follow-up at 3 months is done correctly is really pretty good. So I think that's the positive side. But it's disheartening that there's a disconnect between placing the device and follow-up for the 3-month evaluation, and especially that finances and insurance is part of the holdup. I feel like if you don't have the second part cleared, you shouldn't do the first part. They should be linked.

(Applause.)

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: So if they're going to be linked, then they should be -- it should be

committed to, to begin with, so they should be financing this whole up front so that it's part of the procedure and it's almost guaranteed that it happens.

DR. IGLESIA: Yeah, I think that the actual economic financing and stuff is probably beyond the scope of this particular group; however, the concept of the bundling of the whole method as one procedure, I understand.

Dr. Elser, Dr. Coddington.

DR. ELSER: Denise Elser.

Just for practically for part of the problem, because people are not the clinicians doing this, may not understand some of the implications of that. If the procedure is done in a surgery center and the surgery center accepts public aid because Essure is public aid, pays okay at that surgery center, but that they don't do HSGs there. And so then some places the HSG is done by a radiologist, some places it's done by the gynecologist and radiologist together, but now you're in another facility with another clinician charging, and so it's very complicated to make it a bundled payment if it's not the same facility.

DR. IGLESIA: Good point.

Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

One of the things is we might want to hold on that because, as I understand, there's a study coming up with ultrasound, and I think that that might be something that would be in the hand of the gynecologist and a bundling type of process could take place. So, like you say, we can't control the financial dynamics, but I think they're going to -- we'll have some information here relatively soon, I think. I don't know --

DR. JANIK: But I don't think it's responsible to put it in if you don't have that second part. And if it's not all worked out, I just feel like that should be a "no" barrier to going forward. You just can't offer it if you can't work it out at your system.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I think the bundling is really important, and I think a third component of the bundling should be skill in removing the device. I don't think people --

(Applause.)

MS. CHAUHAN: I think skill in removing should be on the same level of importance as skill in placing, given the problems we've seen.

(Applause.)

DR. JANIK: Can I comment?

DR. IGLESIA: I do think that physician training is Question No. 2, but thank you for that comment.

DR. JANIK: Grace Janik. I just want to comment.

The skill to remove is so different and such a higher level that I don't think you necessarily have to be the same person, but you have to access, you have to have a plan of where in your system they're going to go. It doesn't have to be the same person, but --

DR. IGLESIA: Yeah, I agree.

DR. JANIK: -- it shouldn't be a mystery of now what are we going to do.

MS. CHAUHAN: It's the bundling that matters, yes.

DR. IGLESIA: Dr. Elser, then Dr. Stubblefield.

DR. ELSER: Denise Elser.

So, once again, part of that is the way our payer system works currently that makes it a problem so that -- you know, I'm in Chicago, so let's say a lady has an Essure done at her doctor's office or a clinic in southern Indiana and they know that I may be the closest expert that knows how to remove it. I'm out of pocket because I'm not in her insurance plan. That's a huge barrier. So they might know where to send them. It doesn't make it doable for the patient financially.

DR. IGLESIA: Dr. Stubblefield.

MS. CHAUHAN: May I just respond?

DR. IGLESIA: Sure.

MS. CHAUHAN: Cynthia Chauhan.

It's my understanding we can't consider finances as part of our deliberations, but in the interest of good patient care, I think if you do not have access to someone who can remove successfully, you should not be implanting.

(Applause.)

DR. IGLESIA: Dr. Stubblefield.

DR. STUBBLEFIELD: Stubblefield.

While we're on the topic of the removals, I was really quite amazed to see that so often they are hysterectomies, and it sounds like often hysterectomies and bilateral salpingo-oophorectomies were being done, which is kind of like swatting flies with a cannon. Why do we need to do that? I don't know. Maybe part of the time there is other pathology, and it certainly makes sense if the patient wants to, but the amount of expense

and the amount of risk of doing a total hysterectomy as opposed to a laparoscopy or mini-lap removal with a linear incision, just no comparison.

DR. IGLESIA: All right. And I think some of this is also going to be in one of the questions about the removal. So is there any other discussion for Question 1? And we have the letter (g) as well to consider, if there is any other. I don't want to sort of limit the discussion to (a) to (f).

Dr. Myers.

DR. MYERS: Deb Myers.

Going back to the hypersensitivity events, what is -- and this might get answered later, but what is the current language in the patient insert? You know, is there some language in there that -- or could be added, you know, that this is a possibility, that some hypersensitivity might occur for the patients? In patient info.

DR. IGLESIA: I guess I would have to ask Dr. Fisher about --

DR. MYERS: I don't know. I'm just asking. If it isn't, is that something that we should consider recommending?

DR. IGLESIA: Dr. Milner, while waiting for that question, do you have a comment?

DR. MILNER: I'm not sure how you're going to be able to answer that because since the criteria were not laid out as to what the hypersensitivity is, it couldn't have been captured properly, so how could we answer that in -- the labeling, whatever it says right now, couldn't reflect what's actually being -- what's not captured.

DR. IGLESIA: Well -- you have another? Great.

DR. ELSER: This is not related to autoimmune. Denise Elser.

But while they're looking for the answer, I just want to point out also, yes, getting sterilized is an elective procedure. We always want to weigh the risk and the benefit. But pregnancy is dangerous. Pregnancy is dangerous, and ACOG has recently supported that hormonal contraception should be available over the counter because we felt it was -- or ACOG felt it was safer to let women go to the store and decide to take OCPs without a doctor visit than to be pregnant overall. So we want to just remember that, that yes, having a laparoscopic tubal ligation is not without complications as well, and patients get chronic pain after pelvic surgery, they get abscesses, they can become disabled also. So I just want to remember the context at which we're looking at this.

DR. IGLESIA: Great.

Dr. Yustein.

DR. YUSTEIN: So, in response to Dr. Myers' question, the current patient labeling brochure has the following statements: "The Essure insert is made of materials that include a nickel-titanium alloy. Once placed inside the body, small amounts of nickel are released from the inserts. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash, itching, and hives."

DR. IGLESIA: So it's there as a potential known risk. Okay.

DR. YUSTEIN: And hold on, there's one more.

DR. IGLESIA: Oh. There's more.

DR. YUSTEIN: There's a section in there that says "You should speak to your doctor if," and it has a couple of bullets. One of the bullets says, "You have or think you may have a nickel allergy."

DR. IGLESIA: Dr. Milner.

DR. MILNER: So, again, that just -- that would then narrow it down to nickel when it could be from any number of sources.

DR. IGLESIA: Right.

DR. MILNER: And that's going to miss who knows what by doing that.

DR. IGLESIA: Good point.

DR. MILNER: So, again, when you just talk about hyper-sensitivities, that's any hypersensitivity, and if you narrow it to nickel, then that's going to be misleading.

DR. IGLESIA: We don't know what we don't know.

Dr. Seifer.

DR. SEIFER: I was just going to beg the question about the symptoms that were, I've heard about today, go way beyond that cutaneous reaction, and so I'd like to beg the question if it should be a little more --

DR. IGLESIA: Whole autoimmune?

DR. SEIFER: -- explicit.

DR. IGLESIA: Yeah.

DR. SEIFER: Yeah.

DR. IGLESIA: Okay. Let me see if I can try and summarize, unless there's anyone who has any parting comments on this.

Dr. Chappell.

DR. CHAPPELL: Chappell, right.

DR. IGLESIA: Yeah.

DR. CHAPPELL: Rick Chappell.

I do have a parting comment. Because we are not asked, as part of Question 1 or any other question, to provide FDA with advice under general strategy, but the situation we find ourselves in today absolutely demands it because postmarketing studies behind huge clinical trials, I'd say that postmarketing studies are especially good for detecting rare outcomes. A clinical trial even with a couple of thousand could not detect some rare outcomes. But as Dr. Juran commented today, she showed that many of the medical issues faced by the patients we heard from, as severe as they are, are very common in the general population, pain, et cetera.

And so we find ourselves in a situation, 13 years after this device was approved by the FDA, of asking ourselves about pain and bleeding irregularities and other very common outcomes. And we are doing so because this was approved on the basis of a so-called pivotal trial which was not randomized, not controlled; it was single armed. And I say so-called dismissively because I don't see how a pivotal trial can be a non-randomized, uncontrolled trial. Therefore, I recognize the logistical difficulties, the expense, but therefore, I strongly urge the FDA to abide by its own statement, which it made in 1967, that the gold standard is a randomized clinical trial.

(Applause.)

DR. IGLESIA: I think we can probably address that as well with Question No. 2.

So, to summarize, with regard to the assessment of clinical events, procedural pain, perforation, intra-abdominal device migration, there seems to be a problem for which we have some concern. And the concerns relate to the fact that we need more guidance for

practitioners who are doing this to be able to identify earlier, most early on before long-term complications occur, that we could have a problem. That could be done intraoperatively by assessment of intraoperative imaging to see exactly where these devices are located to mitigate the risk for accidental perforation or migration someplace else.

Or if the symptom of pain persists outside the typical, what one would feel is the typical time period of which one would have the usual procedural related pain, i.e., 7 days or whatever, then an early intervention analysis should take place. Same thing with regard to the development of bleeding and other, maybe unrelated to whether or not a different kind of contraception had been previously used. But if there are signals, then we need some type of protocol to be able to identify that early.

Does that summarize for those three?

(No audible response.)

DR. IGLESIA: With regard to the post-implantation bleeding abnormalities, the range is all over the place because the differential diagnosis for abnormal uterine bleeding is quite large, and there may be other causes that are unmasked because you've stopped other forms of contraception or you may have developed new reasons, i.e., polyp formation or an infection as a cause for bleeding. Again, some type of post-procedural protocol to be able to evaluate that earlier on would be helpful.

With regard to metal, nickel, PET or other -- stainless steel or other allergy or hypersensitivity reaction, this is a pretty significantly high level of concern, and we seem to have only scratched the surface in identifying nickel as a potential problem if someone has already a nickel hypersensitivity. But what we need is more data that's related to testing

pre-implantation, if at all possible, to include patch testing, blood test including -- I'm sorry, the lymphocyte MELISA test, and what I think makes a lot of sense is anything that is actually removed to have post-implantation biopsy/analysis/histopathology and analysis of the actual pathology of the device in relationship to the surrounding tissues to see if that is related to a hypersensitive reaction, inflammation or whatnot.

That being said, we also talked about the need for registries for identification of things that are rare, potentially such as this, a hypersensitivity to something, and even a registry for the common. There seems to be some general consensus that postmarket surveillance with some type of registry would be helpful.

Does that summarize that for that? For the allergy hypersensitivity issue.

Finally, with regard to -- no. Okay. Finally, with regard to pregnancy, seems to be that we need long-term data with good follow-up and some comparator data, I mean, what Dr. Chappell was referring to in terms of a randomized clinical trial, some type of comparator. You know, randomized clinical trials are obviously the gold standard. We had -- since I only saw that there was one study that had a comparator with the gold standard laparoscopic procedure, any type of prospective cohort with the comparator which can be done within the auspices of a registry might be feasible as well.

Now I brought up something else, I probably opened up another can. But go ahead, Dr. Chappell.

DR. CHAPPELL: Thanks. I want to clarify that, alas, I was not recommending a randomized clinical trial right now, in the present instance, because the window of opportunity may well have passed and it would take too long. But I am pointing out that it

was a mistake not to have done so and that I request the FDA not repeat it for future devices.

DR. IGLESIA: Dr. Coddington. I didn't do a great job on that last one.

DR. CODDINGTON: No, I think you did fine. Because I think the reality is, is that to be honest, we don't know what we don't know. And, you know, when you do randomized trials, you have to be able to figure out what you're trying to randomize from what. And we have two expert allergists, and we're not sure where we are there. I mean, I think we need to kind of better define that, if we get a specimen that we can look at the pathology and find different types of reactions --

DR. IGLESIA: Yeah.

DR. CODDINGTON: -- and different types of cells in the histopathology. That's going to make a world of difference. So I think more of a registry is a good place to go.

DR. IGLESIA: Dr. Fisher and Dr. Yustein, is this adequate? Do you have other questions?

DR. JANIK: Sorry.

DR. IGLESIA: Oh, no. No.

DR. JANIK: Dr. Janik. One comment.

You forgot in the pregnancy summary is to have the follow-up study linked with the procedure.

DR. IGLESIA: Correct. Thank you.

DR. YUSTEIN: Dr. Iglesia, we specifically let (g) on there to make sure that we weren't leading the Panel into just a focused discussion of things that we thought we had

focused on. Were there other topics? Because here's the chance to bring those up --

DR. IGLESIA: Okay.

DR. YUSTEIN: -- because the other questions are kind of follow-ons to this question, so if there are other concerns, you heard a lot of different adverse event types discussed today by all the presenters, not just the external presenters, but FDA and the manufacturer as well. Are there other issues of particular concern that we might be looking to in future questions to address in terms of mitigation strategies, labeling changes, et cetera? I just want to make sure that we have that.

DR. IGLESIA: I guess to summarize that some people were talking about the availability of other contraception, making sure that women were informed about options for other contraception, and the bundling. This is a method, that the procedure itself should be linked to the necessary 3-month post-procedural follow-up for, you know, complete analysis. And also if there is a complication that's necessitating a removal, that that also be linked, that, you know, if you can't put it in, you can't -- if you can't take it out, you shouldn't be able to put it in. I think we had those kinds of discussions.

DR. YUSTEIN: Right, I understand. I just want to make sure, like, you heard people talk about, you know, infection. You heard people talk about headache, fatigue, weight gain. There are other adverse events that were mentioned today that we didn't include on that list, but we just want to make sure that there's no other major type of event that people are concerned about.

DR. IGLESIA: Dr. Milner, then Dr. Elser.

DR. MILNER: You can even add -- you should also probably add cancer since -- it may

be more rare but obviously looms quite large to anybody who would be thinking about that. I think the issue that we're all sort of struggling with is that, well, we need some sort of criteria for how we capture any of this, so how can we register an opinion on it if we're not satisfied with the method by which any of this was captured? So I think that that -- so, therefore, if the label needs to reflect, and since we can't capture it, we're going to have to say everything, then that's what it has to say.

But, you know, there are theoretical ways you could explain all of those things in direct relation to nickel or anything, like other theoretical ways. They're not proven necessarily, but there are theoretical ways. And, again, with respect to the functional complaints like -- that can't be pinned down to a pathology, like a headache or a bellyache or something like that, you know, that can go along with a variety of general reactions to things, and this can be one of them.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

I think for "other," we would kind of refer to what might be a new onset of autoimmune disease as we're kind of throwing in with the allergy and hypersensitivity, but it may be a totally separate phenomenon, is that is it related or not? We don't know. And we haven't really talked much about just hypersensitivity disorders in general where we -- you know, some people are hypersensitive; is there a relationship to IBS or fibromyalgia, and would these folks not be good candidates for an implant? And we don't know that either.

DR. IGLESIA: Dr. Fisher.

DR. FISHER: Dr. Janik, I just want to get clarification on your comment about pregnancy. There was talk about the need for long-term follow-up on outcome data, and then you had added something at the end, and I'm sorry, I didn't catch that.

DR. JANIK: That pregnancy oftentimes seems to happen because people don't come to their follow-up study, so there's a gap. But if before the procedure is placed you have your follow-up 3-month study paid for, organized, it's a package, you can't put it in until the second part's organized, so it's not, oh, well I guess we need to set it up, my insurance doesn't cover it, I can't afford it. You just can't start if you can't finish.

DR. FISHER: Got it. Okay, thank you.

DR. IGLESIA: All right. Dr. Coddington.

DR. CODDINGTON: Just one other thing. We've addressed some issues in dealing with the instructions to the person that is implanting the device.

DR. IGLESIA: Yes.

DR. CODDINGTON: The other that I think would be very helpful, and I did not see it, it may be there and if I missed it, I apologize, but is to give some instruction about how to interpret the HSG. In other words, there were some young ladies that brought the films up and showing that said my HSG is abnormal, something you could obviously tell, but --

DR. IGLESIA: This is Question No. 2.

DR. CODDINGTON: Yeah, okay. Sorry.

DR. IGLESIA: So if we're done with Question No. 1, I think we might be able to move to Question No. 2. Thank you.

MS. CHAUHAN: Cynthia Chauhan.

Could I ask one question of the FDA?

DR. IGLESIA: Of course.

MS. CHAUHAN: Following up on Dr. Chappell, I know that it is not usual to go back and say you have to do a randomized control trial, but it seems to me so many of our questions would not be here if that had been done directly in the beginning. Is that something you can never say?

(Applause.)

DR. YUSTEIN: I think one of the questions that we have coming up will ask you if you believe additional clinical information needs to be collected, and that'll give you the opportunity to provide us with further input on what you think it needs to look like and what needs to be collected.

MS. BLYSKUN: Elaine Blyskun.

Question 2: For each of the events of concern discussed in your response to Question #1, please discuss the clinical implications and possible risk mitigation strategies, such as changes to physician labeling, patient pre-operative evaluation or selection, or post-operative monitoring.

DR. IGLESIA: Who would -- we did talk a lot about this, but would someone like to just summarize and have a little bit more of a discussion?

Dr. Gardner.

DR. GARDNER: Yeah, Jim Gardner. So I did have a question related to that.

DR. IGLESIA: Sure.

DR. GARDNER: We discussed quite a few notions about changing practice protocols

and physician training. I think the Sponsor is probably wondering what would their involvement be in that, what should it be, who should be responsible for establishing these protocols and then doing the training. Is that sponsor, FDA, professional societies, medical school, training residencies? Any thoughts about that from the clinicians in the Panel?

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

You know, the question came up earlier when we were asking Bayer about, you know, someone does five procedures with someone watching them, and then who makes the call if they're trained or not trained, should get credentials? So industry manufacturers do not credential physicians; you have a local credentialing board that does. And some hospitals are going to, you know, absolute numbers in order to keep their privileges, so whereas if you don't do 10 of a certain procedure in a year, then you lose your privileges and you have to be proctored again.

Now, that applies to hospital settings, but there is no credentialing oversight in private practice offices and in a lot of clinics, so there's a lot of -- there's a lot -- I've given you a lot of questions to your question, because there is not one board who decides how many you have to do that makes you confident, if you have a problem, what happens. And when I looked at our data at our hospital a number of years ago, I looked at all the Essures done in a year and looked at -- we were looking at follow-up and complications. And we found that over 75% of the perforations were by one physician on a staff of like 45 people doing the procedure, and so that was one reason I asked the geographic to see if there are clusters of problems based on what can we localize into a certain place, a certain type of

hospital. There are so many things that we could learn from better tracking.

DR. JANIK: I agree with individual tracking, but I disagree with a specific *n* number because you can have somebody that does 50 and they're still perfing; somebody who does very few -- so that number correlation, I think, is -- gives a false sense of security. It needs to be tracking of outcome.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: Yeah. But if you have a registry and you review it every 6 to 12 months, you're going to see something like that pop up, it will be a red flag.

DR. IGLESIA: Okay. I'm going to go around the table.

Okay, Dr. Baird.

DR. BAIRD: The tracking also would be much easier for problems if there was this after 7 days kind of an ultrasound or an immediate ultrasound because then you have something to go by, to track with, so it seems like we've discussed things that would make this much easier.

DR. IGLESIA: Great. So I mean, I just want to go around the table to see if anyone has anything additional to add about training, preoperative evaluation, or postoperative surveillance. I'll start this way.

Deb.

DR. MYERS: Deb Myers.

Yeah, thoughts that I've had to try and lessen perforation rates or unrecognized perforation would be like ultrasound, like either post-procedure or like within a week, just to kind of ensure where the placement is. A thought I just had off the top of my head now

is similar to the IUD, it has a string. You know, if you put a string on the end of it and if the string is gone, then you know the coil's gone somewhere. I'm just thinking in my head. Something to think about. I also think that maybe some more bolder, specific information needs to be given to patients. We've been talking a lot about autoimmune responses, what it is, whatever the condition is, but either a patient card, a patient guide, you know, kind of a highlighted bulleted piece as opposed to a big long list of lots of information.

DR. IGLESIA: Thank you.

Dr. Chappell, anything to add?

(No audible response.)

DR. IGLESIA: Dr. Coddington, anything to add to training, pre-op evaluation, or post-op?

DR. CODDINGTON: Sure. Charles Coddington.

I think the post-op aspect that I mentioned regarding the interpretation of the X-ray films would be helpful and then would make things more standardized as far as the post-op process, and I think the results would be all the more clear.

DR. IGLESIA: Can I just ask, is that like a quality control, like somebody's going to actually be a second set of eyes reviewing the films, sending it to --

DR. CODDINGTON: I think -- no, no. All I'm saying is relative to the uterine cavity, when you do an HSG, you can see where the device is.

DR. IGLESIA: Right.

DR. CODDINGTON: And it's -- the device lights up on X-ray, seen it, done it, been there, and it's just a question of is there something that if the device is not in the uterine

cavity, Houston, you have a problem? I mean, you know, in other words, if it's migrated out of the tube and that sort of thing. So that would be the point. And I think also in changing the physician training is to allow the physician to not pursue when the situation is not going to be easy, as you mentioned. If there looks like there's spasm, you can identify spasm when you're looking through the hysteroscope. This is not hard. And/or -- yeah, some of the comments, and forgive me, we've gotten them from everywhere, about looking at not getting good "visualization." If you don't have good visualization, you shouldn't be doing the procedure, or at least not at that time. So I think that giving some guidance allowing people to give up.

DR. IGLESIA: Dr. Janik, anything else to add?

(No audible response.)

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: There were two things that -- we talked about at 3-month procedure to verify that the instrumentation, where it's supposed to be, but we didn't talk anything about the additional contraception that people are supposed to be taking for those 3 months. So I don't know how much of that may or may not contribute to the pregnancy outcome, but it seems that that would be something that we could stress more than maybe what's already being done. The other thing is on the labeling. I think it says give a history of pelvic inflammatory disease, you shouldn't have this placed, but even though it seems so basic, I don't know if there's -- everyone's doing screening for STDs before they place this.

DR. IGLESIA: Ms. De Luca.

MS. DE LUCA: Jo-Ellen De Luca.

Thinking on the autoimmune diseases and being a person with a very limited immune system remaining, looking from M.D. to M.D., every doctor I go to gives me another drug or tries to, and so often, you know, I've gone from methotrexate to Remicade, Imuran, and I've taken the wide gamut; so have a lot of these patients for another reason. And I think maybe the response, if we could somehow make sure that all the physicians are on the same page and recognize what they're doing, because we might be overmedicating with autoimmune problems and then the device itself gets -- comes into question.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I do believe very strongly -- I understand that licensing is not the purview of the company, but I believe training is the ethical responsibility of the company, and part of that training should be what, I believe, was Dr. Coddington touched on, not only how to implant the device but when you refuse to implant the device. I think there needs to be far more rigorous screening of patients, taking into account some of the other risk factors that were briefly mentioned but we haven't gone into in great detail, like obesity, and really being willing to say this is not the best procedure for you and to help the patients look at other options as well as this option with a well-trained circuit of physicians.

DR. IGLESIA: Dr. Gardner, anything to add?

(No audible response.)

DR. IGLESIA: Dr. Wills-Karp.

DR. WILLS-KARP: I guess I'd have to say I'm amazed listening to the speakers today that their physicians allowed a lot of these abnormal events, bleeding, et cetera, to go on

for such a long time. And I just --

(Applause.)

DR. WILLS-KARP: -- think that it requires a lot more physician training. But the patients also should be told if these things persist past a certain period, you know, go and camp out at the doctor's office. Don't just let it go. Not saying they did, but it's also the physicians didn't seem to do the proper follow-up, and I think they absolutely have to.

DR. IGLESIA: Thank you.

Dr. Baird?

(No audible response.)

DR. IGLESIA: Peter. Dr. Schalock.

DR. SCHALOCK: Peter Schalock.

Just a thought. From dermatologic medications, Accutane or isotretinoin, every patient fills, reads, signs off on multiple points on a single consent form that's provided through a program at least monitored by the FDA. Maybe this would be something we could recommend, is develop a consent form, a uniform consent form for the patients that brings up our concerns. I mean, do you think you're nickel allergic? Okay, well, you know, you signed off on it. And that was some things brought up by the community speakers, that if they knew they were metal allergic or if they knew it was metal, they wouldn't use it. So I don't know what's happening, but something like that may be useful where, here are the things we need to know, and put it on a piece of paper that is a formal consent form.

DR. IGLESIA: Dr. Katz?

(No audible response.)

DR. IGLESIA: Dr. Stubblefield.

DR. STUBBLEFIELD: I listened to all those stories for 2 hours. There is a wealth of information there. Perhaps a lot of it is written down, at least on the websites, which I haven't looked at, but seems to me like we really don't have a full grasp of what this problem is. We can't really even agree for sure that there is a problem. It may just be that the device is a red herring, just to let you know you were going to get a fibroid and the fact that you've got this device didn't make you get the fibroid. But there's just a whole lot of details in here, and is there room for a sort of broad epidemiologic analysis, getting together a lot of the stories and writing them down and trying to see what's there and maybe what isn't there and think about other exposures, trying to get a better overall grasp of what the problem is?

DR. IGLESIA: Finally Dr. Milner.

DR. MILNER: So, just quickly, I mean, it was suggested before, but I do think it's important to point out that those who walk in already with -- you called them hypersensitivity. I'm not sure for all of them I would call them that, but if there is a substantial autoimmune history and a substantial history of functional complaint such as headache and IBS or other things of the such, until we have more information that that really isn't a risk factor, it's just -- and it's really the purview of the FDA to decide, you know, what trips that. But I'm sure that in plenty of our experiences, that putting someone like that through another experience, until there's data to prove otherwise, these types of things are going to come up, so at the very least they should be pre-identified, you know, in that regard.

DR. IGLESIA: Okay, thank you very much.

Any comments? I'm going to summarize otherwise.

Dr. Fisher.

DR. FISHER: I just had one follow-up question for Dr. Myers.

Dr. Myers, you suggested that it might be useful to have a patient card, and I was unclear as to if you meant that a card that you give the patient that really outlines what they're about to get into, or if it was a card that says I'm a card-carrying Essure patient, because it sounds like from a lot of these patients, they're getting passed around from doctor to doctor to doctor, and a lot of them don't even really know what this device is about. So I was wondering which one you were suggesting.

DR. MYERS: Deb Myers.

I was actually thinking of the first, more of a patient information, like this is the procedure, these are the kind of like key highlights of things you need to know, are you nickel allergic, do you have autoimmune, you know, history of infection. But, actually, I like your second thought as well. You're talking about "I have an Essure in me."

DR. FISHER: Right.

DR. MYERS: Right.

DR. FISHER: Right.

DR. MYERS: Yeah. I like that as well.

DR. IGLESIA: Okay. Dr. Seifer and Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Following up on that, I like -- they've got a great resource over here at 1-800-CALL-A-

FRIEND, and I heard a number of people went to the ER and they went "huh," and to avoid that, have a card or something, "I've got an Essure; if you don't know what it is, call 1-800." They have that.

(Off microphone comments.)

DR. CODDINGTON: Oh, okay.

DR. FISHER: So it sounds like we have a good idea, but it's not being implemented very well across the board, so -- or it's not being -- or people aren't understanding it when they see it.

DR. SEIFER: So, in terms of patient labeling, it was brought up from the floor about whether or not this is really a nonsurgical procedure. I mean, given what we've seen in terms of the complications and the extent of them, maybe we should consider changing that.

(Applause.)

DR. IGLESIA: Okay. Okay, all right. Let me try and summarize here.

With regard to Question No. 2, in events of concern regarding training, there seems to be some additional training that is necessary, not just in the initial implantation with regard to going through the modules and the didactics, the simulation, and the preceptoring/proctoring of a minimum of five cases; we need to have some type of oversight afterwards so that we can see whether or not, and track whether or not, there are certain surgeons who are implanting who have higher than expected complication rates.

Number 2, the surgeons also need additional training in when to pull out, meaning when this is a contraindication, this is not going well, we should not be putting this in, you

know.

And, number 3, there needs to be additional training and/or resources available for the training for removal and particularly complicated removals for things that are fragmented, migrated, and/or -- you know, complicated with regards to the multi-modalities, the way you can remove this, either hysteroscopically, laparoscopically, and the kinds of dissection, short of hysterectomy.

With regard to preoperative evaluation, we had a lot of discussion about the consent form and whether or not there should be a checklist that includes screening for autoimmune diseases, other hypersensitivities, other -- headache, irritable bowel, history of pelvic inflammatory disease, or even current sexual transmitted screening and -- in order to develop a list of maybe even absolute or relative contraindications to undergoing this. And the patients need to understand that and maybe even have an official consent form which is gone over so we have understanding and signature.

Secondly, the preoperative evaluation, even including the intraoperative evaluation, may include additional imaging relatively soon, that where you placed it is where it's supposed to be, and/or if there are complications in the short postoperative period, that we get that imaging even before the 3-month mark. With regards to the postoperative evaluation, again, imaging comes out; we should have a checklist of complications that would lead to the additional imaging that may be needed. We should have a way to evaluate the quality of the interpretation of even that 3-month HSG or images that occurred that were indicated and taken even before that 3-month time period. Again, this speaks to the registry and to the development not just of the patient cards are given that Essure was

implanted but even perhaps a unique device identification number or some better way of tracking these. And guidance, more guidance is needed on the long-term management of complications.

Did we miss more --

DR. SEIFER: Is it too late to discuss whether or not it should be a surgical procedure or --

DR. IGLESIA: Oh, that's on the patient -- yeah. That's on No. 3. Patient labeling is the next question, so -- okay.

So, Drs. Fisher and Yustein, is this adequate? Or do you have any other questions for the Panel?

DR. FISHER: No, good. Thank you very much.

DR. IGLESIA: Oh, you're welcome.

Elaine.

MS. BLYSKUN: Elaine Blyskun.

For the events of concern discussed in your response to Question 1, please provide any additional general recommendations for modifications to the physician and/or patient labeling which might help to address that concern. If there are any additional other general labeling recommendations which do not pertain to a specific type of event, please provide those as well.

DR. IGLESIA: Who would like to begin this discussion?

Dr. Elser.

DR. ELSER: Denise Elser.

So I would like to respond to what Dr. Seifer said. I think there is certainly a precedent for plenty of intra-office procedures that we do that are not labeled as surgeries because there's no incision but certainly can have some serious adverse effects. So calling it a surgery, I don't think changes that you have to be aware of what serious events can occur and how closely to monitor for them and what to do if they occur.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

But a hysteroscopy is surgery. I mean, so just because --

(Applause.)

DR. JANIK: -- it doesn't have to have an incision doesn't make it nonsurgical, so to me all hysteroscopies are surgery. You could say placing an IUD is not surgery, but I think anything that's hysteroscopy is surgery.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: And the sorts of complications that come with hysteroscopy fluid overload and all the ramifications of that. And to Bayer's credit, they say, you know, if you have a 1500 cc deficit or it's taking more than 30 minutes, you should stop. I mean, those are the same kind of warnings that we give for doing hysteroscopy in the OR.

DR. IGLESIA: Are there -- oh. Anything on this side with regard to patient labeling?

Dr. Baird.

DR. BAIRD: Dr. Baird.

It seems to me that the current labeling, which I read the whole material, is very benign, and there's no indication of the possible need for removal and what the

ramifications of that can be. And so I think at least more information needs to be given about possible adverse events.

(Applause.)

DR. IGLESIA: Dr. Milner, do you want to piggyback?

DR. MILNER: Yeah, I just -- so I guess we mentioned it, but here is where the appropriate time is, which is that you can't limit the hypersensitivity warning to nickel allergy.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Is it appropriate for part of the patient labeling to be to tell the patient be sure that you have discussed in detail the risk of this procedure with the physician before proceeding? And the --

DR. IGLESIA: Sure. That's part of the informed consent.

MS. CHAUHAN: The risk factors.

DR. IGLESIA: Yeah. Yeah, so part of the informed consent would be talking about not only the benefits of a procedure but also the risks and the potential alternatives as well.

MS. CHAUHAN: I agree. That's -- and I've got that down in my notes, informed consent is very important. But this is even pre. This is when you're looking at the label. In case someone got sloppy and went through the informed consent too quick or said here, this is really good, you know. That's just another stop to say this is a serious procedure, to be thought about seriously, and to put something like that in the patient labeling.

DR. IGLESIA: And so I just want to just put -- so are you talking about, like, mentioning the development of new pain, abnormal bleeding, plus the potential for

migration/perforation?

MS. CHAUHAN: I wasn't even being that specific. I certainly don't object to that.

DR. IGLESIA: Okay.

MS. CHAUHAN: What I was saying is something in the patient labeling saying be sure you have discussed with your physician the risk --

DR. IGLESIA: Okay.

MS. CHAUHAN: -- and issues in this procedure before proceeding.

DR. IGLESIA: Got it.

Dr. Katz.

DR. KATZ: Just to elaborate -- David Katz.

I think the take home message here is that we want to provide information for the woman that she can acquire going into that visit where she has that interaction with the physician about the possibilities so that she already has relevant and necessary information to be self-informed as she goes into that first experience, that consult.

MS. CHAUHAN: Cynthia Chauhan.

Exactly. So that she goes in with a knowledgebase.

DR. KATZ: Right.

DR. IGLESIA: Ms. De Luca, do you have any other recommendations for patient labeling?

(No audible response.)

DR. IGLESIA: Okay, all right. I think I'll summarize.

Oh. I'm sorry, Dr. Stubblefield. I didn't see you back there.

DR. STUBBLEFIELD: We've had a lot of talk about, too, lumping things all together to begin with. Autoimmune disorders, some people appear to have developed them while wearing the device. Are we concerned about people that already have these autoimmune disorders? Should they know that this perhaps might predispose them to something else?

(Applause.)

DR. STUBBLEFIELD: That said, the downside of that is people that are already sick are going to be much safer having a hysteroscopy under a local than -- or general anesthesia for an alternative tubal ligation.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

The main thing that concerns me about that, it may be true, but we really don't know. So I hate to write something down that's saying, you know, if you have autoimmune, you shouldn't have this; we really can't say it. So I think you can say possibly, because we have some possible indications, but I don't think we should overstate without data.

DR. IGLESIA: Okay. Any more comments?

(No response.)

DR. IGLESIA: I'm going to try and summarize with regard to patient labeling and even general labeling, that this is a surgical procedure that requires the insertion of an instrument called a hysteroscope to place a device, and that's a permanent implant. I think that people need to understand that, you know, that -- what that implant is made of and that that implant may need to possibly be removed at some time, and sometimes the removal can be complicated. In addition, there may be some possible concerns for people

who have known hypersensitivities to X or underlying autoimmune diseases and that more data is needed for that. And I think that's it. I think the most important thing, though, is what Ms. Chauhan said, is that there has to be some kind of checklist to say that this discussion actually happened and so that, you know, the patients are aware and some documentation made.

Dr. Yustein, Dr. Fisher.

DR. YUSTEIN: So if I can just address a comment that Ms. Chauhan made and that you just talked about, Dr. Iglesia. We do have a couple of examples where we have patient information brochures for some PMA products where the last page is kind of a checklist that recommends that the patient and the physician both initial by each item and it goes down several different things and says we discussed this and the patient initials it, the doctor initials it. We do have a couple of examples where we have asked companies to do that at the back on the last page of the brochure. Now, again, FDA doesn't intervene in patient informed consent procedures and whether or not that takes place at the office level between the patient and the physician. You know, the document would help promote that, but it wouldn't guarantee that that discussion takes place.

MS. CHAUHAN: So that's not within -- Cynthia Chauhan.

That's not within the purview of the FDA's authority?

DR. YUSTEIN: We can ask the company to put something like that on the patient brochure, but we certainly can't be in the room watching the patient and the physician initial each item and make sure that that takes place.

MS. CHAUHAN: Cynthia Chauhan.

So you cannot mandate an informed consent, beyond the brochure? You cannot mandate an informed consent --

DR. YUSTEIN: Right. The brochure is more of an informed decision making; it's giving information. But the informed consent process is really the patient-physician process.

DR. IGLESIA: Dr. Fisher, then Dr. Seifer.

DR. FISHER: Yeah. We're splitting hairs here, and it is kind of an informed decision form because informed consent is really, it's really tied to an investigational device. I mean, that was the intent, that's our authority for informed consent, actually deals with an investigational device. So this is something that we're talking about, it would be an informed decision form or something, but it wouldn't be called an informed consent.

DR. YUSTEIN: So I think what -- sorry. Dr. Yustein.

I think what Dr. Fisher is clarifying is that in the case of an IDE study, certainly FDA reviews the informed consent document and has input with the company on what should be in those informed consent documents, but for a procedure like this for an approved device, we don't regulate the informed consent document that a physician and a patient would have in their office.

MS. CHAUHAN: Cynthia Chauhan.

So if it gets moved to being a surgical procedure, then can you demand it?

DR. SEIFER: You don't have to.

MS. CHAUHAN: You don't?

DR. SEIFER: Sorry. David Seifer.

You won't have to because it's a surgical procedure, and that requires informed consent.

MS. CHAUHAN: That's what I was saying.

DR. SEIFER: Yeah.

MS. CHAUHAN: Yeah.

DR. IGLESIA: Okay. Dr. Fisher, Dr. Yustein, is this adequate or do we have other -- for Question No. 3?

DR. FISHER: I think we're good. Thank you.

DR. IGLESIA: Okay.

Elaine.

MS. BLYSKUN: Elaine Blyskun.

For the events of concern discussed in your response to Question #1, please discuss whether you believe any additional post-market bench and/or clinical data should be collected by the sponsor to better understand the events or inform mitigation strategies.

If so, for each outcome, please comment on the following:

a. The patient population to be evaluated

b. The clinically relevant endpoint(s) to be assessed

c. Appropriate duration of follow-up

d. Ancillary tests (e.g., labs, imaging, etc.) that should be conducted

DR. IGLESIA: Okay.

DR. SEIFER: So if you have a registry, I wonder who should be in charge of that. It may not be the best option to have the sponsor running that, but I don't know who the best

monitor of that would be.

DR. IGLESIA: You know, I have been involved in the development of several registries, and I'll just disclose that vaginal mesh was one of them. And the industry as well as the FDA, as well as the relevant medical societies and patient representatives, as well as insurers were all involved in the development of that for the postmarket surveillance and to answer some of the 522 orders that were then eventually initiated, so it is possible to be done. So that point is well taken, a registry of the relevant parties, including patient representatives. For the patient-centered outcomes.

Other discussion? Grace?

MS. CHAUHAN: Cynthia Chauhan.

Is this where we talk about another clinical trial?

DR. JANIK: That's exactly what I was going to say.

MS. CHAUHAN: I am mindful that there are a large number of women who use this device successfully, and we're not addressing those today, but I'm mindful that they exist, that sterilization is an important option for women. I would really like to see a randomized control trial done with a population, a control population, and that would, I think, address some of the issues that Dr. Milner brought up about some of these symptoms happen to people because of trauma, whatever the trauma is, and if you've got a control set, you could begin to clarify some of that. I think given the large population that's affected, the differences in outcomes, another randomized -- not another, there wasn't one. A randomized control trial would be an appropriate thing to look at for this device.

DR. IGLESIA: Dr. Janik, then Dr. Elser.

DR. JANIK: That's really what I was going to start to say, and I think that it's more important; I think we have pretty good pregnancy outcome data. I don't necessarily think that's what our endpoint is. I think our endpoint is more what kind of complications and symptoms do we have coming off of one form of birth control going to tubal ligation, standard tubal ligation versus Essure. Is it the same, this bleeding profile? How many people go on to develop autoimmune issues, reactive issues? We assume it's the device, but unless we compare, we'll never answer the question.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

My concern would be that we don't really know that denominator or the incidence of how many people may or may not have autoimmune problems. Could we power a study to be able to capture rare events, you know, given the expense of an RCT? And how many patients, how long do you follow up, how do we figure out how to power it?

DR. IGLESIA: Other comments?

Dr. Stubblefield.

DR. STUBBLEFIELD: Just a little wild guessing. I mean, if the phenomenon we're talking about, if this is 1 or 2 per 1,000 patients and the sample size gets us something that the Defense Department would have to support, no one else could afford it.

DR. IGLESIA: Okay.

DR. WILLS-KARP: Some power issues. I think some of this information may come out of --

DR. IGLESIA: Just state your name, sorry.

DR. WILLS-KARP: I'm sorry. Marsha Wills-Karp.

I think some of the information that's needed or in the complications may come out of the registry.

DR. IGLESIA: Yeah.

DR. WILLS-KARP: Prospectively.

DR. IGLESIA: Not necessarily RCT.

Dr. Katz.

DR. KATZ: David Katz.

Another question would be is there any more that we can learn from the ongoing studies? Now, the big study is in Europe, it's not here, that the Sponsor is conducting. And we asked all the questions that need to be asked from the data that exists to date and from anything that's ongoing now. It's already underway.

DR. IGLESIA: Okay.

Final comments? Let me --

Oh, Dr. Gardner.

DR. GARDNER: This is on a somewhat different topic. We've been talking about needing histopathologic evidence.

DR. IGLESIA: Yeah.

DR. GARDNER: And I'm wondering, is it standard of care today if there's an explant done, is that specimen sent off to path for assessment? And if so -- I see some heads going up and down and some -- if so, are we sitting on that data now, and can we work with the patient groups and identify people and get their consent to share their records and get that

information?

DR. IGLESIA: Okay. All right, let me try and summarize Question -- the answer to Question No. 4, then.

DR. FISHER: Before you do --

DR. IGLESIA: Oh.

DR. FISHER: Sorry. Dr. Fisher.

DR. IGLESIA: That's okay, Dr. Fisher. Go ahead.

DR. FISHER: Yeah, Ben Fisher.

We have (a), (b), (c), and (d) up there, and I really didn't hear anything specific. I heard randomized control clinical trial --

DR. IGLESIA: Got it.

DR. FISHER: -- but I didn't hear anything about patient population, I didn't hear anything about endpoints, duration, and we would really like to have your input on if you're to say that you want another randomized control trial. What exactly would you be looking for?

DR. IGLESIA: We talked a little bit about the endpoints with regard to complications versus pregnancy rate, and we really didn't talk a lot about the duration or ancillary tests.

DR. FISHER: Or the population.

DR. IGLESIA: Or population.

DR. CHAPPELL: At the risk of repetition and giving words that burn in my mouth as they leave it, this is too late for a randomized controlled clinical trial, and that I agree with Dr. Katz' and others' suggestions that we piggyback and get the best information we can in

2015. But to those at the FDA, perhaps I shouldn't mention Congress, I would suggest that a randomized clinical trial is the way to go for the future. Other devices.

(Off microphone comment.)

DR. IGLESIA: Oh, put your mike on.

MS. CHAUHAN: I'm sorry. Cynthia Chauhan.

Could you clarify why you think it's too late? Because we're talking about a device that will be used for a long, long time if it stays approved.

DR. CHAPPELL: Rick Chappell.

Perhaps I shouldn't be so negative, but I really worry about accrual. I do have some practical intuition, and if I were to try to convince a clinician or her patients to enroll in a clinical trial because we have grave concerns about the safety of a device, that would not be a big selling point. It's hard enough to randomize device trials, surgical trials at any rate. It's easier to randomize two pills, but there's enough challenges. I just don't think it would accrue.

DR. IGLESIA: Dr. Seifer, Dr. Coddington.

DR. SEIFER: I mean, maybe we approach this in stages. We do the registry, we see what the real incidence is, we get real numerators, denominators, then we think about doing an RCT that's going to cost and take so much time to do. We'll see if it's really determined if these are real recurring issues.

DR. IGLESIA: Do you have an opinion about the patient population or the length of follow-up?

DR. SEIFER: With regard to the registry? I think it should be, for now, pretty much

indefinite. I mean, until -- or at least for the foreseeable future, and it should be reviewed every 6 to 12 months so you can see what's coming up.

DR. IGLESIA: Yeah. I know that the vaginal mesh registry was a 3-year endpoint. I mean, there's some feasibility issues here. And it was not a randomized trial. The 522 studies are actually prospective cohorts with a shared -- tissue arm and the vaginal mesh arm. It's every 6-month follow-up for 3 years with real patient-centered outcomes that patients can populate regardless of which position they're seeing.

DR. SEIFER: Some of the comments we've heard here, they have developed over some long period of time, so I --

DR. IGLESIA: Yeah.

DR. SEIFER: You know, depending upon the reality of the situation, I would think 3 years a minimum. I'm thinking more like 5.

DR. IGLESIA: Five years.

DR. SEIFER: Yeah.

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Thank you for bringing up the mesh because, I mean, that's a perfect model to -- perfect model. Not paralleling, but in other words, every 6 months for 3 years we've got some 5-year data here that may guide us a little bit about whether there were things that came up. I haven't looked at that data specifically to see if you had some increased incidence of problems and that type of thing. But I think looking at it in that regard will help us. So I think, you know, patients that have the Essure, patients -- I think if we want to go 1

to 5 years with the aspect, we could be more specific if we see something at 1 year, if there are things that really jump out at us in regards to either application or complications of the way in which the device is implanted, that's going to come out quicker than something dealing with autoimmune.

DR. IGLESIA: Yeah.

DR. CODDINGTON: So I think that this is something that can be done in a very positive and ongoing way to help evaluate, as well as patient care.

DR. IGLESIA: Thank you.

Dr. Wills-Karp. And do you have -- any other ancillary tests? Okay.

DR. WILLS-KARP: First, I was going to say I don't think it makes sense to do a randomized trial at this point because you're not going to have the power to pick up some of these events with the size studies that are generally done, so I don't think that would change the data that's obtained. I think it's more relevant to follow the registry of these folks and see what's happening actually. And it's the length of time that sort of revealed the number of these issues, complications. Other tests, I think we've sort of said it several times, but trying to figure out exactly what some of these immune changes are, adding those on. Certainly, nickel and whatever the types of tests, we probably need to have more extensive conversation about that. But just put that in the record that they need to find out more carefully what are these actual immune responses.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Just briefly, just to follow up. It was brought up, I think, by someone else, but to put it into here, which was that, you know, the standard for nickel leaching, and

honestly, we probably should look for everything else, is to put it in water or saline, I forget what it is, but it would seem to me that the better assay here would be to put it into -- whether it's, I don't know, an animal or something like that and to actually try to measure within the tissue if the amount that's being released is more than you would have thought it would have been instead of just putting it in water, which doesn't -- not really what's happening here.

DR. IGLESIA: Okay. Dr. Janik.

DR. JANIK: I do think that patients that are having these removed are a very useful source of information, and maybe we should do something expanded with that subgroup.

(Off microphone comment.)

DR. JANIK: I thought it's No. 4.

DR. IGLESIA: No, it's part of it. Patient population.

DR. JANIK: Okay. No, no. As far as a population --

DR. IGLESIA: Yeah.

DR. JANIK: -- to follow the path, maybe we want more than standard path. I don't know what testing you guys would recommend with the tubes that are removed. Also, some expanded history of what brought them to that situation, then their outcome of removal.

DR. IGLESIA: Okay.

DR. JANIK: I would add that onto that subgroup.

DR. IGLESIA: Okay, I'm going to try and summarize now, then.

So the question regards postmarket, bench, and/or clinical data that should be

collected by the Sponsor to better understand events in order to inform mitigation strategies. Population of patients to be evaluated include patients who have had complications and have had removal, that necessitate removal, and we would want to know what -- their symptomatology, the history, and what -- obviously, an evaluation of the actual pathology of the removed device and/or tissue surrounding it. Another population of patients are those who are currently enrolled in clinical trials and trying to extend that past, beyond, the 3- to 5-year duration, specifically looking for outcomes that are a little bit more rare like some of the autoimmune disorders in addition to the ones we've already mentioned with the complications.

It seems that, in terms of a clinically relevant endpoint, we're all aware that if properly done in a proper -- the method has been completed and the follow-up imaging shows occlusion, that the pregnancy rate is okay, may be comparable, but the complications are something that we're a little bit more interested in, in terms of a clinically relevant outcome. Is that correct? Overall and general. But it is a process that needs to be looked at, so complications even over pregnancy prevention.

And then, finally, in terms of study design, we have some concerns about whether or not a randomized clinical trial is practical or even feasible at this point, given the social media and the negative outcome on this. However, we do feel that postmarket surveillance of these devices is necessary and that a registry would be useful in that way, and the registry should include pretty significant close follow-up, whether it be every 6 months, every 1 year, and if we can extend it past 3 years to even 5 years or longer, if feasible, particularly for some of the more rare outcomes. I think -- you know, we talked about

seeing some of that with regard to the ongoing studies, but the problem is, is that we would like to compare that, have some kind of comparison group, which you can do in a registry with prospective cohorts, which we can't do currently with the PMA trials and the premarket studies that we have in place.

Dr. Baird.

DR. BAIRD: I'd like to consider also adding some sort of imaging to the ongoing study for a later time --

DR. IGLESIA: Oh, right.

DR. BAIRD: -- other than just the standard imaging.

DR. IGLESIA: Yes, I didn't mention the ancillary tests and the other imaging. You know, we need some other, not just post-procedural, the 3-month, but possibly even some delayed imaging to understand better the migration/perforation issues and also the blood tests, skin test, bench, xenografts or whatever we're using in terms of animal models for how the tissues act, the device is acting in vivo in animate and human subjects.

Dr. Yustein, Dr. Fisher, does that summarize, or do you have more questions?

DR. YUSTEIN: So can I make one comment and then a couple questions? So I believe that the TVU study is a 10-year study?

DR. FISHER: Yes.

DR. YUSTEIN: So that study still has many years to accumulate data, just to point that out.

DR. IGLESIA: That's good.

DR. YUSTEIN: So, in terms of outcomes that would be evaluated in a prospective

trial, whether -- whatever form that looks like, can we get a little bit more definition from the Panel in terms of are they the items that we've generally been speaking about for the last couple of hours? Are there other patient-centered outcomes or adverse events that we haven't mentioned that should be particularly tracked in a registry or whatever form that we do this?

And then my other question is there seemed to be a lot of talk earlier today about various bench testing related to allergies and nickel testing and things like that. Are there any other nonclinical evaluations that the Panel believes is necessary to further evaluate?

DR. IGLESIA: Dr. Chappell.

DR. CHAPPELL: Rick Chappell.

Removal.

DR. YUSTEIN: Right. That's the ultimate rejection of the intervention, is to have it reversed.

DR. CHAPPELL: Right.

DR. YUSTEIN: And I heard that that was one outcome that, in particular, we want to be following, and the outcome of the patient symptoms following removal, so certainly we heard that. Are there other particular ones other than the items we've kind of focused on throughout the day? Are there other outcomes or adverse event types that should be specifically captured?

MS. CHAUHAN: Cynthia Chauhan.

DR. IGLESIA: Yes.

MS. CHAUHAN: When you say the ones we focused on today, are you talking about

the small group or the long list?

DR. YUSTEIN: Well, I was referring to the ones that we've been speaking about during the question and answer session. We've been focusing on things like vaginal bleeding irregularities, metal hypersensitivity. I don't want to, you know, mischaracterize that, that quote. Perforation, migration, removal. Those are the things we've been focused on, but certainly you saw the longer list, you've heard other issues from patients in the audience, so I just want to make sure that we have that discussion.

MS. CHAUHAN: Cynthia Chauhan.

I think -- I don't mind giving you work. I think it should be the long list because that's going to filter out, to help filter out where focus needs to be. If we just do the top five, then you may be losing some really important information.

(Applause.)

DR. IGLESIA: I think what you're referring to or alluding to is some more of the quality-of-life issues. I mean, there was some concern about dyspareunia, the overall fatigue, the depression, the headache. And, you know, certainly we have validated questionnaires like the SF-36, and we have validated questionnaires like the Female Sexual Function Index, you know, that can be added, because you don't know what you don't know.

DR. YUSTEIN: On the other hand, you know, I'm not a registry expert, but if you have a list of 400 things that you're asking a physician to check off, how accurate is that going to be? So somewhere along the way we need to focus it down to --

DR. IGLESIA: Yeah.

DR. YUSTEIN: -- a feasible set of items, and I just wanted to try to get an idea from the Panel which they thought were the most feasible, because although I agree the list of several dozen things would be nice, I don't think that's going to be realistic.

MS. CHAUHAN: Cynthia Chauhan.

That's why PROs are important because you don't just filter through the physician; you get direct information from the patient that's validated.

DR. IGLESIA: Yeah. Patient reported outcomes.

Dr. Fisher, do you have any other questions or comments that we --

DR. YUSTEIN: I'm sorry, can I?

DR. IGLESIA: Oh. I'm sorry, Dr. Yustein.

DR. YUSTEIN: Can we go back to the -- was there anything from the preclinical standpoint? I just want to make sure we covered that.

DR. IGLESIA: Oh.

DR. YUSTEIN: Was there any --

DR. IGLESIA: Dr. Milner.

DR. MILNER: It's hard to know what the question is to ask. I mean, make up a great model in vivo, intra-organ model for nickel hypersensitivity, that would be great. I don't know when that's going to happen, you know; that's not an easy thing to accomplish.

DR. YUSTEIN: So you're not aware of anything that's obvious and easy right off?

DR. MILNER: There are plenty of models of surface sensitivities which lead to some of the stuff that's being discussed here, but this is a different story. And certainly, you know, implanting this into mice or something else for a longer period of time and really

following it and seeing what happens, but I don't even know that you're going to get the outcome you're looking for when you do that. So without a model, you know, I -- it's certainly worth -- I should make it clear that, you know, we're not complete experts on nickel allergy, and so diligence should be done that if such a model does exist, that that should be found.

DR. YUSTEIN: And, sorry, can I ask Dr. Milner one more question?

Sorry, Dr. Milner. I'm going to ask you the same thing you asked us earlier. How would you define, if you're asking clinicians to check off a box that said hypersensitivity or allergic reaction, how would you define that?

DR. MILNER: So I think what I was more asking was, was there a standard that was being held? What my definition is and what everybody else's definition is, it's going to be different for different people, but the fact that an a priori standard didn't exist was what was disturbing me. And so I think that it's well known what an immediate hypersensitivity looks like, it's well known what a delayed type hypersensitivity looks like; when it's inside of your body, that's not well known. And so at least to be able to capture the things that are known, you'll be able to report them. What bothered me is that we said that the hypersensitivity rate was zero, and there were four things in there which I would have called a hypersensitivity.

DR. YUSTEIN: Thank you.

DR. IGLESIA: Dr. Fisher, are you satisfied?

DR. FISHER: Yes, thank you.

DR. IGLESIA: Okay.

Elaine, Question No. 5.

MS. BLYSKUN: Elaine Blyskun.

The current physician labeling provides information related to "Insert Removal," focusing on the technique of removal of an intra-fallopian insert via salpingotomy or salpingectomy or of an intraperitoneal insert with the use of fluoroscopy.

Please discuss and provide any further recommendations regarding the decision to pursue hysteroscopic or laparoscopic removal of Essure inserts.

In particular, please consider the following scenarios:

a. Patient having persistent abdominal/pelvic pain without objective evidence of insert malpositioning, migration, or perforation
b. Patient having persistent abdominal/pelvic pain with evidence of malposition, migration or perforation
c. Asymptomatic patient found, or suspected, to have device malpositioning, migration, or perforation on standard follow-up imaging (e.g., 3 months or following unintended pregnancy)
d. Other scenarios you deem relevant

In addition, please provide any comments regarding the current instructions for removing inserts.

DR. IGLESIA: Okay, Dr. Elser. And if you want to take a particular scenario, let us know.

DR. ELSER: Okay. Just a few comments. Denise Elser.

I want to make sure that we don't say that if a patient develops pelvic pain, that we

assume immediately that it's caused by the implant. So even if it looks like it's not in the perfect position on ultrasound, do we want to make this patient undergo a major abdominal surgery if other causes of pain haven't been addressed? So keep in mind that we, as pelvic specialists, see all the time kidney stones, constipation, myofascial disorders that occur in women with or without implants. So we don't want to say pelvic pain, get an ultrasound; doesn't look like perfect position, operate. And then, secondly, I would say that consensus among hysteroscopists, I've often heard is that if there's more than the eight trailing coils, more than expected, and you're relatively recent to the implant, you would attempt a hysteroscopic removal, and otherwise you would attempt it laparoscopically or by laparotomy.

DR. IGLESIA: Other comments?

Dr. Janik.

DR. JANIK: I think if the problem is relatively immediate, it's different than chronic, and chronic is when endometriosis, all the other things you mentioned, get to be more of the issue. It's immediate, it doesn't seem in the patient's best interest to make it go on when, you know, it happened right after the event, it's not clearing, and especially you get more problems with all other types of infectious issues and gets more -- or inflammatory issues. It's more difficult to operate, too, when you get past that window. So I think we have to think of it as two different problems. And I also think it's difficult to have one way of removing it. This is where I think you just need to have a very high skill level surgeon because it depends on what it's poking into and what's tangled up with it. So you can't have a formula of how to remove it.

DR. IGLESIA: Should we just tackle the question and let's do patient, let's do (a) and let's talk about it, immediate. So you have a patient with abdominal pain, it looks like it's in -- the device is in good position. She has pain and it's immediately after, not chronic.

(Off microphone comment.)

DR. IGLESIA: Under 3 months because chronic pelvic pain is generally defined as greater than 3 months, right?

Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

I was thinking that we have the data that Grace alluded to earlier, of a week. So I mean, you know, if there's -- obviously, if there is extreme pain and there's concern by the physician of perforation, one has to have clinical suspicion and do probably an ultrasound right then and there.

DR. IGLESIA: Okay.

DR. CODDINGTON: If there is a comfort level of 3 to 5 over 10, then maybe okay, wait a week and then see where you are. I think there has to be some clinical aspect to that. I know that's not very specific, I apologize, but I think that the week is where we have some data to work on.

DR. IGLESIA: Okay. So immediate pain, we'd need some kind of imaging.

DR. CODDINGTON: Um-hum.

DR. IGLESIA: We would probably want to try some type of medical management of pain, assuming that there's no acute hemodynamically --

DR. CODDINGTON: Agree.

DR. IGLESIA: -- unstable situation going on like sepsis or something.

DR. CODDINGTON: Yeah.

DR. IGLESIA: And then -- but if it persists despite medical management and it's in the right position and it's in the wrong position, those are -- how would you like to proceed?

DR. JANIK: Grace Janik.

I think if it's the wrong position, on you go. That's the easy one.

DR. IGLESIA: Yeah.

DR. JANIK: And I think if it's in what -- I think our confidence of cracked position maybe isn't as great as we think, so I think if you're out past -- I'd give it at least a week because 99% were okay within a week. But if you're out a week, then I think it's -- I think you need to require 3 months or --

DR. IGLESIA: Yeah.

DR. JANIK: -- leave people go on and on.

DR. IGLESIA: Or maybe we should just get a second opinion with regard to the review of the imaging, you know. It seems like some people had some issues with the interpretation of the imaging. So that might be another thing to recommend.

Other comments on this side?

Dr. Myers.

DR. MYERS: Deb Myers.

Not really having expertise in this particular thing, but if you have just done a procedure, you are now a month -- it looks like it's in the right place but the patient's having severe pain, I would think you'd just go take it out. I mean, assuming ultrasound and

everything else --

DR. IGLESIA: And potentially go to Plan B with another form of like a laparoscopic tubal ligation. And I think that that conversation, you know, we probably need to have that kind of conversation so that that's not a failure of the surgery; it's just this wasn't the right procedure for this patient.

DR. SEIFER: You could potentially have that discussion in your informed consent, right?

DR. IGLESIA: Yeah, yeah. So I think that the asymptomatic patient with it in the wrong place is going to be a little tricky. Does anyone want to bring up this discussion?

Good. Dr. Stubblefield.

DR. STUBBLEFIELD: Doesn't this describe some of the pregnancies?

DR. IGLESIA: Yeah.

DR. STUBBLEFIELD: Isn't this the group that's going to be rich in unwanted pregnancies? So maybe you should go ahead and evaluate these people laparoscopy, if needed, now.

DR. IGLESIA: They're not having any problems, but the 3-month follow-up was not conclusive that this was close.

DR. STUBBLEFIELD: Right.

DR. IGLESIA: Or you know that this is in the wrong spot. You think it's better to preemptively go ahead and remove and do something correct, like --

DR. STUBBLEFIELD: Yes,

DR. IGLESIA: -- for pregnancy prevention?

DR. STUBBLEFIELD: Yes.

DR. IGLESIA: Okay.

Dr. Milner.

DR. MILNER: Yeah, it's on the point, although it really, in the end, is a question. And that is, are we already missing some of that data in the intent-to-treat, those who were missed in the intent-to-treat data? I mean, it's not an insignificant number of folks who were missed, and is it possible that that would be -- by missed, I mean they didn't complete the study, not that they weren't followed up. Is it possible that that data exists and they just have not been fully, properly made public? That is to say, meaning that there has been an examination of those who dropped out, either because of pregnancy, and was looked at. You know, the ultrasound was looked at, or at some point in time it was looked at in some way or another. Might we have a bit of a clue already that it exists right now?

DR. IGLESIA: So you're looking at it from a research question, what can we do on a secondary analysis of these failures with regard to the device location and the cause for the failure.

Dr. Janik.

DR. JANIK: Grace Janik.

I have other concerns because it's something that's reactive, so even if they're not asymptomatic at the moment, you're reactive in the peritoneal cavity, how do you know that it's inert and nothing is going to happen down the road? I feel like you have an obligation to take it out by the nature of what it is. Also, do we have any sense of how many people are like this? Asymptomatic but not positioned?

(Off microphone response.)

DR. IGLESIA: Yeah, we can't -- we're not addressing that. It's -- the question right now. But that's, you know, that's a scenario that is likely to exist because again, you know, we don't know.

Okay. Dr. Katz.

DR. KATZ: That goes into this question of what data do we need to acquire.

DR. IGLESIA: Right.

DR. KATZ: And, in fact, what we could learn, that's number -- is in 4. It's one of the questions that --

DR. IGLESIA: Right.

DR. KATZ: -- we would need to ask.

DR. IGLESIA: Yeah. And that's another where some prospective cohort registry would be able to answer those kinds of questions as well, because you'd have another outcome, being the imaging that is done post-op.

Okay, so that was all acute. How about the chronic? I guess, like -- how about chronic pain past the 3-month mark and a perfectly positioned device?

You would take it out.

DR. JANIK: I think you have to have your mind very open to other possibilities.

DR. IGLESIA: There you go.

DR. JANIK: You can't just assume it's the device. So you have to work them out, as any other chronic pain patient, and rule things out and -- but it's on your list. But it can't be so exclusive.

DR. IGLESIA: But it does bring up the question as to, you know, whether or not chronic pelvic pain may even be considered a relative contraindication, you know, to getting this device in the beginning. I mean, it is something that we're very aware with when we're doing implant as a pelvic reconstructive surgeon, so just something else to consider.

DR. SEIFER: I think that's a great point. I mean, that should be a contraindication in putting the device in.

DR. IGLESIA: Relative, relative. Okay.

DR. JANIK: Grace Janik.

Because it may be somebody's had multiple laparotomies, so I think you have to think it out, but it just adds confusion, so you want to --

DR. IGLESIA: Okay.

DR. JANIK: -- definitely weigh it.

DR. IGLESIA: Okay. Any more discussion? And I'll try and summarize.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I think that points to the importance of a really good pre-procedure history-taking where you bring up things that people may have begun to have some issues, but they don't know how to name them yet, and so you bring that up. And just a really good history beforehand.

DR. IGLESIA: How about the other scenarios that we may deem relevant and the way to remove these things? I think we probably need to discuss that.

DR. JANIK: I think the allergic and autoimmune will be a reason to remove also.

How do you determine when the hypersensitivity person should be removed? General unwellness, want to remove. I think that's a difficult question, but if --

DR. IGLESIA: I know. All right.

DR. JANIK: I think it's on the list.

DR. IGLESIA: Let's summarize. So with regard to removal, and we know the general comment with the approach, maybe there isn't the number of coils that are actually showing and the way that the imaging is, if this is very distally migrated, it may dictate the approach. It would be probably the rarer thing that you can probably just easily redo it hysteroscopically if some of these are very distally migrated or you have very few coils that are able to be seen outside the tubal ostia.

So for those who have abdominal pain that is in duration related to the insertion and it's something that was temporarily related to the insertion of this and it's failed the medical management, we would probably recommend removal. For those who have pain in a perfectly positioned device, then -- and it's past -- you know, we've done all the testing and it's past the 3-month mark, we may want to just think about the differential diagnosis for chronic pelvic pain and think about that. But it begs the question as to whether or not chronic pelvic pain, in and of itself, would be a relative contraindication for device insertion to begin with.

For those who have pain with evidence of device malposition, removal is recommended, whether that be acute or chronic. And then for those who are asymptomatic with a device that is not in the right spot, i.e., found because they became pregnant, device removal and another form of birth control is recommended. In terms of

the other scenarios, if you develop a de novo autoimmune hypersensitivity, some type of reaction, we feel that some consideration to device removal sooner than later should be given.

(Off microphone comment.)

DR. IGLESIA: Tweak it, yeah.

DR. MILNER: I would just throw in there that there is a significant risk in making that worse, as well, by going through that procedure, as well. So until we have a better sense of who the people are who are developing it versus in whom this is, you know, sort of a ball that's rolling, that recommendation could end up being harmful.

DR. IGLESIA: And so would you be so bold as to say that that would be a relative contraindication to putting this, if you know you have --

DR. MILNER: Beforehand, fine.

DR. IGLESIA: Yeah, okay.

DR. MILNER: But if someone has developed it de novo, I'm just saying I would be careful about how strong of a statement one makes --

DR. IGLESIA: Okay.

DR. MILNER: -- about whether to advise to remove at that point of time.

DR. IGLESIA: Point well taken. More data needed on the de novo development of autoimmune or hypersensitivity reaction, both basic science translational model.

Any further comments, Dr. Yustein or Dr. Fisher, before we proceed with the last question? Because I know patients, some people, members, have some planes to catch.

DR. YUSTEIN: No, but can I make a correction to something I said earlier?

DR. IGLESIA: Oh, of course.

DR. YUSTEIN: I just want to -- the eye in the sky kind of caught me on a mistake, so it goes back to the issue that Ms. Chauhan and I were discussing back and forth about patient informed consent, so we actually do have, apparently have the authority to put some restrictions on devices where we can insist that patients receive informed -- but that's by regulations and rule making, so that's not a quick process to take place, but we can do something like that. It's just a long, prolonged issue.

DR. IGLESIA: Elaine.

MS. BLYSKUN: Elaine Blyskun.

Question 6, the last one: Considering the information presented and discussed today, your own experience and knowledge of the device and the conditions for which it is used, as well as alternatives to its use, please discuss the overall benefit-risk profile for the Essure System. Within your discussion, please specifically describe the particular patient populations, if any, for whom the benefit-risk profile is acceptable (there is a reasonable assurance of safety and effectiveness) or the benefit-risk profile is unfavorable (device use is not recommended).

DR. IGLESIA: Who would like to lead that discussion? The ideal patient for the Essure implantation.

DR. JANIK: I can start.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

I think it's the patient who has -- is a high risk for laparoscopic procedures from

previous surgery, other health issues, obesity, so multiple reasons why laparoscopy would be a negative is the perfect patient for this type of a procedure, so I think that's the ideal patient.

DR. IGLESIA: Somebody who's failed the LARC method and has relative contraindication to general anesthesia.

DR. JANIK: Um-hum, exactly. And infavorable patients, that's the harder one to answer. I think we have suspicions that people who have history of hypersensitivity, potentially autoimmune issues would be ones that -- to think a little more deeply until we have more data.

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: I think it was described in there about patients with pelvic inflammatory disease, prior surgery to the tube, would be, you know, a consideration. And we might say tube and uterus because there may be some alterations, as far as the uterus goes, if you've done a multiple myomectomy. The tube may not be right in the anatomic spot we think. So I would say surgery to --

DR. IGLESIA: Okay.

DR. CODDINGTON: -- uterus and tube. One could put as a possible is those that have had prior pelvic inflammatory disease. And the reason I say that is because there may be scar tissue in the fallopian tube that would make the application difficult.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

So any patient who desires permanent contraception, who's had a discussion of the

alternates, including LARC and including laparoscopic tubal, and chooses to have the device. But if the device, if you start the procedure and there's difficulty placing it, consider aborting early and not proceeding; do not force the procedure to go to its end.

DR. IGLESIA: Right.

Any other comments? And then I'll summarize.

(No response.)

DR. IGLESIA: Okay.

(Off microphone comment.)

DR. IGLESIA: No, I think we have to -- this is a closed discussion. So I'm going to --

MS. CHAUHAN: Cynthia Chauhan. Oh.

The risk-benefit, I like what you said. I would add to that. Risk-benefit should be discussed in great detail with patients prior to the procedure.

DR. IGLESIA: Okay.

Let's try and summarize and then -- so the question, in terms of the benefit-risk profile is acceptable, are patients who desire permanent contraception for whom a complete discussion of the risk and benefits as well as alternative forms of contraception has been done. And this may include patients who are at high risk to undergo general anesthesia or laparoscopy who may be obese and who have failed other reversible forms of contraception. However, for those who are unfavorable, these are patients who have a history of known hypersensitivity to something like nickel or metal who have chronic pelvic pain, perhaps, who have autoimmune disorders not otherwise specified or specified who have a history of pelvic inflammatory disease, either past or current, who have prior uterine

surgery that maybe have entered the uterine cavity like a myomectomy or tubal surgery, and in whom you do the procedure and it is not going straightforward and you have to abort, you know, that we need to make sure that we've had that discussion, that this may not be the right thing for you based on your anatomical -- or the situation at hand.

Denise.

DR. JANIK: Just one more quick comment. Vasectomy is also included in our list of options for a patient with a stable partner, and that anyone who's on hormonal contraceptives, part of the counseling is what may happen to your bleeding pattern or painful menses.

DR. IGLESIA: Oh, yes. The favorable patient has to be willing to be on a reliable form of birth control for the first 3 months, correct.

DR. SEIFER: And also if they have a history of DUB, maybe you might not want them to use this. I don't know.

DR. IGLESIA: Okay. History of abnormal uterine bleeding may be a relative contraindication as well.

UNIDENTIFIED SPEAKER: Undiagnosed.

DR. IGLESIA: Undiagnosed. Untreated, yeah.

Dr. Katz.

DR. KATZ: I'm reading this question and the two parts of it, and our mandate is to be responsive to what the question asks to the extent that we are able to. And the first part of the question involves what are the elements of the risk and benefit of Essure, and that's essentially what we've been talking about.

DR. IGLESIA: Yeah.

DR. KATZ: The second part of the question says the risk-benefit profile is acceptable for a subset of potential users, and it may be unfavorable. And I think it should be clear in our response to FDA and to the users of this device, in the audience, our participants and elsewhere, that this is how we're interpreting that statement because we're -- the adjective "acceptable" and "unfavorable" is in that question.

DR. IGLESIA: Correct. Would that -- with that caveat, would that change the discussion that we just had? Would that change anything?

DR. KATZ: That's my question.

DR. IGLESIA: Okay.

Dr. Yustein, Dr. Fisher, do you have other questions to the Panel about this? Has this question been answered satisfactorily?

(No audible response.)

DR. IGLESIA: Okay. So do you have something else to say?

(Pause.)

DR. IGLESIA: Well, then at this time the Panel would like -- we would like to thank the Panel. Is this it? Okay. At this time the Panel will hear summations, comments, or clarification from Bayer Healthcare. Bayer Healthcare, you have 5 minutes.

DR. ZAMPAGLIONE: Great, thank you.

So thank you very much, everybody. I would definitely like to thank Madam Chair, members of the committee, and truly all the participants. Really kudos to you guys for coming here to share your stories. We learned a lot, and we thank you for coming here.

As I stated in my opening comments, we really want to ensure the safe and appropriate use of all of our products. We don't deny that adverse events occur, and we make every attempt to mitigate them as best as possible. And we sympathize with any patient who has experienced an adverse event. We look forward to working with the FDA on these recommendations that you have made and on the next steps really to ensure that both physicians and patients really understand the benefits and risks of Essure, but not just Essure, all permanent methods of contraception and just contraception in general. The experience of today reinforces the diversity of needs and perspectives in the area of female reproductive health and argues for more options, not less.

Thank you very much.

DR. IGLESIA: Thank you.

At this time the Panel will hear summations, comments, or clarifications from the FDA. FDA, you have 5 minutes.

DR. FISHER: Thank you very much.

FDA is constantly faced with the challenge of trying to ensure that devices that show favorable benefit-risk profiles in controlled premarket clinical trials continue to perform with reasonable assurance of safety and effectiveness when they get out into routine clinical practice. And to try to accomplish this task, it's critical that FDA continues to listen to physicians, advocacy groups, professional societies, industry, advisory panels, to the patients themselves throughout the entire lifespan of the device. In addition, we review the required annual reports and the MDR reports.

Over the past few years, FDA has become aware of the growing number of safety

concerns with Essure that's been raised by women implanted with these devices and some of the physicians who have experience with the Essure device. We felt that it was important to hold this panel meeting to hear directly from the women implanted with the devices and to get the recommendation from the Panel based on the clinical and scientific data that's available. So the Panel members were asked to address a number of questions regarding the clinical events, additional data needs, labeling, and removal, as well as the benefit-risk associated with the Essure device.

In regards to clinical events, it was said that there are signals of concerns, but we don't seem to have a long-term patient management protocol. With persistent pain and late-developing pain, it's an issue, and we need to have an early patient intervention procedure, possibly a protocol change for patient management, which would include imaging after placement and even after confirmation. Bleeding alteration, they're a little bit more problematic, but -- because it's hard to determine if they're directly tied to the insert. But a regular and persistent bleeding warrants an interventional protocol on patient management.

Nickel sensitivity, wow. More data is needed. Could it be more than just nickel sensitivity? We've talked about hypersensitivity, autoimmune, immunocompromised patients. How do we define all these? Which patient populations overlay with other patient populations? Simple blood tests might be a good start, but is it going to be enough? There was talk about the possibility of a registry to address allergy and hypersensitivity concerns, and with pregnancy, there's some need for longer follow-up outcome data.

There was a comment made that we should be looking at bundling these procedures,

that patients that have access -- that need to have access to the entire process. If you can't have the device removed, then you shouldn't have it placed. And this also includes confirmation procedures.

We talked about risk mitigations and training physicians. The training should go beyond physician training. We need to have some type of -- there was a suggestion that we need to have some type of proficiency assessment. Patient counseling was stressed over and over to better define the rules for when you get an implant of a device and more rules on when you should not get an implant of a device. So we need to have better patient counseling to define these options.

We need to be able to clearly convey the real issues to the patients before they agree to the procedures, and there was a lot of talk about having an informed consent or a checklist for the patients and the physicians to discuss so that everybody's on board with what they're facing going into it.

With labeling, there was the comment that this should be considered a surgical procedure with a permanent implant. There's need for more information for the general risks and the issues associated with general hysteroscopy, and there needs to be something to capture the unknowns of this issue that we're calling nickel allergy or hypersensitivities. Patients need to be able to go into this procedure knowing a basic amount of information as to what the true risks and benefits of this device are.

The need for additional data, instead of another randomized control clinical trial, which would probably have to be too big and too expensive, there was a suggestion that we should try to get as much additional information from the studies that are already ongoing.

And there was a suggestion of a registry with close follow-up, that we might be able to use these to gather more useful postmarket data. We need to have patient evaluation on those who have had removals, and there's much need for ancillary tests for helping us get our heads around what these immunological issues are that we're faced with. And there was also discussion about more bench testing and clinical data that's needed for these autoimmune/immunocompromised/hypersensitivity issues.

When it comes to removal, we need to be able to provide information to physicians and patients on how these devices should be removed and how they can be safely removed. The physician that inserts the device may not be the one that removes it, so patients need to have access to both. There's a need for follow-up data on patients that have had these devices removed; if there's immediate pain, we should be talking about imaging.

For benefit-risk, we said that there are suitable populations, and these may include patients that are high risk for laparoscopic procedures, failed the LARC, but we have to have thoroughly informed patients if issues arise, and we should be aborting these procedures earlier and be discussing alternatives with the patients. Risk-benefit needs to thoroughly be discussed before the procedures are initiated.

Not suitable patients. There's a lot of questions about these metal allergies, hypersensitivities; until there's more data available, I think that we need to consider these patients carefully. We also said non-suitable patients may be those who have had prior uterine surgery that might complicate the insert itself. And patients need to be able to go on alternate birth control for at least 3 months.

So where do we go from here? I think that, and I hope that everyone understands,

that we saw the actions that FDA has already taken, and I'm talking about some of the labeling changes, some of the meetings that we've had with the patients and the advocacy groups prior to this, and even this panel meeting itself, that everyone realizes that FDA considers this to be a high priority issue. So, moving forward, the Agency will consider all the comments as well as the scientific presentations, the public testimony, the Panel recommendations in determining our next steps. And, of course, any next steps will be publicly communicated.

I'd like to remind everyone that the docket is still open until October 24th, so for those patients who did not have an opportunity to present today, FDA would like to remind everyone that the docket remains open, and we encourage members of the public to post their comments to the public docket announcing this meeting until the comment period closes.

I would like to thank the Panel members for providing their input; for the company, Bayer, for your presentations today; the professional societies and the advocacy groups for providing their comments. Our primary concern continues to be the safety and well-being of the patients, and with that, I would like to thank the patients and their families and the physicians who traveled to our agency today to share their personal stories or professional experiences. Many of you came today, and we really appreciate your attendance at this meeting. You traveled a large distance, and it's not easy getting up in front of a large crowd and presenting before a panel. It can be difficult. But I want you to know that to us, it's very important. So thank you very much.

And with that, Madam Chair, that's all I have.

DR. IGLESIA: I would like to thank the Panel, FDA, Bayer Healthcare, and all Open Public Hearing speakers for your contributions to today's meeting.

Dr. Yustein, do you have any final comments?

(No audible response.)

DR. IGLESIA: So the September 24, 2015 meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee is thus adjourned. Thank you very much, and good evening.

(Whereupon, at 8:08 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

September 24, 2015

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter

EXHIBIT F

Essure Problems

FOR IMMEDIATE RELEASE – January 12, 2015

January 14th, seven administrators from the Essure Problems Facebook Campaign, two of their attorneys, and Dr. Diana Zuckerman, President of The National Center for Health Research, will be meeting with several of their congressional leaders to discuss issues faced by thousands of women who have had complications due to Essure, a form of "non-surgical" permanent birth control.
The group will also be discussing the FDA's role in the approval and monitoring of Essure, pre-market approval for Class III medical devices, and concerns with Medicaid's coverage of Essure. The goal of these meetings is to ultimately have Essure removed from the market for further study and to encourage change in the drug and device approval process by the FDA in order to better protect public health.
Meetings are scheduled with the following offices:
Senator Chuck Grassley (Iowa), Senator Roger Wicker (Mississippi) Senator Lamar Alexander (Tennessee) of the republican HELP committee, and members of the democratic HELP committee.
The group had reached out to the FDA to schedule a meeting and discuss their concerns, but it was ultimately denied by the FDA claiming too short of notice.
More meetings are still being coordinated.
For more information on the group, please visit www.essureproblems.webs.com. For questions you may contact the group administrators via email at essureproblems@yahoo.com.

Donate

We have started a grassroots movement to get an unsafe medical device off of the market. Our fight to get PMA revoked from Essure is gaining rapid traction. There are many times when we need to get to meetings and rallies and press conferences last minute. Traveling at our own expense has become quite a financial burden on many of us. When we have funds available, it makes it so much easier to take those trips!!

We appreciate any help that you can offer! Click the "donate" button above to make a donation.

All donations are tax deductible!

Our nonprofit organization is called ASHES. Advocating Safety in Healthcare E-Sisters

Essureproblems.webs.com presents information about Essure.

EXHIBIT G

FDA Review Document

Review of the
Essure System for Hysteroscopic Sterilization

Prepared for the
September 24, 2015 meeting of the
Obstetrics and Gynecology Devices Advisory Panel
Center for Devices and Radiological Health (CDRH)
United States Food and Drug Administration

Table of Contents

I. Introduction and Purpose of the Committee Meeting

Sterilization for permanent birth control may be accomplished in a variety of ways. One method, hysteroscopic sterilization, began to be widely used in the United States after the 2002 FDA approval of the Essure System (P020014; original applicant, Conceptus, Inc.). Since initial approval, FDA has continued to monitor the safety and effectiveness of the Essure System and the, safety concerns that have been raised within the patient and healthcare provider community. FDA believes that, in keeping with its public health mission, it is appropriate to do the following:

- have an open and transparent dialogue among FDA and its stakeholders, including the device manufacturer, health care providers, researchers, patients, and the public,
- review and discuss available data regarding the benefits and risks associated with the use of the Essure System, and
- obtain FDA Advisory Committee and public input on the safety and effectiveness of the Essure System.

As such, FDA's Obstetrics and Gynecology Devices Advisory Panel is being convened to review and discuss current information related to the effectiveness of the Essure System, adverse events associated with, or suggested to be associated with, the Essure device, and the overall benefit-risk profile of the device. The Committee will be asked to provide input regarding the need for product labeling changes, the collection of additional post-market safety data, or other mitigation steps, and the overall benefit-risk profile of the device based on current available information

The discussion at the Advisory Panel will focus on the Essure device, its approved use, effectiveness, and select reported complications. It will not focus on other cleared or approved medical devices (e.g., endometrial ablation devices) or, un-approved uses of Essure (e.g., treatment of hydrosalpinx).

This review memo will provide information for the Panel's consideration, including:

- Background on female sterilization
- Overview of the Essure System
- Summary of clinical data supporting the original PMA of the Essure System
- A description of the sources of data used to perform FDA's review of post-market information
- Information related to procedural and effectiveness outcomes
- Information related to post-procedural safety outcomes (including deaths)
- Information related to insert removal
- Outside the US (OUS) post-market information

II. Background on Female Sterilization

In 2015, elective (i.e. non-medically indicated) female sterilization is one of the most commonly performed surgical procedures in the United States. Approximately 650,000 elective procedures were performed in 2006 in the US.[1]

The first report in the medical literature describing surgical sterilization by tubal occlusion (at the time of repeat cesarean section) appeared in 1881.[2] In 1930, the Pomeroy method of tying off a loop of the Fallopian tube was first described as a method of elective surgical sterilization.[3] Also in the 1930s, the first report of a laparoscopic tubal occlusion procedure appeared in the literature.[4] However, elective sterilization remained uncommon until the 1960s, when many U.S. hospitals screened women requesting elective sterilization on the basis of age and parity.[5] In the 1970s, laparoscopic instrumentation was becoming increasingly available and, by 1978, approximately one third of all tubal occlusions were being performed laparoscopically, as compared to 1% in 1970.[6]

Evolution of Methods for Laparoscopic Tubal Occlusion

Prior to the widespread availability of laparoscopic instruments and electrosurgical accessories (e.g., electrocautery), elective tubal occlusion by partial salpingectomy (i.e., removal of a section of the Fallopian tube) was typically performed post-partum through a mini-laparotomy incision or in the setting of cesarean delivery. One of the earliest reports describing electrosurgical tubal coagulation using unipolar electrode during laparoscopy appeared in 1962.[7] Reports of serious burn injuries to both the patient as well as the surgeon appeared shortly after the unipolar procedure was adopted.[8] Bipolar electrodes were introduced in the early 1970s to mitigate the risk of thermal injury and began to replace unipolar electrodes for laparoscopic tubal occlusion.[9, 10]

Alternative laparoscopic sterilization methods that did not utilize electrocautery appeared in the literature in the mid-1970s with the introduction of the first implantable device, the Hulka Clip, which comprises two plastic jaws made of polycarbonate hinged by a stainless steel pin.[11] The Falope Ring, made from silicone rubber band became available in 1976.[12] The Filshie Clip, a titanium and silicone clip, was described in 1981.[13]

Regulation of Devices for Female Sterilization

FDA began to have premarket regulatory authority over medical devices with the enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetics Act in 1976. Medical devices marketed prior to the 1976 Amendments, such as laparoscopes and accessories, the Falope Ring, and Hulka Clip, were permitted to remain on the market while FDA determined where the devices fit in FDA's three-tiered classification scheme (Class I devices were deemed low risk, Class II, moderate risk, and Class III high risk).

Laparoscopes and electrosurgical accessories were deemed moderate risk and assigned Class II status. The Hulka Clip and Falope Ring tubal occlusion devices, designed and manufactured specifically for laparoscopic tubal occlusion, were deemed high risk and classified into Class III with their own unique device regulation (21 CFR 884.5380 – Contraceptive Tubal Occlusion Device and Introducer). On October 1, 1987, FDA ordered manufacturers of devices under this classification to obtain approval through the premarket approval (PMA) process in order to continue marketing their devices. A "grace period" was granted to provide opportunity for preparation and FDA review of the submissions. The Filshie Clip, which was developed after the 1976 Amendments, was not marketed in the US until premarket approval was obtained in

1996. These three devices received premarket approval during 1993-1996 based on clinical trial data that showed the devices were effective (0.0 to 2.7% failure rate at 12 months) and had acceptable safety profiles.

Annual Incidence of Tubal Sterilization Prior to Approval of Essure System

The annual number of inpatient female sterilizations performed in the US rose sharply during the early 1970s from approximately 200,000 in 1970 to approximately 702,000 in 1977. Between 1975-1978, the proportion of sterilizations being performed laparoscopically was greater than 30%.[6] The US Collaborative Review of Sterilization (CREST) Study was a prospective, multicenter, longitudinal study that enrolled 12,138 women. This landmark study enrolled women from nine US cities who were scheduled for interval tubal sterilization (i.e., sterilization not performed during c-section or within the postpartum period) between 1978-1986. Peterson, et al. analyzed outcomes for 10,685 of these women for eight to fourteen years following sterilization. 41% of women underwent laparoscopic sterilization by electrocautery, 37% by Falope Ring, and 18% by Hulka Clip. Five percent had sterilization by partial salpingectomy (via laparotomy). Life-table cumulative probability of pregnancy at one year ranged from 0.7 to 18.2 per thousand women. At ten years, cumulative probability of pregnancy ranged from 7.5 to 36.5 per thousand. **[14]** Data on the distribution of laparoscopic sterilization by technique (e.g., electrosurgery, Hulka clip, Falope Ring) for more recent years prior to Essure approval are not readily available.

The number of female sterilizations performed annually in the US is estimated to have declined slightly from the mid-1970s to approximately 650,000 in 2002, the year that Essure System was approved. Approximately 30% of married couples in the US using a contraceptive method, use female sterilization as their method of family planning.[15] During 2002, slightly more than half of female sterilization procedures were performed in a hospital.[1] A large number of these inpatient procedures were likely post-partum sterilization (at cesarean delivery or by mini-laparotomy usually within 24 hours of a vaginal delivery), whereas many outpatient procedures were likely interval sterilizations that occur separate from pregnancy.[10]

Female Sterilization in the US Following Approval of Essure System for Permanent Birth Control

As discussed below, the Essure System for hysteroscopic sterilization received FDA approval in November 2002. From 2002 to 2007, uptake of the Essure procedure grew from 0% to 51% of all interval sterilization procedures at Detroit Medical Center hospitals.[16] A recent analysis of hysteroscopic sterilization in the US between 2005 and 2012 found that hysteroscopic sterilization represented 38% of interval sterilization procedures over this time.[17] While Essure is the only hysteroscopic sterilization method presently available in the US, the Adiana System was also legally marketed from July 2009 to May 2012, when it was withdrawn from the market (for reasons unrelated to safety and effectiveness). The Adiana method consisted of hysteroscopic delivery of RF energy to a small portion of the Fallopian tube lumen followed by placement of a cylindrical silicone matrix within the interstitial portion of the tube. Like Essure, the Adiana method required a three-month waiting period and confirmation of tubal occlusion prior to discontinuation of alternate contraception.

More than 750,000 Essure procedures have been performed worldwide since FDA approval in November 2002 through early 2013.[18] The number of Essure procedures worldwide has grown since that estimate was released, with approximately 80% of 2011 global revenue for this product coming from US sales. [19]

Complications Following Interval Laparoscopic Sterilization

The rates of intraoperative or postoperative complications following interval laparoscopic surgical sterilization also were evaluated by Jamieson, et al. using outcomes from the CREST study.[20] The analysis population was 9475; women undergoing concurrent surgeries other than diagnostic D&C or simple biopsies were excluded. Surgical sterilization was performed by one of the following methods: silicone band (3659), spring clip (1709), bipolar coagulation (2288) and unipolar coagulation (1485). This study collected outcomes data at one- and 12 months postoperatively. Six categories of complications were evaluated:

- Unintended major surgery
- Transfusion
- Febrile morbidity
- Life-threatening event
- Rehospitalization
- Death

The rate of women who experienced any of the above events was 153/9475 (1.6%). No deaths were reported; however, the risk of death following surgical sterilization has been estimated elsewhere at 3.4-4.0 per 100,000 procedures.[20]

Unintended major surgery (i.e., conversion to laparotomy) due to laparoscopic complications in this study occurred in 14 subjects and were due to bleeding from Fallopian tube or mesosalpinx (4), transection of the fallopian tube (3), bleeding from laparoscopic puncture site (2), stomach perforation (1), bowel perforation (1), bleeding from sacral promontory caused by Veress needle injury (1), bleeding not further described (1) and perforation of a structure believed to be an adhesion (1). There were 37 other conversions to laparotomy attributed to difficult Fallopian tube visualization or manipulation of which adhesions were cited as the cause in 27 cases. Fifty-six women (0.6%) were re-hospitalized. The most common reasons for re-hospitalization were pelvic infection, heavy vaginal bleeding, pregnancy complication, and abdominal or pelvic pain.

When the category of unintended major surgery was limited to true laparoscopic complications, the overall rate of complications in the above six categories was 0.9%. Independent predictors of any complication included diabetes mellitus (adjusted OR 4.5; 95%CI 2.3, 8.8), general anesthesia (OR 3.2; CI 1.6, 6.6), previous abdominal or pelvic surgery (OR 2.0; CI 1.4, 2.9), and obesity (OR 1.7; 1.2, 2.6).[21]

III. Overview of the Essure System

The Essure System for Permanent Birth Control is a medical device used for permanent sterilization by bilateral occlusion of the fallopian tubes. The Essure device includes an implantable insert and a delivery system for the placement of the insert. In contrast to other permanent sterilization procedures, Essure inserts are placed into each fallopian tube through the cervix, i.e. hysteroscopically. Once in place (Figure 1), fibers within the insert elicit a local, fibrotic reaction from the patient, which causes fibrous tissue to grow in and around the implant. Over a period of several months, this tissue ingrowth blocks the fallopian tubes, which prevents contact between oocytes (eggs) and sperm and fertilization. As part of the Essure procedure, patients undergo a radiologic confirmation test three months after insert placement in order to assure the proper placement and/or occlusion of the fallopian tubes.

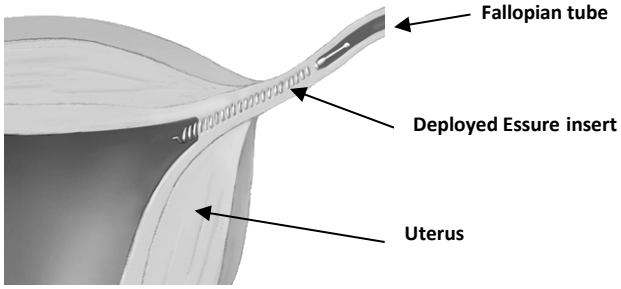


Figure 1: Essure System for permanent birth control

Description of the Use of the Essure System

The Essure System comprises a disposable delivery system, described below, and a wound-down insert. A disposable introducer is also provided to facilitate delivery system entry into the operating channel of a hysteroscope. The Essure insert consists of a super-elastic nickel-titanium (Nitinol) outer coil and a stainless steel inner coil wrapped in polyethylene terephthalate (PET) fibers. The wound-down insert is approximately 4 cm in length and 0.8 mm in diameter (Figure 2A). When released, the outer coil expands up to 2.0 mm in diameter, conforming to the varied diameters and shapes of the fallopian tube (Figure 2B). When expanded, the outer coil pushes against the fallopian tube wall, conforming itself to the diameter and shape of the fallopian tube, and acutely anchoring the insert in the utero-tubal junction. Once in place, the PET material surrounding the inner coil stimulates the fibrotic reaction and tissue ingrowth, leading to pregnancy prevention.

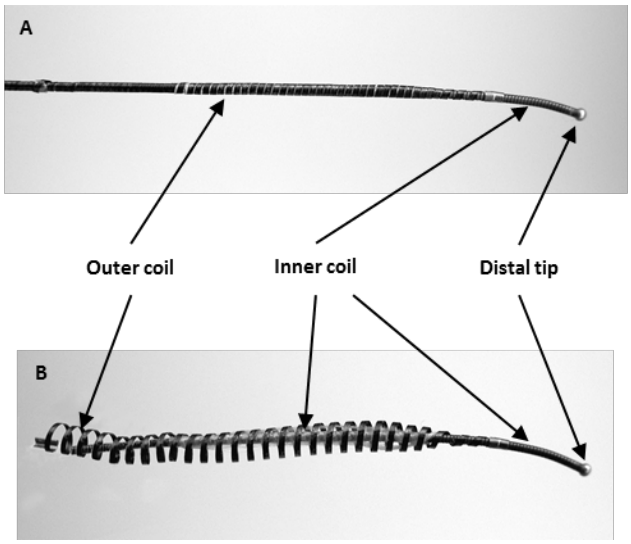


Figure 2: A) Essure insert in wound configuration. B) Essure insert with outer coil deployed.

The Essure insert is delivered into each fallopian tube via a disposable delivery system, which consists of a delivery catheter and handle (Figure 3). At the distal tip of the delivery catheter, the wound-down insert is attached to a delivery wire and sheathed by a flexible release catheter. The delivery handle controls the device delivery and release mechanism. During a placement procedure, the physician inserts the delivery catheter through a hysteroscope port with the aid of an introducer and guides the catheter to the fallopian tube under observation. Once the distal tip of the delivery catheter is in place, the physician uses the thumbwheel and button on the delivery handle to retract the delivery wire and deploy the insert. The physician must use two pre-loaded catheters to achieve bilateral placement.

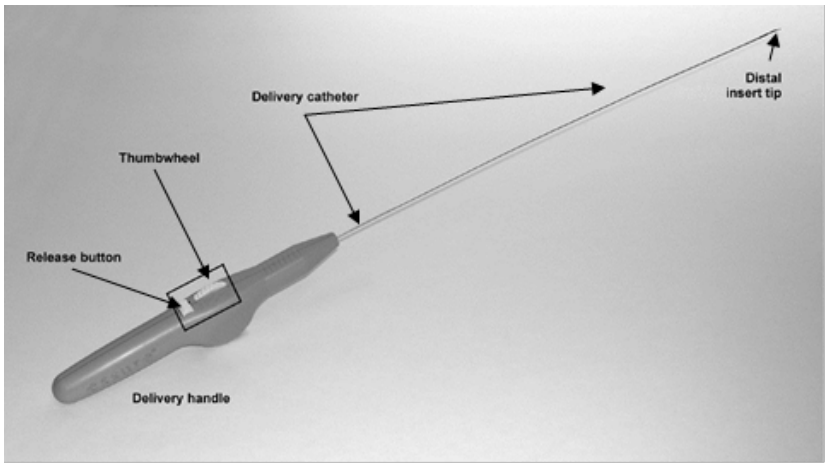


Figure 3: Essure System (delivery handle, catheter, and wound insert tip)

The insert placement does not require entry into the peritoneal cavity or general anesthesia, and can often be performed as an outpatient office procedure.

The Essure Confirmation Tests

The tissue ingrowth process into and around the inserts is gradual and may take several months to elicit full occlusion of the fallopian tubes. Therefore, patients who have the Essure procedure must continue to use alternate contraception, until occlusion has been confirmed by their physician, and the physician informs the patient that she may rely on the device. A patient must have a confirmation test performed three months after device placement to confirm proper insert location and/or occlusion of the fallopian tubes. Only after a satisfactory confirmation test can a patient rely on the Essure inserts alone for permanent contraception.

Until June 2015, the FDA-approved Essure confirmation test had been limited to a modified hysterosalpingogram (HSG) in which radiologic contrast dye is deposited in the uterus through the cervix. Fluoroscopy is utilized to visualize the Essure inserts and the dye within the uterus and fallopian tubes. If the tubes are fully occluded, the dye should not be able to pass into the distal portions of the fallopian tubes, and the dye will not be visualized on the radiograph distal to the Essure inserts. With this test, physicians determine if the inserts are appropriately located, and that tubal occlusion has occurred.

In June 2015, FDA approved an algorithm that allows transvaginal ultrasound (TVU) to serve as the confirmation test in lieu of the modified HSG when multiple criteria are satisfied (PMA Supplement 41). When these criteria are not met, or when the results of the TVU are unsatisfactory, the modified HSG must be performed before a patient can be advised to rely on Essure. The TVU method of confirmation utilizes a transvaginal ultrasound probe to generate images of the uterus, proximal fallopian tubes, and the Essure inserts. Physicians use these images to evaluate the suitability of the inserts' location; if the TVU demonstrates satisfactory insert location bilaterally, the patient may be advised to rely on Essure. The Essure TVU procedure, however, does not provide confirmation of occlusion. Individual physician training and assessment of comprehension is required before users may adopt the TVU/HSG protocol. TVU has been an accepted method for the Essure confirmation test in several countries in the EU and elsewhere since 2011.

Indications for Use and Contraindications to Use

Essure is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

The Essure system is contraindicated for patients who:

- Are uncertain about ending fertility.
- Can have only one insert placed
- Have previously undergone a tubal ligation.
- Are pregnant or suspect pregnancy.

- Have delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure.
- Have an active or recent upper or lower pelvic infection.
- Have a known allergy to contrast media.

Regulatory History

The Premarket Application (PMA) for the Essure System for Permanent Birth Control was submitted to the FDA for review in April 2002. The PMA application was supported by clinical data from two studies including one with 2 years of follow-up (Phase II study) and 1 year of follow up in the other (Pivotal study). These studies will be described further in Section IV, Summary of Clinical Data Supporting the Original PMA of the Essure System.

When the PMA was submitted, the Essure System was commercially available in Australia, Austria, Belgium, Canada, Denmark, Finland, Germany, Holland, Indonesia, Italy, Norway, Portugal, Singapore, Spain, Sweden, Switzerland, Turkey, and the U.K. The Essure System was approved for marketing in Europe by the notified body TÜV in February 2001 and in Canada by Health Canada in November 2001. Information regarding outside of the US (OUS) post-market experience is described in Section XI, below.

As a first-of-a-kind device, the Essure System was presented to the CDRH Obstetrics and Gynecological Devices Advisory Panel on July 22, 2002. After deliberating on the information in the application and presentations at the panel meeting, the panel voted to recommend "approval with conditions" for the Essure PMA with 8 affirmative votes and 1 abstention. The panel recommended the following conditions for approval: 1) performance of mandatory HSG confirmation testing after placement of the device, 2) the training program to train physicians on the placement procedure be a prerequisite to performing the procedure, and 3) several modifications to the labeling be included, including addition of prominent information on failure/success rates, warnings about metal allergy, electrocautery, and pregnancy occurring while the device is in place, and training requirements.

In accordance with the recommendations of the advisory panel, the FDA approved the original PMA on November 4, 2002. As a condition of approval, FDA required that Conceptus continue gathering data from patients in the ongoing Phase II and Pivotal studies out to 5 years after discontinuation of alternative contraception, and conduct a new study to document the bilateral placement rates for newly-trained physicians.

Since approval of the original Essure System in 2002, there have been numerous modifications to the device. These changes did not change the basic design of the insert, the primary insert materials, or the device mechanism of action. Most of the changes were intended to improve device deployment and usability during the Essure placement procedure. The current model Essure (ESS305) was approved in 2007 (PMA Supplement 12) and was modified to include a new introducer design to prevent backsplash of distension fluid during hysteroscopy onto the surgeon and/or surgical field, a modification to the catheter/insert interface to improve insert detachment, and visual updates to ease device deployment and usability. As a condition of

approval for Supplement 12, Conceptus was required to perform a post-approval study (PAS) to evaluate the rate of successful bilateral insert placement on the first attempt.

Several labeling modifications have been made to the Essure System since approval of the original PMA. (See Appendices B and C for the current physician and patient labeling.) Principally, the labeling updates have added long-term efficacy and safety information from the Phase II and Pivotal clinical trials as they became available. The labeling was also updated to reflect information on pregnancies in commercial use of Essure. In 2011, the labeling was modified to remove the contraindication for nickel allergies, replacing it with a revised warning. In 2012, the physician's instructions for use and the patient brochure were updated to include information about device effectiveness and reasons for pregnancies based on commercial use of the device. In 2013, following an internal FDA review of post-market data, the patient brochure was amended to better reflect the adverse event information available in the physician labeling, including reports of chronic pelvic pain and device migrations. In the most recent labeling change (Supplement 41, approved in June 2015), transvaginal ultrasound (TVU) was added as a possible confirmation test in certain cases. One-year effectiveness data were added from the ongoing TVU clinical study and the discussion of device removal was expanded.

Beginning in late 2013, FDA has received a significant increase in the number of adverse event reports related to Essure; in particular, from patients who have received the device. The Agency has also been cognizant of complaints related to the device being conveyed in traditional and social media outlets. Accordingly, FDA has recently conducted an additional review of data related to the Essure system and determined that the information should be vetted and discussed in an open forum, i.e., this panel meeting.

IV. Summary of Clinical Data Supporting the Original PMA of the Essure System

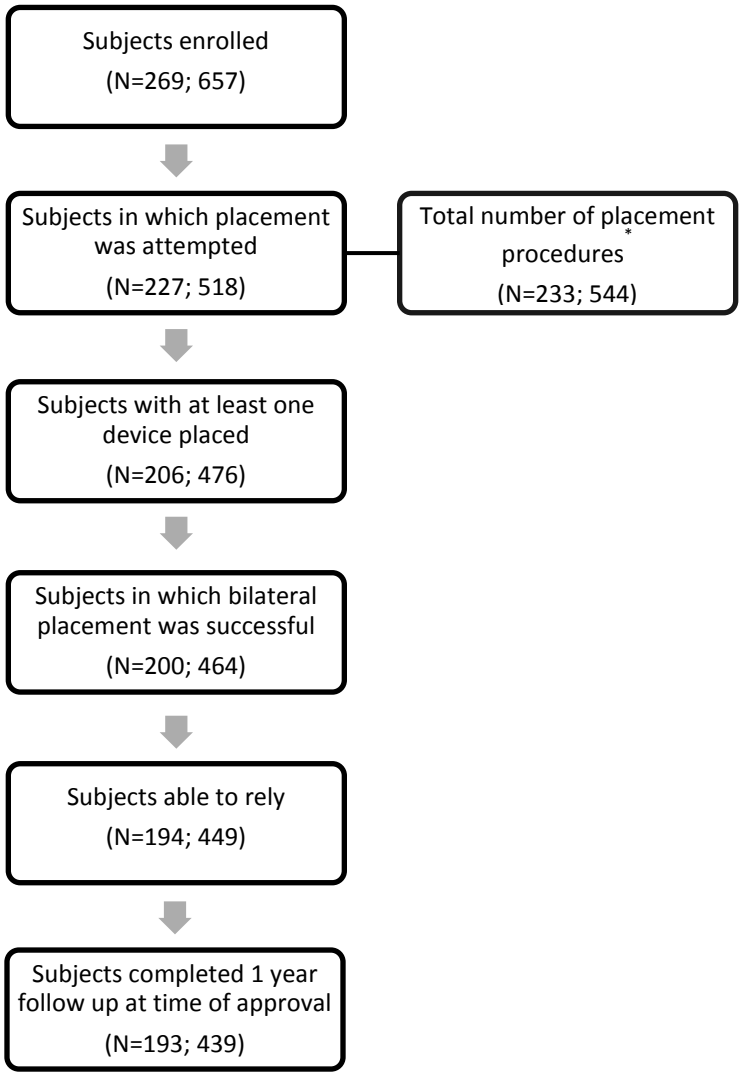
Prior to submitting the application for market approval ("original PMA"), the sponsoring firm, Conceptus, Inc., performed several clinical studies under the Investigational Device Exemption (IDE) program. As discussed in this section, at the time of original PMA approval, 2 year safety and effectiveness data were available from the Phase II study, and 1 year safety and effectiveness data were available from the Pivotal study. Additional data following the patients in these two studies for 5 years was collected postmarket as part of the conditions of approval.

Prior to the Phase II and Pivotal studies, beginning in 1996, preliminary investigations of different versions of the device were conducted with the devices placed either concurrently or in advance of hysterectomies. These studies, which included 99 and 63 patients for peri-hysterectomy and pre-hysterectomy studies, respectively, yielded data on device placement, patient comfort, as well as histological data to support the mechanism of action of the device.

In 1998, FDA approved Conceptus' IDE for a prospective, multi-center, non-randomized, single arm Phase II clinical study. In this study, the long-term safety and effectiveness of the device was to be evaluated for the first time in 227 women who were not undergoing hysterectomy. Devices were implanted bilaterally in women, who were then followed for up to 5 years post-placement for evaluation of adverse events and pregnancy rates. During the Phase II study,

Conceptus also began a larger, prospective, multi-center, non-randomized, single arm pivotal study of the device, also under an IDE. The placement procedure was attempted in 518 women in the Pivotal study, which investigated safety and effectiveness endpoints similar to the Phase II study, including evaluation of adverse events and pregnancies in subjects for a period up to 5 years. Figure 4 provides a patient accountability chart for the Phase II and Pivotal studies.

Figure 4. Phase II and Pivotal Study Patient Accountability Chart



Numbers of subjects in each category (N) are displayed as the number of subject in the Phase II and Pivotal study as (N=patients from Phase II; patients from Pivotal)

*Some subjects had more than one placement procedure, and so the total number of placement procedures is in excess of the number of subjects in which placement was attempted

All of the participants in the Phase II and Pivotal studies were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had at least one live birth, had regular, cyclical menses and were able and willing to use alternative contraception for 3 months following Essure placement. Table 1 provides patient demographics for these studies.

Table 1. Demographics of Study Subjects in Phase II and Pivotal Clinical Trials of Essure

	Phase II N=227	**Pivotal Trial N=518**
Race	(not collected)	
White/Caucasian		428
Latin		31
Black		24
Other		9
Mean Age	35	32
Age < 28	7%	17%
Age 28-33	23%	47%
Age ≥ 34	70%	36%
Gravidity	Mean = 2.6 (0 – 10)	Mean = 3.03 (1 – 11)
Parity	Mean = 2.2 (0 – 5)	Mean = 2.26 (1 – 6)
BMI	Mean = 26 (17 – 57)	Mean = 27 (16 – 52)

The data from these IDE studies were used to support the PMA application, which was submitted to the FDA in 2002 as the "Essure System for Permanent Birth Control."

Adverse events

Adverse events in the original PMA application were reported from the Phase II and Pivotal IDE trials. When asked immediately after the procedure, the majority of women stated that they experienced mild to moderate pain during the procedure. As shown in Table 2, the most common adverse events reported during the recovery period the first day following device placement were cramping, pain, and nausea/vomiting. In addition, it was reported that the majority of women experienced spotting for an average of 3 days after the procedure.

Table 2: Adverse Events Reported During Recovery on Day of Placement

Phase II Study (N=233 procedures)		
Adverse Event	**Number**	**Percent**
Band detachment (device malfunction)	3	1.3%
Vaso-vagal response	2	0.9%
Pain	2	0.9%
Pivotal Study (N=544 procedures)		
Adverse Event/Side effect	**Number**	**Percent**
Cramping	161	29.6%
Pain	70	12.9%
Nausea/vomiting	59	10.8%
Dizziness/light headed	48	8.8%
Bleeding/spotting	37	6.8%
Vaso-vagal response/fainting	7	1.3%
Hypervolemia	2	0.4%
Band detachment	2	0.4%
Other*	16	2.9%

*Includes: ache (3), hot/hot flashes (2), shakiness (2), uncomfortable (1), weak (1), profuse perspiration (1), bowel pain (1), sleep (1), skin itching (1), loss of appetite (1), bloating (1), allergic reaction to saline used for distension (1).

Lower rates of adverse events were reported post-procedure. As seen in Table 3, the most commonly reported adverse events in the first year of reliance on Essure in the Pivotal trial were back pain (9.0%), abdominal pain/abdominal cramps (3.8%), and dyspareunia (3.6%). In addition to the reports from the Pivotal trial, 12/206 (5.8%) of women in the Phase II trial with at least one insert reported episodes of dysmenorrhea, ovulatory pain, or changes in menstrual function.

Table 3: Adverse Events by Body Systems, First Year of Reliance on Essure in Pivotal Trial*

Adverse Events by Body System	Number (N=476)	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Gas/Bloating	16	1.3%
Muscolo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Nervous/Psychiatric:		
Headache	12	2.5%
Premenstrual Syndrome	4	0.8%
Genitourinary:		
Dyspareunia	17	3.6%
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Persistent increase in menstrual flow	9**	1.9%
Vaginal discharge/vaginal infraction	7	1.5%
Abnormal bleeding – timing not specified	9	1.9%
(severe)	5	1.1%
Menorrhagia/prolonged menses (severe)		
Pain/discomfort – uncharacterized:	14	2.9%

* The patients in this table (N=476) were implanted with at least one device, and events occurred in the first year of reliance (up to 15 months post-procedure). Percentages presented reflect the number of events in the numerator and the number of women in the trial wearing at least one insert in the denominator. [2]Only events occurring in ≥ 0.5% are reported

** Eight women reported persistent decrease in menstrual flow

In addition to the events listed above, the adverse or other events listed in Table 4 delayed or prevented reliance on Essure for contraception.

Table 4: Events that delayed or prevented reliance on Essure for contraception

Phase II Study		
Event	**Number**	**Percent**
Perforation	6/206	2.9%*
Expulsion	1/206	0.5%
Other unsatisfactory micro-insert location	1/206	0.5%
Initial tubal patency	7/200	3.5%**
Pivotal Study		
Event	**Number**	**Percent**
Perforation	5/476	1.1%
Expulsion	14/476	2.9%***
Other unsatisfactory micro-insert location	3/476	0.6%
Initial tubal patency	16/456	3.5%**

*Four of the six perforations occurred with use of the since-discontinued Support Catheter

**Tubal patency was demonstrated in 7 women (Phase II) and 16 women (Pivotal) at the 3-month HSG, but all women were shown to have tubal occlusion at a repeat hysterosalpingogram (HSG) performed 6 months after Essure placement.

***Fourteen women experienced an expulsion, however nine of these 14 women chose to undergo a second micro - insert placement procedure, which was successful in all nine cases.

Effectiveness

The primary effectiveness endpoint of the Pivotal trial was the one-year contraceptive efficacy rate among relying subjects (e.g., those subjects who had a confirmation test that showed bilateral occlusion and location, and were told to rely on the device for contraception). Additional indicators of device performance included bilateral placement rate and reliance rate (i.e., the rate at which women with successful bilateral placement were confirmed to have tubal occlusion and location by HSG and told to rely).

In the Phase II and Pivotal trials, bilateral placement was achieved in approximately 90% of subjects who underwent hysteroscopy for device placement; some required a second procedure when bilateral placement was not achieved in the first. Of the women with bilateral placement, 97% were ultimately able to rely on Essure for contraception (Table 5).

Table 5: Essure Placement and Reliance Rates from Phase II and Pivotal Clinical Trials*

Outcome	Phase II N=227		Pivotal N=518	
	Number	**Percent**	**Number**	**Percent**
Bilateral Placement: After one procedure	196/227	86%	446/518	86%
Bilateral Placement: After two procedures**	200/227	88%	464/518	90%
Reliance rate: Among women with bilateral placement	194/200	97%	449/464	97%

* Note that the data above represents the rates based upon available information at the time of approval

** Four women in the Phase II study and 18 in the Pivotal study had successful additional placement procedures after failure to achieve bilateral placement on first attempt.

Since the original approval, the sponsor has made changes to the catheter to facilitate placement, although data on Essure placement rates have generally demonstrated a high rate of bilateral placement. In post-approval studies, higher bilateral placement rates were reported (>95%), and since approval of the Essure system, there has been consistently high bilateral placement rates (80-100%) reported in the literature. Appendix A provides post-market information on bilateral placement rates, the physician learning curve for device placement, and patient compliance with the confirmation testing requirement.

At the time of PMA submission, of the 745 subjects in whom placement was attempted in the Phase II or Pivotal trials, 643 subjects were told they could rely on Essure. In these women, there were no reported pregnancies. There were four luteal phase pregnancies reported in the Pivotal trial (pregnancies occurring prior to Essure placement but not detected on the day of placement). None of these women became pregnant while relying on Essure for contraception, and the luteal phase pregnancies were not reflected in the device failure rates. The cumulative failure rate for subjects relying on Essure for contraception in the Phase II trial at one and two years and for the Pivotal trial at one year was 0% (Table 6). As a comparison, a life-table 1-year cumulative probability of pregnancy among women undergoing tubal sterilization by six surgical methods of

0.55% was found in the large, prospective U.S. Collaborative Review of Sterilization (CREST) study, as reported by Peterson et al.[14]

Table 6: Essure Effectiveness Results of Phase II and Pivotal Clinical Trials at Time of Approval

Cumulative Failure Rates	Phase II N=193	Pivotal Trial N=439	Both Trials Combined N=632
One-year	0% (95% CI 0 – 1.53%) (Adj 95% CI 0-2.19%)*	0% (95% CI 0-0.68%) (Adj 95% CI 0-0.78%)*	0% (95% CI 0-0.47%) (Adj 95% CI 0-0.57%)*
	Phase II N=181	**Pivotal Trial N=16**	**Both Trials Combined N=197**
Two-Year	0% (95% CI 0-1.54%) (Adj 95% CI 0-2.36%)*	0% (95% CI 0-0.86%) (Adj 95% CI 0-0.93%)*	0% (95% CI 0-0.55%) (Adj 95% CI 0-0.67%)*

The data above represent the failure rates based upon available information at the time of approval. Although the failure rate established in the clinical trials of Essure ™ was 0%, no method of contraception is 100% effective, and pregnancies have occurred in the commercial setting.

*Adjustment using indirect method (CDC CREST study population) based on the age groups: <28 years, 28-33 years, and =34 years.

Five-Year Follow-Up of PMA Cohort

FDA has the authority to require sponsors to perform a Post-Approval Study (PAS) at the time of approval of a PMA to help assure continued safety and effectiveness of the approved device. As a Condition of Approval in 2002, FDA ordered two PAS's for the Essure original PMA, one of which required additional follow-up of the Phase II Study and Pivotal Study premarket cohorts for a total of five years of follow-up. This extended follow-up was completed in 2008, and the device label was updated to include 5-year performance data. The following information, from the complete 5-year reports of the Phase II and Pivotal studies, is arranged by the topics of interest outlined in Sections VI and VII of this executive summary.

Pregnancies

In the five-year follow up of the Phase II and Pivotal clinical trials, no pregnancies occurred in women relying on Essure. As described above, there were four luteal phase pregnancies reported in the Pivotal trial (pregnancies occurring prior to Essure placement but not detected on the day of placement).

Patient Comfort/Satisfaction

In the Phase II and Pivotal trials at follow up time points of 3, 6, 12, 18 24, 36, 48, and 60 months, at least 99% of women were reported to have rated comfort of wearing the Essure inserts as "good" or "excellent." In the Pivotal trial, at least 97% of women were reported to be "somewhat" to "very satisfied" at all visits through 5 years.

The FDA is aware of allegations from women who participated in the original Essure clinical trials that the feedback they provided about the comfort wearing the device was not recorded accurately by clinical staff. As part of the original PMA approval, FDA performed inspections at Conceptus and one clinical site. These inspections audited data provided in support of the PMA, as well as sponsor activities during the studies, and did not report findings concerning the case report forms or patient comfort/satisfaction data submitted in support of the PMA.

Post-market literature assessing patient comfort and satisfaction is discussed in Section VI.B of this document and also shows high patient satisfaction rates.

Post-procedural Pain (Chronic/Persistent Pain)

Patient pelvic and other pain was reported at follow-up visits up to 5 years for the Phase II and Pivotal trials. Follow up visits were recorded as either post-device placement (PDP) or post-alternative contraception (PAC; when alternative contraception was discontinued). Patients reported if they experienced pain in the previous follow up period. Unless noted, reports do not indicate duration, severity, or persistence. The pain reported at follow-up visits in the Phase II and Pivotal studies are summarized in Tables 7 and 8, respectively, below:

Table 7: Reports of pain at follow up visits of the Phase II study

Follow-up visit	Pelvic Pain			Other Pain
	Dysmenorrhea	Dyspareunia	Other Pelvic	
3 month N=203	29 (14%)	17 (8%)	5 (2%)	2 (<1%)
6 month N=199	11 (6%)	3 (2%)	3 (2%)	1 (<1%)
12 month N=196	5 (3%)	0	5 (3%)	0
18 month N=193	2 (1%)	0	10 (5%)	2 (1%)
24 month* N=194	8 (4%)	0	6 (3%)	6 (3%)
36 month* N=182	7 (4%)	1 (<1%)	2 (1%)	1 (<1%)
48 month* N=176	9 (5%)	2 (1%)	2 (1%)	2 (1%)
60 month* N=171	4 (2%)	1 (<1%)	3 (2%)	2 (1%)

Numbers are based upon the number of subjects reporting at that visit
* No data reported for some women that indicated unusual pain (N=2 at 24 months; N=1 at 36, 48, 60 months)

In the Pivotal study, additional analysis of recurrent and persistent pain was reported. Recurrent pain was defined as pain reported at more than one visit during the follow up period. Persistent pain was defined as pain reported at all visits during the follow up period.

Table 8: Reports of pelvic pain in the follow up visits of the Pivotal study

Follow-up visit	Pelvic Pain			
	Dysmenorrhea	**Dyspareunia**	**Ovulatory Pain**	**Other Pelvic**[†]
Baseline N=518	183 (35%)	22 (4.2%)	n/a	n/a
3 months PDP N=467	29 (6.2%)	29 (6.2%)	5 (1.1%)	32 (6.9%)
3 months PAC N=440	20 (4.5%)	10 (2.3%)	6 (1.4%)	26 (5.9%)
6 months PAC N=436	15 (3.4%)	8 (1.8%)	3 (0.7%)	16 (3.7%)
12 months PAC N=460	17 (3.7%)	15 (3.3%)	5 (1.1%)	27 (5.9%)
18 months PAC N=410	14 (3.4%)	9 (2.2%)	10 (2.4%)	11 (2.7%)
24 months PAC N=435	22 (5.1%)	9 (2.1%)	22 (5.1%)	13 (3.0%)
36 months PAC N=422[***]	14 (3.3%)	7 (1.7%)	12 (2.8%)	6 (1.4%)
48 months PAC N=402	3 (0.7%)	5 (1.2%)	6 (1.5%)	11 (2.7%)
60 months PAC N=386	14 (3.6%)	8 (2.1%)	10 (2.6%)	9 (2.3%)
Recurrent[*] N=473	29 (6.1%)	18 (3.8%)	14 (3.0%)	25 (5.3%)
Persistent year 1[**] N=460	0	0	0	1 (0.2%)
Persistent year 2[**] N=435	0	0	0	1 (0.2%)
Persistent year 3[**] N=422	0	0	0	0
Persistent year 4[**] N=402	0	0	0	0
Persistent year 5[**] N=386	0	0	0	0

[†]Other pelvic is defined as pain not reported to be dysmenorrhea, dyspareunia or ovulatory pain

[*] Recurrent: symptom reported at more than one visit during the follow-up period (i.e., symptoms do not have to be reported on consecutive visits).

[**]Persistent: symptoms reported at all visits during the follow up period

[***]Data missing on one patient

While reports of various types of pelvic pain ranged from < 1% to 7% throughout the follow up of the Pivotal study, persistent pelvic pain was reported in only 1 case at one and two year follow up appointments.

Changes in Vaginal Bleeding, Menstrual Patterns or Characteristics

Changes in menstrual patterns and bleeding were reported at various times during the Phase II trial. Rates of reports of irregular menses, spotting, and changes in flow ranged from 2-9% (Table 9).

Table 9: Reports of menstrual irregularities during the Phase II trial

Follow-up visit	Irregular menses	Spotting	Changes in flow	Other
3 month	Not asked	Not asked	Not asked	Not asked
6 month N=199	3 (2%)	6 (3%)	3 (2%)	0
12 month N=196	6 (3%)	5 (3%)	4 (2%)	0
18 month N=193	9 (5%)	4 (2%)	5 (3%)	0
24 month* N=194	4 (2%)	4 (2%)	10 (5%)	1 (<1%)
36 month* N=182	4 (2%)	3 (2%)	4 (2%)	2 (1%)
48 month* N=176	4 (2%)	3 (2%)	9 (5%)	2 (1%)
60 month* N=171	16 (9%)	3 (2%)	11 (6%)	2 (1%)

Numbers are based upon the number of subjects reporting at that visit

* No data reported for some women that indicated unusual bleeding (N=2 at 24 months; N=1 at 36, 48, 60 months)

In the Pivotal trial, changes in vaginal bleeding and menstrual patterns were recorded throughout the study over a period of 5 years (Table 10). Additionally, recurrent and persistent menstrual irregularities were reported.

Table 10: Reports of menstrual irregularities, rates of recurrence, and persistence during the Pivotal trial

Follow-up visit	Irregular menses	Bleeding between menses	Heavier than usual menstrual flow	Less than usual menstrual flow
Baseline N=518	9 (1.7%)	12 (2.3%)	n/a	n/a
3 months PDP	48 (10.3%) N=467	110 (23.6%) N=466	89 (19.2%) N=463	56 (12.1%) N=463
3 months PAC	36 (8.2%) N=440	40 (9.1%) N=440	96 (21.9%) N=439	55 (12.5%) N=439
6 months PAC	36 (8.2%) N=437	29 (6.6%) N=437	94 (21.6%) N=435	57 (13.1%) N=435
12 months PAC	35 (7.7%) N=455	31 (6.7%) N=460	77 (16.8%) N=458	67 (14.6%) N=458
18 months PAC	19 (4.6%) N=410	42 (10.2%) N=411	70 (17.0%) N=411	63 (15.3%) N=411
24 months PAC	20 (4.6%) N=435	32 (7.4%) N=435	89 (20.6%) N=432	53 (12.3%) N=432
36 months PAC	31 (7.4%) N=420	25 (6.0%) N=420	83 (20.2%) N=411	47 (11.4%) N=411
48 months PAC	33 (8.4%) N=393	33 (8.3%) N=396	69 (17.9%) N=386	52 (13.5%) N=386
60 months PAC	45 (11.7%) N=386	29 (7.5%) N=386	74 (19.6%) N=377	40 (10.6%) N=377
Recurrent*	70 (14.8%) N=473	89 (18.8%) N=473	177 (37.5%) N=472	110 (23.3%) N=472
Persistent year 1**	3 (0.7%) N=455	2 (0.4%) N=460	7 (1.5%) N=458	12 (2.6%) N=458
Persistent year 2**	0 (0%) N=435	1 (0.2%) N=435	4 (0.9%) N=432	3 (0.7%) N=432
Persistent year 3**	0 (0%) N=420	1 (0.2%) N=420	4 (1.0%) N=411	2 (0.5%) N=411
Persistent year 4**	0 (0%) N=393	0 (0%) N=396	3 (0.8%) N=386	1 (0.3%) N=386
Persistent year 5**	0 (0%) N=380	0 (0%) N=386	2 (0.5%) N=377	0 (0%) N=377

* Recurrent: symptom reported at more than one visit during the follow-up period (i.e., symptoms do not have to be reported on consecutive visits). The denominator (N) is the sum of all unique patients who responded over the course of their follow-up period. Not all women responded at all follow-up visits

** Persistent: symptoms reported at all visits during the follow up period

Irregular menses were reported at rates ranges from 4-12%. Heavier than usual menstrual flow was more commonly reported at 16-22% while less than usual menstrual flow was reported at rates ranging from 10-15%. Menstrual irregularities that were persistent occurred at rates ranging from 0-3% with the highest rate being changes reported as "less than usual flow."

Headache

Eleven cases of headaches were reported in 10/206 (4.9%) of subjects in the Phase II trial over the duration of the study. In the Pivotal trial, 226 cases of headaches were reported in 98/518 (18.9%) of subjects over the duration of the study.

Nickel Allergy/Hypersensitivity

There were no reported cases of nickel or metal allergy reaction identified in the Phase II and Pivotal clinical trials. Subjects were not tested for nickel or metal sensitivity at baseline or subsequent to Essure placement as part of the study.

Perforation and intraperitoneal migration

In the Phase II and Pivotal studies, perforations were discovered on the day of placement (on x-ray), at the Essure confirmation test, or during subsequent laparoscopic surgery. Details surrounding these perforations included surgical and histological findings when available.

In the 5-year follow-up of the Phase II trial, one perforation was identified in addition to the 6 identified premarket. Therefore, the rate of perforation at 5 years reported in the Phase II study was 7/227 (3.1%). In the Pivotal trial there were 5 perforations reported in the first year of reliance (Table 4). There were no additional perforations reported in the post-approval follow up. The rate of perforation at 5 years was therefore 5/476 (1.1%).

Of the 7 perforations reported in the Phase II study, 6 of the devices were reported as "intraperitoneal." Intraperitoneal devices were those either partially or completely within the peritoneal cavity. No other intraperitoneal devices were reported in this study.

Deaths

There were no deaths reported in the final 5-year report for the Phase II trial. A single death was reported secondary to leukemia during the post-market follow up of the Pivotal trial.

Essure insert removal

Information on device removal in the Phase II and Pivotal trials was not systematically reported and was compiled from various investigator reports. In the 5 year data from the Phase II and Pivotal trials, a total of 32 women were reported to have devices removed. Of these cases, 12 occurred in the Phase II trial (12/206, 5.8%) and 20 occurred in the Pivotal trial (20/476, 4.2%) (Table 11).

Table 11: Number of women in which device removal was performed during the Phase II and Pivotal Studies up to 5 years of follow up.

	Phase II	Pivotal
Total device removals	12	20
Laparoscopic removal	4	5*
Hysteroscopic removal	1**	-
Hysterectomy	5	15
Other removal	2***	-

*Inserts were removed laparoscopically prior to IVF in a woman who desired pregnancy, four others at time of sterilization

**In one woman, device removal was attempted hysteroscopically during the placement procedure

***Includes one woman in which devices were removed via cornual resection and one woman in which devices were removed via laparotomy.

Circumstances leading to the hysterectomies with device removal in Table 11 were:

- Abnormal bleeding (7)
- Heavy bleeding and pain (2)
- Pain (3)
- Prolapse (2)
- Asherman's Syndrome (1)
- Uterine myoma (1)
- Unknown (4)

Circumstances surrounding the laparoscopic, hysteroscopic, and other device removals in Table 11 were:

- Tubal ligation following unsatisfactory placement (8)
- Pain (2)
- Desire for fertility (1)
- Unsatisfactory location during placement procedure (1)

In addition to the above, there was one case in the Phase II study and four cases in the Pivotal study in which salpingectomies for sterilization were performed, but information regarding device removal was not available

V. Post-Market Data: Sources

As described in Section IV, FDA ordered post-approval studies for the Essure original PMA, including but not limited to follow-up of the Phase II Study and Pivotal Study premarket cohorts for a total of five years.

The remainder of FDA's memo will summarize safety and effectiveness data for the Essure device which has been developed since the original PMA approval in 2002 and outside of the original corresponding post approval studies which were discussed above and which collected

data out to 5 years on the IDE cohorts. A particular emphasis will be placed on specific events or outcomes of interest which have become a significant concern to the patient community.

This section of the memo describes the sources of the data which FDA reviewed – the results will be presented in Sections VI and VII below. These sources of data, which will be described in more detail, include the ongoing ESSTVU prospective clinical trial used to support approval of TVU as an alternate confirmation tool (PMA Supplement 41), clinical studies cited in the recent peer-reviewed medical literature, published or presented case reports/series, Medical Device Reports (MDRs) submitted to the FDA's Manufacturer and User Facility Device Experience (MAUDE) database since approval, current product labeling, and information from social media listening tools and outside-the-US regulatory bodies.

ESSTVU Study Safety Data ("TVU Study")

As noted previously, FDA recently approved a change to the Essure confirmation test protocol to allow TVU as a possible test in certain cases. This change was approved in Supplement 41 to the PMA and was supported by the ongoing ESSTVU Study 16974 prospective, multi-center, international study, which includes 597 women ages 21-44. Enrollment took place from May 2011 – October 2012; data for subjects with 1 year follow-up supported the approval of the PMA Supplement. The subjects in this study continue to be followed; the results are reported to FDA annually. Pertinent safety information from the ESSTVU study current to the most recent annual report (data up to June 2015) will be presented for the outcomes of interest in Section VII.

Literature: Peer-Reviewed Studies

A PubMed search was conducted on June 26, 2015, using the strategy "Essure OR (hysteroscop* AND sterili*)" in order to identify articles pertaining to the following topics:

1) Pregnancy-related outcomes including unintended pregnancies after Essure placement;
2) Safety issues and adverse events after Essure placement;
3) Patient satisfaction with the Essure procedure and device;
4) Confirmation testing, including patient compliance;
5) Placement rates and problems, including migration and expulsion, and physician learning curve.

The literature studies reviewed and summarized in Sections VI and VII had a number of limitations. Many studies were retrospective reviews which may be more susceptible to study bias than prospective studies, and which can lead to biased estimates of incidence rates. Very few articles reported data for a comparison group receiving an alternate sterilization procedure, such as tubal ligation. Therefore, it was difficult to assess incidence rates and device-relatedness of events such as menstrual irregularities as compared to the general population or women who receive other sterilization procedures. Publications were often single-site studies which reported results obtained by physicians with extensive device experience and some publications may have been reporting on the same study or patient population from a given center at different time points. Study enrollment varied considerably in numbers of patients included. In addition, some studies provided limited follow-up in terms of duration and/or percentage of patients completing follow-up. Details (such as timing after procedure and intervention) about events such as device

migration and perforation were lacking in many articles. Multiple studies and authors listed affiliation with the manufacturer of Essure (Conceptus or Bayer), which may introduce a publication bias toward publishing positive results. Multiple (10) articles were translated to the best of our ability from French, Spanish, or Finnish to English, in order to better assess the effectiveness and safety profile of Essure (especially in light of differing confirmation test protocols in Europe), but there was a possibility for translation error. Finally, one article presented combined data for Essure and Adiana sterilization devices, and results were not stratified by device.[17]

Literature: Case Reports/Series

Using the criteria above, PubMed, Embase, and Google Scholar were also searched for case reports and series, as well as abstracts, posters, and presentations which cited safety-related outcomes following Essure placement. Information from these sources will be summarized separately from peer-reviewed clinical studies within each safety outcome section below although similar limitations (e.g., retrospective reviews, single-site reports, limited follow-up, etc.) apply.

Medical Device Reports (MDRs)

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters, such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/ environment, including:

    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs include, but are not limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

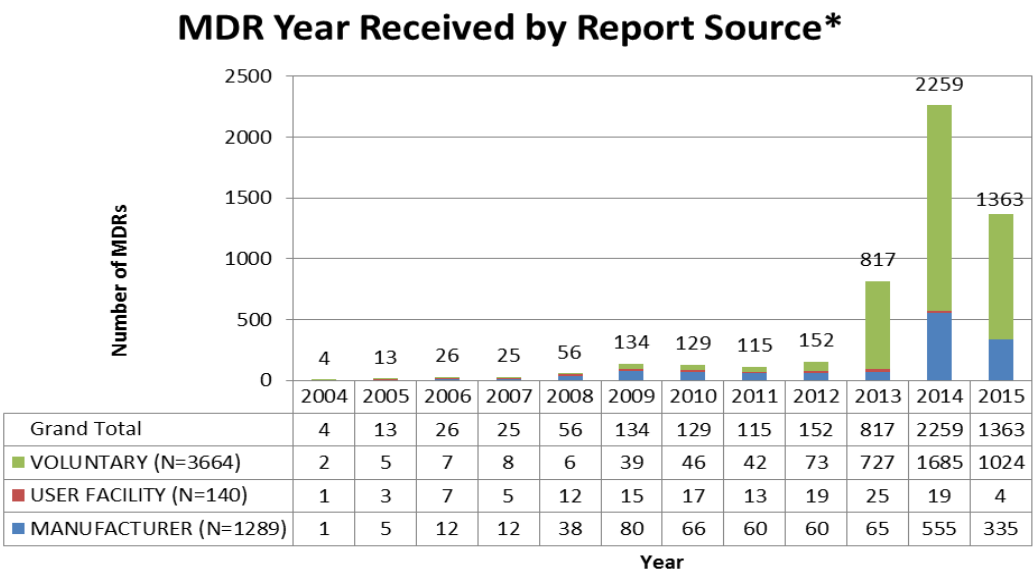
As such, MDR numbers and data should be taken in context and along with other scientific information.

Within the MDR sections of this memo, reference will occasionally be made to "patient problem codes or PPCs." A given PPC is intended to indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis. It should be noted that a given report may contain more than one PPC (no maximum) and that a report may not have every event captured as a coded PPC.

For the purpose of this review memo, the MAUDE database was queried for all reports related to Essure entered into FDA's database prior to June 1, 2015. This resulted in a total of 5,093 reports since approval. Figure 5 below provides an overview of the number of reports received per year broken down by the report source. As can be seen, there was a sharp increase in the number of MDRs received starting in 2013, largely due to a large number of voluntary reports being submitted. However, it should be noted that many of the MDRs received in/after 2013 described events from earlier years.

Note: FDA sends copies of voluntary reports to the device manufacturer, who evaluates the data and submits MDRs for those it considers to meet the mandatory reporting criteria. Because of this, there are many instances in which multiple MDR reports have been submitted for the same event. It is not usually possible to accurately match voluntary reports to manufacturer reports. Due to the potential duplicative reporting of adverse events, as well as the known limitation of underreporting, it is not possible to use MDR data to determine the actual number of incidents that have occurred in clinical practice.

Figure 5 – Number of MDRs Received per Year, Prior to June 1, 2015, by Report Source



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Grand Total	4	13	26	25	56	134	129	115	152	817	2259	1363
VOLUNTARY (N=3664)	2	5	7	8	6	39	46	42	73	727	1685	1024
USER FACILITY (N=140)	1	3	7	5	12	15	17	13	19	25	19	4
MANUFACTURER (N=1289)	1	5	12	12	38	80	66	60	60	65	555	335

Of the reports received, 4608 were coded as patient injury reports, 474 as device malfunctions, and 11 as deaths (discussed in Section VIII)

Essure Product Labeling

In Sections VI and VII, parts of the currently approved physician labeling and patient labeling relevant or pertinent to the topic being discussed are provided within each section. The exact content from the labeling is provided in *italics*, and all tables are "cut-and-pasted" from the labeling brochure to provide relevant information in one place. (Table numbers from the labeling may be removed so as not to cause confusion with numbering within this memo). Complete physician and patient labeling can be found in Appendices B and C, respectively.

VI. Post-Market Effectiveness Outcomes (Non-PAS)

The risks associated with a given therapeutic product or modality cannot be viewed in isolation. An assessment of a device's overall performance and benefit-risk profile must include consideration of the effectiveness of the device. As such, Section VI provides a review of literature and MDRs related to pregnancy outcomes and patient satisfaction for the Essure System.

A. Unintended Pregnancy

For the Essure System, effectiveness depends on procedural outcomes, including the rates at which devices can be placed (i.e., bilateral placement rate) and the rates at which patients who had devices placed successfully can rely on the device (i.e., reliance rate). As with any surgical or interventional procedure, outcomes may be dependent on the training or experience of the physician or device user. FDA also sought to assess information related to the "learning curve"

associated with the use of the Essure System, published since the original PMA and its PAS. Appendix A addresses the post-market literature regarding device placement rates, physician learning curve, and patient compliance with confirmation testing requirements.

The effectiveness of a permanent birth control procedure is determined by its ability to prevent unintended pregnancies while the woman or partner is not using any other methods of contraception. As discussed previously, surgical tubal ligation is considered an effective permanent sterilization procedure, but it is not 100% effective. It is important to note that, unlike surgical tubal ligation, which is effective immediately, the Essure System relies on the following:

- patient compliance with utilizing alternative birth control until a satisfactory confirmation test
- performance of the alternative birth control
- patient compliance with undergoing a confirmation test
- correct interpretation of the confirmation test.

The premarket studies used to support original PMA approval of the Essure System had zero pregnancies among 632 patients who relied on the Essure device for one year following confirmation testing (and out to 5 years of follow up). However, pregnancies may occur in the commercial setting because of device failure or because of patient compliance or other issues related to confirmation testing.

Literature on Unintended Pregnancy

When assessing rates of unintended pregnancies after Essure placement, it is important to differentiate among:

- luteal phase pregnancies that are already present but unrecognized at the time of the Essure procedure,
- pregnancies that occur between Essure placement and the three month confirmation test, and
- pregnancies that occur after the three month confirmation test.

Previous systematic reviews have concluded that unintended pregnancy is rare in women with successful confirmation tests[22] with rates comparable to other methods such as tubal ligation.[23] Retrospective analysis of worldwide data from FDA's MAUDE database, literature, and manufacturer reports has suggested that many unintended pregnancies are associated with patient or physician noncompliance and misinterpreted or misleading confirmation tests[24,25] and that failure rates of Essure are likely to vary by "perfect use" versus "typical use".[26] For example, FDA's literature review showed that compliance rates with confirmation testing ranged from 28.8% to 100% (see Appendix A for additional information regarding patient compliance with confirmation testing).

Tables 12 and 13 present data on occurrences of unintended pregnancy after Essure placement from published articles that were identified by the current review in addition to select articles identified by the FDA's 2009 literature review. Table 12 focuses on unintended pregnancies

occurring in the first 3 months following device placement, usually before confirmation testing. Most studies were retrospective reviews, so follow-up time may vary. Table 13 provides unintended pregnancies occurring in studies with follow-up of more than one year; some of the pregnancies in these studies may also be in the first 3 months.

Most articles reported low rates of unintended pregnancy, including zero pregnancies in the post-approval five year follow-up study (excluding luteal phase pregnancies).[27] However, this study suffered from high rates of loss to follow-up of the original intent-to-treat population (~30%). Several authors reported unintended pregnancies after patient noncompliance with confirmation testing or using alternative contraception in the three month period before confirmation testing.[28,29,30,31,32,33] There were also a number of unintended pregnancies that occurred after an apparent successful confirmation test.[34,35,36,37] Of note, Povedano, et al., reported one pregnancy that occurred 32 months after Essure placement and successful x-ray and ultrasound confirmation testing; after delivery, HSG showed apparent bilateral occlusion, but a tubal perforation of the insert, rather than occlusion was found upon laparoscopy. [36] Sakinci, et al., reported one pregnancy nine months after abandoning alternative contraception; after termination of the pregnancy, subsequent repeat HSG again showed bilateral occlusion. The patient chose to undergo laparoscopic tubal sterilization; no perforation was noted.[37]

An analysis of French hospital discharge data reported that 39,169 Essure procedures were performed between 2006-2010, and Essure patients became pregnant at a statistically significantly lower rate (143 unintended pregnancies, or 0.36%) than laparoscopic ligation patients (0.46%; hazard ratio 0.62, 95% CI: 0.40-0.96).[38] Information regarding confirmation test results or time interval between sterilization and pregnancy was not presented.

Table 12. Unintended pregnancies occurring before or near the time of confirmation testing (Studies with three months of follow-up).

Author	Country	n	Unintended Pregnancy
Anderson, 2013[39]	U.S.	638	Multiple pregnancies before confirmation
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517	6/467 (1.3%) with successful confirmation test** 1/41 (2.4%) without confirmation test**
Connor, 2011[40]	U.S.	118	0/40 in women with additional follow-up
Duffy, 2005[29]	U.K.	55	1/55 (1.8%): noncompliant with confirmation test, possibly due to immediate expulsion of 1 device
Grosdemouge, 2009[41]	France	1061	2 pregnancies: 1 luteal phase, and 1 after unsatisfactory confirmation test
Lazarus, 2012[35]	U.S.	235	1 after successful confirmation test**
Legendre, 2011[30]	France	311	2/293 (0.7%): both noncompliant with confirmation
Levie, 2006[31]	U.S.	96	1/96 (1.0%): noncompliant with using alternative contraception
Panel, 2011[42]	France	382	0/382
Rajecki, 2014[43]	Finland	120	0/120
Rodriguez, 2013[44]	U.S.	229	0/229
Savage, 2009[32]	U.S.	884	8 pregnancies: 4 unsuccessful HSG, 3 misread HSG, 1 noncompliant HSG
Shah, 2011[45]	U.K.	18	0/17
Veersema, 2010[46]	Netherlands	47	0/47

* NR=Not reported.

**Timing of pregnancy not reported.

Table 13. Long term data for unintended pregnancy (Studies with > 1 year of follow-up).

Article	Country	n	Length of F/U	Unintended Pregnancy
Andersson, 2009[47]	Sweden	57	Mean 23 months	0/57
Arjona, 2008[28]	Spain	1615	Up to 42 months	3/1615 (0.2%): at least 1 due to patient noncompliance (did not use alternative contraception)
Chern, 2005[48]	Singapore	77	1218 woman-months total	0/77
Chudnoff, 2015[27] Cooper, 2003[49]	Europe, U.S., Australia	518	5 years	0/453 for women with follow-up data at 5 yrs 4 luteal phase pregnancies
Donnadieu, 2007[50]	France	20	Mean 14 months	0/20
Franchini, 2011[51]	Italy	45	5 years	0/45
Kerin, 2003[52]	Europe, U.S., Australia	198	21-45 months	0/198
Lopes, 2008[53]	France	140	18-58 months	0/140
Povedano, 2012[36]	Spain	4306	1 year	7/4242 (0.2%): 3 before confirmation test, 4 after confirmation test
Rios-Castillo, 2013[54]	Spain	1321	5 years	3/1200 (0.3%): 2 luteal phase, and 1 before confirmation test due to device migration
Sakinci, 2015[37]	Turkey	32	8 years	1/30 (3.3%): 9 months after successful confirmation test
Shavell, 2008[33]	U.S.	79	Up to 4 years	1/79 (1.3%): noncompliant with confirmation test
Syed, 2007[55]	U.S.	20	2 years	0/20
Thiel, 2011[56]	Canada	610	6 years	2 pregnancies: both diagnosed before confirmation test
Veersema, 2011[57]	Nether-lands	1145	2 years	4/1037 (0.4%): 2 due to device expulsions, 1 due to placement failure, 1 due to perforation
Wittmer, 2006[58]	U.S.	52	10-26 months	0/52

*NR=Not reported.

MDR Reports on Unintended Pregnancy

Since the Essure System was approved in 2002 through June 1, 2015, FDA has received 337 MDR reports related to unintended patient pregnancy associated with Essure use. This includes 21 reports which cite more than one pregnancy in a given patient post-Essure placement and 69 involving ectopic pregnancy.

Of the 127 MDRs which cited a pregnancy and provided a fetal outcome, 76 reported a live birth, 32 reported a miscarriage, and 19 reported electively terminating the pregnancy.

Essure Physician Labeling Related to Pregnancy

The following information regarding pregnancy is provided in the Essure Physician Labeling (Appendix B).

Warnings

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place. Some of these pregnancies were due to patient non-compliance, which included failure to:*

    - *Use alternate contraception during the 3-month "waiting period" prior to Essure Confirmation Test (modified HSG);*
    - *Return for the Essure Confirmation Test (modified HSG) to determine if the inserts are in the correct location and tubal occlusion is present; and*
    - *Use alternate contraception or undergo sterilization by another method if the Essure Confirmation Test (modified HSG) reveals tubal patency. In this case, the clinician should inform the patient of the Essure Confirmation Test (modified HSG) finding and counsel her not to rely on the Essure System for contraception.*

  Therefore, it is critical that clinicians properly counsel patients regarding the risk of pregnancy (including ectopic pregnancy) attributable to non-compliance during all stages of the Essure procedure.

Clinical Trial Results

Effectiveness Results as of December 2007

CUMULATIVE FAILURE RATES Phase II and Pivotal Trials Combined				
One-Year[C]	**Two-Year**[C]	**Three-Year**[C]	**Four-Year**[C]	**Five-Year**[C]
0% **N=635** (95% CI 0 – 0.10%)[A, B]	**0%** **N=605** (95% CI 0 – 0.20%)[A, B]	**0%** **N=586** (95% CI 0 – 0.30%)[A, B]	**0%** **N=567** (95% CI 0 – 0.40%)[A, B]	**0%** **N=567** (95% CI 0 – 0.50%)[A, B]

[A] 95% confidence intervals are based on a "constant-hazard" exponential failure-time model, whose parameter is determined by the total number of woman-months accumulated during the trial.

[B] Combined effectiveness data obtained using Bayesian statistics.

[C] The number of women "N" were considered to have completed follow-up at 1 year if patient contact occurred at ≥11 months, 2 years if contact occurred at ≥23 months, 3 years if contact occurred at ≥ 35 months, 4 years if contact occurred ≥ 47 months and 5 years if contact occurred at ≥ 59 months.

No pregnancies were reported in the clinical trials. However, no method of contraception is 100% effective and pregnancies have occurred in the commercial setting.

Commercial Setting Data

In the commercial setting, unintended pregnancies have been reported in women who have worn the inserts.

[The table below] summarizes the reasons for pregnancy from reports received by Bayer HealthCare LLC and additional reports from the published scientific literature.

Potential Contributing Factor	United States		Outside the United States**		Total	
	n	% of US causes	n	% of OUS causes	n	%
Patient Non-compliance (e.g., failure to use alternate contraception or return for **Essure** Confirmation Test)	213	32%	16	18%	229	31%
Perforation*** / #	91	14%	4	5%	95	13%
Unsatisfactory Placement***	32	5%	13	15%	45	6%
Physician Non-compliance	22	3%	13	15%	35	5%
Pregnant at time of Placement (Luteal)	26	4%	6	7%	32	4%
Inadequate Confirmation Test***	28	4%	0	0%	28	4%
Expulsion***	20	3%	4	5%	24	3%
Tubal Patency***	19	3%	1	1%	20	3%
Insufficient Information to determine	209	32%	31	35%	240	32%
Total	660		88		748****	

*Table includes pregnancy reports received directly by Bayer HealthCare LLC, recorded in the FDA MAUDE database and reported in the scientific literature; data reported to FDA in PMA Annual Reports. Pregnancies in **Essure** patients may be underreported.

Outside of the United States, the **Essure Confirmation Test may be an x-ray or transvaginal ultrasound; device location alone, not occlusion, is primarily used to determine whether the patient may rely on **Essure**. Use of an x-ray or transvaginal ultrasound in the United States is not in accordance with approved labeling.

*** Most of these pregnancies are due to misinterpreted **Essure** Confirmation Tests. Please note that many misinterpretations are due to the fact that occlusion is seen on the HSG films even though the insert is not properly located.

****Number of pregnancies reported from worldwide commercial launch in 2001 through end of 2010. 497,306 **Essure** kits sold during this time. Note that an accurate pregnancy rate is difficult to obtain as the number of devices actually implanted is not known.

#The causal association cannot be established between the perforation and the pregnancy. However, perforations have been identified in pregnant women who were relying on **Essure** for contraception.

The majority of unintended pregnancies are preventable. Most unintended pregnancies are related to patient non-compliance and physician misinterpretation of the Essure Confirmation

Test. In order to ensure maximum contraceptive effectiveness by Essure, the physician should ensure that the patient is properly counseled in accordance with Section XI. It is also important to evaluate both insert location and occlusion carefully before telling the patient that she may rely on Essure for contraception.

Essure Patient Labeling Related to Pregnancy

The following information regarding pregnancy rates is provided in the Essure Patient Labeling (Appendix C).

- *The Essure procedure is 99.83% effective, based on five-year clinical study data.*
- *No birth control method is 100% effective. There is a chance that you can become pregnant after completing the Essure procedure. In the original premarketing studies for Essure, no pregnancies were reported for women who had Essure inserts for up to 5 years. Although successful pregnancies have been reported with Essure devices, if you do become pregnant after Essure, the risks to you, the fetus, the pregnancy and childbirth are unknown.*
- *The risks to you and your fetus if you get pregnant after the Essure procedure are not known*

B. Patient Satisfaction

In the Pivotal study, at all study visits after the 1-week phone visit, 99% of women rated their comfort with wearing Essure as "good" to "excellent" and > 97% rated their overall satisfaction as somewhat to very satisfied (including women not able to rely on Essure).

Literature

In FDA's review of the current published literature, 8 articles reported rates of patient satisfaction after the procedure by asking patients to rate their level of satisfaction with Essure, or state whether they would recommend Essure to a friend or relative (see Table 14).[27,30,37,41,43,59,60,61] All articles reported satisfaction rates of 93% or higher. Five articles measured satisfaction at the time of the three month confirmation test.[30,41,43,60,61] The other three articles measured satisfaction at up to one year,[59] five years,[27] and eight years[37] of follow-up.

Table 14. Patient satisfaction

Article	N	Time of F/U	Satisfaction Rating Scale	Satisfaction Rate
Grosdemouge, 2009[41]	1061	3 mos	Scale: 1 (dissatisfied) to 5 (very satisfied)	93% satisfied or very satisfied
Legendre, 2011[30]	311	3 mos	Very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied	95% very satisfied
Ploteau, 2009[60]	168	3 mos	Very satisfied, satisfied, somewhat satisfied, or not satisfied	93% (145/156) satisfied or very satisfied
Rajecki, 2014[43]	120	3 mos	Scale: 1 (very dissatisfied) to 5 (very satisfied)	96% satisfied
Rufenacht, 2015[61]	143	3-16 mos	• Satisfied (yes/no) • Whether they would recommend the procedure to a friend	• 89.2% (107/120) satisfied • 95.8% (115/119) would recommend to friend
Sakinci, 2015[37]	32	3 mos 8 yrs	• To what extent they were satisfied • If they recommend the method to anybody else	• At 3 months: 100% (30/30) happy with procedure, would recommend to friend • At 8 years: 100% (26/26) happy with result of procedure, would recommend to friend*
Levie, 2010[59]	209	1-12 mos	• Rate satisfaction on a scale from 1-5, with 1 being “not satisfied” and 5 being “very satisfied” • Whether they would have the procedure done again • Whether they would recommend the procedure to a friend	• Average satisfaction score: 4.7 (SD 0.71) • 93% (164/176) would do procedure again • 98% (173/176) would recommend to friend
Chudnoff, 2015[27]	518	5 yrs	Very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied	98% (376/384) somewhat or very satisfied

*One patient who became pregnant after the three month confirmation test was excluded from eight year follow-up.

VII. Post-Market Safety Outcomes (Non-PAS)

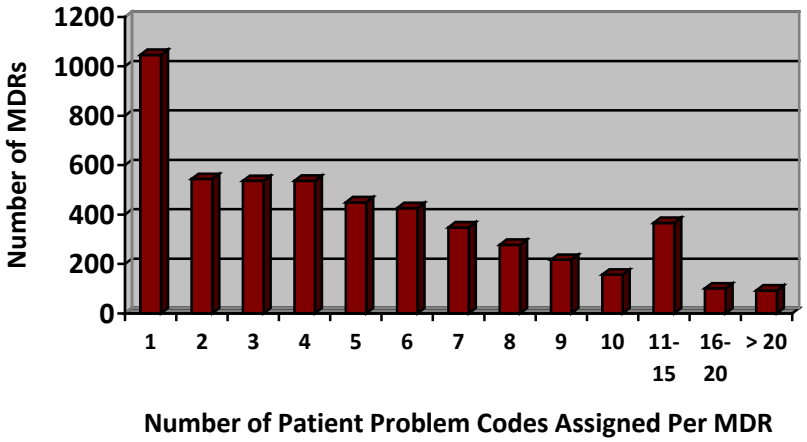
As indicated previously, FDA has noted a significant rise in the number of adverse event reports submitted in the past 1-2 years, in particular from women who had been implanted with the device. There have been different types of events or symptoms reported in those MDRs and Table 15 below provides a summary of many of those, listed by body system or symptom complex.

Table 15. Symptoms Reported in Essure MDRs

GYNECOLOGICAL			
• Menorrhagia • Menstrual irregularities • Amenorrhea • Constant spotting • Metorrhagia • Polymenorrhea • Dysmenorrhea • Hot flashes • Premenstrual Dysphoric Disorder • Loss of libido	• Pelvic pain • Cramping • Abdominal spasms • Dyspareunia • Breast tenderness • Breast engorgement	• Pregnancy • Miscarriage • Early menopause • Endometriosis • Adenomyosis • PCOS • PID • Adhesions	• Ovarian cysts • Uterine cysts • Uterine fibroids • Fallopian tube cysts • Uterine infection • Bacterial vaginosis • Yeast infections • Vaginal discharge • Urinary tract infections • Cervical dysplasia
GENERAL	**PAIN**	**NEUROLOGICAL**	**GASTROINTESTINAL**
• Fatigue • Weight gain or loss • Edema/swelling • Excessive sweating • Fevers • Night sweats • Insomnia • General aches/pains • Vitamin D deficiency • B12 deficiency • Dental caries, chipping • Changes in vision • Changes in hearing	• Abdominal pain • Pelvic pain • Low back pain* • Leg pain • Joint pain	• Headache/Migraine • Dizziness • Vertigo • Paresthesia • Weakness • Tremors • Cognitive (“fog”) • Memory loss • Seizures • Stroke symptoms • Syncope • Myasthenia gravis • Multiple sclerosis	• Nausea • Vomiting • Diarrhea • Constipation • Metallic taste in mouth • Heartburn • Metallic taste • Abdominal pain • Abdominal cramping • Gallstones • Pancreatitis
RENAL/URINAY	**DERMATOLOGICAL**	**MUSCULOSKELETAL**	**PSYCHIATRIC**
• Polyuria • Incontinence • Hematuria • Kidney stones • UTIs	• Rash, hives • Alopecia • Pruritis • Easy bruising • Dry skin • Acne	• Back pain • Joint pain • Tendonitis • Muscle spasms • Rheumatoid arthritis	• Mood changes • Depression • Anxiety • Panic attacks • Mood swings • Irritability
HEMATOLOGICAL	**IMMUNOLOGICAL**	**CARDIOVASCULR**	**RESPIRATORY**
• Anemia (IDA) • Blood clots, emboli • ITP	• Food, chemical, metal sensitivities • Difficulty fighting infections • Frequent infections	• Palpitations • Chest pain	• Sleep apnea • Pulmonary embolism
ENDOCRINE	**AUTOIMMUNE**		
• Hypoglycemia • Thyroid disease • Adrenal problems • Degenerative bone disease	• SLE • Rheumatoid arthritis • Fibromyalgia • Raynaud’s • Myasthenia gravis		

The majority of MDRs received by FDA (particularly since late 2013) each contain multiple, concurrent symptoms believed to be associated with, or a consequence of, having the Essure device implanted. Figure 6 below depicts the number of Patent Problem Codes (PPC) contained within a given MDR. As can be seen, many listed more than 10, and some, more than 20.

Figure 6. Number of Patient Problem Codes per MDR Report



FDA sought to focus our review on available data related to specific adverse events which have been more commonly discussed or reported in the patient community and in our MDR database including

- Pain and cramping (abdominal, pelvic) – with a focus on chronic/persistent pain
- Abnormal bleeding or menstrual irregularities
- Headache
- Metal allergy/sensitivity.

A. Post- Procedural Pain (Chronic/Persistent Pain)

Pain is a well-known and commonly reported complaint *during* the Essure insertion procedure and recovery period. In the Pivotal study, almost 30% of women reported cramping during the recovery period, and 13% reported pain. However, the pain/discomfort experienced during the procedure typically resolves within hours or days. Kerin, reporting data from the Phase II trial[52], noted that of those patients who did experience procedural or peri-procedural pain, 59% had the pain resolve within 1 day, 88% within 3 days, and 99% within 1 week. Two patients had pain last longer than 1 week – but both resolved within 2 weeks. In Arjona's prospective study of over 1600 women at one Spanish site, 7% of patients needed oral analgesics for 1-2 days after the procedure.[28] Mino, reporting on a population of 857 patients from the same institution, noted that of the fewer than 10% of patients who took oral analgesics following the procedure, 43% took the drugs on the day of the procedure alone, 30% for 2 days, 13% for 3 days, and 12% for 4 or more days. This latter group accounted for only 1% of the overall population. [62]

Abdominal and pelvic pain are common symptoms, and both acute and chronic pain may arise from multiple sources, including organs of the digestive, genitourinary reproductive, musculoskeletal, and nervous systems. As such, in many cases, it may be challenging to definitively link persistent or new abdominal or pelvic pain to the Essure System. However, several potential Essure device-related causes of post-procedural pain have been suggested, including, but not limited to:

- Malpositioned device within the fallopian tube, including subserosal placement or a kinked insert
- Uterine or fallopian tube perforation (discussed below)
- Migration with intra-abdominal or pelvic organ damage (see below)
- Infection
- Tubal pressure from > 1 insert within a tube (not consistent with device labeling)
- Nickel allergy with or without local inflammation
- Concurrent procedure (e.g., endometrial ablation, not consistent with device labeling).

It should be emphasized that the presence of any of the above does not necessarily mean the device recipient will have/develop pain, and likewise, pain may develop in the absence of any of these.

ESSTVU Study Safety Data Related to Pain

In the most recent annual report for the ESSTVU study (including data current to June 2015), pelvic pain was recorded in 4.7% of subjects and abdominal pain in 2.7%. In addition, dysmenorrhea was noted in 2.5% of subjects, and dyspareunia in 0.7%. These rates do not include procedural pain, but do include events that occurred any time during the first year after the procedure.

Literature Related to Persistent Pain

In 2013, Al-Safi, et al., reported that there were 217 reports of Essure-related pain within the MDR database from 2002-2012. The onset of the pain ranged from immediately after placement to years after the procedure, and in 54 cases, perforation was discovered during subsequent imaging or surgery.[63] However, post-procedural pain has not been a common outcome reported in the literature. In the current review, there were several articles that specifically looked at the occurrence of Essure-related chronic pain after the three month confirmation test (i.e., not intraoperative or postoperative pain). Conover, et al., used claims data from a large cohort of U.S. women with employer-provided health insurance plans who received hysteroscopic sterilization with either Essure or Adiana devices (no longer available in the U.S. market), and reported that 236 of 26,927 women (0.88%) experienced opioid-managed pelvic pain at a mean follow-up time of 275 days. This rate was comparable to a similar cohort of women who underwent laparoscopic sterilization, of which, 420/44,948, or 0.93% experienced pelvic pain with a mean of 283 days of follow-up (between-group differences were not statistically significant, OR= 0.97 (0.83;1.14)). The authors defined the pelvic pain outcome with the following criteria: (1) at least two diagnoses relating to pelvic pain, including dysmenorrhea, abdominal pain, or symptoms associated with female genital organs, and (2) at least two opioid

prescriptions filled on separate days. This study excluded women who experienced childbirth within six months of sterilization, underwent concurrent endometrial ablation, or had a history of opioid use or pelvic pain.[17] Results were not stratified by type of device (Essure vs. Adiana).

A retrospective cohort study using data on 458 subjects with successful bilateral Essure placement at a U.S. university medical center recently reported a higher rate of chronic pain (4.2%), defined as pain lasting >3 months after insertion. Of those with chronic pain, 75% reported pain within 130 days of the procedure, and 91% had appropriate tubal occlusion confirmed with HSG. The authors reported that those with a previous diagnosis of any chronic pain before the Essure procedure (chronic pelvic pain, chronic low back pain, chronic headache, and fibromyalgia) were six times more likely to report chronic pain after Essure (OR=6.15, 95% CI: 2.09-18.05). The authors did not identify causes of pain (such as perforation) for each individual, but suggested that a causal relationship between Essure and chronic pain was likely in these patients due to the temporal relationship of procedure and pain onset, and suggested that HSG may not enable discernment of small perforations or malpositioning that may cause pain.[64]

Arjona-Berral reviewed the medical records of 4,274 women who received Essure in a hospital in Spain and published findings in 2014. Seven women (0.16%) returned to the hospital seeking device removal for "chronic pelvic pain" which started either immediately or one week post-op, increased with time, and was not responsive to standard analgesic drugs. At the time of the procedure, the surgeon reported satisfactory placement in six patients and unsatisfactory placement in one. The procedure was rated as difficult by the surgeon in three cases although subsequent HSG demonstrated correct placement. The other four patients received an x-ray confirmation test (results not given). The Essure devices were removed either hysteroscopically or laparoscopically in all seven patients, with time between procedure and removal between 4-57 months. All seven patients reported immediate resolution of pelvic pain after removal.[65] This publication did not specifically comment on whether additional patients experienced chronic pain but were responsive to pain medications and/or did not seek device removal. In addition, the rate of women experiencing pelvic pain in this study may have been an underestimate as it relied on the patient's self-report of pain to the hospital and its peripheral centers. Another publication from this same Spanish facility two years earlier noted one patient out of 4,306 implanted over a 7-year period who experienced "persistent abdominal pain" (0.02%). However, this patient's symptoms did not resolve with administration of NSAIDs or after device removal.[36]

Additionally, Sakinci, et al., recently reported that at five years follow-up of 30 patients, no patients reported persistent pelvic pain, and 2 patients reported a slight groin pain from time to time that they were unsure was related to the device.[37]

Earlier, in 2007, Sinha published on a prospective cohort of 122 women who received the Essure device at a single site in the UK.[66] Postal questionnaires were sent to 84 women who had completed 3 months of follow-up. Of the 76 patients who responded, 5 (6%) reported "new pain or discomfort since the procedure" and two (3%) described "new pain or discomfort with sexual intercourse." In 2005, Duffy reported a cohort controlled comparative study which included 48 women with successful bilateral Essure placement and 24 women undergoing laparoscopic sterilization.[29] Of the 35 women in the Essure group providing data at 3 months follow-up, 4 (11.4%) reported abdominal or pelvic pain. However, information regarding the timing of the events and whether any represented persistent/chronic pain was not specified.

Case Reports/Series Related to Persistent Pain

Several published case reports describe patients with persistent pain following Essure placement – even if it was not the primary reason for publishing the report. In many of these reports, the onset of pain was at the time of the procedure, but some reports noted a period where the patient was asymptomatic for weeks or even months before it started[67,68,69,70] Duration of symptoms was variable although some note pain that persisted for months and even years before either presenting for evaluation or having symptomatic relief. [69,71,72,73,74,75,76] The abdominal or pelvic pain may have been unilateral or bilateral, constant or intermittent, and, in cases, unresponsive to traditional analgesics.[36, 65, 67, 73, 75,77]

Difficult or improper placement and perforation were noted in some cases[78,79, 70, 75,76, 81] while in others, the authors specifically noted correct insert placement with no procedural difficulties and no evidence of malpositioning or perforation.[65 67, 77, 80, 72 73, 79, 74 75,81]

Multiple case reports note that the patients underwent removal of their inserts as a treatment for pain presumed to be secondary to the device. Several describe hysteroscopic removal as far out as 55 months from placement.[65, 67, 79, 74] Others describe laparoscopic removal via salpingectomy or salpingotomy[65, 77, 71, 82, 72, 73, 83, 84] or hysterectomy/oophorectomy[71, 75] – up to 4 or more years after insert or start of pain. Many of the case reports which described insert removal for pain noted resolution of symptoms following the procedure.[36,67,77,71,72,73,74,76,85,83,84] When time to resolution was provided it ranged from "immediately" to several weeks. However, other cases noted only partial resolution of pain symptoms[84], unchanged symptoms[36,65,71] or even worsening of pain following removal.[71]

MDR Reports Related to Pain

The majority of MDRs received by FDA note the presence of abdominal or pelvic pain and/or cramping. The numbers of reports coded with each of these pain-related Patient Problem Codes (PPC) are shown below in Table 16. Some reports were coded with multiple pain-related PPCs. There were a total of 3,516 reports which were coded with at least one of these PPCs indicative of pain. Over 69% (3516/5093) of the reports mention pain or cramping of some sort.

Table 16. MDRs Coded with Pain/Cramps*

PPC	Number of MDRs
Pain	2907
Pain, abdominal	1012
Cramps	529
Abdominal cramps	491

*Each MDR report may contain more than 1 patient problem code.

There was variability in the type and amount of information provided in the MDR reports regarding the symptom of pain including specific information related to the timing of the onset of pain relative to the placement procedure, location of the pain within the abdominal/pelvic region, the intensity and quality of pain, the consistency of the pain (continuous versus cyclical/intermittent), and the duration of pain (including some beyond 8 years). Although it is not possible to determine which were primarily or solely done for persistent pain, 452 total MDRs for Essure described women having their devices removed. As will be discussed in a later section (Section IX), women who underwent device removal *and* provided information related to symptom outcome generally reported improvement or resolution to their symptoms (176/196, or 90%).

Essure Physician Labeling Related to Pain

Warnings

- *Some Essure patients have reported pelvic pain that may be device related. If device removal is indicated, this will require surgery.*

Precautions

- *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up patient for possible perforation.*

Other Statements/Study Results

- *Table (Pivotal Trial Adverse Events by Body Systems, First Year of Reliance (N=476 patients implanted with at least one insert))* – NOTE: Table modified to include only pain events

Adverse Events by Body System	Number	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Musculo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Dyspareunia	17	3.6%
Pain/discomfort - uncharacterized:	14	2.9%

Essure Patient Labeling Related to Pain

- *You may experience mild to moderate pain and/or cramping, vaginal bleeding, and pelvic or back discomfort for a few days after the procedure.*
- *There are reports of chronic pelvic pain in women, possibly related to Essure*

Summary for Persistent/Chronic Pain

Reports of various types of pelvic pain ranged from < 1% to 7% throughout the follow up of the Pivotal study. However, persistent pelvic pain was reported in only 1 case at one and two year

follow up appointments. When reviewing data from these studies, it is important to recognize that patients with chronic pain syndromes were excluded from enrollment, and a recent retrospective study suggested that patients with such conditions are at significantly higher risk for post-procedural chronic pain.[64] In addition, lack of a control group may make the assessment of causality or association difficult for such a common symptom. There is a paucity of clinical studies within the peer reviewed literature regarding persistent or chronic abdominal/pelvic pain following Essure placement. Several of these have reported rates of < 1%, although these were largely based on retrospective data collection/review. One recent retrospective single-site study, however did report a rate of chronic pain of 4.2%.[64] Limited data were often available in these studies regarding the onset of pain, pain characteristics, and associated findings or causes (e.g., presence of perforation). Interpreting chronic or persistent pain in the literature is made more difficult by the lack of consistent terminology and what is included in the case definition of pain. Multiple case reports in the literature and MDRs submitted to FDA cite pain – and when the information was provided, the pain often resolved with device removal. However, information from case reports and MDRs cannot be used to calculate rates of the event, and considering the large volume of device use, it is not possible to assess whether the number of individual reports noted fall within the range which might be expected based on data from the prospective IDE studies.

B. Changes in Vaginal Bleeding, Menstrual Patterns or Characteristics

Many of the voluntary MDRs which have been received by FDA for the Essure System note changes related to vaginal/uterine bleeding and/or menstrual symptoms. In the Pivotal study, irregular menses were reported at rates ranging from 4-12% throughout the 5 year follow up period after subjects had discontinued alternative contraception. However, persistent menstrual irregularity rates were significantly lower, ranging from 0-3%, with the higher rates of persistent changes reported as "less than usual flow."

ESSTVU Study Safety Data Related to Bleeding and Menstrual Changes

Table 17 below lists the rates of various vaginal bleeding and/or menstrual symptoms (per MedDRA coding) reported in the most recent annual report from the ESSTVU study (including data current to June 2015).

Table 17. Menstrual Symptoms from ESSTVU Study

Event	Rate
Menorrhagia	3.9%
Dysmenorrhea	2.5%
Vaginal hemorrhage	2.3%
Uterine hemorrhage	1.5%
Metrorrhagia	0.8%
Dyspareunia	0.7%
Menstrual irregularity	0.5%
Amenorrhea	0.5%
Dysfunctional uterine bleeding	0.3%

The most commonly reported of these events has been menorrhagia with heavy and/or prolonged menstrual bleeding. A total of 23 women (3.9%) reported this in the study report.

Literature Related to Bleeding and Menstrual Changes

Two recent articles reported information about menstrual irregularities. In one clinical trial published in 2015 (published results of the 5-year Pivotal IDE cohort), one subject reported lower abdominal pain and very heavy periods at her 18- and 24-month follow-up visits; she ultimately underwent hysterectomy at 34 months. Another subject in that trial experienced irregular menstrual bleeding, which resolved following dilation and curettage. Overall, 29/473 patients (6.1%) reported dysmenorrhea at one or more follow-up visits. At the five year follow-up visit, 12% of subjects reported irregular menses, 8% reported intermenstrual bleeding between menses, 20% reported heavier than usual menstrual flow, and 11% reported lighter than usual menstrual flow.[27] Fifteen women underwent hysterectomy as of the five-year visit – with bleeding being a reason in seven of those cases, and dysmenorrhea in two. As noted previously, this study suffered from a high rate of loss to follow-up, which could result in biased rates. In a Turkish study, also reported in 2015, 4/30 (13.3%) patients reported an increase in menstrual bleeding, while 5/30 (16.7%) patients reported a decrease at eight year follow-up.[37]

In 2009, Andersson reported a retrospective review of 61 women implanted with Essure at one Swedish site, 58 of whom had successful bilateral insert placement.[47] Fifty (50) women responded to an outcomes questionnaire with a mean follow-up of 23 months (range, 7-67). Heavier periods were reported in 9 women although none sought medical attention. Eight patients reported lighter periods. In 2007, Kerin published a multi-center retrospective review of a subset of women undergoing repeat hysteroscopy 4-43 months following Essure placement. Of 545 women who had undergone the procedure at the facilities, 20 required a diagnostic second-look due to abnormal and/or heavy bleeding. However, it is unknown how many other women experienced abnormal bleeding but did not undergo a second look.[86] Also in 2007, Sinha reported on outcomes for 76 of 84 Essure patients who responded to a 3-month questionnaire, noting that 26% had persistent changes in menstrual pattern including heavier-than-normal menses in 18%, amenorrhea in 4%, irregular bleeding in 3% and intermenstrual bleeding in 1%.[66]

Mino, however, reported no changes in volume or pattern of menstruation in a survey of 857 women after 3 months.[62]

Case Report/Series Related to Bleeding and Menstrual Changes

In 2013, Levie presented an abstract report describing 193 women who had undergone Essure placement and 139 who had surgical BTL between 2004 and 2011 at a single U.S. center.[87] Irregular cycles were experienced by 30% of Essure patients and 28% of BTL patients, and menorrhagia was reported in 36% and 46% respectively.

MDR Reports Related to Bleeding and Menstrual Changes

Irregularities in vaginal bleeding, menstrual patterns or symptoms were noted in the MDR reports. Many reports were coded with multiple menstrual-related PPCs which resulted in a total of 1,580 reports which were coded with at least one of these PPCs. Table 18 lists the more commonly reported PPCs related to this topic.

Table 18 MDRs Coded with Menstrual Signs/Symptoms*

PPC	Number of MDRs
Heavier menses	867
Menstrual irregularities	807
Hot flashes	187
Intermenstrual bleeding	182

*Each MDR report may contain more than 1 patient problem code.

When described in the MDRs, changes in vaginal bleeding patterns after Essure placement included prolonged, frequent, and/or heavy menstrual bleeding when compared to prior experiences, irregular bleeding, intermenstrual bleeding or spotting, bleeding that was less frequent and/or less severe than in the past, as well as amenorrhea. However, as seen in Table 18 above, over half of the reports noted heavier menses.

Essure Physician Labeling Related to Bleeding and Menstrual Changes

Observed Adverse Events from Pivotal Trial

Pivotal Trial
Adverse Events by Body Systems, First Year of Reliance*
(N=476 patients implanted with at least one insert)

Adverse Events by Body System	Number	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Gas/bloating	6	1.3%
Musculo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Nervous/Psychiatric:		
Headache	12	2.5%
Premenstrual Syndrome	4	0.8%
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Persistent increase in menstrual flow	9**	1.9%
Vaginal discharge/vaginal infection	7	1.5%
Abnormal bleeding - timing not specified (severe)	9	1.9%
Menorrhagia/prolonged menses (severe)	5	1.1%
Dyspareunia	17	3.6%
Pain/discomfort - uncharacterized:	14	2.9%

* Only events occurring in ≥ 0.5% are reported
** Eight women reported persistent *decrease* in menstrual flow
In the Phase II trial, 12/206 (5.8%) women with at least one insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.

Essure Patient Labeling Related to Bleeding and Menstrual Changes

- *Will I still get my period after the Essure procedure? Yes, you will still have a period. Some women find that their period may become slightly lighter or heavier after the procedure. These changes are often temporary. They may also be due to you stopping your previous hormonal birth control, rather than the Essure procedure.*

Summary for Vaginal Bleeding and Changes in Menstrual Patterns

General menstrual irregularities were reported at rates ranging from 4-12% throughout the 5 year follow up period of the Phase II and Pivotal trials after subjects had discontinued alternative contraception. Heavier than usual menstrual flow was more commonly reported at 16-22%; however, less than usual menstrual flow was reported at rates ranging from 10-15%. Irregularities that were *persistent* occurred at rates ranging from 0-3%. Few peer-reviewed publications have addressed the issue of changes in bleeding patterns following Essure placement although longer term follow-up from the Pivotal study reported higher rates for several pattern changes (e.g., up to 20% reporting heavier menses).[27] Several case reports and abstracts – largely single center experiences – have also reported these higher rates. However, these have included higher rates of both increased/heavier menses (some over 30%) as well as *lighter* menses or even amenorrhea (close to 20%). Numerous MDRs describe bleeding irregularities, ranging from heavy, prolonged, frequent bleeding to amenorrhea. Again, rates of these events cannot be determined by the numbers of case reports and MDRs. In addition, much of the data related to Essure and menstrual changes do not provide information related to prior menstrual history and do not take oral contraceptive use, or its discontinuation, in to account. Furthermore, most studies lacked a control group to account for natural progression of symptoms as the woman ages. These limitations may make it more challenging to ascribe the changes to the device.

C. Headache

FDA evaluated current data related to post-procedural headaches as this symptom was one of the more commonly reported events in MDRs. In the initial pre-market data, headaches which were deemed at least possibly related to the device or procedure were reported in up to 2.5% of subjects whereas those that were rated as unlikely or not related were reported in up to 19% Headaches were reported in 4.9% of women in the 5-year follow up of the Phase II study and 18.9% of patients through 5 year of follow-up in the Pivotal trial. However, it is not clear whether the latter rate represents all headaches, or only those which were deemed by the investigator to be possibly related to the device or procedure.

ESSTVU Study Related to Headaches

In the most recent annual report for the ESSTVU study, the rate of reported headache was consistent with that seen in the original PMA cohort; traditional headache was reported in 0.7% of subjects, migraine headache in 0.5% and premenstrual headache in 0.3%.

Literature Related to Headaches

FDA has been unable to locate any significant scientific literature which specifically evaluated headaches following Essure treatment. Yunker's 2014 publication evaluating risk factors for chronic pain in Essure patients found that women with previous diagnoses of chronic pain syndromes, including headaches, were at increased risk for chronic pain post-Essure.[64] However, this study did not report on the occurrence or rates of headaches or migraines post-operatively. In Duffy's 2005 publication, one subject out of 48 who had bilateral Essure placement reported a headache.[28] This was documented at the 1-week follow-up visit.

Case Reports/Series Related to Headaches

In 2010, Hurskainen submitted an abstract describing a retrospective cohort from one Finnish hospital which evaluated 103 patients who had undergone Essure placement, and 104 who had undergone surgical BTL with Filshie Clips.[88] Patients were assessed via questionnaires and review of medical records. The patients receiving Essure had a lower rate of post-operative headaches ($p=0.05$) through the first week, although exact values were not provided.

MDRs Related to Headaches

Approximately 1400 MDRs received list the presence of headache (including migraine headaches) as a symptom following Essure placement. However, as headaches were often one of several symptoms noted in a given report, additional details regarding the headache were limited. The frequency of headaches varied considerably – from constant/every day to monthly or just occasionally. Reports did not usually provide significant information related to prior headache history, or information regarding evaluation and treatment specific to the headache, although a handful of reports did note improvement in headache symptoms after device removal.

Summary for Headaches

Headache has been noted in a significant proportion of voluntary MDR reports submitted to FDA, although limited details were available. No significant data are available from the published literature regarding the rates of post-procedure headaches, and data from the prospective IDE studies have shown rates that varied considerably. Because these prospective studies did not have a control group, and because headaches are common, it is difficult to assess causality.

D. Nickel Allergy/Hypersensitivity

Although allergic reactions were not specifically identified in the Pivotal and Phase II studies, many of the MDRs which have been received by FDA related to the Essure product claim an allergy to the nickel in the device and/or a general allergic-type of reaction following placement.

It is estimated that about 10 to 25% of all women in the United States have a general nickel allergy.[89] The most common manifestation is a contact dermatitis which appears in a previously sensitized patient after future cutaneous contact as a result of a Type IV delayed hypersensitivity process. However, symptoms are also possible in a sensitized individual following exposure

through other routes, including intravenous and oral ("systemic contact dermatitis").[90,91] In addition, some authors have suggested that non-dermatological allergic symptoms may be associated with nickel hypersensitivity, including chest pain, migraine headache, palpitations, edema, respiratory issues, and digestive symptoms.[92,93]

Nitinol, a combination of nickel and titanium, is present in the Essure System and is a common alloy used in medical implants, including intravascular cardiac devices (IVC filters, septal occluders, etc). Nitinol tends to have low levels of nickel leaching - approximately 0.14 µg/day in Essure – possibly because of the formation of a titanium oxide coating.[89]

The results of *in vitro* nickel release testing conducted on Essure devices can be compared with nickel release information of other nitinol devices. Nickel release is expected to be highest initially, and then to taper off over time. Data presented at a 2012 FDA Public Workshop entitled "Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching" [94,95] are summarized in Table 19. The peak rates in the table reflect release rates on the first day; the chronic rates reflect rates measured up to 60 days; the totals reflect the total amount released in 60 days. These data demonstrate that the release of nickel from two Essure inserts is comparable to or lower than the release from selected cardiovascular nitinol devices.

Table 19. Nickel release from Essure compared to other selected implant devices.

	Peak rate (µg/day)	Chronic rate (µg/day)[a]	Total (µg)[a]
Selected cardiovascular implant devices	0.043-4.8	<0.015 – 1.31	0.11-110
Essure (2 inserts)	< 0.77[b]	< 0.007[c]	< 1.4

[a] Most of the testing reported at the workshop was conducted at 60 days.
[b] Based on seven day *in vitro* measurements; as a worst case, the 0.77 µg/day is based on all of the nickel in the seven day test being released in a single day.
[c] Based on longer-term *in vitro* testing, in which nickel release was not detected (for days 30-60); the worst case estimate of 0.007 µg/day in the table is based on the detection limit.

The mechanism of hypersensitivity reaction to implanted metal devices has yet to be fully elucidated. Although presumed to be the mechanism, there is insufficient evidence to confirm a delayed Type IV reaction.[93] As such, there is currently no proven method to prospectively identify individuals who will develop adverse events to their implant.[96] A correlation between serum nickel levels and allergy has not been demonstrated and self-reporting of nickel allergy is unreliable.[93,89] Although patch testing is standard for identifying Type IV delayed hypersensitivity in the skin to external allergens, it is unknown whether it can reliably identify sensitivity to *internal* materials, or can predict/identify peri-implant or systemic reaction to nickel.[89, 96,97] Because of the relatively high prevalence of nickel allergy (in women particularly), as well as nickel's common presence in consumer products, the results of a positive patch test can not necessarily attribute causation to the presence of an implanted device and do not necessarily correlate with a clinically significant reaction.[90,98] Likewise, a negative result does not preclude the development of a complication.[98] An alternative to patch testing is the

lymphocyte transformation test (LTT) which measures the proliferation of peripheral blood lymphocytes in the presence and absence of given allergens. However it is rather expensive, complex, and has limited availability. Several authors have instead proposed a clinical set of "criteria" for assessing a potential allergic reaction to a metal implant.[97,98] These have focused on dermatological symptoms or findings and include a dermatologic eruption on the skin overlying the metal implant (weeks to months after placement) with the absence of other contact allergens or systemic cause, a positive skin patch test, and recovery following removal of the implant.

ESSTVU Study Safety Data Related to Allergic/Hypersensitivity Reactions

In the most recent annual report from the ESSTVU study, only 1 subject (0.2%) was reported to have an "allergy to metal." This was rated as a mild event, and no treatment was rendered. In addition, one patient (0.2%) was diagnosed with dermatitis and two (0.3%) with a rash – all of which were rated as mild and resolved with medical therapy.

Literature Related to Allergic/Hypersensitivity Reactions

Zurawin & Zurawin performed an analysis of the MAUDE database for the years 2001-2010 as well as data published from the Phase II and Pivotal clinical trials. During this period, 436,927 Essure kits were sold, and sixty-three reports of nickel hypersensitivity were identified. The authors used these numbers to suggest a rate of 0.014%. Thirteen of twenty patients who underwent patch testing tested positive for nickel allergy; these patients reported symptoms including rash, hives, pain, nausea, swelling, increased symptoms of asthma, and arthritis. Device removal performed in 9/13 positive patch test patients resulted in resolution of symptoms for four patients, no resolution of symptoms for two patients (one case of pelvic pain two years post-procedure that was judged to be unrelated to Essure and one case of rash and hives four years post-procedure that was judged to be unrelated to Essure), symptom resolution that occurred before device removal for one patient, and unknown resolution for two patients lost to follow-up. In 3/13 positive patch test patients who did not undergo device removal, symptom resolution was achieved by oral medication in two patients with rash and skin reaction, and the third patient had confirmed nickel allergy but no symptoms. Of the seven negative patch test patients, two with post-procedure total body itching underwent device removal and reported symptom resolution. Overall, in this sample of twenty women with potential nickel-related reactions, not all symptomatic women were patch-test positive, not all patch-test positive women were symptomatic, and most adverse events were not judged by the physician to be device-related. The authors concluded that despite the likelihood of underreporting, the incidence of nickel-related reactions is very low, lower than the proportion of women with contact nickel allergy in the population, and suggested that the relationship between Essure devices and nickel-related reactions is not a clinically relevant consideration for placement of nitinol-containing micro-inserts.[89]

Al-Safi's review of the MDR database alone, published in 2013[63] found 20 reports of what was considered an allergic or hypersensitivity reaction (including such symptoms as itching, nausea and abdominal pain). The disparity in numbers compared to Zurawin's review may be the result of the use of different sources to identify the cases, but also may be reflective of a difference in the definition of an allergic or hypersensitivity reaction.

During our review of the literature, cases of nickel allergy were noted in two large cohort studies conducted in Spain. The first article reported two cases of nickel allergy out of 4,306 patients. The first case was a woman with history of atopy who presented shortly after the procedure with papular urticarial and erythema; symptoms disappeared after device removal. The second case was a woman with history of persistent general pruritis, who was referred one year post-procedure; she underwent device removal as well (information about symptom resolution not reported).[36] The second article reported one case of nickel allergy out of 517 patients. The patient experienced eczematous skin lesions and underwent hysterectomy with salpingectomy; this patient was then lost to follow-up.[34]

A systematic review by Adelman, et al., reviewed these articles among others and concluded that severe nickel allergy requiring Essure removal is rare, and universal patch testing before placement is not cost-effective and not recommended, except possibly in women in whom nickel allergy is suspected preoperatively.**Error! Bookmark not defined.**

Case Reports/Series Related to Allergic/Hypersensitivity Reactions

In addition to the studies and cases noted above, several individual case reports have cited suspected nickel reaction in patients implanted with the Essure device. In 2010, Al-Safi published a report on a 27 year-old who developed generalized pruritus and intermittent nausea 3 days following insertion. Skin patch testing was positive to nickel and symptoms resolved following hysteroscopic removal of both inserts at day 8.[99] In 2013, Bibas reported a woman who presented 3 months post-placement with a generalized rash unresponsive to steroids.[91] A patch test was positive and, within 3 days of being removed, the rash began improving. By 3 months, it had resolved. In 2014, Goldwaite reported on a patient with a prior history of metal sensitivities who developed an abdominal rash 3 days after Essure placement.[100] After an unsuccessful trial of steroids, she underwent hysteroscopic removal of the implants and her rash resolved within 36 hours. More recently, Lane reported a case involving a woman experiencing recurring rash (pelvis, neck, axilla) for 10 weeks post-placement in addition to facial edema and pruritis.[101] The patient was patch-test positive for nickel but had only a partial response to steroids. The patient underwent laparoscopic removal of the device and had resolution between 2 and 6 weeks after surgery.

Published abstracts have attempted to address the question as to whether pre-placement patch-test *negative* patients convert their patch-test status after device insertion. In one Dutch study, patch testing was done pre-operatively and 3 months after Essure placement.[102] Only 1 woman (of 97) who was negative at baseline tested positive at 3 months. In another report describing 50 women, there were no conversions from negative at baseline to positive at 3 months and no allergic symptoms were reported.[103]

For Essure recipients who were known to be patch test-*positive* prior to the procedure, one abstract reported a retrospective cohort review of patients at one Spanish site implanted 2003-2010 and noted no documented side effects among 25 such patients.[104]

MDR Reports Related to Allergic/Hypersensitivity Reactions

As noted above, the signs and symptoms which constitute an allergic reaction to an implanted medical device is ill-defined and may vary by author/reporter. This makes the determination of which MDRs reflect a real or potential allergic or hypersensitivity reaction extremely difficult. For this review of MDRs, all reports containing reference to a metal or nickel allergy or hypersensitivity (e.g., patient stating they had an allergic reaction or hypersensitivity reaction), or skin manifestations were included for evaluation – regardless of the specific symptoms the patient noted. For example, many reports described pain, headache, and/or menstrual changes as the symptoms associated with the presumed allergic reaction. With these considerations, a total of 878 MDR reports were coded as allergies/hypersensitivities.

When cited, there was variability in time to onset of symptoms (hours to weeks after insertion), duration of symptoms (weeks, months, years), and whether dermatological manifestations such as rash or pruritis were present. Limited information was provided regarding formal evaluations for the suspected nickel hypersensitivity or how the events were managed clinically and whether they responded to medical therapy. However, 212 of these MDRs describe device removal at least in part due to the presumed allergic reaction. The status of symptoms following removal was provided in 117 of these reports – and all of these noted symptom improvement or resolution. The remaining reports provided no follow-up information related to post-removal symptoms.

Of the 878 MDRs which were coded as allergy/hypersensitivity, 407 (46%) stated that the patient had a history of nickel allergy prior to device placement.

Essure Physician Labeling Related to Allergic Reactions

Warnings

- *The Essure micro-insert includes nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.*

Essure Patient Labeling Related to Allergic Reactions

- *The Essure insert is made of materials that include a nickel-titanium alloy. Once placed inside the body, small amounts of nickel are released from the inserts. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash, itching, and hives.*

Summary for Allergic/Hypersensitivity Reactions

Although cutaneous nickel allergy is known to be present in a substantial percentage of women, what constitutes an allergic or hypersensitivity reaction to a metallic medical implant and the role of patch testing in predicting or diagnosing such a reaction is not well-defined. The prospective IDE studies supporting approval of the original PMA or PMA Supplement have reported very few specific metal allergy reactions or dermatological events. Few studies in the peer-reviewed literature have addressed this symptom complex, and although they typically cited rates of < 1%, the data was obtained from retrospective reviews at single sites, or was based on MDR numbers divided by kits sold (which has significant limitations as a method to calculate or estimate event rates). A handful of case reports in the medical literature have noted individuals who developed a rash following placement (as early as 3 days), subsequent positive patch test results, and timely resolution of the rash following device removal, all of which are suggestive of a traditional hypersensitivity reaction. Little information is available in the literature related to "conversion" of patch-test status after placement, or the development of symptoms in patients known to be patch-test positive prior to placement. The MDRs received by FDA citing allergic reactions to the device, are numerous, including some noting resolution of symptoms with device removal. However, the limited information provided, and the variety of symptoms reported to represent the reaction make interpretation more difficult.

E. Perforation

Due to the technique and location of placement of the device, it is possible that the Essure insert may penetrate either partially or wholly through the wall of the uterus or fallopian tube during or after insertion. In the latter case, the device may migrate into the intraperitoneal cavity (see "Intra-Peritoneal Migration" below). Multiple factors have been suggested to increase the risk for a difficult or incorrect insert placement, which may in turn lead to perforation. These factors include the following: [78, 79,66, 105,106,107,108,109,110]

- Poor visualization or obscuring of tubal ostia by endometrium, adenomyosis, fibromas
- Tubal spasm
- Anatomic abnormalities including tubal obstruction, stenosis, tortuosity, retroverted uterus
- Uterine or abdomino-pelvic adhesions
- Prior history of STD
- Larger uterine size
- Patient procedural pain/discomfort

Perforation due to the hysteroscope itself is also possible. Furthermore, Essure kits distributed soon after approval included a "support catheter" which may have contributed to early cases of perforation.

It is important to note that perforations may not always be detected or diagnosed. In the Phase II and Pivotal clinical trials, perforations were suspected due to abnormal device position observed on the day of placement procedure via x-ray or during the Essure confirmation test (modified HSG). Perforations were also detected as a result of adverse events, such as pain or abnormal

bleeding, or upon observation in later surgical procedures. Perforations may not be diagnosed if they are not found during placement or confirmation tests and if there are no associated symptoms. Additionally, perforations may not be explicitly reported as adverse events and may only be reported by the symptoms or outcomes resulting from the perforation (e.g., pain or a failed confirmation test).

Perforation is a known risk with use of the device, and, in the complete 5 year report from the Phase II and Pivotal studies, uterine or fallopian tube perforation was reported at rates of 3.1% and 1.1%, respectively.

ESSTVU Study Safety Data Related to Insert Perforation

In the most recent annual report for the ESSTVU study (including data current to June 2015), three events of perforation were described in 2 unique subjects. One subject presented 16 months after device placement with a positive pregnancy test and, upon laparoscopic evaluation, was noted to have bilateral perforation – one uterine, one fallopian. Both devices were left in place during laparoscopic bilateral tubal ligation. The second patient also presented with pregnancy – approximately one year after placement. This patient was diagnosed with a unilateral fallopian tube perforation. The insert was removed at the time of laparoscopic bilateral tubal ligation.

Literature Related to Insert Perforation

A rate of perforation was reported in several articles as presented in Table 20.

Table 20. Rates of Perforation (Literature)

Author	Country	N	Perforations (%)
Aparicio-Rodriguez-Minon[34]	Spain	517	1 uterine (0.2%)
Grosdemouge[41]	France	1061	2 (0.2%)
Gerritse[78]	Netherlands	100	1 (1%)
Langenveld[79]	Netherlands	149	3 (2%)
Legendre[30]	France	311	1 uterine (0.3%)
Levie[31]	U.S.	578	2 uterine* (0.3%)
Panel [42]	France	382	1 (0.3%)**
Povedano[36]	Spain	4306	1 (0.02%)
Sakinci[37]	Turkey	30	1 uterine*** (3.3%)
Sinha[66]	U.K.	112	1 (1%)
Thiel [56]	Canada	610	22 (3.6%)
Veersema[57]	Netherlands	1145	7 (0.6%)

* one during insertion of hysteroscope
**underwent concomitant endometrial ablation
***asymptomatic, identified at HSG

The highest rate, 22/610 (3.6%), was seen in a retrospective medical chart review performed in the Saskatchewan province of Canada. The authors reported that 2/7 proximal, 1/3 distal, and 12/12 uterine perforations were associated with tubal patency on HSG.[56] These rates may be underestimates due to the varying study designs and method of follow-up data collection; in addition, not all perforations may have been discovered or documented (especially in asymptomatic cases).

The systematic review by Adelman, et al., identified 166 cases of perforation, and reported that many cases of perforation were associated with a difficult placement.**Error! Bookmark not defined.** Al-Safi's review of the MDR database through February 2012 noted 90 cases of suspected or confirmed perforation.[63]

Case Reports/Series Related to Insert Perforation

Since Thoma's report in 2006[111], multiple case reports or series describing uterine or tubal perforation during or following Essure placement have appeared in the literature. The timing of the perforation relative to the insertion is often difficult to determine as the reports often describe the time at which the event was *diagnosed* – and this may have been after prolonged periods of time (with or without symptoms). Some note a diagnosis of perforation within days of placement, and others, out to several years afterwards.[36,104,76] Although a difficult insertion procedure is often cited in these cases, multiple reports note perforation in the setting of an uncomplicated procedure.[67,68,112, 69, 75,113] In addition, several reports note that a perforation was diagnosed sometime after a confirmation imaging exam demonstrating proper placement and successful bilateral tubal occlusion.[36,69,75,113] In other words, proper placement at the 3-month confirmation did not preclude subsequent perforation diagnosis.

Patient presentation at diagnosis of perforation varied in the case reports, and in general can be categorized into three types:

- *Abdominal/pelvic pain*
  Several case reports note the presence of abdominal or pelvic pain preceding the diagnosis of uterine or fallopian tube perforation. For some, the pain was persistent following placement and may have lasted months or years before the diagnosis was made.[67,78,79,75,76,81] In others, the pain started after a period where the patient was asymptomatic following placement – sometimes out to one year.[69,70] Although abdominal or pelvic pain was the only (or major) symptom in most of these reports, a few noted patients also presenting with nausea and vomiting.[68,114,85] All of these latter cases involved perforation complicated by insert migration to, or entanglement of, the small bowel with subsequent small bowel obstruction. In one of these cases, the insert perforated through the fundus of the uterus, into and through the wall of the small bowel to the mesenteric aspect, causing small bowel (terminal ileum) perforation.[85] This patient required an ileocecectomy as part of the treatment.

- *Asymptomatic perforation found at confirmatory HSG*

Multiple reports note asymptomatic patients presenting for their confirmatory HSG who were found to have a patent fallopian tube and then, upon further evaluation, diagnosed with perforation[69,72,79,70,110,81,115,116]

- *Pregnancy*
  A handful of reports noted a woman eventually being diagnosed with a perforation after presenting to their physician with an ongoing pregnancy[36,79,113,117] or after a spontaneous miscarriage[118] but without pain.

Most reports were unilateral events, but a few noted bilateral perforation.[67,118,81] Although most described penetration through the organ wall, some noted perforation which remained "subserosal."[79,70] Multiple reports of insert perforation note migration of the insert (or fragments) to the abdominal or pelvic cavity (See below under "Intra-Peritoneal Migration").

MDR Reports Related to Insert Perforation

FDA has received reports related to Essure which describe perforation events including but not limited to reproductive organs. Table 21 below describes the number of reports for each location.

Table 21 – Perforation MDR Reports

Perforation	Voluntary Reports	Manufacturer/User Facility Reports	Total
INTRA-PROCEDURAL PERFORATION			
Uterus	4	12	16
Fallopian Tube	2	10	12
Uterine Horn	0	1	1
Cervix	1	0	1
Unknown	0	3	3
INTRA-PROCEDURAL Totals:	7	26	33
POST-PROCEDURAL PERFORATION			
Fallopian Tube	46	92	138
Uterus	24	40	64
Uterine Horn	0	18	18
Bowel	1	11	12
Amniotic Sac	1	4	5
Other**	1	2	3
Unknown	2	24	26
POST-PROCEDURAL Totals:	75	190	266*

PERFORATION Grand Total:	**82**	**216**	**299***

* 14 reports included two different perforation locations.
** Other included: abdominal cavity, small intestine, ostium, terminal ileum and ovary

As was the case for the reports in the literature, patient presentation varied and subjects may have been diagnosed upon evaluation of abdominal/pelvic pain or a patent tube on HSG – either at the scheduled confirmation test time, or following a pregnancy.

In addition to perforations of the uterus and fallopian tubes, several reports have been received which describe insert perforation involving other organs or structures. FDA has received 5 MDRs in which the reporter alleges that an Essure implant may have been involved in the perforation of the amniotic sac or uterus of a pregnant woman. No additional information supporting the events was provided. Although 5 reports were submitted, it is difficult to determine to what degree the reports overlap. However, all 5 note the preterm death of the fetus.

In addition, 12 MDRs have been received which describe bowel perforation. These include cases where the insert was free within the abdomen (e.g., migrated) or was still within, but perforating through the uterus or fallopian tube. One of these reports notes a "full thickness perforation" through the small bowel wall, requiring an ileo-cecectomy. Two other reports describe the insert ensnaring a loop of small bowel, causing small bowel obstruction in addition to perforation, and the need for an ileo-cecectomy. It is possible that these two latter reports represent the same event reported from 2 sources, and may overlap with the case reports described..

<u>Essure Physician Labeling Related to Insert Perforation</u>

Warnings

- *Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity. Attempted removal with less than 18 trailing coils may result in fractured insert, fallopian tube perforation or other injury.*
- *To reduce risk of uterine perforation, terminate procedure if excessive force is required to achieve cervical dilation.*
- *Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. A false positive HSG and pregnancy have been associated with tubal perforation by insert in the literature; evaluate Essure Confirmation Test for perforation if excessive resistance is experienced during procedure. Only 1.8% (12/682) of clinical trial patients had device related perforations. If necessary, retrieval of perforating inserts requires surgery.*

Precautions

- *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up patient for possible perforation.*

Clinical Trial Description

- *Phase II trial, the following adverse events prevented reliance: Perforation (7/206; 3.4%),*
- *Pivotal trial, the following adverse events prevented reliance: Perforation (5/476; 1.1%);*

Section on Potential Adverse Events Not Observed in Phase II/Pivotal Clinical Studies
The following adverse events were not experienced by Phase II/Pivotal clinical trial participants prior to marketing but are still possible and/or have occurred in the commercial setting:

- *Perforation of internal bodily structures other than the uterus and fallopian tube.*

Essure Patient Labeling Related to Insert Perforation

- *In rare cases, part of an Essure insert may break off. Your doctor may remove the piece or let it leave your body during your period.*
- *In rare cases, part of an Essure insert may puncture the fallopian tube. Surgery may be necessary to repair the puncture.*
- *Your doctor may be unable to place one or both Essure inserts correctly.*

Summary for Device Perforation

The Phase II study of the Essure device noted a uterine/fallopian perforation rate of 3.1% in the full 5 year report. Subsequent prospective IDE studies (Pivotal Trial, ESSTVU) have reported rates of ≤ 1.1%. Most of the peer-reviewed literature which was assessed also cite rates of 1% or less. However, many of those studies were retrospective, single-site experiences, and/or of short-term follow-up (e.g., 3 months). Other, but fewer studies have reported rates of perforation up to 3.6%. Case reports and MDRs have appeared describing perforations of the uterus and/or fallopian tube – some diagnosed at the time of placement, but many others in the post-procedural window, including some beyond confirmation testing with positive bilateral occlusion.. Perforations were typically diagnosed during evaluation of abdominal pain or evaluation in asymptomatic women following an HSG which revealed patent tubes. Because pain is not always indicative of a perforation and because perforations may be asymptomatic, it may be difficult to detect or confirm such an event on clinical grounds alone, and this may in turn impact reporting of the event and calculations of event rates.

F. Intra-Peritoneal Migration

Proximal insert migration or expulsion into the uterine cavity is a well-known event following the Essure procedure – in particular during the first months following placement. However, reports of insert (or insert fragment) migration into the *intra-peritoneal* space (thought to largely occur as a result of perforation) is also possible. In 7 cases of perforation in the Phase II study, 6 devices were reported as "intraperitoneal," meaning that at least a portion of the device was identified to be in the peritoneal cavity.

ESSTVU Study Safety Data Related to Insert Migration

In the ESSTVU study, locations of devices in the two reported perforations were described by investigators during follow up procedures. In one of the two cases, per the investigator, the

insert had "migrated" from the fallopian tube to the pelvis. In the second reported case of perforation, the investigator observed the perforated devices during a laparoscopic sterilization procedure. The investigator described one insert as sticking through the utero-tubal junction, and the other as sitting "in the left ovary." No other instances described as "migration" were reported.

Literature Related to Insert Migration

In our evaluation of published studies or reviews in the medical literature, the occurrence of device migration into the intra-peritoneal space has been described as rare.**Error! Bookmark not defined.** Cases of migration in such are listed in Table 22. Information regarding timing of device migration was not commonly available; however, in many cases, device migration was noted upon confirmation testing and was associated with unintended pregnancy in at least one case.[54]

Table22. Insert Migration – Literature

Article	Country	n	Migrations
Arjona[27]	Spain	1630	3 migrations to the abdominal cavity
Aparicio-Rodriguez-Minon[34]	Spain	517	1 case: migration of both devices into abdomen
Grosdemouge[41]	France	1061	8 migrations (location not specified)*
Panel[42]	France	382	5 migrations: 1 peritoneal cavity, others unspecified
Povedano[36]	Spain	4306	2 asymptomatic migrations into abdomen
Rios-Castillo[54]	Spain	1321	1 (location not specified)*
Thiel[56]	Canada	610	14 proximal or distal migrations noted on HSG*
Gerritse[78]	Netherlands	100	1 migration to the abdominal cavity

*May have included migration within the fallopian tube, or expulsion into the uterine cavity

Case Reports/Series Related to Insert Migration

In addition to cases described as part of clinical studies, several individual case reports describing intra-peritoneal migration have been presented. Like perforations, the timing to the diagnosis has been presented in some of the cases, but the time of the actual migration event cannot be easily assessed. Several migrations were noted in the days/weeks following placement.[112,114,81] These were often noted after evaluation of symptomatic patients (e.g., abdominal pain, nausea, vomiting). Many insert migrations, however, were noted in asymptomatic women during confirmation test imaging which showed patent fallopian tube(s).[115,69,72,116,110]

Although uterine or fallopian tube perforation was documented or presumed to be associated with the device migration, in some cases authors specifically noted that no perforation was present at the time of laparoscopic evaluation and retrieval of the device.[68,116,110] At least one

author suggests the possibility the device may have migrated distally through the fallopian tube into the peritoneal space.[110]

In the case reports, the device or device fragments migrated to the:

- Abdominal cavity[104,63,69]
- Omentum[78,76,110,81]
- Small bowel serosa or mesentery[68,112,115,114,116]
- Large bowel mesentery[112]
- Cul-de-Sac[72]

Several complications or intra-operative observations were reported in association with the migrated device (fragments) including:

- Small bowel obstruction due to insert entanglement or inflammation[68,114]
- Small bowel perforation[114]
- Adhesions[68,112,69,72]
- Local inflammation[68]

In the majority of the reports, the inserts were removed laparoscopically without complications. However, in several, intra-operative fluoroscopy was required to locate the insert or insert fragments.[112,69,76] Some patients required more than one laparoscopy because fluoroscopy was not used in the initial retrieval procedure and unsuspected fragments were unintentionally left behind.[72,76] In addition to insert removal, patients may have undergone concurrent BTL or lysis of adhesions[68,112,72] and, as previously described, one patient required an ileocolectomy for small bowel obstruction and perforation.[114] Some surgeons, however, elected to leave the inserts/fragments in place if the patient was asymptomatic.[115,116]

MDR Reports Related to Insert Migration

FDA has received a total of 227 reports which discuss migration outside the uterus. Table 23 shows the location of migration as noted in those reports.

Table 23 – Migration MDR Reports

Location of Migration	Voluntary Reports	Manufacturer/User Facility Reports	Total
Abdominal cavity/ Peritoneal cavity/Pelvic cavity	21	51	72
Bowel (Colon/Small Intestine)	9	26	35
Fallopian tubes	16	6	22
Omentum	0	10	10
Other	3	1	4

Unknown	57	27	84
Total	**106**	**121**	**227**

Although FDA attempted to delineate reports which involved intra-peritoneal migration from proximal or vaginal expulsion, it is possible that some of the reports noted above, in particular the "unknown" reports represent the latter. In cases where the device migrated to, or around, the small bowel, the patient may have presented with signs or symptoms of bowel perforation and/or bowel obstruction (e.g., abdominal pain, nausea, vomiting, and/or fevers). At least one report noted that a patient required surgical ileocecectomy because of a full thickness perforation of the terminal ileum secondary to the migrated insert. This case may overlap with one of the literature case reports.

In May-June 2013, FDA conducted an inspection that included an evaluation of Conceptus/Bayer's complaint handling and adverse event reporting practices. When any firm receives complaints, the firm is required to investigate each event and make a determination whether the complaint represents an event that is required to be reported to FDA under the medical device reporting regulations (21 CFR Part 803). The firm is then responsible for submitting such reportable events to FDA as medical device reports (MDRs). As part of the inspection process, part of FDA's review focused on 16,047 complaints the firm received on the Essure device between January 2011 and the date of the inspection. From these complaints, the firm identified 183 reportable MDRs and submitted them to FDA. Of these, 22 reports were associated with insert perforations and/or insert expulsions involving the Essure device. In several of these cases, it was reported that the insert was located in the peritoneal cavity. During the inspection, FDA assessed whether the firm's general investigation and MDR reporting practices were compliant with FDA regulations and concluded that, based on available information, the firm's reporting practices were consistent with the FDA's mandatory reporting requirements.

<u>Essure Physician Labeling Related to Insert Migration</u>

Section on Insert Removal

- *The technique for removal of an insert that has perforated the uterus or tube or is within the peritoneal cavity will depend on the location of the insert. Localization should be assessed with imaging prior to the surgical procedure and confirmed intraoperatively. Availability of intraoperative fluoroscopy and/or intraoperative x-ray is recommended to identify the location of the insert or fragments of the insert during surgery.*

<u>Essure Patient Labeling Related to Insert Migration</u>

- *There are reports of the Essure insert migrating into the lower abdomen and pelvis. If this happens, it may be necessary to surgically remove the migrated device.*

<u>Summary for Device Migration</u>

Prospective studies conducted under IDE for the Essure PMA reported 6 cases of perforations that resulted in at least a portion of a device being in the peritoneal cavity. Limited reports of intra-peritoneal device migration have been published – either as part of prospective or retrospective studies, or as individual case reports/series. Although it is presumed that a perforation had occurred prior to migration, not all authors noted evidence of perforation at time of laparoscopic evaluation. Insert migrations were often asymptomatic and detected at follow-up confirmation test imaging, or in some cases, earlier when associated with symptoms related to entanglement or perforation of the small bowel. Most authors elected to remove the migrated components via laparoscopy, although the potential for device fragmentation led some to suggest the importance of intra-operative fluoroscopy to ascertain that all components had been retrieved. Other clinicians elected to not retrieve the device if the patient was asymptomatic. Information within MDR reports received is consistent with the reports noted in the literature.

G. Pregnancy-Related Safety Outcomes

Ectopic Pregnancy

An ectopic pregnancy occurs when a fertilized egg implants outside the uterine cavity. Women with a history of damage to fallopian tubes from PID, previous tubal surgery, and/or previous ectopic pregnancy are at increased risk for ectopic pregnancy.[119] Without treatment, an ectopic pregnancy can lead to a ruptured fallopian tube, which can result in life-threatening bleeding for the mother. No pregnancies, including ectopic pregnancies, were reported in the original PMA studies.

ESSTVU StudySafety Data Related to Ectopic Pregnancy
In the ESSTVU study, no ectopic pregnancies have been reported.

Literature Related to Ectopic Pregnancy

Our review of the medical literature revealed little in the way of clinical studies reporting on rates of ectopic pregnancy following Essure. Of 61 pregnancy-related adverse events noted in Al-Safi's review of the MDR database through 2012, 29 ectopic pregnancies were noted.[63]

Malacova, et al., recently published a population-based retrospective cohort based on extraction of data related to all women aged 18-44 undergoing tubal sterilization between 1990 and 2010 from hospital records in Western Australia.[120] The set of 44,829 women included 278 who had undergone hysteroscopic sterilization with Essure. No ectopic pregnancies were reported in this group.

Case Reports/Series Related to Ectopic Pregnancy

In 2011, Bjornsson reported a patient who presented with acute abdominal pain, nausea, and dizziness – approximately 2-3 years after Essure placement (with documented bilateral occlusion on 3-month HSG).[121] The patient was found to be in hypovolemic shock, with a positive urine pregnancy test, and free fluid in the abdomen by ultrasound. She underwent an emergency

laparotomy, and an ectopic pregnancy in the left fallopian tube was identified – even though both Essure inserts appeared to be in proper location.

In 2013, Huguelet reported on a woman who presented with acute pelvic pain and positive pregnancy test 4 years after her Essure procedure despite having bilateral tubal occlusion documented at 3 month HSG.[122] An ultrasound showed a questionable 3.3-cm left adnexal mass and the patient underwent laparoscopy where no adnexal/tubal pathology was found, but the left insert was seen perforating the uterus. Post-laparoscopy, the patient continued to have rising hCG levels and was treated with methotrexate for a presumed ectopic pregnancy of unknown location.

MDR Reports Related to Ectopic Pregnancy

Of the 337 MDR reports FDA has received for Essure related to pregnancy, 69 involved ectopic pregnancy (including one MDR reporting a woman who experienced two ectopic pregnancies).

Product Physician Labeling Related to Ectopic Pregnancy

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place.*
- *Section on Potential Adverse Events Not Observed in Phase II/Pivotal Clinical Studies The following adverse events were not experienced by Phase II/Pivotal clinical trial participants prior to marketing but are still possible and/or have occurred in the commercial setting:*
- *Pregnancy and ectopic pregnancy in women relying on Essure inserts.*

Product Patient Labeling Related to Ectopic Pregnancy

- *Women who have the Essure procedure are more likely to have an ectopic pregnancy if they get pregnant. Ectopic pregnancy is when the pregnancy occurs outside of the uterus. The pregnancy usually happens in one of the fallopian tubes. Ectopic pregnancies can be very serious or life- threatening.*

Premature Rupture of Fetal Membranes (PROM) /Fetal Death

When premature rupture of membranes (PROM) occurs prior to the 37th week of pregnancy, it is referred to as preterm premature rupture of membranes (PPROM). PPROM may lead to significant perinatal morbidity, including respiratory distress syndrome, infections/sepsis, placental abruption, and fetal death. Although not seen in the premarket PMA trials or the ESSTVU Study, one potential concern for women who become pregnant following Essure placement is the possibility for the trailing coils within the uterus to interfere with the pregnancy.

Literature Related to PROM

The potential risk of a trailing coil of the Essure insert leading to preterm premature membrane rupture has been discussed in the literature.[123] Live full term birth outcomes have been reported

in women seeking pregnancy via assisted reproductive technology who underwent the Essure procedure in order to isolate the uterine cavity from hydrosalpinx fluid prior to embryo transfer.[124]

Veerseema reported on 50 intended and unintended pregnancies which occurred after unilateral or bilateral Essure insertion.[125] This included 2 reports of stillbirth in one IVF patient: one singleton pregnancy at 19 weeks of gestation due to premature rupture of membranes, and then later, one twin pregnancy at 18 weeks of gestation due to premature rupture of membranes with evidence of chorioamnionitis. The second pregnancy and stillbirth occurred after the hysteroscopic removal of the Essure inserts. The authors stated that "the cause of both fetal losses was not likely related to the presence of micro-inserts." There was one additional case of premature rupture of membranes at 37 weeks gestation, resulting in vaginal delivery of a healthy infant. Two additional studies which reported on IVF results noted cases of PROM.[124,126] Both cases resulted in a healthy infant.

MDR Reports Related to PROM

As noted above ("Perforations") FDA has received 5 MDR reports describing pre-term death of a fetus for which the reporter felt that the presence of the Essure insert may have contributed to the perforation of the amniotic sac or uterus.

Summary for Adverse Outcomes of Pregnancy

No cases of ectopic pregnancy or premature rupture of membranes were reported in the IDE studies used to support PMA or PMA Supplement approval. Within the literature, limited reports exist describing ectopic pregnancy or PROM in women with unintended or intended pregnancies following Essure placement. However, FDA has received 69 MDRs describing cases of ectopic pregnancy. In addition, 5 reports related to PROM (all resulting in fetal death) have been submitted in which the reporter suggests the Essure device may have contributed to the event. The limited data for these latter reports make it difficult to assess causality.

VIII. Reports of Death

During the IDE studies that supported approval of the original PMA or PMA Supplement, no deaths were reported. In the post-approval follow up in these studies, two deaths were noted. One death, secondary to leukemia, occurred in a woman from the Pivotal study during the 5 year follow up. The other death was a woman in the ESSTVU study that occurred during the post approval follow up period. This second patient died of a myocardial infarction following coronary artery bypass surgery. Both events were classified as unrelated to the device.

Prior to June 1, 2015, FDA has received 11 MDRs which were coded as involving a patient "death" and which note such an event. The 11 reports represent 9 unique events, as duplicate reporting occurred. It is crucial to remember that the coding of a report as a death does not necessarily prove the causality between the device and the event. In many cases it is difficult to come to that conclusion based on the information available. Of the 11 reports, 5 describe fetal

death (discussed above, Perforation). The remaining 6 reports describe 4 unique events including the following:

- A 30 year old woman with Group A Streptococcal infection 2 days following placement.
- A 31 year old woman experiencing cardiopulmonary arrest during insertion. Autopsy revealed probable paradoxical air embolism with a patent foramen ovale. (Two reports received for one event)
- A woman who died 13 days after undergoing a hysterectomy to remove the Essure implants. This was suspected to have resulted from a pulmonary embolism. (Two reports received for one event)
- One woman who committed suicide (No additional information provided)

IX. Essure Insert Removal

Essure is intended to be a permanently implanted device. However, removal of devices did occur in the follow-up of the original clinical trials. Twelve of 206 (5.8%) women had devices removed in the Phase II trial and 20/476 (4.2%) of women had devices removed in the Pivotal trial. As noted in previous sections, several publications, case reports/series, and numerous MDRs describe patients seeking and having surgery for implant removal. Reasons for seeking removal have included:

- Identification of an incorrectly placed or perforated insert
- Displaced/migrated implant
- Persistent pain
- Persistent menstrual symptoms
- Presumed allergic reaction

<u>ESSTVU Study Safety Data Related to Insert Removal</u>

In the ESSTVU study, information on device removals was obtained based upon the association with adverse events. To date, with 2-3 years of follow-up, 11 of the subjects enrolled in the ESSTVU Study (1.8%) have undergone device removal associated with adverse events. Reasons for removal included:

- Abdominal or pelvic pain or cramping (8)
- Intermenstrual bleeding (1)
- Fibroids (1)
- Worsening endometriosis (1)

The majority of device removals (64%, 7/11) was performed via laparoscopic salpingectomy and was performed for symptoms related to pain. Five involved bilateral insert removal, and 2, unilateral. Four other removals (36%) were accomplished via hysterectomy with bilateral salpingectomy.

In terms of symptom status following device removal, 8 of the 11 subjects reported resolution of the symptoms. The one patient with fibroids continued to have symptoms despite hysterectomy and the status of two patients who reported pain as the indication for removal are unknown as the patients both exited the study.

Literature on Insert Removal

Chudnoff's publication of the 5-year follow-up for the Pivotal IDE cohort (described above) noted 15 hysterectomies (of 397 evaluable patients) to remove the devices, including two which the investigators felt were possibly due to the Essure implants. Arjona-Berral reported that 7/4274 (0.16%) patients presented with chronic pelvic pain requiring device removal by hysteroscopy in two cases and by laparoscopy in five cases.[65] Zurawin & Zurawin reported eleven cases of device removal noted in adverse event reports submitted to FDA.[89] Two additional articles describing cohort studies, noted a few cases of device removal before confirmation testing due to post-procedural pain: 1 removal (laparoscopically) out of 638 patients in one study, and no rate given for the second study of 458 patients (did not report how devices were removed).[64,39]

Case Reports/Series on Insert Removal

Several case reports have been published noting successful and uncomplicated hysteroscopic insert removal out to 55 months.[28,118,74,127,128] More case reports and series describe laparoscopic surgical removal via salpingotomy or salpingectomy and in some cases, hysterectomy years following placement.[72,73,128,84,129] At least one author found that the ease of removal was not influenced by the duration implants were in place.[84]

In the case of removal of inserts that had migrated into the intra-abdominal space, several authors have suggested the use of intra-operative fluoroscopy to assist in the location of the implant, particularly in cases in which the coil is suspected to have fragmented and be in multiple pieces.[112,76]

As noted in sections above, the removal of the implants may or may not have completely resolved the symptoms which were suspected to be associated with the presence of the device.[67,71,74,84]

MDR Reports on Insert Removal

As noted previously, multiple MDRs describe women who sought removal of their devices for one or more symptoms or events. FDA reviewed 1202 Essure reports which included any of the following terms: "hysterect", "salpingec", "laparo", or "remov". Of these, 452 describe device removal including 265 being performed by hysterectomy. The majority of the hysterectomy removals were related to device removal due to perforation and migration issues. The device removals related to allergy/hypersensitivity symptoms were nearly evenly split between hysterectomy and non-hysterectomy removal.

Less than half of the 452 device removal reports provide further information related to symptom outcomes following surgery. Of those that do provide that information, 176 reports state that the symptoms originally attributed to the Essure device either resolved or significantly improved following device removal. Many noted improvements soon after surgery. A given report describing such resolution may have mentioned several improved signs/symptoms including: abdominal/pelvic pain, back pain, joint pain, headaches, rash, hair loss, fatigue, weight gain/loss,

dyspareunia, irregular menstrual bleeding, nausea, mood swings/ irritability, edema, visual changes, and more. Conversely, 20 of the 452 reports specifically noted that the woman's symptoms did not improve or resolve following the hysterectomy. All of these women still reported pain after the device removal with a few reporting the continuation of other symptoms such as fatigue, weight gain/loss, and headaches.

In addition to the 452 reports describing device removal, many additional reports cited women who were already scheduled for, or actively seeking, removal surgery.

Essure Physician Labeling on Removal*

Warnings

- *Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity. Attempted removal with less than 18 trailing coils may result in fractured insert, fallopian tube perforation or other injury.*
- *Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated. Risks to the patient, fetus and continuation of pregnancy are unknown.*
- *The Essure procedure should be considered irreversible. Safety or effectiveness of reversal surgery is unknown.*

Section on Insert Removal

- *WARNING: Essure inserts are intended to be left in place permanently. Do not remove insert(s) unless patient is experiencing an adverse event(s) associated with its presence, or if removal is demanded. If insert removal is indicated, patient should be counseled on unknown risks as techniques for insert removal post-placement have not been evaluated in clinical studies.*

  For all surgical device removal procedures, care should be taken to avoid transecting the insert during removal. Avoid use of any instrument that is likely to result in fragmentation of the insert. Application of electrocautery to the outer coil should be avoided. During removal, grasping both the inner and outer coils together may help prevent excessive stretching of the outer coil, which could result in fragmentation.

  Location of Essure inserts should be confirmed through imaging prior to any attempted surgical removal.

  Limited case reports describe hysteroscopic insert removal up to seven weeks following placement. In these cases the proximal coils were visible within the uterine cavity and were easily removed with gentle traction. When hysteroscopic removal is not feasible, linear salpingotomy or salpingectomy via laparoscopy or laparotomy can be used to remove an insert within the tube. In some cases, a cornual resection of the proximal fallopian tube may be required for insert removal. In these cases, patients should be counseled about the risk of hysterectomy in order to achieve hemostasis.

1. *To perform a linear salpingotomy, make a small incision (approximately 2 cm in length) along the antimesenteric border of the fallopian tube overlying the insert. Use of vasoconstrictive agents is at the discretion of the operating surgeon. The insert needs to be exposed and may need to be freed from the surrounding tissue prior to grasping the coils. Once the insert is exposed, a grasping instrument may be used to extract the insert using gentle traction. Removal may be along with, or independent of, an incisional sterilization procedure.*

2. *When removing insert via salpingectomy, the location of the proximal and distal portions of the insert within the fallopian tube should be reconfirmed intraoperatively by palpation and/or imaging prior to transecting the tube. The insert may be exposed and visualized via salpingotomy prior to transection or removal of the fallopian tube.*

3. *The technique for removal of an insert that has perforated the uterus or tube or is within the peritoneal cavity will depend on the location of the insert. Localization should be assessed with imaging prior to the surgical procedure and confirmed intraoperatively. Availability of intraoperative fluoroscopy and/or intraoperative x-ray is recommended to identify the location of the insert or fragments of the insert during surgery.*

*Note: Labeling provided here reflects major changes to the labeling that were approved in June 2015, via Supplement 41.

<u>Essure Patient Labeling on Removal</u>

- *Is Essure reversible? No, the Essure procedure is not reversible. Like having your tubes tied or a vasectomy for men, Essure is permanent birth control. You need to be sure you are done having children before you decide to have the Essure procedure.*
- *The safety and effectiveness of reversing the Essure procedure are not known*
- *The safety and effectiveness of in vitro fertilization after the Essure procedure are not known*
- *The risks to you and your fetus if you get pregnant after the Essure procedure are not known*

<u>Summary for Insert Removal</u>

Complete 5-year follow-up of patients in the Phase II and Pivotal study has reported that 5.8% of women had devices removed in the Phase II trial and 4.2% of women had devices removed in the Pivotal trial. In addition, recent data on the ESSTVU study demonstrate device removal in approximately 2% of subjects. In this study, the most common reasons for undergoing device removal were abdominal/pelvic pain or abnormal bleeding. Limited data are available from peer-reviewed studies, although several case reports have been published citing hysteroscopic or laparoscopic removal or hysterectomy out to several years past insertion to remove the device for a variety of symptoms, and/or for a migrated device. Many MDRs received by FDA describe

women who were seeking or scheduling a hysterectomy to remove the device, or women who had already had the devices removed – many by hysterectomy. For those women who underwent device removal, and for whom symptom status was provided, the majority noted improvement or resolution of their symptoms after the hysterectomy. Several case reports and data from the ESSTVU study also note improvement in symptoms following removal.

X. Social Media

The Food and Drug Administration has been exploring various tools for "social listening" as a means to expand our ability to identify and refine new safety signals. Among those efforts was a pilot program with Epidemico, Inc's MedWatcher Social program which is intended to review public posts on several popular patient and consumer web sites including Twitter, Facebook, and select patient forums. The program uses a Bayesian classifier which identifies "posts with resemblance to adverse events" or "Proto-AEs" based on a probability score. The internal classifier has been trained with over 350,000 manually coded posts and an internal dictionary is able to translate vernacular to MedDRA terms.

The Agency recognizes that these types of social listening tools are still evolving, and the data they provide has important limitations that may significantly impact the ability to interpret the inforation. These limitations include but are not limited to the potential for patients to incorrectly assign symptom causality to the device and the potential for large volumes of posts which may be duplicative or include "false positives." Despite these known limitations, within the pilot evaluation, early data on Essure was collected from postings between September 2013 and July 2015. Of the approximately 350,000 mentions of Essure, the software identified 20,000+ posts which it classified as containing Proto-AEs. The vast majority of these Proto-AEs were from Twitter posts. Keeping in mind that this is preliminary data (e.g., false positives not yet removed, reports not unduplicated, retweets not consolidated), the top Proto-AEs for Essure posts were as follows:

- Pain
- Hysterectomy
- Malaise
- Pregnancy
- Medical device removal
- Device dislocation
- Pelvic pain
- Surgery
- Abdominal distension
- Hemorrhage
- Allergy to metals

Although raw information, these are consistent with the types of events or complaints received by FDA through the MDR reporting process.

XI. Outside-the-US (OUS) Post-market Experience

During its review of post-market information related to Essure, FDA contacted several of its larger global regulatory counterparts where the Essure device has been approved/marketed for more than 10 years. The types of adverse events and safety outcomes reported to those bodies have also been reported within the United States. No new issues were being reported abroad that were not included in the information provided above. However, the number of reports received yearly by our foreign colleagues through their adverse event reporting processes has been significantly less. On average, the OUS regulatory organizations were receiving fewer than 20-30 reports per year regarding Essure.

XII. Summary

The Essure device has been approved for marketing within the United States (and many other nations) for over 10 years. Two prospective clinical trials were performed by the sponsor, and reviewed by FDA and its Obstetrics and Gynecology Devices Advisory Panel in support of the approval decision in 2002.

Over the past 2 years, FDA has seen a dramatic increase in the number of adverse events submitted in relation to the Essure device. The majority of these reports have come from women implanted with the device.

FDA has recently conducted a review of effectiveness and safety performance data from several sources as related to the Essure device. As part of the preparation for this panel meeting, FDA has summarized that post-market data and information – focusing largely on specific commonly reported safety issues and concerns raised by portions of the patient community.

FDA has provided information in this memo related to Essure safety and effectiveness from several different sources, including studies done under IDE as well as studies within the peer-reviewed literature. The IDE studies were prospective, multi-center studies, each conducted with several hundred subjects and performed in line with FDA regulations. Two of those studies followed patients out to 5 years, and the third has provided data out to 2-3 years and is still ongoing. These studies did/do not have a control arm which limits interpretation of some of the outcomes of interest, and data was not available on all subjects at the 5-year point for two of the studies. Peer-reviewed literature was reviewed and numerous publications related to the effectiveness of the device were included. Fewer publications specifically addressed many of the adverse outcomes selected for discussion. Although relatively low rates were reported in many of these publications, significant limitations must be taken into account when reviewing the data, including a large amount of data being generated from retrospective studies (chart reviews, physician or patient surveys or phone interviews, etc.), single-arm cohort studies, studies from single institutions, separate studies from the same institutions reporting on patient populations with significant overlap, studies with limited follow-up (e.g., 3 months), studies with notable loss to follow-up, and/or reviews using MDR data to estimate rates.

FDA also attempted to summarize information from case reports – both from the medical literature (including abstracts and posters) as well as MDRs received into our MAUDE database. Limitations to the literature case reports and abstracts are similar to those described for the peer-reviewed literature. As noted, most of the MDRs received by FDA have been voluntary reports from patients themselves, and many of the reports describe numerous symptoms or side effects following device placment. A number of these events have not previously been presumed to be associated with the device and which, if true, may call in to question a "systemic" process. MDRs are a valuable source of information to FDA, but in general, can also have limitations including under-reporting, and biased or incomplete/unverified reporting. In addition, MDR data alone cannot be used to establish rates of events, or confirm whether a device actually caused (or worsened) a specific event. Because rates of events cannot be determined by MDR data, it is not possible to determine whether the numbers of reports represent a true increase in rates of particular known or expected events, or rather represents an increase in the reporting of adverse events or increase in the number of devices in clinical use.

The Committee will be asked to review this data, along with other information provided by the device manufacturer and members of the clinical and patient communities at the day of the panel meeting. The Committee will be asked to provide input and recommendations regarding the benefit-risk profile of the device, specific safety issues, and potential mitigating actions, if any, which should be considered by the FDA and public.

Appendix A. Device placement, physician learning curve, and patient compliance; post-market information

The effectiveness of the Essure system depends on successful bilateral insert placement and patient compliance with the confirmation testing requirement. If the devices are not correctly placed, a woman may not rely on the device for contraception. Successful placement is dependent on a variety of factors, including but not limited to device design (e.g., catheter), physician training and experience, and patient anatomy. In the Phase II and Pivotal Trials, which supported the original approval of the Essure System, rates of bilateral placement, and the reliance rates were measured. In the post-market, there have been numerous additional studies of bilateral placement rates, physician learning curve for successful placement, and patient compliance with confirmation testing requirements.

Successful Device Placement

Since the original approval, the sponsor has made changes to the catheter to facilitate placement, although data on Essure placement rates have generally demonstrated a high rate of bilateral placement. In the initial premarket study, successful bilateral placement rates were reported to be ~86-90%. In subsequent post-approval studies, higher bilateral placement rates were reported (>95%), and since approval of the Essure system, there has been consistently high bilateral placement rates (80-100%) reported in the literature. Subsequent post-approval studies showed higher rates.

The second PAS, ordered at the time of original PMA approval, evaluated the bilateral placement rate at first attempt for *newly* trained physicians in the U.S., and evaluated factors predictive of bilateral placement failure. The target sample size was 40 physicians and 800 women, per protocol. In 2005, after reviewing data in a PAS report, FDA considered this condition of approval to be satisfied, with 514 women enrolled in the study. The sponsor used Bayesian statistics to demonstrate that enrolling additional women would not change the observed results for the main study endpoint. There were 476 women in whom bilateral placement was possible and bilateral placement was achieved in 458 women, for 96.2% success rate. Placement rates did not change by calendar time, place where procedure was performed, device configuration, hysteroscope shape, or patient characteristics (age, body mass index, education level, income, and race). There were 13 adverse events that included perforation (2 cases, one secondary to hysteroscope), pelvic pain, bleeding, light headed, increased blood pressure and temporary decreased pulse. The device labeling was updated based on the results of this PAS.

In addition, FDA approved a PMA supplement for the model ESS305 design in 2007. A PAS was ordered at that time to evaluate if design changes and material modifications affected the bilateral placement rate. This PAS was an observational cohort study with 76 sites in the US that enrolled 584 women. The new model had a bilateral placement rate of 97.2%, excluding placement non-attempts.

Literature

Essure placement rates from studies included in our literature review are summarized in Tables 24 and 25. Placement was generally assessed at the time of the procedure by the number of coils trailing into the uterine cavity. It was commonly reported that more than one attempt was sometimes needed to successfully place the inserts. The most common reasons reported for unsuccessful Essure placement were poor visualization of the tubal ostia, tubal stenosis, tubal spasm, previous tubal occlusion, anatomical irregularities, and patient discomfort during the procedure.

A number of studies investigated potential factors that could be associated with Essure placement success or failure, such as patient age, body mass index, parity, history of sexually transmitted infection, or procedure setting;[39,130,32,131] however, no patient characteristic emerged as a definitive risk factor for placement failure. One group of authors from Spain reported that use of the oral contraceptive desogestrel before Essure placement was associated with decreased endometrial thickness and subsequently, better visualization of the ostia and higher placement rates; however, the sample size was not large enough (16 women in each group), and the physician was not blinded to treatment group.[134] Methods to improve success rates included placement during the follicular phase of the menstrual cycle (i.e., before ovulation) to improve visualization of the tubal ostia,**Error! Bookmark not defined.** and premedication with nonsteroidal anti-inflammatory drugs (NSAIDs).[106]

Table 24. Successful placement rates in articles with no three month follow-up data.

Article	Country	Successful bilateral placement		Reasons for unsuccessful placement
		First Attempt	Second Attempt	
Chapa, 2015[132]	U.S.	43/45 (95.6%)	3/4 (75%)	Suspected tubal spasm
Chudnoff, 2010[133]	U.S.	74/80 (92.5%)	n/a	Not Reported
Haimovich, 2013[134]	Spain	28/34 (82.4%)	n/a	Visualization of ostia (n=4) Menstruation (n=2)
Isley, 2012[135]	U.S.	54/58 (93.1%)	n/a	Visualization of ostia (n=2) Coil could not advance into one tube (n=1) Patient unable to tolerate (n=1)
Leyser-Whalen, 2012[131]	U.S.	292/324 (90.1%)	n/a	Tubal stenosis or spasm (n=18) Visualization of ostia (n=9) Cervical stenosis (n=3) Severe uterine prolapse (n=1)
Panel, 2010[106]	France	440/492 (89.4%)	13/15 (86.7%)	Visualization, tubal stenosis, or spasm (n=23) Salpingectomy or tubal occlusion (n=23) Previous tubal occlusion (n=2) No additional information given (n=4)
Thiel, 2011[136]	Canada	84/85 (98.8%)	n/a	Not Reported

Table 25. Successful placement rates in studies with ≥ 3 months of follow-up.

Article	Country	Successful placement[a]
Anderson, 2013[39]	U.S.	95.5%
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517/534 (96.8%)
Garcia-Lavandeira, 2014[137]	Spain	55/61 (90.2%)
Gauchotte, 2011[138]	France	88/94 (94%)
Grosdemouge, 2009[41]	France	992/1051 (94.4%) first attempt
Howard, 2013[139]	U.S.	131/136 (96.3%)
Legendre, 2010[140]	France	73/78 devices (93.6%)
Legendre, 2011[30]	France	293/311 (94.2%)
Pachy, 2009[141]	France	22/25 (88%)
Paladini, 2015[142]	Italy	27/27 (100%)
Panel, 2011[42]	France	321/341 (94.1%)
Povedano, 2012[36]	Spain	4075/4306 (94.6%)
Rajecki, 2014[43]	Finland	103/120 (85.8%)
Rios-Castillo, 2013[54]	Spain	1166/1200 (97.2%)
Sakinci, 2015[37]	Turkey	24/32 (75%)
Savage, 2009[32]	U.S.	850/884 (96.2%)
Tatalovich, 2010[143]	U.S.	48/48 (100%)
Thiel, 2014[144]	Canada	30/30 (100%)
Veersema, 2011[57]	Netherlands	1034/1145 (90.3%)

* NR=Not reported.
[a] Overall placement rates including placements that required multiple attempts

Essure Physician Labeling Regarding Insert Placement

Clinical Trial Results Section

Insert Placement Rate at first attempt in the Commercial Setting Using the Essure System ESS305

Placement Status	ESS305 Post Approval Study	
	Number	Percent
Bilateral Placement*:	593/612	96.9%
Intent-to-Treat Bilateral Placement**:	593/619	95.8%
Unilateral Placement or No devices placed***:	26/619	4.2%

*Bilateral placement rate excludes seven patients in whom insert placement was not attempted.

** Intent-to-treat bilateral placement rate includes all participants who underwent hysteroscopy regardless of whether insert placement was attempted.

*** Unilateral placement occurred in 10 participants; 6 participants had no placement in either fallopian tube; insert placement was not attempted in 7 participants. Tubal obstruction and visualization problems due to uterine anatomy were the most common reasons for placement failure.

Physician Learning Curve

Literature Regarding Physician Learning Curve

In our current literature review, 3 articles reported on the physician learning curve for the placement of Essure.[130,145,146] A Dutch study that collected data from 631 procedures performed by 15 gynecologists inexperienced with the Essure procedure found that increasing experience was significantly associated with decreasing procedure time through the physician's 15th procedure; however, experience was not associated with placement success, pain scores, or complication rates. Successful bilateral placement (confirmed by TVU or x-ray) was achieved in 480/631 (76.1%) patients at first attempt, and the overall rate of sterilization success was 537/631 (89.5%). The authors reported 40 complications such as vasovagal collapse and nausea/vomiting, but no cases of perforation, migration, or expulsion.[145]

A French study classified 498 surgeons into four groups according to experience with hysteroscopy. At the surgeons' first Essure placement, failure rates ranged from 4.7% for the most experienced group to 16.3% for the least experienced group of surgeons. The presence of an instructor from Conceptus (previous manufacturer of Essure) during the procedure was associated with faster improvement during the surgeons' second and third placements. Overall the placement success rate (bilateral and unilateral) was 1054/1144 (92.1%). Complication rates were not reported.[146]

Levie & Chudnoff published the results of the "Newly Trained Physicians" post-approval study. The group of 39 experienced physicians had each performed ≥25 Essure placements, while 37 newly trained physicians had each performed 3-5 proctored placements. The successful placement rate (bilateral and unilateral) was 339/346 (98%) vs. 223/232 (96.1%) for experienced versus newly trained physicians ($p>.05$); procedural time was 7.9 minutes versus 10.7 minutes, respectively ($p<.01$). Six subjects experienced adverse events, including two cases of uterine perforation (one at the time of cervical dilation, and one during hysteroscope insertion); it was not reported whether these procedures were performed by newly trained or experienced physicians.[130]

Patient Compliance with Confirmation Test

As described previously, although surgical tubal ligation may be considered effective immediately, due to the mechanism of action of the Essure device, a period of time is required to ensure that the fallopian tubes are occluded. A woman must have a successful "confirmation test" before she can stop alternative birth control and rely on the Essure device. As noted above, failure to comply with this confirmation testing has been cited as a factor in a significant percentage of reported unintended pregnancies. As such, adherence to this step is crucial to the device's effectiveness.

Literature on Confirmation Test Compliance

FDA's literature review showed that patient compliance rates with the confirmation testing ranged from 28.8% to 100% (Table 26). Health insurance coverage was an important factor in

patient compliance; in multiple studies, privately insured women were more likely to be compliant with HSG confirmation testing than women with public insurance or no insurance. Only 53% of women were compliant with HSG testing in one study of mostly publicly insured women from Kansas City, Missouri.[139] Another study with a very low compliance rate (28.8%) reported that insurance issues were the most frequently reported reason for noncompliance in their urban-based clinic population in Detroit, Michigan.[147] Comparatively, a sample of 884 women in the Kaiser Permanente Northern California healthcare system had a compliance rate of 86.5%, and more than a third of those lost to follow-up were no longer Kaiser Permanent Northern California members at the end of the study period.[32] In a study conducted at Vanderbilt University Medical Center, patients were 2.05 times more likely (95% CI: 1.22, 3.43) to undergo HSG testing if they had private insurance compared with Medicaid insurance.[39]

Two articles reported on methods implemented in order to increase patient compliance. Mahmud, et al., reported an increase in compliance from 68.6% to 78.4% using an electronic reminder for staff.[148] Guiahi, et al., reported an increase in compliance from 71.1% to 87.3% after hiring a dedicated staff nurse to schedule HSG appointments and track compliance.[149]

Outside the U.S., it is general practice to use pelvic x-ray or TVU to assess device placement, rather than tubal occlusion. Multiple authors recommend ultrasound as the first line of confirmation testing, followed by the modified HSG, when indicated by an inconclusive result.[56,137,142] In a large Dutch prospective cohort, three-month TVU results were satisfactory for 892/944 women (94.5%); of the 52 unsatisfactory results, subsequent HSG confirmed bilateral occlusion in 50 cases. However, the authors noted that two of four observed pregnancies were possibly due to misinterpreted TVU results that appeared satisfactory (no HSG performed).[57] Similarly, a retrospective Canadian study reported that 524/610 (85.9%) women had satisfactory TVU results and 86/610 women underwent HSG due to inconclusive or abnormal TVU results. There were two pregnancies during six years of follow-up, both due to non-compliance.[56] In two articles, there was a case where TVU or x-ray showed correct placement of the devices, but HSG showed that one or both tubes remain patent.[45,46]

Table 26. Confirmation test compliance data

Author	Country	n	Confirmation Compliance	Successful Completion of Confirmation Test[b]
Anderson, 2013[39]	U.S.	638	58.7%	88%
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517	476/517 (92.1%)	X-ray/US: 467/476 (98.1%) HSG: 67/76 (88.2%)
Connor, 2011[40]	U.S.	118	101/118 (86%)	Contrast infusion sonography: 53/57 (93%)
Franchini, 2011[51]	Italy	45	NR	45/45
Garcia-Lavandeira, 2014[137]	Spain	61	55/55 (100%)	Ultrasound: 43/55
Gauchotte, 2011[138]	France	94	58/94 (62%)	X-ray/US: 53/58 (91%)
Grosdemouge, 2009[41]	France	1061	1014/1015 (99.9%)	X-ray: 982/1014 (97%)
Guiahi, 2010[149]	U.S.	228	78% before intervention (hiring staff to schedule) 90.9% after intervention	123/173 (71.1%) before and 48/55 (87.3%) after
Howard, 2013[139]	U.S.	132	70/132 (53.0%)	61/70 (87.1%)
Lazarus, 2012[35]	U.S.	235	NR	218/240 (90.8%)
Legendre, 2010[140]	France	40	39/40	61/64 devices
Legendre, 2011[30]	France	311	257/305 (84.3%)	US: 195/227 (85.9%)
Leyser-Whalen, 2013[150]	U.S.	286	243/286 (85.0%)	NR
Mahmud, 2015[148]	U.S.	211	68.6% before eReminder 78.4% after	NR
Pachy, 2009[141]	France	25	24/25 (96%)	US: 21/21
Paladini, 2015[142]	Italy	27	27/27 (100%)	US: 35/51 devices HSG: 50/51 devices
Panel, 2011[42]	France	382	317/341 (93.0%)	NR
Povedano, 2012[36]	Spain	4306	4108/4242 (96.8%)	X-ray (plus [137,142]TVU or HSG when indicated): 4095/4108 (99.7%)
Rajecki, 2014[43]	Finland	120	NR	X-ray or US: 85.8%
Rodriguez, 2013[44]	U.S.	229	229/281 (81.4%)	221/229 (96.5%)
Sakinci, 2015[37]	Turkey	32	30/30 (100%)	30/30 (100%)

Author	Country	n	Confirmation Compliance	Successful Completion of Confirmation Test[b]
Savage, 2009[32]	U.S.	884	739/854 (86.5%)	687/739 (93.0%)
Shah, 2011[45]	U.K.	18	18/18 (100%)	17/18 (94.4%)
Shavell, 2010[147]	U.S.	14	21/73 (28.8%)	NR
Tatalovich, 2010[143]	U.S.	48	38/48	37/38
Thiel, 2011[56]	Canada	610	NR	US: 524/610 (85.9%) HSG: 85/86
Thiel, 2014[144]	Canada	30	30/30 (100%)	30/30 (100%)
Veersema, 2010[46]	Netherlands	47		X-ray: 44/47
Veersema, 2011[57]	Netherlands	1145	1051/1072 (98%)	TVU: 892/944 (64.5%) HSG: 150/164 (91.5%)

*NR=Not reported

.[a]Confirmation test used was HSG unless otherwise noted. US=Ultrasound.

MDR Reports Related to Confirmation Testing

As noted previously, FDA has received 337 MDRs which cite unintended pregnancy following Essure placement. A large number of those MDRs (175) did not provide any information related to whether the confirmation test was performed, when, and/or what the results were. Of the remaining reports, 131 specified that the HSG test had been completed, 4 noted that a TVU was done, and 27 specifically stated that no confirmation testing had been completed.

Essure Physician Labeling Regarding Patient Non-Compliance

Warnings

- *Physicians performing the Essure procedure must adhere to the Essure Confirmation Test (modified HSG) protocol in these Instructions for Use. The protocol for interpretation of the Essure Confirmation Test (modified HSG) is different from a standard HSG for infertility. In addition to patient noncompliance, incorrect interpretation of the Essure Confirmation Test (modified HSG) has led to pregnancy.*

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place. Some of these pregnancies were due to patient non-compliance, which included failure to:*

    - *use alternate contraception during the 3-month "waiting period" prior to Essure Confirmation Test;*
    - *return for the Essure Confirmation Test (modified HSG) to determine if the inserts are in the correct location and tubal occlusion is present; and*
    - *use alternate contraception or undergo sterilization by another method if the Essure Confirmation Test is (modified HSG) reveals tubal patency. In this case, the clinician*

should inform the patient of the Essure Confirmation Test (modified HSG) finding and counsel her not to rely on the Essure System for contraception.

Therefore, it is critical that clinicians properly counsel patients regarding the risk of pregnancy (including ectopic pregnancy) attributable to non-compliance during all stages of the Essure procedure.

Essure Patient Labeling Regarding Patient Non-Compliance

- *You can rely on Essure for birth control only after your doctor has reviewed your Essure Confirmation Test results and told that you may rely. If you rely on Essure for birth control before having your Essure Confirmation Test, you are at risk of getting pregnant*
- *Talk to your doctor about which method of birth control you should use for the 3 months after the procedure. Some women can remain on their current birth control. Other women, such as those using an intrauterine device or contraceptive, will need to switch to another method.*
- *It can take longer than three months for the Essure procedure to be effective. In rare cases, it has taken up to 6 months. Make sure to continue using an alternate form of birth control up until your doctor has reviewed your Essure Confirmation Test results and confirmed that you can rely on Essure for birth control*
- *After 3 months, a doctor administers the Essure Confirmation Test using contrast dye and a special type of x-ray. The test confirms that the inserts are placed correctly, your fallopian tubes are blocked, and pregnancy will be permanently prevented. Until you receive confirmation from your doctor, you must continue to use another form of birth control to prevent pregnancy. Essure inserts do not contain hormones, so you'll continue to have your normal period and your ovaries will continue to release eggs. Since the eggs cannot be fertilized, they are simply absorbed back into your body.*

Appendix B: Physician Labeling for the Essure System

Appendix C: Patient Labeling for the Essure System

Appendix D: Mandatory Medical Device Reporting

Appendix E: Summary of Safety and Effectiveness Data, Original Approval (P020014)

Appendices B, C, D, and E are provided in separate pdf files.

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EXHIBIT H

Essure Problems:

Utilizing Facebook and Mobile Apps in Pharmacovigilance

Chi Y Bahk1, Melanie Goshgarian2, Krystal Donahue2, Clark C Freifeld1, Christopher Menone1, Carrie Pierce1, Harold Rodriguez1, John S Brownstein1, Robert Furberg3, Nabarun Dasgupta1

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2 “Essure Problems” Facebook Group
3 RTI International, NC, USA

Chi Bahk, MS

epidemico

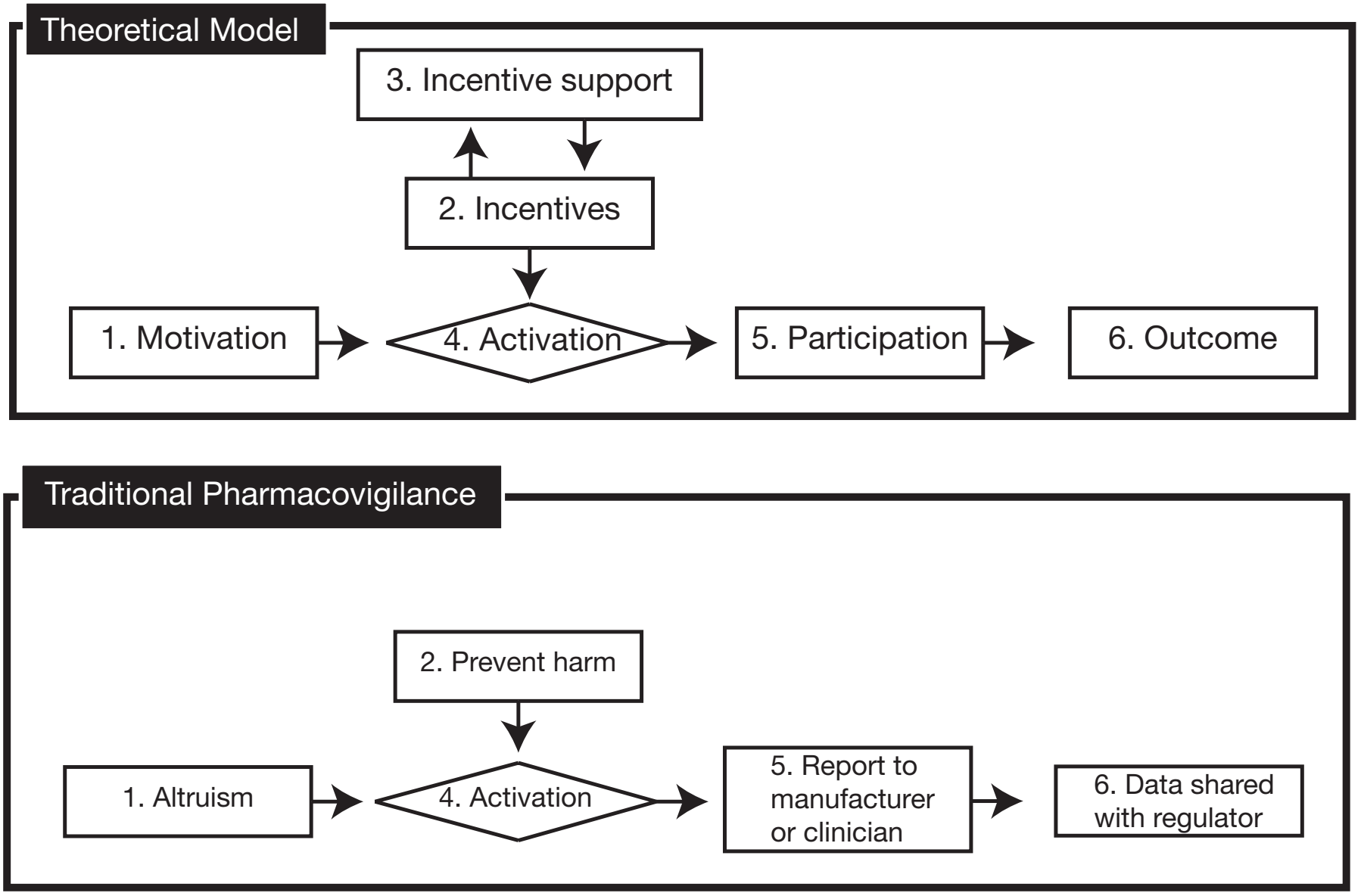
Aug 25 2015
ICPE

Disclosures

- This research was funded in part by the Center for Devices and Radiologic Health of the US Food and Drug Administration.
- Presenter is an employee of Epidemico, developer of MedWatcher App. Epidemico does not commercially benefit from the public's downloading or use of the App. We do commercialize the information technology aspects of this research.
- This presentation contains adverse event information for a product manufactured by Bayer HealthCare Pharmaceuticals. Epidemico has no relationship with Bayer, and the manufacturer was not notified ahead of time about this presentation.
- This presentation contains patient-related information, which has been approved for presentation purposes by patient group.

"I forget. If I have an adverse reaction, do I call my doctor or my lawyer?"

MIAB Model for successful crowdsourcing



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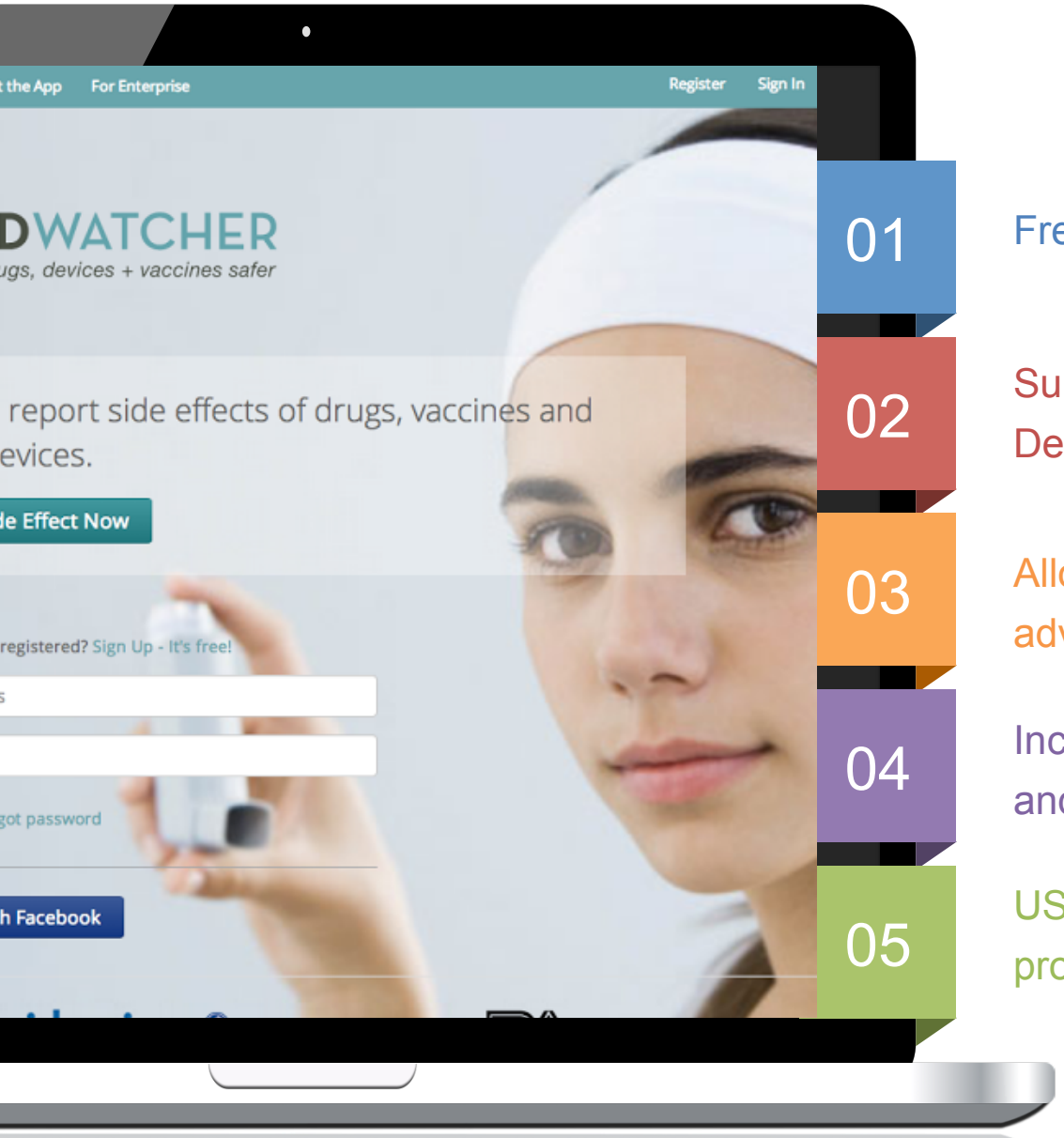
MedWatcher App



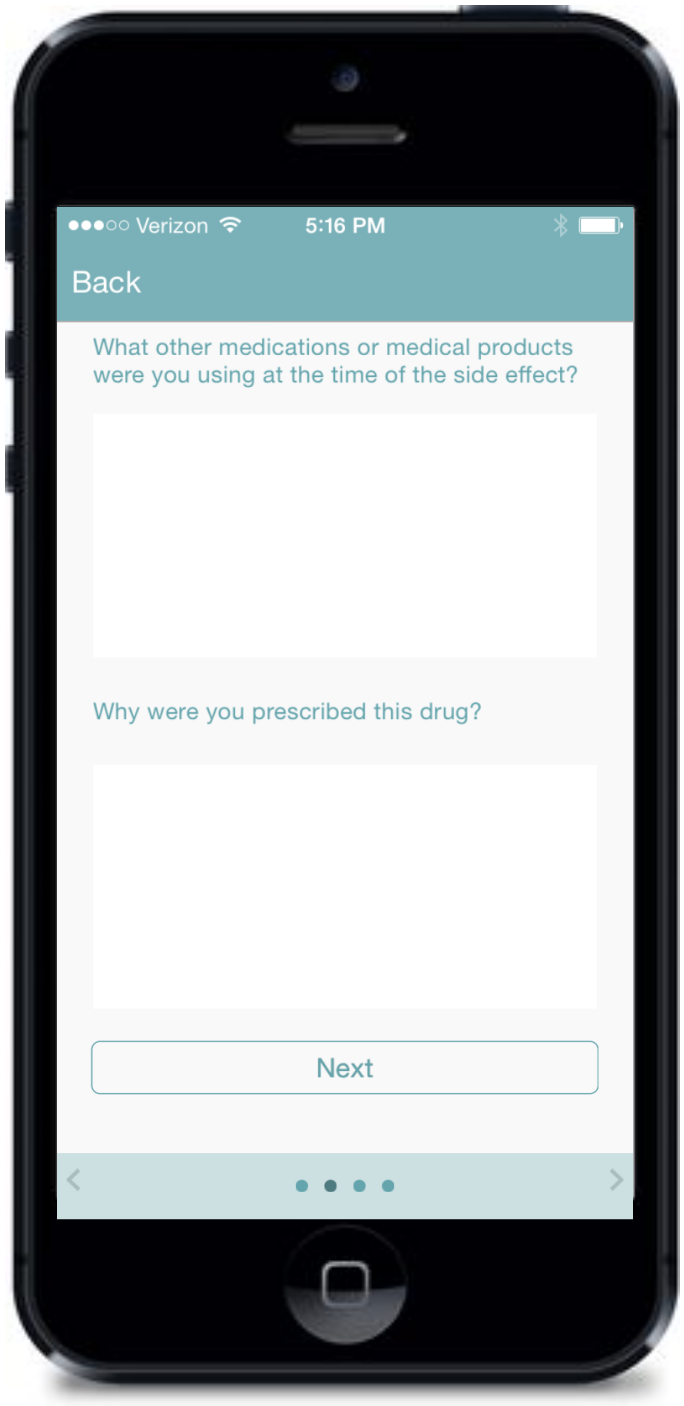
01 Free, user-friendly Web & mobile app

02 Supported by US FDA Center for Devices and Radiologic Health

03 Allows for rapid reporting of suspected adverse events

04 Increase public access to drug, device, and vaccine information

05 US launch in 2010; EU expansion in in progress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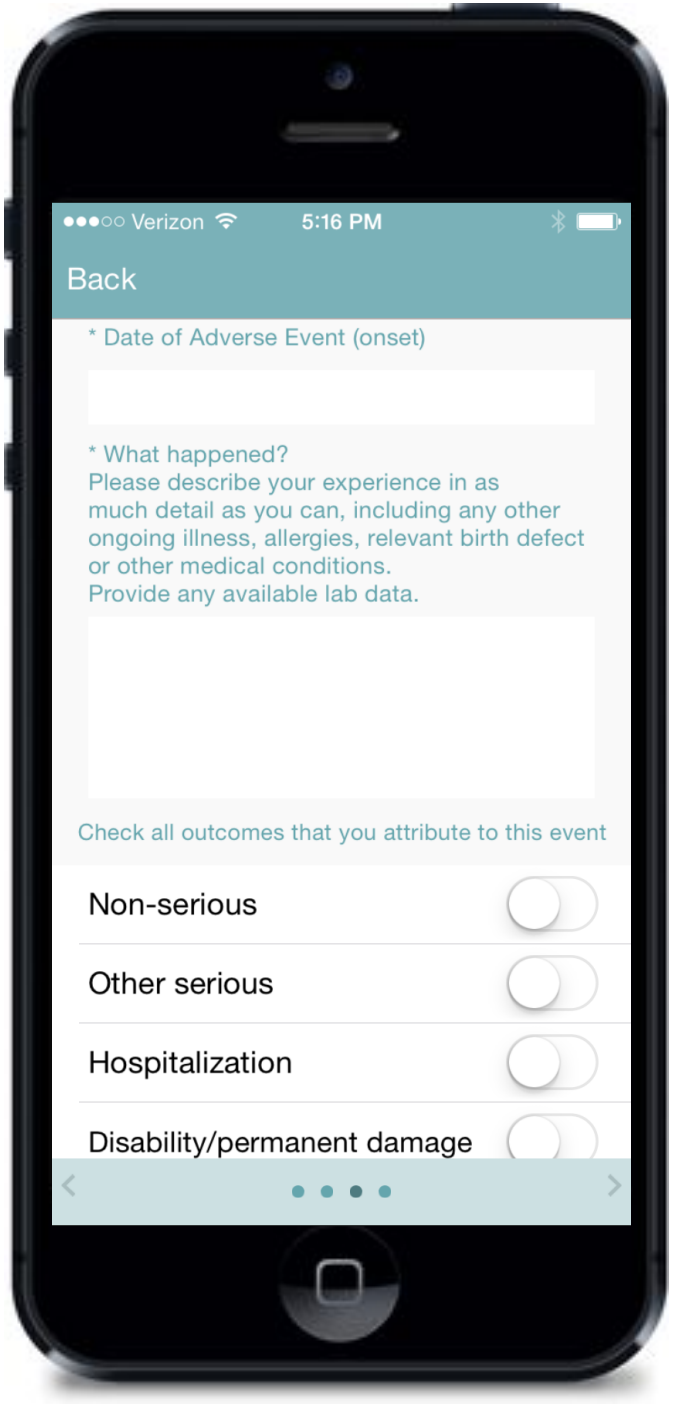
Back
What other medications or medical products were you using at the time of the side effect?
Why were you prescribed this drug?
Next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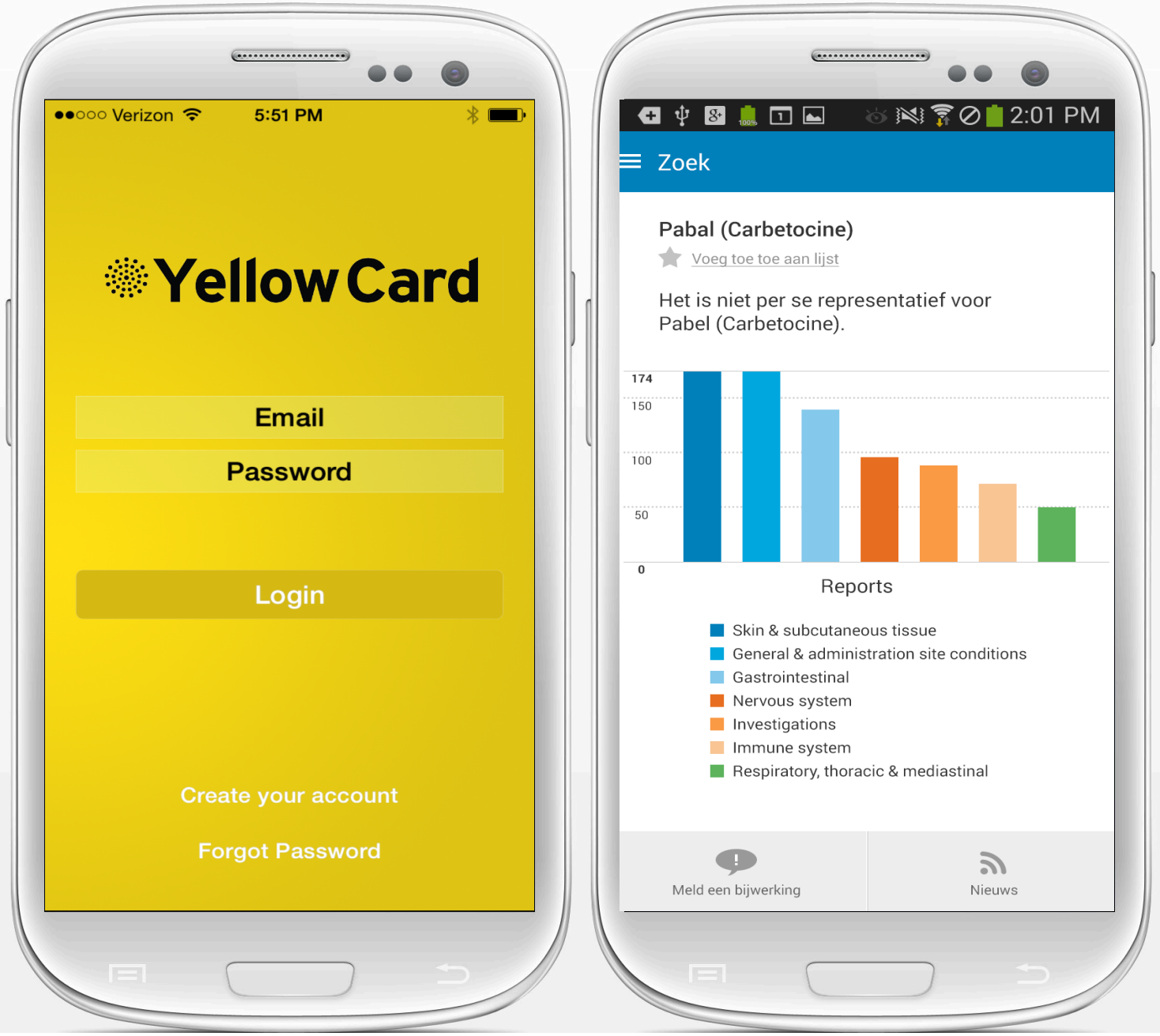
Back
* Date of Adverse Event (onset)
* What happened?
Please describe your experience in as much detail as you can, including any other ongoing illness, allergies, relevant birth defect or other medical conditions.
Provide any available lab data.
Check all outcomes that you attribute to this event
Non-serious
Other serious
Hospitalization
Disability/permanent damage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174
150
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50
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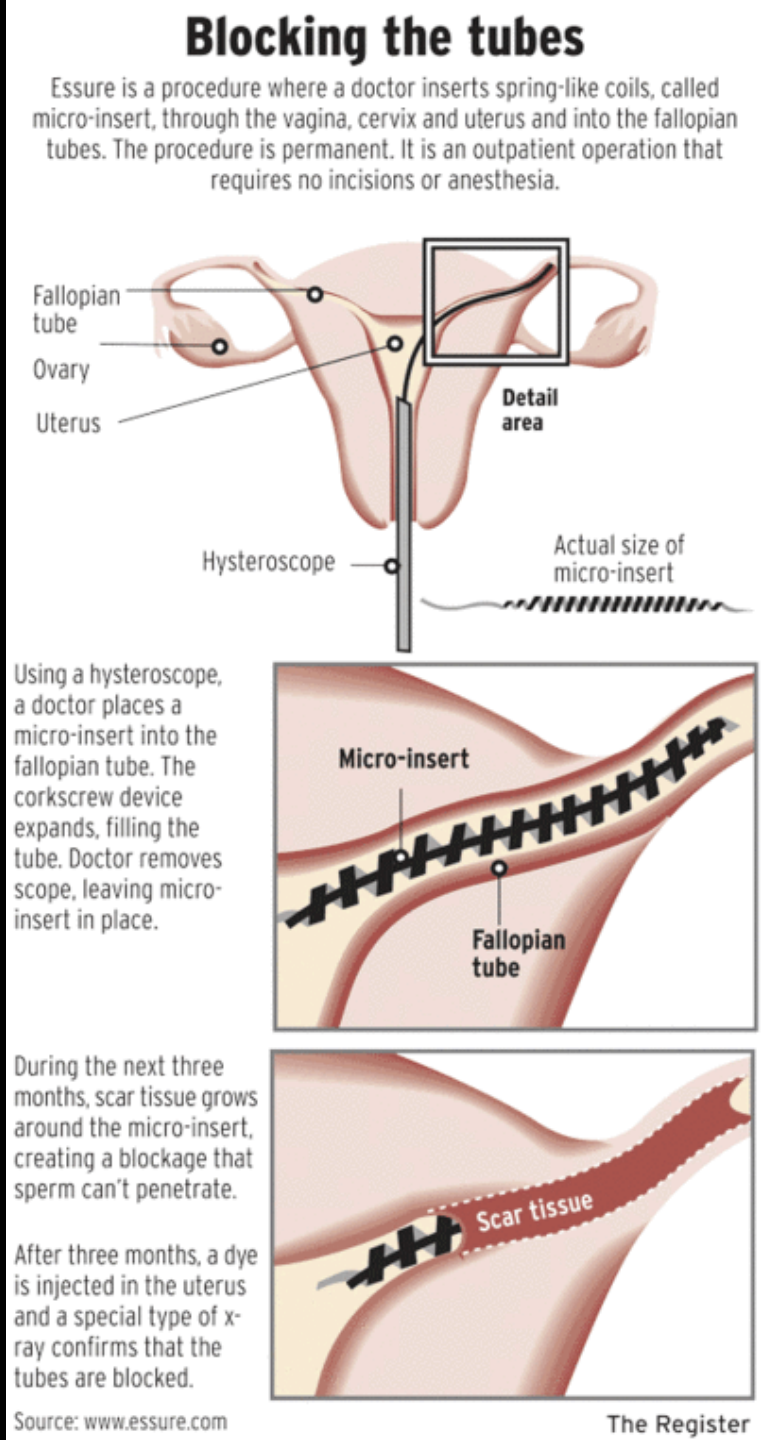
Reports
Skin & subcutaneous tissue
General & administration site conditions
Gastrointestinal
Nervous system
Investigations
Immune system
Respiratory, thoracic & mediastinal
Meld een bijwerking
Nieuws

Essure

- Implantable, permanent birth control for women
- Coils made of polyester fibers, nickel-titanium and stainless steel, implanted into fallopian tubes
- US FDA approved 2002
- 5-year fail rate: 0.27%
- Common and notable AEs: abdominal pain, pelvic pain, abdominal distension, vaginal haemorrhage, alopecia, allergy to metals, device dislocation, pregnancy with contraceptive device, salpingectomy, hysterectomy



“Essure Problems” Facebook Group

01

Launched in March 2011 by patient, Angie Firmalino

02

As of August 2015, more than 19,000 members

03

Environment where patients can share information and experiences

04

Managed by 11 volunteer administrators; 2 elected as co-authors

05

Engaged by MedWatcher team starting October 2013

Methods

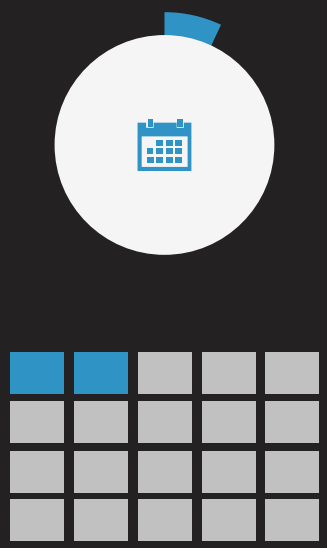
Outreach to Facebook group “Essure Problems”

Work with administrators to promote AE reporting via mobile app

1,349 AE reports (May 2013 – Dec 2014) coded & analyzed

WHO-UMC VigiGrade completeness scores calculated & MIAB model for successful crowdsourcing applied

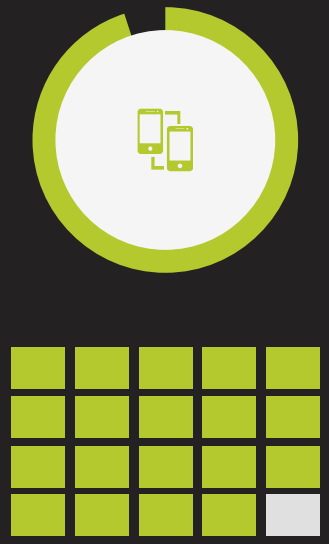
Findings: Essure Reports per Month



7 per month

FDA MAUDE

132 months marketing authorization



103 per month

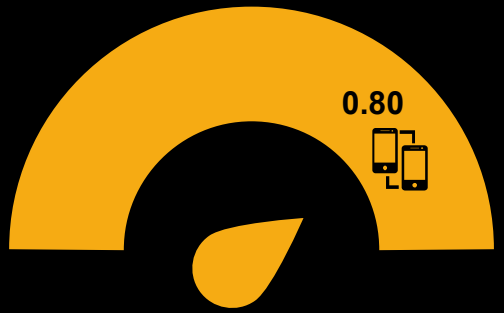
MedWatcher Mobile App

19 months collaboration with patient community

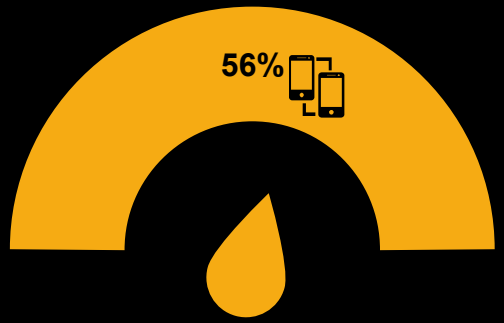
Findings: Crowdsourcing vs. Traditional Pharmacovigilance

Comparison of Essure mobile app submissions with WHO-UMC database

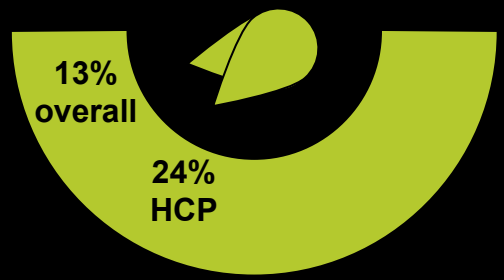
Average Time for Submission
App users submitted in 11.4 minutes compared to 40 minutes via traditional forms



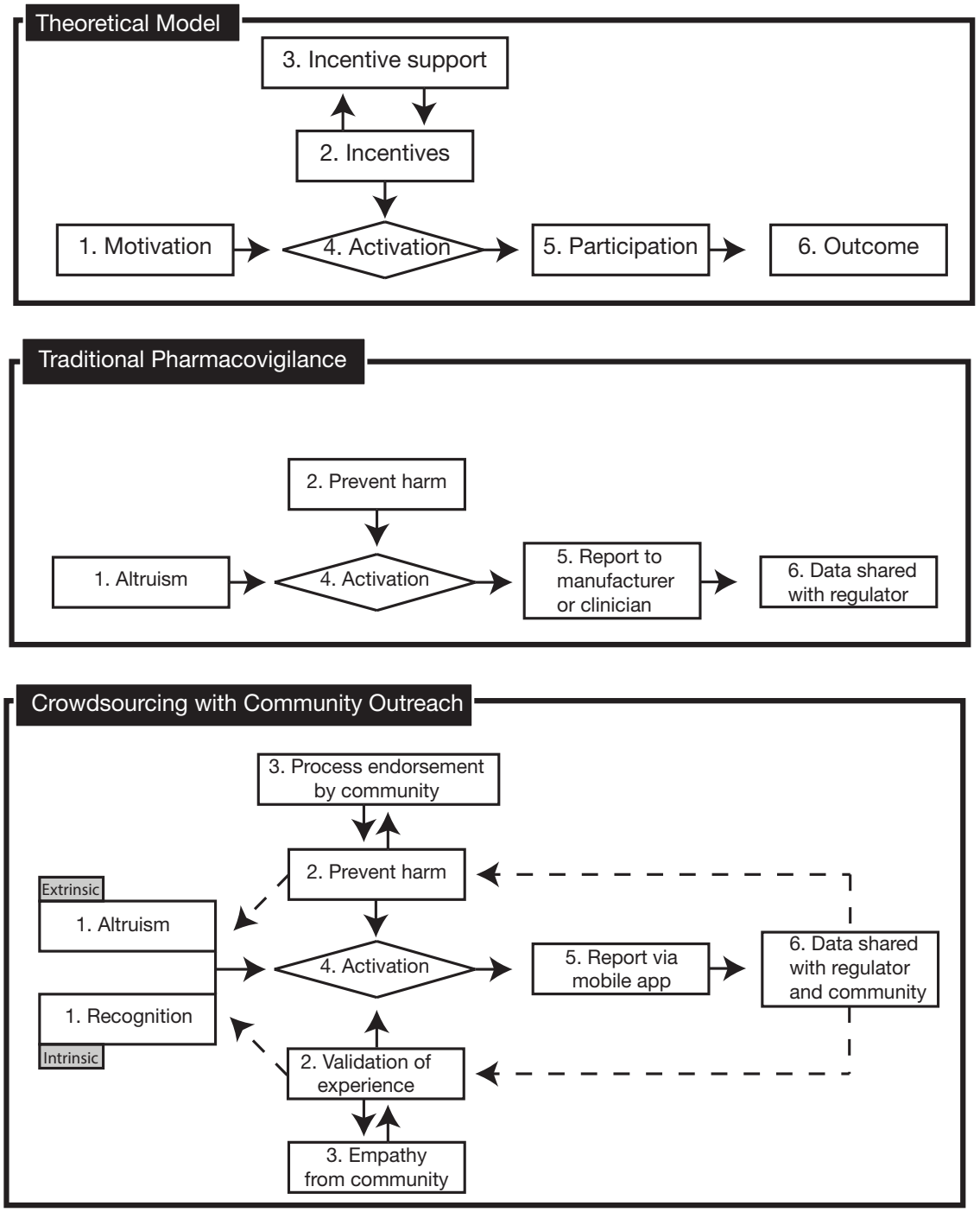
Average VigiGrade Score
App submissions were more complete than global avg in VigiBase.



"Well-documented" Reports
App reports were considered "well-documented" 4x more often than global avg in VigiBase



Bergvall T 2013 *Drug Safety*



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Amanda Douglass

Come on ladies, do we want the FDA to hear us? Or do we want to spend the next 10 years in a FB group complaining about not being heard. Want the product off the market? Read the pinned post and follow the link to report your symptoms to the FDA. Even if they are NOT confirmed yet by your doctor, even if you are not having surgery, even if your essure caused you to trip and get a splinter in your toe. We have an obligation to our daughters to report it, if we don't, this could be a viable birth control option for them when they come of age.

Unlike · Comment · Unfollow Post · about an hour ago

You and 15 others like this.

Debbie Ezra Reporting it might help those without insurance get some help.
about an hour ago via mobile · Like

Debbie Ezra Can I triple like this!!!
about an hour ago via mobile · Like · 1

Chi Bahk Easiest way to report to the FDA:
www.medwatcher.org

MedWatcher – Make drugs, devices + vaccines safer
www.medwatcher.org
MedWatcher is a new way to track and report side effects of drugs, medical devic...
See More

about an hour ago · Like · 1 · Remove Preview

Write a comment...

Crystal Mays

Unlike · Comment · Unfollow Post · 6 minutes ago near Fortson, GA

You, Angela Desa and 3 others like this.

Angela Desa Woot woot! AWESOME!!
5 minutes ago via mobile · Unlike · 2

Angela Desa I swear I love this app
4 minutes ago via mobile · Unlike · 2

Crystal Mays Me too!!!
about a minute ago via mobile · Unlike · 1

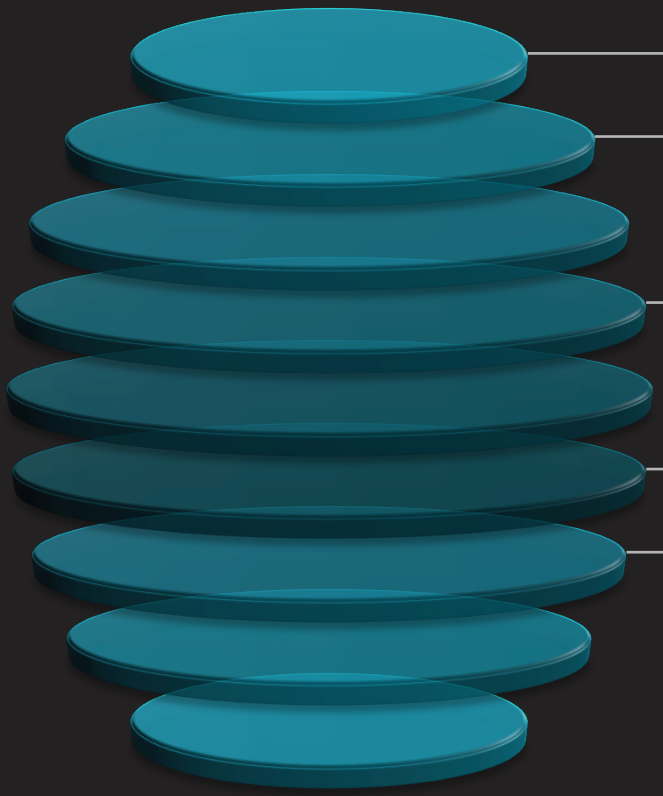
Chi Bahk This is awesome, thank you ladies. I'm glad MedWatcher can help get your stories heard!!
a few seconds ago · Like

Write a comment...

To Date

- June 24, 2015: FDA announces Advisory Committee meeting on Essure
- "The majority of reports received since 2013 have been voluntary reports, mostly from women who received Essure implants"
- 5093 reports on MAUDE through May 31, 2015; 2087 through MedWatcher app
- To date, 3592 reports received through MedWatcher app

LIMITATIONS OF SOCIAL MEDIA & MOBILE APPS



01

CAUSALITY

Patients may not correctly assess causality. *Define methods to measure probability of real world significance.*

02

VOLUME

Volume of reports likely to be large. *Reduce false positives and create automated tools to triage information.*

03

SIGNAL DETECTION

Very limited statistical methods to detect problems. *Collaborate with academia, industry and regulators to refine methods.*

04

PRIVACY

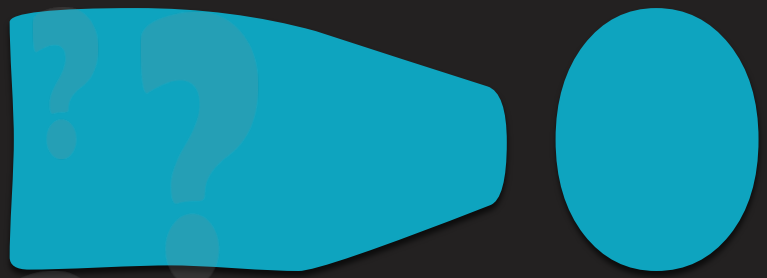
Patient privacy expectations and fear of government oversight. *Use publicly available data only.*

05

REGULATION UNCLEAR

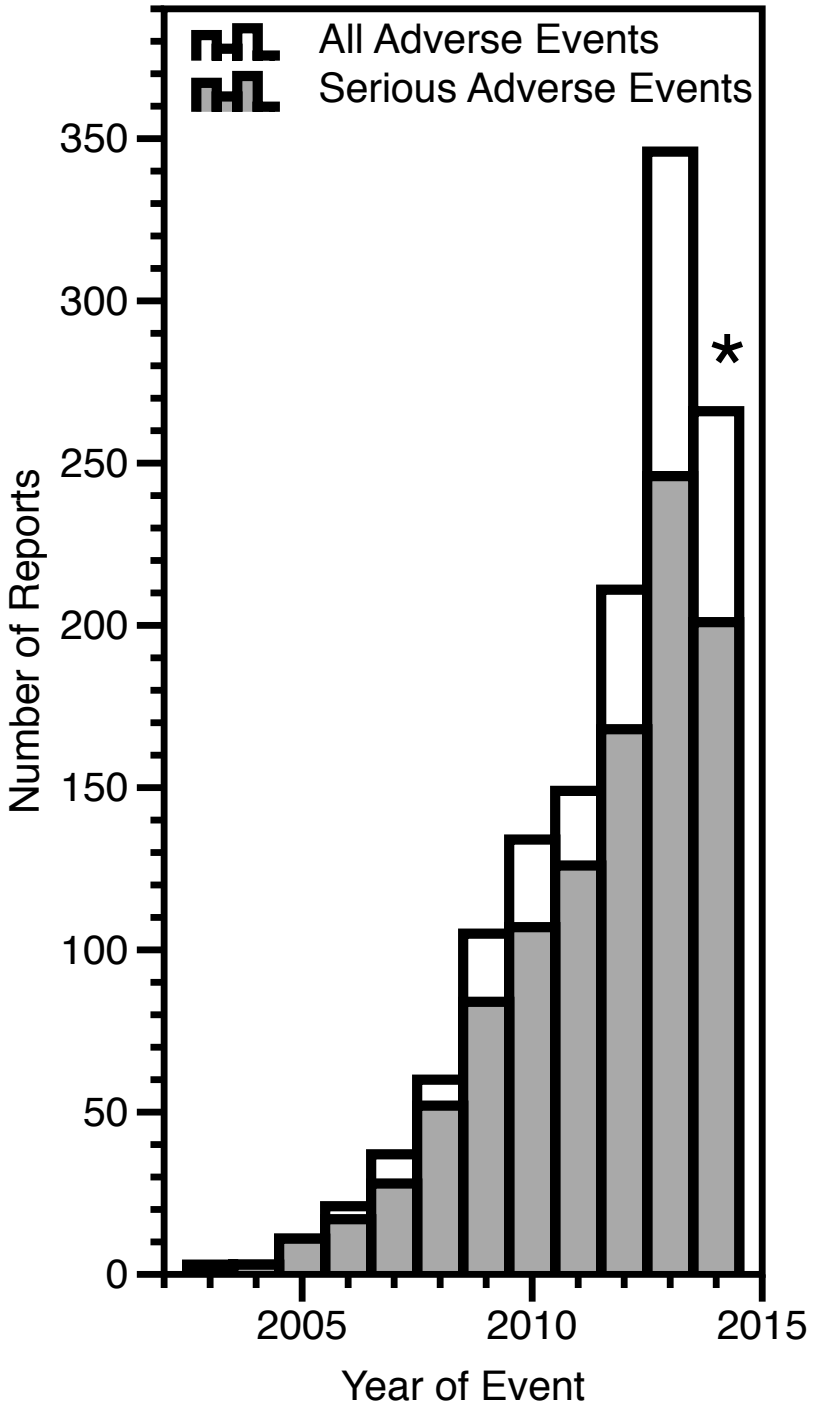
When is there an obligation to monitor or report? *Work with regulators and industry to clarify guidance.*

QUESTIONS?



chi@epidemico.com

www.medwatcher.org
@med_watcher
info@medwatcher.org


All Adverse Events
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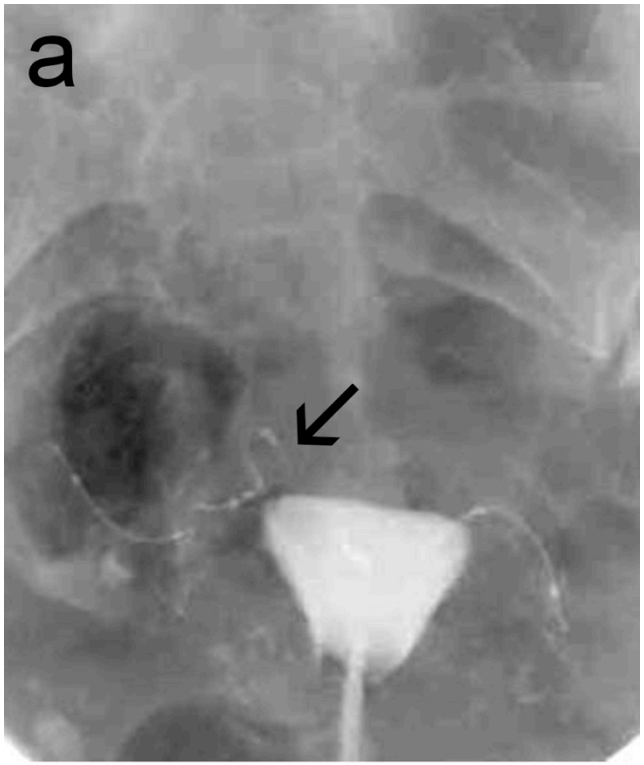
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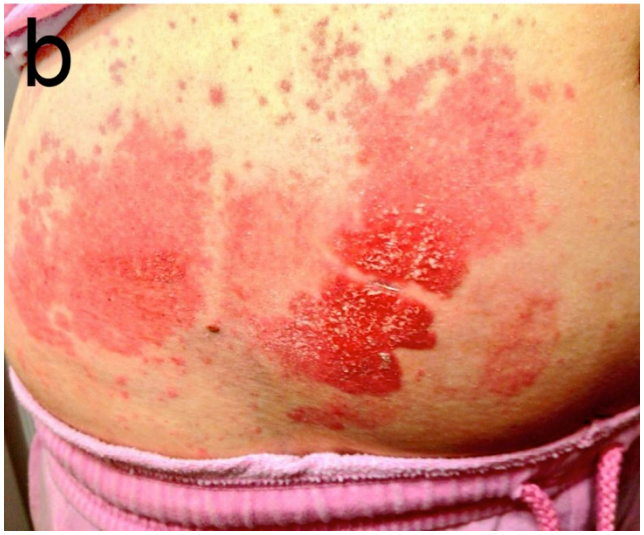
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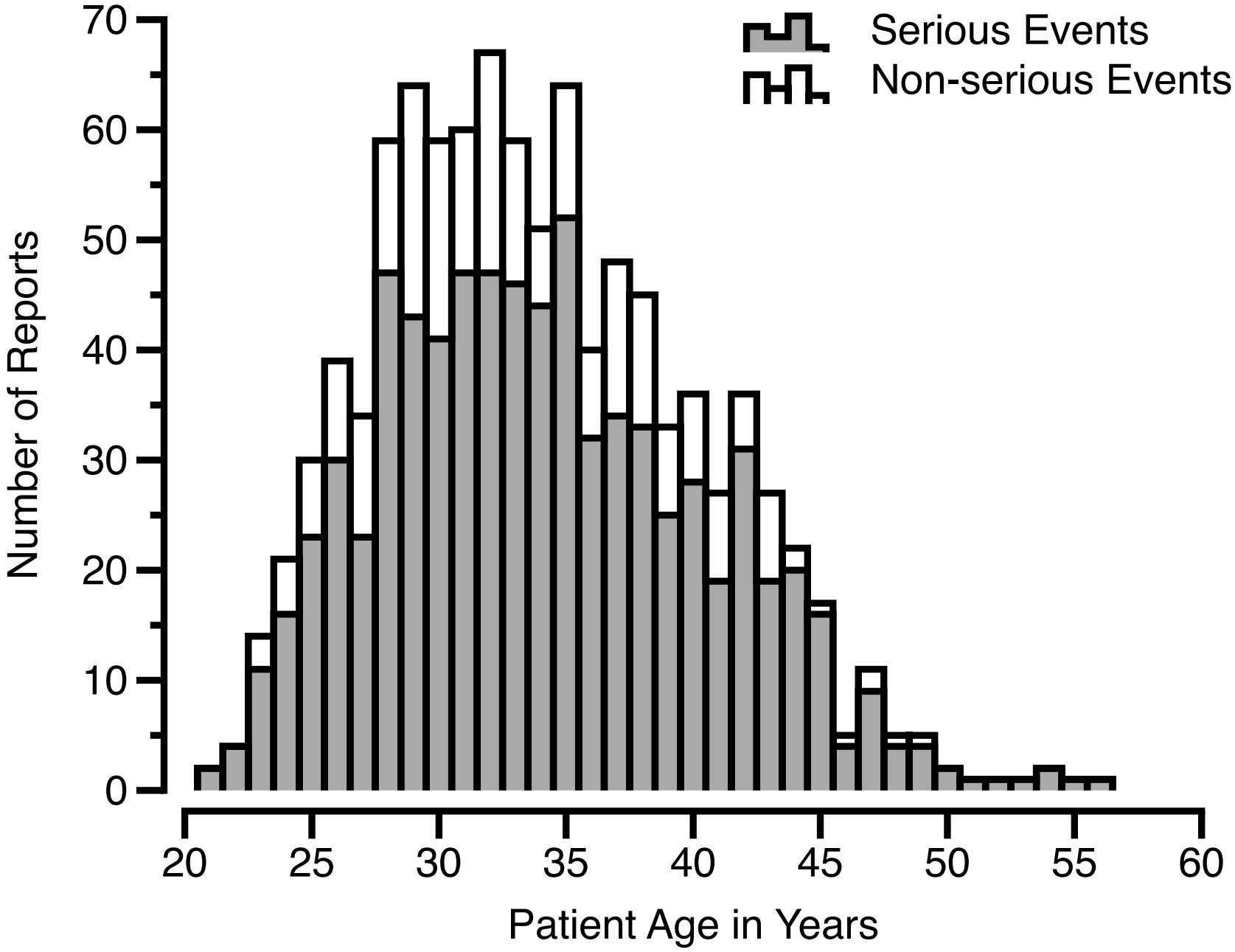
Serious Events
Non-serious Events
Number of Reports
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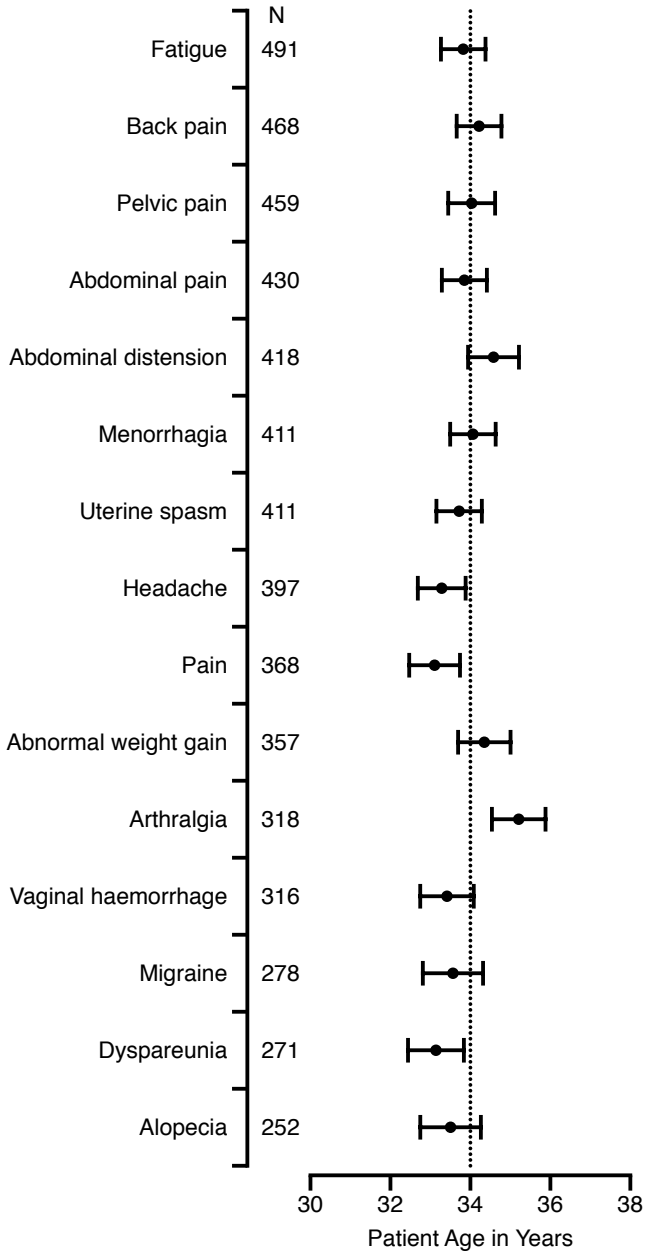
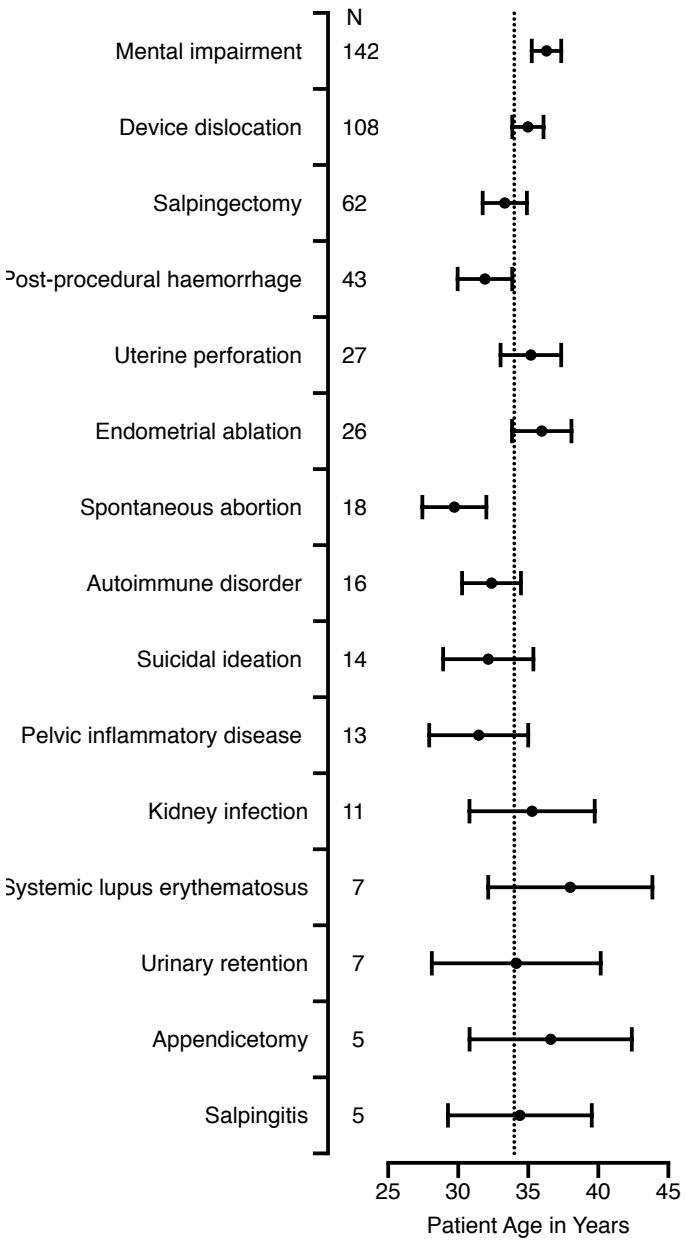
Patient Age in Years

Most frequently reported AEs

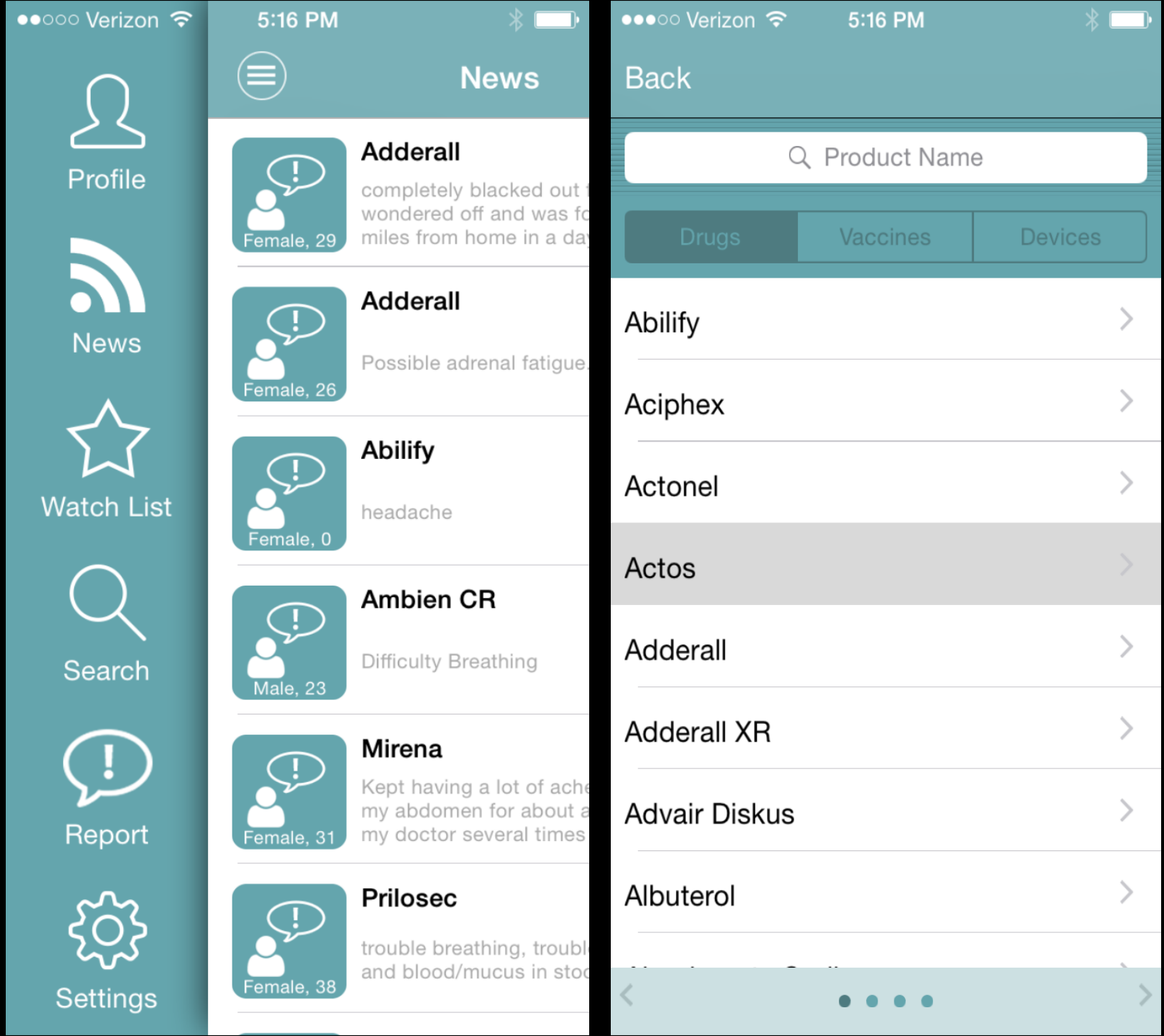


Most frequently reported important medical events



Data Flow for MedWatcher App

Transmission to FDA using electronic gateway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Adderall
Possible adrenal fatigue.
Female, 26
Abilify
headache
Female, 0
Ambien CR
Difficulty Breathing
Male, 23
Mirena
Kept having a lot of ache
my abdomen for about a
my doctor several times
Female, 31
Prilosec
trouble breathing, troubl
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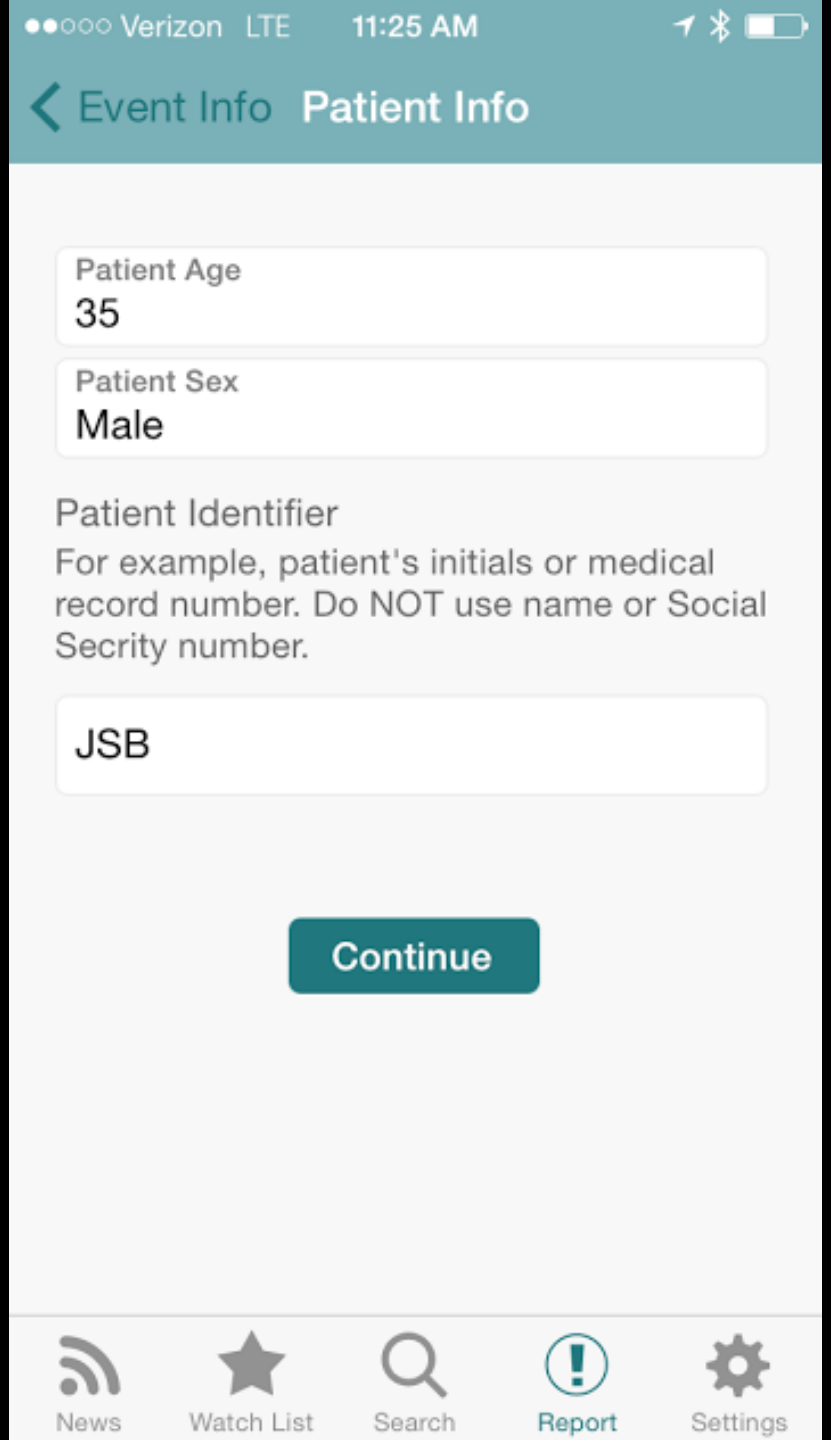
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Event Info
Patient Info
Patient Age
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Patient Identifier
For example, patient's initials or medical record number. Do NOT use name or Social Secrity number.
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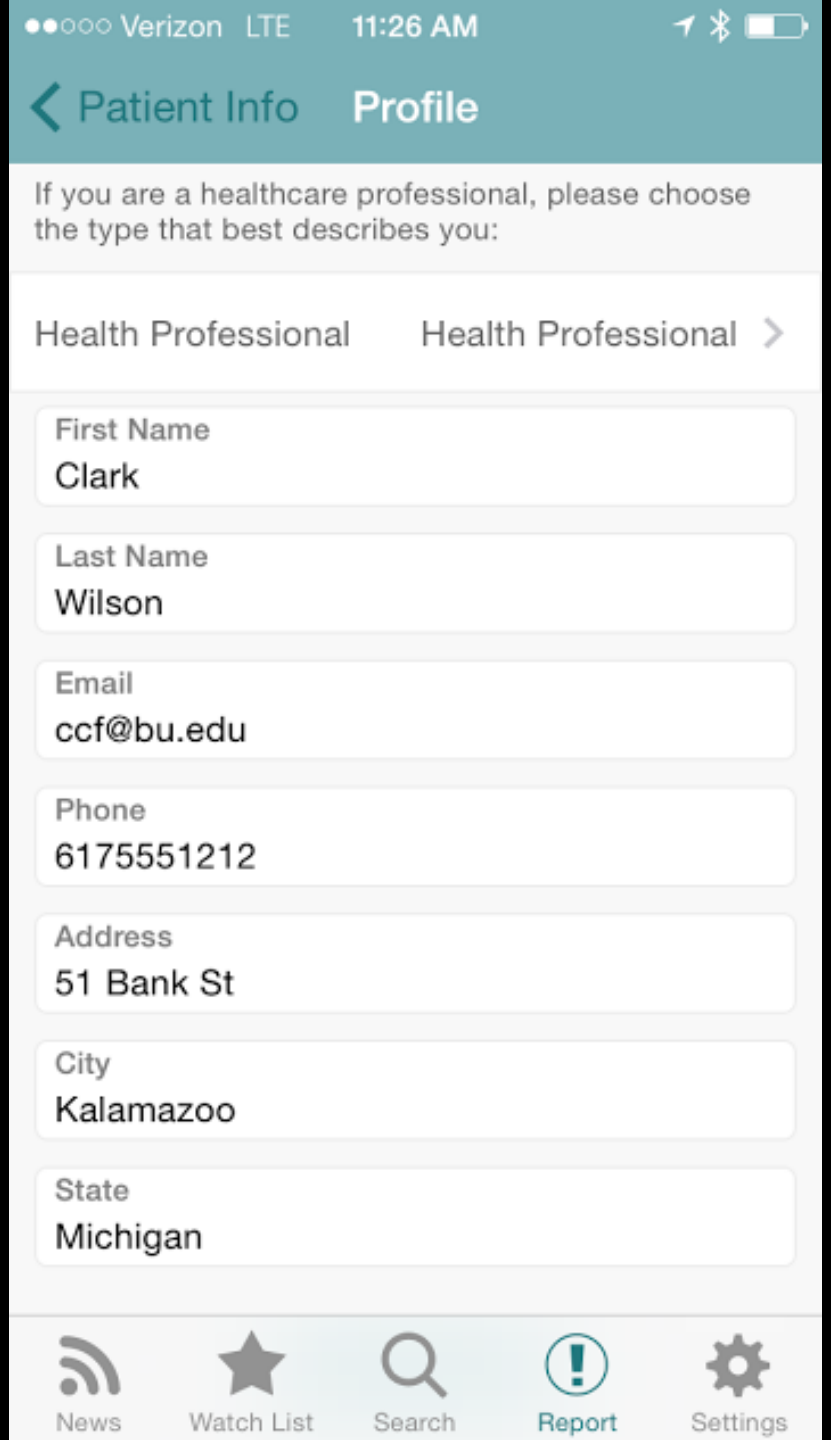
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Thanks for reporting to MedWatcher * Epidemico x

MedWatcher info@medwatcher.org via amazonses.com 4:18 PM (1 minute ago)

to me

My Newsfeed
My Account

Thanks for your report.

Dear Carrie,

Thank you for your recent submission to MedWatcher. Our team is reviewing it now.

Sharing your report helps make drugs, devices and vaccines safer for everyone!

We may follow up with you by email if any questions come up, but for now, your work is done. We'll let you know when we've transmitted your report to the FDA (via electronic gateway for devices, fax for drugs) or CDC for a vaccine report.

Feel free to email us at info@medwatcher.org if you have any questions.

Best,
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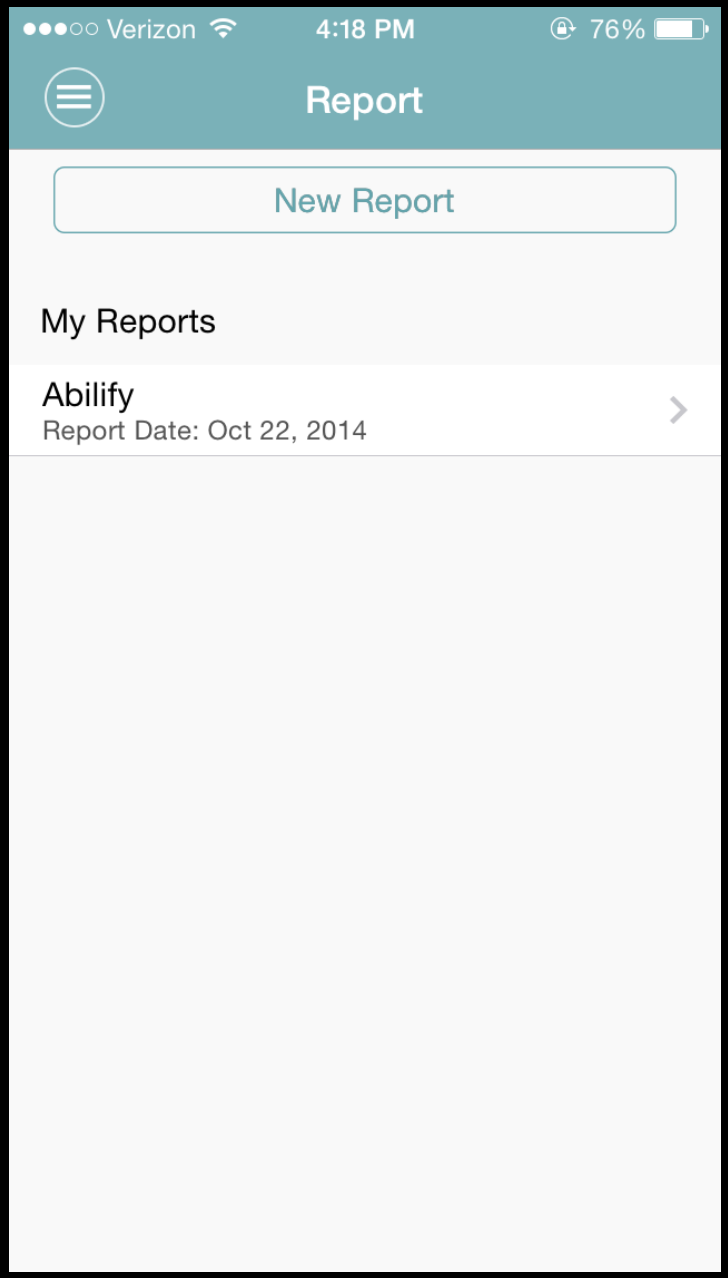
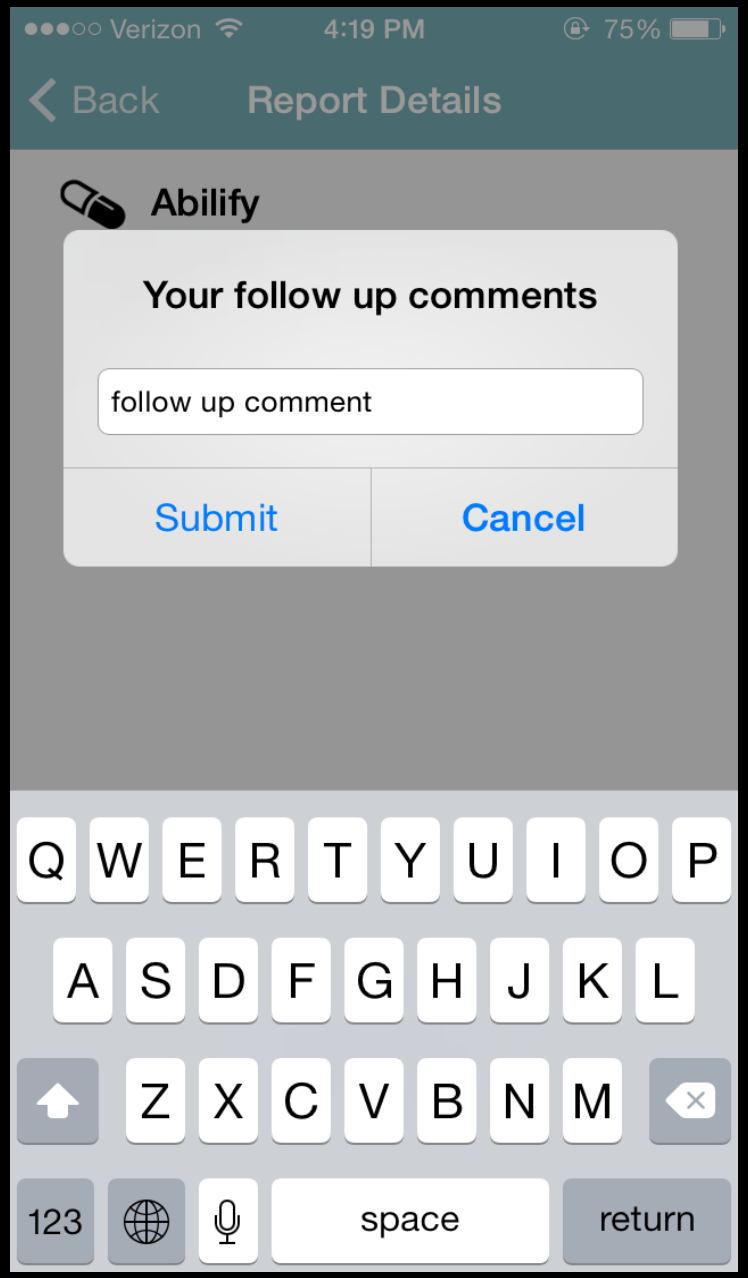
Twitter: @med_watcher

Manage email preferences


Verizon
4:18 PM
76%
Report
New Report
My Reports
Abilify
Report Date: Oct 22, 2014


Verizon
4:19 PM
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Report Details
Abilify
Your follow up comments
follow up comment
Submit
Cancel
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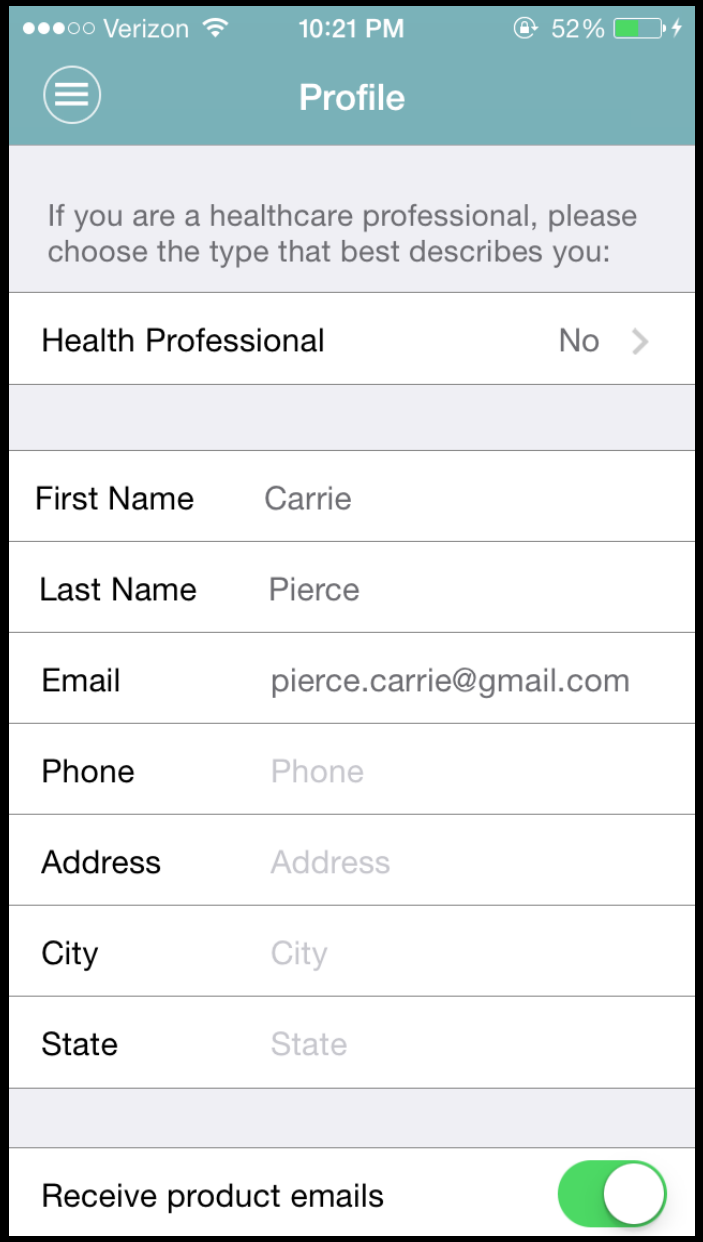
Verizon
10:21 PM
52%
Profile
If you are a healthcare professional, please choose the type that best describes you:
Health Professional
No
First Name
Carrie
Last Name
Pierce
Email
pierce.carrie@gmail.com
Phone
Phone
Address
Address
City
City
State
State
Receive product emails

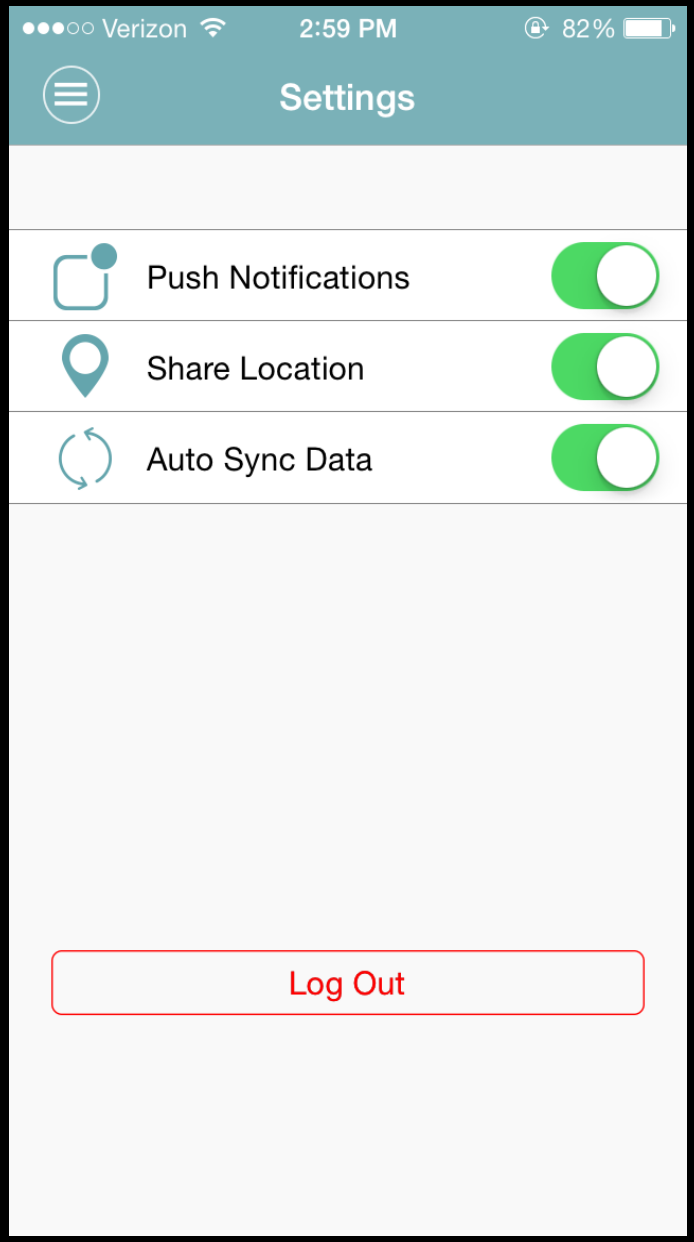
Verizon
2:59 PM
82%
Settings
Push Notifications
Share Location
Auto Sync Data
Log Out

EXHIBIT I

Shelly Thompson

Shelly Thompson

SPREAD THE WORD, DON'T BE SILENT.
SPEAK UP,SPEAK OUT, SILENCE KILLS!
#SecertsKeepUSICK

Please be kind and feel free to share, because that's what we do is care.

Nov 12, 2017, 9:16 PM

Attachment(s):

- `messages/inbox/ShellyThompson_pmdtZzz44g/photos/23602174_10214570828043548_888422003_n_10214570875764741.jpg`

Shelly Thompson

Ok sounds like a plan thank you again

Jun 7, 2016, 4:52 PM

Angie Firmalino

lol thats funny, thanks! ill let you know if i see your name in the filed cases. i have to find them.....

Jun 7, 2016, 4:52 PM

Shelly Thompson

Ok i most certainly will. Thank you so much for answering my concerns. Im glad you Ladies had fun on your trip. I get all your updates on here, you're like the reason i keep a phone with internet,for fb.lol
I'm your biggest fan

Jun 7, 2016, 4:51 PM

Angie Firmalino

they were very strategic with who they filed and why..... i wasnt in the first two filings, just got in on the third one

Jun 7, 2016, 4:48 PM

Angie Firmalino

conact marcus directly. ill check the thee cases filed to see if your name is in there or not. but if its now, it will be soon. but shoot him an email anyway in the meantime for an update. susen@kpw.law.com

Jun 7, 2016, 4:47 PM

Shelly Thompson

I was like one of the first100. That you enailed the paperwork to, and i printed it off and mailed to them the next day, which was like yrs ago,it feel like. But you contacted me and let me know before it went public in group. So i was just curious. I have their numb i believe so I'll call but they really never give me much info the secretary is only one i can ever get. ?

Jun 7, 2016, 4:45 PM

Angie Firmalino

I just got back from meeting with Marcus in Florida over the weekend. If you are not already filed as of right now, you should be by months end. Dont ever feel shy contacting the firm for an update. If you want Marcus's email just let me know!

Jun 7, 2016, 4:41 PM

Angie Firmalino

KPW? yes. they have three sets of clients filed in PA and are prepparing to file the remainder by the end of June.

Jun 7, 2016, 4:40 PM

Shelly Thompson

Has our attorney made any movements yet do you know.

Jun 7, 2016, 4:39 PM

Shelly Thompson

Absolutely, agree.

Mar 22, 2014, 2:16 PM

Angie Firmalino

I don't think anything that THEY say can be used against anyone else. all the cases are individual, so only you can be held accountable for your actions and posts. some of the women were going to bayers facebook page and harassing them basically, and that kind of behavior may come back to haudnt them. I think the attoneys have a lot of strong evidence and will be able to get some settlements out of them. time will tell. I know the positive power of the group is only going to continue to grow and lift us up. we will persevere and be heard, that's for sure!

Mar 22, 2014, 2:09 PM

Shelly Thompson

Yeah I was wondering what the heck was going on,I left their group when the grab started a week or so ago,I never posted there hardly ever, but notice the hostility and was but comfortable being acquainted with them. That's another concern I had,I know something happened with files before being deleted or what have you. Thank you for the insight. I think I got past my anger with them as far as posting anything,. I'm glad you ladies are on TOP OF EVERYTHING. I ADMIRE EACH OF YOU ADMINISTRATION, and grateful that you deeply have concern for each of us. But thank you for the validation. I hate to think what if,bc you know how that can go, but what if the other group by some odd sense of behavior gets wind back to BAYER,etc is our ground strong enough to up hold without them covering anything up? I personally don't feel so,bc how I read and understood it. But either way I feel this is our time and the universe is moving all in our favor and time for them to be held accountable and responsible. And no worries,I know you will get back with me as you may. :-) thank you again

Mar 22, 2014, 2:06 PM

Angie Firmalino

we don't want bayer to know what weve found ot

Mar 22, 2014, 1:55 PM

Angie Firmalino

also, we do not share a lot of the research and information on the page anymore, regarding what we know and what we are sharing with the lawyer

Mar 22, 2014, 1:54 PM

Angie Firmalino

it would only come back to bite us in tha ass

Mar 22, 2014, 1:54 PM

Angie Firmalino

as far as moles fro bayer or conceptus or the fda, we assume we are being watched. so it is always important to watch what youa re saying. especially now that we are entering litigation. people should not post threatening or humiliating things about bayer or essure

Mar 22, 2014, 1:54 PM

Angie Firmalino

but I think the admins have handled it and removed them.

Mar 22, 2014, 1:53 PM

Angie Firmalino

we seem to have some women from the awareness group causing issued in our group again

Mar 22, 2014, 1:53 PM

Angie Firmalino

sorry for the delay,michelle called me raight as you sent that

Mar 22, 2014, 1:53 PM

Shelly Thompson

Just concerned if there is a certain person to be aware of, or alias? As I read in the one group. It's hard for me to tell sometimes,bc I do have slight paranoia. I do try to watch what I say and how I word it, lol. But I noticed one and she seems to be page jumping with the same question s and maybe she's legit, maybe not. Do I guess what I should ask , is.. if there is a more what information exactly would or could they be looking to gain? I'm sorry if this is a asinine concerns, but I couldn't help but to ask. So I apologize in advance,I know you ladies are busy and have your hands full. I just want to be helpful but at the same time cover my butt by not sticking my feet in my mouth.lol , sorry my phone internet being slow again

Mar 22, 2014, 1:07 PM

Angie Firmalino

im here, whats going on?

Mar 22, 2014, 12:36 PM

Shelly Thompson

Good afternoon. :-) thank you ,I must of had a brain fart and went straight to you. I apologize, but good to see your recovering well. I did join the ptls page, and learning more,sigh. just was concerned in this mole thing, so if and when you have a moment, no big hurry. Or if there is andmin that maybe able to help, would any one do.

Mar 22, 2014, 12:35 PM

Angie Firmalino

Morning, I was sleeping. Still have an issue on the page to discuss? If you are on when I'm off, u can usually find wither Angela Desa, Amanda Dykeman, or Kim Myers on.

Mar 22, 2014, 8:00 AM

Shelly Thompson

Angie ,I hate to bother you but are you up or busy. I have a concern about a group post

Mar 22, 2014, 1:28 AM

Shelly Thompson

I love you sister :-)

Mar 14, 2014, 5:12 PM

Shelly Thompson

Never mind I see it thank you

Mar 13, 2014, 1:48 AM

Shelly Thompson

Just wanted to make sure I send this to the fort Lauderdale office

Mar 13, 2014, 1:44 AM

Shelly Thompson

Hello angie , are you up by chance

Mar 13, 2014, 1:42 AM

Angie Firmalino

you are welcome!

Mar 11, 2014, 1:06 PM

Shelly Thompson

Ok thank you

Mar 11, 2014, 1:04 PM

Angie Firmalino

just put essure question in the subject, he will get right back to you

Mar 11, 2014, 1:03 PM

Angie Firmalino

his email is susen@kpwlaw.com

Mar 11, 2014, 1:03 PM

Angie Firmalino

but i would contact MArcus directly with that last question to clarify.

Mar 11, 2014, 1:03 PM

Angie Firmalino

each individual would have their own settlement depending on injuries. if you lose, there are no costs to you. with certain claims, if the defendant wins, they can sue you for their costs. in this case, our attoneys are not filing any of those types of claims, so bayer cannot sue us for their legal costs. as far as i know there is no statute of limitations on personal injuries against the manufacturer, only medical malpractice against your doctor.

Mar 11, 2014, 1:02 PM

Shelly Thompson

Ok,just curious if it's an individual and not class action , due to some research the more envolved the less would be dispensed after spilt between all, correct? And if we lose do I have to pay court cost? If I lose can they sue me for Bill of cost to recover their legal fees? Any and all other cost that I would have if I lose? What is my statue of limitation,?

Mar 11, 2014, 12:57 PM

Angie Firmalino

individual

Mar 11, 2014, 12:51 PM

Shelly Thompson

Am I individual , or is it a class action?

Mar 11, 2014, 12:51 PM

Angie Firmalino

sure whats up?

Mar 11, 2014, 12:47 PM

Shelly Thompson

Thank you

Mar 11, 2014, 12:47 PM

Shelly Thompson

Hey angie ,I have a few questions if your not busy

Mar 11, 2014, 12:47 PM

Shelly Thompson

Ok thank you.

Mar 10, 2014, 7:33 PM

Angie Firmalino

then you just sign and mail back

Mar 10, 2014, 7:31 PM

Angie Firmalino

you can call him and ask him to mail you one with your name and info printed on it

Mar 10, 2014, 7:31 PM

Angie Firmalino

you will have to print it out to sign it.

Mar 10, 2014, 7:31 PM

Shelly Thompson

So am I able to fill this out on line and email back or do I need to print it out? Sorry, I don't have a printer so I was wondering if it can be done electronically.

Mar 10, 2014, 7:21 PM

Angie Firmalino

no prob

Mar 10, 2014, 7:19 PM

Shelly Thompson

Got it, that account goes straight to my cell. I'm reading it now. Thank you again. Your awesome

Mar 10, 2014, 7:18 PM

Angie Firmalino

let me know if you got it

Mar 10, 2014, 7:17 PM

Angie Firmalino

ok, no problem!

Mar 10, 2014, 7:15 PM

Shelly Thompson

For some reason I'm not being able to open my Yahoo mail account, would you care to send it to shellythompson30@gmail.com I'm sorry. I'll keep trying but it's telling me page can't be displayed. Im so anxious I think it's giving me a hard time.lol

Mar 10, 2014, 7:14 PM

Angie Firmalino

thanks. let me know ifyou have any questions. you can call marcus as well.

Mar 10, 2014, 6:54 PM

Shelly Thompson

O sweet Jesus,bc im awating ssi and ssd right at the moment. But if I needed to I would of made it happen. Thank you so much with all my heart. You ladies are so amazing.

Mar 10, 2014, 6:53 PM

Angie Firmalino

no costs to us at all. lawyer gets paid only if he wins

Mar 10, 2014, 6:51 PM

Shelly Thompson

I totally understand. Retainer is that in the email, getting ready to open it, just finished cooking dinner for kids. Do I need money to retain,. . Let me read it ill brb

Mar 10, 2014, 6:50 PM

Angie Firmalino

we have all mailed in our retainers, and have contacted about 125 people so far. lots of work to do

Mar 10, 2014, 6:43 PM

Angie Firmalino

you are so welcome! let me know if you have questions

Mar 10, 2014, 6:42 PM

Shelly Thompson

O no worries,I will not it leave my knowledge. I know nothing. Thank you so very much for thinking of me, ive been praying for this news. And you delivered it. I can't thank you enough.

Mar 10, 2014, 6:41 PM

Angie Firmalino

please do not share this with anybody yet. or post in the group. they want to surprise bayer. one they file the first action with a few hundred women, it will open the doors for everybody else to join in. ok ill send it now

Mar 10, 2014, 6:39 PM

Shelly Thompson
Thank you so much. Ellysha83@yahoo.com is my email
Mar 10, 2014, 6:39 PM

Angie Firmalino
your email address
Mar 10, 2014, 6:38 PM

Shelly Thompson
What do you need hun. I will do it right now
Mar 10, 2014, 6:38 PM

Shelly Thompson
I'm lost for words
Mar 10, 2014, 6:38 PM

Shelly Thompson
O boy this is wow,o my goodness
Mar 10, 2014, 6:38 PM

Shelly Thompson
Absolutely
Mar 10, 2014, 6:37 PM

Angie Firmalino
would you be interested in me emailing you the info?
Mar 10, 2014, 6:34 PM

Angie Firmalino
weve been asked to reach out to a few hundred women
Mar 10, 2014, 6:34 PM

Angie Firmalino
but it has to be kept confidential for now
Mar 10, 2014, 6:34 PM

Angie Firmalino
we have found a law firm willing to file a claim against bayer
Mar 10, 2014, 6:34 PM

Angie Firmalino
bearer
Mar 10, 2014, 6:34 PM

Angie Firmalino
oh good i get to be the brearer of good news then
Mar 10, 2014, 6:34 PM

Shelly Thompson
No. I wasn't aware they were going to
Mar 10, 2014, 6:33 PM

Angie Firmalino
Hi Shelly. HAs any other admin contacted you yet?
Mar 10, 2014, 6:32 PM

EXHIBIT J

FDA Activities

September 2015 Advisory Committee to discuss Essure Safety and Effectiveness

The FDA has been examining safety concerns about Essure raised by patients and cited in Medical Device Reports (MDRs). We convened a meeting of the **Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee (/7993/20170111065822/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm463457.htm)** on September 24, 2015 to:

- discuss currently available scientific data pertaining to Essure's safety and effectiveness,
- hear expert scientific and clinical opinions on the risks and benefits of the device, and
- hear concerns and experiences of women implanted with Essure.

Meeting participants and the panel also discussed recommendations for:

- Additional prospective clinical data collection to better understand adverse events such as allergic reaction and autoimmune response, persistent pain, device removal, migration, perforation or fragmentation and bleeding;
- Improved physician training and education;
- Improved patient counseling and education to facilitate informed decision-making; and
- Labeling modifications.

The Advisory Committee meeting provided valuable information and perspectives the FDA considered to inform our next steps.

FDA's Review of Available Information after the September 2015 Advisory Committee Meeting

After careful review of concerns identified by the public speakers and the feedback and recommendations provided by the panel (See **Advisory Committee meeting summary (/7993/20170111065822/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM464487.pdf)** and **panel transcript (/7993/20170111065822/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM467456.pdf)**), comments submitted to the public docket, and additional medical literature and adverse event reports that have been published or received since the Advisory Committee meeting. The FDA:

1. Ordered Bayer to conduct a postmarket surveillance (https://wayback.archive-it.org/7993/20170111065822/https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm) study to obtain more data about Essure's benefits and risks.

Like the Advisory Committee panel, the FDA believes more clinical data is needed to better define and understand certain outcomes and events that may be associated with Essure when compared to women who undergo tubal ligation. Findings from the study will inform any future FDA action.

On March 29, 2016, Bayer submitted a postmarket surveillance study plan to the FDA for the Essure device and the agency approved the study plan on September 2, 2016. The FDA believes that results collected from the approved study plan will help the agency better understand complications associated with the Essure device, as well as the underlying reasons inhibiting the completion of the three steps of the Essure System method (device insertion/gplacement, use of alternative contraception for three months, and a confirmation for proper location/occlusion). Additional information on the postmarket surveillance study are available on the **522 Postmarket Surveillance Studies webpage (https://wayback.archive-it.org/7993/20170111065822/http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm)**.

2. Issued the final guidance (/7993/20170111065822/http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM488020.pdf), "Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization" after carefully considering public comments on the language in the boxed warning and Patient Decision Checklist for inclusion in the product labeling.

Advisory Committee meeting and comments received through the public docket indicated that patients are not reliably receiving and/or understanding appropriate information about the device and associated risks prior to making a sterilization decision – for Essure as well as other sterilization methods. Panel members recommended changes to the patient and physician labeling and more aggressive methods to ensure patients are well-informed of risks. FDA will require a boxed warning and Patient Decision Checklist as part of the labeling to help ensure that a woman receives and understands information regarding the benefits and risks of this type of device. The FDA issued draft guidance on the content and wording to be included in the product labeling for permanent hysteroscopically-placed tubal implants with respect to:

- A boxed warning with safety statements to better communicate to patients and providers the significant side effects or adverse outcomes associated with these devices and information about the potential need for removal;
- A Decision Checklist with key items about the device, its use, and safety and effectiveness outcomes, which the patient should be aware of as they consider their sterilization options.

The 60-day comment period on the draft guidance ended on May 3, 2016. After the comment period closed, the FDA reviewed all comments, made the necessary and appropriate revisions and issued the final guidance. To view comments, go to the **Public Docket (https://wayback.archive-it.org/7993/20170111065822/http://www.regulations.gov/)** and search Docket # FDA-2016-D-0435.

3. Completed its evaluation of the trade complaint regarding allegations initially made in a Citizen Petition (https://wayback.archive-it.org/7993/20170111065822/https://www.regulations.gov/document?D=FDA-2015-P-0569-0001).

The Citizen Petition, which included allegations related to Essure, was referred to the Office of Compliance within the Center for Devices and Radiological Health (CDRH). CDRH closed the Citizen Petition and reviewed the allegations as a trade complaint. The Office of Compliance completed its investigation of the **trade complaint (https://wayback.archive-it.org/7993/20170111065822/http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-0569-0005)**.

Allegations in the trade complaint included clinical trial misconduct, notably that clinical trial participants' medical records were altered to reflect more favorable data about participants' experiences, and that the sponsor violated the terms of the PMA approval order and violated laws that relate to the manufacturing and marketing of Essure.

The FDA inspected Bayer as part of the complaint investigation. In addition, Bayer provided the FDA with the available case report forms that documented patient experiences during Essure clinical trials.

The FDA analyzed these forms to evaluate the incidence of cross-outs and discrepancies regarding patient-reported pain, comfort and satisfaction ratings to assess whether modifications favored Essure safety and effectiveness. The Agency found that less than 1 percent of case report form data pertaining to pain, bleeding, device placement/movement and pregnancy were changed during the clinical trials. Although modifications to the case report forms were identified, our analysis did not find evidence the sponsor purposefully modified patient responses to reflect more favorable data for Essure. More information about the Agency's case report form analysis can be found in the **Summary and Key Findings document (/7993/20170111065822/http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/UCM488062.pdf)**.

Also as part of the Agency's complaint investigation, CDRH evaluated Bayer's labeling of the device, taking into account the allegations in the complaint, as well as the feedback received during the September 2015 Advisory Committee meeting and from public comments received in response to the public docket. With the issuance of the final guidance and the subsequent approval of Bayer's labeling changes that are consistent with the recommendations in the guidance, the Agency considers its investigation of the trade complaint completed. CDRH Office of Compliance will ensure that Bayer's revisions to their marketing and promotional materials are consistent with the updated labeling.

FDA's Review of Reported Problems

Problems that were reported during clinical studies are addressed in the Essure product information (labeling for physicians and patients). Some women have reported to the FDA that they have experienced pain or other health problems after Essure placement. Other reports that are not included in the labeling, were not observed in post-approval studies, or described in the clinical literature include extreme fatigue, depression, weight gain, allergy and hypersensitivity reactions. Many of these outcomes were discussed at the Advisory Committee meeting and cited in docket comments.

The FDA relies on a variety of postmarket surveillance data sources to monitor the safety and effectiveness of medical devices. The FDA conducted a thorough review of the available information about Essure and the experiences of patients who have had Essure since the FDA approved it in 2002. This includes experiences of patients who have had positive outcomes with Essure as well as those who have experienced problems. For this review, the FDA:

- ***Analyzed Essure patient reports of problems (including Web-based testimonials) and reports of problems submitted to the FDA from other sources, including doctors, patients, and the manufacturer of Essure.***

  Adverse event and product problem reports submitted to the FDA are one source we use to monitor marketed medical devices. These reports may contribute to the detection of potential device-related safety issues as well as to the benefit-risk assessments of these devices. While such reports are a valuable source of information, this type of reporting system has notable limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Complaints or adverse event reports do not necessarily directly indicate a faulty or defective medical device, and adverse event reports alone cannot be used to establish or compare rates of event occurrence. Additionally, we may receive multiple reports related to the same event making it difficult to determine actual numbers of events.

  The FDA conducted a search of the Manufacturer and User Facility Device Experience (MAUDE) database. From Nov. 4, 2002, Essure's approval date, through December 31, 2015, the FDA received 9,900 medical device reports related to Essure. The majority of reports received since 2013 have been voluntary reports, mostly from women who received Essure implants.

  The most frequently reported patient problems during this period were pain/abdominal pain (6989), heavier menses/menstrual irregularities (3210), headache (2990), fatigue (2159), and weight fluctuations (2088). Most of the reports received listed multiple patient problems in each report. The most frequent device problems reported were patient-device incompatibility (2016) (for example, possible nickel allergy), migration of the device or device component (854), device operating differently than expected (490), device breakage (429), device difficult to remove (280), malposition of the device (199), and device difficult to insert (187). Multiple device problems can also be listed in each report.

Through December 31, 2015, there have been 32 reports coded by the submitter as death. Six of these were incorrectly coded, as there was no indication of death in the report. Of the remaining 26, six relate to four adult deaths; 18 reports relate to 15 incidences of pregnancy loss; and two reports related to two incidents of a death of an infant after live birth.

FDA has received 631 reports of pregnancies in patients with Essure. Of these, 150 were reported to result in a live birth; 204 did not indicate whether the pregnancy resulted in a live birth or pregnancy loss; and 294 resulted in pregnancy loss.

Among the 294 reports of women who experienced a pregnancy loss, 96 were reported as ectopic pregnancies; 43 were reported as elective terminations of pregnancies, and 155 were other pregnancy losses.

Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. The Agency continues to monitor adverse event reports associated with Essure and will periodically update this page.

- ***Reviewed the results from two Post-Approval Studies (PAS) conducted by Conceptus as part of the product's 2002 approval.***

  PAS I (https://wayback.archive-it.org/7993/20170111065822/http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm?t_id=90320&c_id=260#tt) was conducted to gather five-year follow up information on the participants in two groups of patients that were part of premarket clinical trials (known as Phase 2 trial and Pivotal Trial). The study evaluated:

  - how well Essure prevented pregnancy;
  - the safety of the procedure used to place Essure; and,
  - the safety of Essure once implanted, including patient comfort.

  Although there is evidence of complications, as there are with many medical devices, overall results from this study did not demonstrate any new safety problems or an increased incidence of problems since the time of device approval.

  PAS II (https://wayback.archive-it.org/7993/20170111065822/http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm?t_id=90320&c_id=23#tt) was conducted to evaluate bilateral placement rate (insert placement in both the right and the left Fallopian tubes at first attempt) for newly trained physicians in the U.S. Data from this study were used to evaluate the training procedures and to update labeling.

  You can view a **summary of Essure PAS results (/7993/20170111065822/http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/UCM452291.pdf)** for the two studies ordered in conjunction with the PMA approval, which have been extracted from the **Post-Approval Study Status web page (https://wayback.archive-it.org/7993/20170111065822/http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm)**.

  Subsequent to the product's approval in 2002, three PMA supplements were approved with post-approval studies required as conditions of approval. One supplement was related to device modifications; the other two supplements supported labeling modifications. Details on the study protocols and status are posted on the **Post-Approval Study Status web page (https://wayback.archive-it.org/7993/20170111065822/http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm)**.

- ***Evaluated the available clinical literature to better understand long-term complications.***

  FDA sought to determine what long-term complications may be associated with Essure more than five years after placement, because the post-approval study evaluated safety and effectiveness only up to five years. To date, we have found no conclusive evidence in the literature indicating any new or more widespread complications definitely associated with Essure occurring more than five years after Essure placement.

The **Executive Summary (/7993/20170111065822/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM463486.pdf)** prepared for the Advisory Committee meeting provides a comprehensive overview of Essure and the FDA's review, including post-market information, clinical literature and information from ongoing studies. FDA continues to monitor the safety of Essure to ensure it does not pose an increased risk to public health and that its benefits continue to outweigh the risks.

More in Essure Permanent Birth Control (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/default.htm)

Essure Benefits and Risks (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452250.htm)

Esssure Permanent Birth Control: Information for Patients (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452251.htm)

Essure Permanent Birth Control: Information for Health Care Providers (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452252.htm)

FDA Activities (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452254.htm)

Essure Permanent Birth Control: Reporting Problems to the FDA (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452269.htm)

Regulatory History (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452270.htm)

Essure Labeling Information for Patients and Health Care Providers (/7993/20170111065822/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452280.htm)

EXHIBIT K

Essure Problems

*****Disclaimer. Minutes were taken to the best of my ability. FDA statements are not word for word or quotable. They are a general overview of what was stated. Essure Patients that spoke had pre-written script that is contained in these minutes. If any media wish to quote these statements, please get approval ahead of time so we can tell you if it is an exact quote or not. The FDA will be providing its own official minutes in a few days.*****

Peper Long "got housekeeping" out of the way. The call will be 1 hour. It will be a venue to communicate and express your concerns. We hold these calls frequently with patient groups. No information not already available on our website or released to the media will be available. No recording is allowed. It lessens the value of the conversation by interfering with the freeflow of ideas.

Short Introductions:

FDA:

Peper Long, Associate Director Public Affairs
Paula Silberbrg, Public Health Adviser
Karen Jackler ,Public Affairs Specialist

Media:

Lauren Gilger
Christina Mendoza
Dave Elias
Kim Chappell

Patient Advocates:

Angie Firmalino
Michelle Garcia
Amanda Dykeman
Angela Desa
Krystal Donahue from Bel Air, MD I had to have a hysterectomy after dealing with 2 years of pain and am here to support other patients suffering.
Carrie Hirmer
Kim Myers
Melanie Gosgarian
Mishelle Moore Hi, My name is Mishelle... I live in Mukilteo Wa.. I had Essure for 2 yr 2 mos...before I needed a hysterectomy because of a hypersensitivity to nickel...Essure cost me two years of my life due to illness, my reproductive organs, and my career as an airplane builder.
Jerri Lynn Silver from Long Island, NY I am here for my Daughter Stacy who has become very ill since having essure
Kim Hudak

Peper Long I appreciate and take this call and complaints seriously. We use all premarket and postmarket literature to review the safety and efficacy of the device. We continue to use post market surveillance and patients play a significant role in how we decide a products benefit/risk analysis. Turn the time over to you.

Kim Hudak It is my understanding that one of the roles of the FDA is to evaluate, not only the efficacy of new pharmaceuticals and medical devices, but also the safety of these products. I do not find any evidence that the safety of the STOP device was evaluated by Conceptus during the clinical trials. In fact, quite the opposite is true. I expressed serious concern about my rapidly declining health the entire duration of the study yet no specialized tests were ever done to evaluate my claims. The information that was relayed back to Conceptus was that I was "highly satisfied" with the product on almost every single account yet my office follow ups as well as my phone interviews during the course of the trials are in sharp contrast to this information.

In addition to the safety, I question the known efficacy of the product at the time of approval as well. With such a small group and such a short duration for the study, I have a difficult time believing that the data was correct. Upon entering the study, women were required to agree to have intercourse a specified number of times each month. This is impossible to verify and it was not a requirement to be in a verifiable long term relationship.

With all of this in mind, my question to you is how was it determined that this product was safe and effective? How did a medical device with such little verifiable data and limited duration of study get the FDA's approval?

Peper Long Safety and effectiveness was determined by significant amounts of data from 2 studies given to the FDA prior to approval.

Angie Firmalino

Good morning. I'd like to thank the members of the FDA for giving us this opportunity to speak about our experiences after being implanted with Essure, and for the chance to present our information and research to you. It has taken a lot of time, and thought, and preparation to collect and arrange a presentation for you. One that included everything that we wanted or needed to say, while keeping it within an hour long phone call. So we have tried to keep it as short as possible, while including the main topics of concern.

My name is Angie Firmalino; I was implanted with essure in 2009. I am the founder of the FB group Essure Problems. I started the group in 2011 after finding out my coils were embedded in my uterus. I have had three surgeries since being implanted, and I am scheduled for my forth surgery, a complete hysterectomy, on February 13th 2014, to remove the remaining fragments of essure. The surgery involves removing the remainder of my tubes, both ovaries, my uterus and cervix. While I am hopeful it will resolve all of the pelvic pain, I do not know if the chronic inflammation, headaches, or joint deterioration will subside. I am 41 years old.

I'd like to begin my part of this presentation by pointing out the number of women included in the clinical trials for essure. As of the last update to the pma at the time of the initial meeting between Conceptus, the FDA, and the advisory panel, there were 281 women who had successfully relied on essure for contraception for 18 months, 149 women who had relied on essure for 24 months, and 5 women who had relied on essure for 36 months. A total of 435 women. (Of those women from the clinical trials, 4 are in our FB group, and 2 women from the trials are here on the phone with us today, and we will get to their stories shortly)

During the PMA meeting, several questions were raised by the advisory panel that either went unanswered, or could not be answered, because there was not enough data at the time to provide an answer. So here we are, 12 years later and capable and willing to answer those questions. We have almost 6000 women currently in our group suffering from the essure device. At the present time, we add about 150 women a week, however that number is continually and rapidly rising. We recently made an essure survey for our members to fill out, so that we could start to collect some data and present to you some numbers. Currently, 920 members have finished the survey. So already, our group has more women that have taken our survey, than were in clinical trials.

Some questions raised during the PMA meeting that I would like to focus on are

1. Hypersensitivity to metals, particularly nickel
2. What does a doctor do about perforations or migrations, meaning proper protocol of removing a coil
3. What is the long term wearing safety of the PET fibers, specifically if the coils perforate or migrate out of the fallopian tubes?
4. How do we know an accurate rate of pregnancy amongst women relying on essure?

Let me start with the hypersensitivity to nickel. Initially, there was a contraindication for women with a known hypersensitivity to nickel. The same contraindication remains on labels for similarly made devices such as cardiac and cerebral stents. On Aug 4th 2011, Conceptus received FDA approved for the removal of the nickel hypersensitivity contraindication from the Essure procedure Instructions for Use ("IFU").

(The removal of a contraindication for patients with known hypersensitivity to nickel as confirmed by a skin test

The removal of a warning for patients with a suspected hypersensitivity to nickel to pursue a confirmatory skin test

The addition of a warning for patients with suspected hypersensitivity to nickel)

The instructions also state that physicians will be advised to continue to counsel patients about the risks and benefits of the Essure procedure, including the possibility of an allergic reaction to the micro-insert or development of an allergy to nickel.

Of the 920 women who took our survey, when asked the question "did your doctor ask you if you were allergic to nickel", 18% said yes and 82% said no.

When a woman reports an adverse event report to the FDA regarding an allergic reaction to essure….. This is the manufacturer's response on that event.

"Manufacturer Narrative

The essure ifu contains the following warning statement: the essure micro-insert includes nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device. Pts who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some pts may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives."

So the manufacturer knows and admits that hypersensitivity is a problem. Yet, they requested, and the FDA approved, the removal of the contraindication to simply corner the market on hysteroscopic sterilization. Many of the clinical trails that followed the initial market approval had hypersensitivity to nickel as an exclusion criterion.

Here are some published statements, regarding the label change….The label was changed to expand the number of potential patients for Essure. The president and chief executive officer of Conceptus said "This FDA label decision will further strengthen our competitive advantage and leadership in the permanent birth control market, and we are pleased that we were able to secure it, the upgraded label change significantly diminishes the biggest competitive selling point of our competitor's hysteroscopic sterilization product against Essure, which was the nickel hypersensitivity contraindication." "We will be aggressively marketing this IFU change to the OB/GYN community, and especially to those physician

accounts that are trialing the competitor's product primarily because of potential nickel allergy in patients."

The motivation for this change was not based on patient safety but on the manufacturer's financial interest. Not only are women not being informed of the possibility of an allergic reaction or becoming allergic, the allergic reactions that ARE happening are being downplayed! We have countless images of women who are suffering severe allergic reactions that leave their bodies with welts, rashes, blemishes and possibly long term scars; this is a living nightmare for these women who are allergic to this Essure device that is implanted in them. The constant pain, irritation, and inflammation that they are forced to live with, because the manufacturer thought that this adverse event was insignificant or extremely rare, is unacceptable. Also, their implanting doctors will rarely make the connection or admit that the essure device is the cause of these reactions, so the women are sent on to dermatologists and specialists and undergo test after test, only to be denied any type of logical explanation. And removal of the essure devices seems like a never-ending quest. Currently, only a handful of allergists are stepping up and offering essure specific allergy testing. It is only very recently that women have been able to use a diagnosis for a nickel allergy as justification for essure removal.

During the PMA meeting, Dr. Sharts-Hopko asked the question about sensitivity to metals, immediately following her statement, the topic of conversation is changed, and she is never answered. Her statement was: "A concern that I have, also not on the list, is related to the question I raised earlier today about sensitivity to metals. I am a person with an extreme sensitivity to metals other than 14k gold, which is a great problem."

This was followed by (Laughter.)

The chairman DR. BLANCO says "You sure it's not 18?"

DR. SHARTS-HOPKO replies: "Eighteen is better. So I don't know what happens to people with metal sensitivity when you implant metals in them. "

They move on with the meeting, never to bring it up again.

Those are my concerns regarding the nickel hypersensitivity issue. If this device is to remain on the market, the nickel contraindication must return to the labeling to protect women from future harm. As part of title 21 volume 8 part 814 the label change constitutes that reapplication of pma is permitted by federal law and the fda has authority to enforce Bayer's requirements to ensure the modification of the device does not pose serious adverse health consequences. Enough women are already suffering from just this one complication. One of many complications.

On to my next question often raised at the PMA meeting, what does a doctor do about perforations or migrations, meaning proper protocol on removing a coil?

Panel member DR. ROY asks: "Okay. Inasmuch as Dr. Wright described the profound inflammatory response that does occur with this device, what was done when perforations were noted?"

Conceptus rep DR. COOPER replies: "When perforations were noted, traditional methods of sterilization followed. The devices were retrieved at laparoscopy."

DR. ROY asks: "With I suppose a bit more surgical intervention that traditionally would occur or did they just slip out?"

DR. COOPER replies: "No, the diagnosis of perforation was in most cases made at the time of device placement. In a small number of cases, perforation was not noted until the three-month post-procedure x-ray. Retrieval of the device at laparoscopy was not found to be problematic. In a couple of the cases, the device was found lying in the omentum but could be easily removed from the omentum."

DR. ROY responds: "Okay. Because it's sort of like the situation with copper IUDs being perforated. They produce such an inflammatory response, that it is somewhat problematic, depending on where you ultimately find them, whether the omentum is able to sequester them or other peritoneal or intraabdominal contents, such as bowels. So I was just curious to what extent the inflammatory process, even at a three-month interval, was sufficiently problematic, and I guess you're telling me that it was not, it was easy to find and remove without resorting to laparotomy, for example, to do so."

Then they go on to discuss the 11 women who had device migration or perforation and the 9 who had the devices retrieved. They claimed only one required laporatomy and one underwent a cornual resectioning. They said of the women whose devices had not been retrieved, they've not had any reports of unusual pain that can be attributed to the device location. .

Chaiman DR. BLANCO replies: "A follow-up on that, because I had that as a question. On the patients that had continual symptomatology of cramps and pains and so forth. What other experience except other than this one case do you have for someone who has chronic complaint, desires the removal of the device, in terms of removing the device? Is cornual section the only option for removal of the device if someone wants it removed? Do you see what I'm saying?

In other words, can you go back, do you have any experience going back with hysteroscope trying to pull the device out or do you have to resect the corneum?"

Conceptus DR. CARIGNAN then comes to the podium and states: "When a device is well positioned across the utero-tubal junction, because of the extensive fibrosis, it does require a minimal cornual resection to remove the device. The only time that we ever actually recommend removal of the device hysteroscopically is if during the procedure, you recognize that you haven't positioned it far enough into the tube or you inadvertently deploy it into the uterus that you would then remove it and replace the device. Subsequent to placement, we do not recommend hysteroscopic removal of a well-positioned device."

Within the clinical trials, with the devices that had perforated and ended up elsewhere, the manufacturer claimed device retrieval was easy. They also claim that the ones they left in the body, could not be attributed to any pain or problem. However, as the study was not long term, there was no evidence to speak to about the long term effects of having a coil migrate and embed in another part of

your body. There were also no incidents reported in the clinical trials where the patient had the device migrate outside of the reproductive system. Within our group, we now have evidence of long term wearing of this device after it has migrated or perforated. I for one, am an example. Mine were embedded in my uterus for two years. I suffer pelvic pain, chronic inflammation, chronic headaches, and joint deterioration, just to name a few issues going on. We've seen women with severe pelvic adhesive disorder due to migrated coils. We've seen xrays, cat scans, ultrasounds, and MRIs of coils ending up in the abdominal wall, the bowels, the kidney, the liver, the ovaries…… The damages are extensive and in many cases requires multiple surgical procedures to repair the injury. Many of our group members have been diagnosed with autoimmune diseases ranging from lupus and crohns disease to myasthenia gravis. Other common symptoms amongst us include debilitating pelvic pain, headaches, joint pain and joint deterioration, chronic inflammation, extreme fatigue, severe bloating, blood disorders and skin conditions. Adverse events that the FDA continues to state cannot be directly related to the device. For most of us, irregular bleeding has become a way of life. There is not a man on earth who would risk wearing a colostomy bag as a possible adverse event from a vasectomy, but this is a possible risk passed on to every woman implanted with essure. And we can say this, because we have seen it happen. Bowel perforation is a common occurrence within our group. However, in the manufacturers presentation, a slide show indicated that the list of adverse events reported by clinical trial participants included…… abdominal pain/abdominal cramps, back pain/low back pain, headache, premenstrual syndrome, dysmenorrhea/ menstrual cramps (severe), pelvic/lower abdominal pain (severe), persistent increase in menstrual flow, vaginal discharge/vaginal infection, abnormal bleeding-timing not specified (severe,) menorrhagia menses (severe), dyspareunia, and uncharacterized pain/discomfort. ……. But that only eight events were rated as definitely related to the Essure device. The FDA allowed the company to dismiss these other adverse event because they were only "possibly" related. The FDA has required no long term follow up on patients beyond the five year mark. And even those studies are still not yet available to the public.

This brings me to the next question regarding the long term safety of being implanted with PET fibers. This topic was brought up several times during the PMA meeting as well. They discussed the expected response of the pet fibers. The acute followed by chronic inflammatory response, and the giant cell growth. Dr. Roy asked about a possibility for a neoplastic process to the pet fibers, and the presenter remarked on this possibility.

DR. ROY asks: "The last concern would be, is there any reason for us to be wondering whether these giant cells that infiltrate this area or are produced are in any way precursors for a neoplastic process?"

Conceptus rep DR. WRIGHT replies: "Right, and I didn't answer to that. It's the same sort. The pictures I showed you with giant cells could be from any vascular graft in the body, and we have a very long history of use of devices using PET fibers for long-term implants and they have been shown to be neoplastic."

A neoplasm is an abnormal proliferation of benign or malignant cells. In laymen's terms, it is the growth of a tumor.

PET fibers have been proven to have a connection to autoimmune disease. We have seen research proving this in the forms of vaginal mesh or other mesh applications. http://tvtno.org/the-facts/surgical-mesh-and-autoimmune-disease-connection/

The hope is that the pet fibers will remain as part of the essure coil encased in the fallopian tube. However, the high instance of migration, perforation, and coil breakage is allowing the pet fibers to become loose in the body, where we are seeing devastating results.

Finally, I come to the last topic, pregnancy. Essure boasts a pregnancy prevention success rate at less than 1%. And I quote "Following successful insertion and occlusional response, the Essure procedure is 99.74% effective based on 5 years of follow-up, with zero pregnancies reported in clinical trials." Only the women who achieved successful bilateral placement on the first attempt AND had successful occlusion at three months were included in the pregnancy statistics. Every other woman in the clinical trial was excluded from this calculation.

The manufacturer blames the doctor or patient for non-compliance in most situations resulting in pregnancy. The pregnancy rate that was added to the label raised concern amongst panel members.

Panel member MS. LUCKNER states : "Speaking as a consumer rep here, I think when you use the word "permanent sterilization" and we are showing a one-year level of great compliance and great doing the job it's supposed to do, I don't see how you can call this permanent. I don't think there's a woman in the audience or here on the panel who would like to buy into that system for just one year. It's a little risky if you are going for permanent sterilization".

DR. BLANCO responds: "Well, but let me not let you off the hook so easy. So then, do you think that more data needs to be gathered in terms of length of time of efficacy before you would want to see the device approved?"

MS. LUCKNER: "Or very, very careful labeling that the permanent implies one year or restrictive labeling so that people understand. The woman who elects it with her gynecologist understands that his confidence is based on the data that states X and Y."

Currently on the maude database, under product problems, there is no way to report pregnancy or miscarriage. That's a problem.

The pregnancy data in our group is as follows:

In our group there have been

192 Pregnancies

26 women are Currently Pregnant

71 Pregnancies resulting in births

76 Total e-babies including 4 sets of twins

2 babies that died shortly after birth one due to Uterine rupture causing early delivery and one caused by an infection due to essure.
1 Stillborn Baby
81 Miscarriages
3 Terminations
10 Unknown outcomes
Out of the 155 Pregnancies we know the outcome of (total pregnancies minus those still pregnant and unknown outcomes):
55% resulted in Miscarriages
.01% Terminated
46% Resulted in a Live Birth
Out of those 72 pregnancies resulting in live births:
76 Babies
5% twins
2% Deaths that can be linked to Essure

Gabriella Avina

My name is Gabriella Avina and I thank you for this opportunity to be heard for a second time. In July, 2002, I stood before you in Washington, DC to express my support for Conceptus and the Essure Device. I was on their panel to request FDA approval for this new, revolutionary device. I am here today, almost twelve years later, to say I was wrong. So please listen carefully to me and to these women with me today. Time has changed my thoughts, my beliefs and most importantly, my health.
I am a registered nurse with a Master of Science degree in Women's Health Nursing. I was involved in the clinical trials at both a professional and personal level. I assisted in the placement of the devices in the operating room with Dr. Don Galen and I became a clinical trial participant in October, 2000. In January, 2001 I had the testing completed that documented placement and confirmed sterilization. Because of my experiences, both as a clinician and a patient, I was asked by Conceptus to speak at the annual AAGL convention in San Francisco and share these experiences. This began a professional relationship as a spokesperson that lasted until 2008.
I traveled the country speaking to large groups of doctors, nurses, patients and Conceptus employees, managed a link on the Essure website known as Ask Gaby where I answered thousands of questions regarding this product, adverse events, fears, concerns, and general information. As I became the face of Essure Women, my health was in a grave tailspin, and I had failed to connect the dots.
In April, 2001, not six months following placement, I was diagnosed with Hashimoto's Thyroid Disease - an autoimmune disease whereby the body attacks the thyroid, believing it to be foreign.
In 2003 I was hospitalized with an acute onset of Immunological Thrombocytopenia Purpura (ITP) - an autoimmune disease, whereby the body attacks the platelet cells thinking they are foreign and the body is left with no ability to clot. I was hospitalized for nearly two weeks with several transfusions, treatments and tests. One year later and several hospital admissions and complications, I was started on chemotherapy to suppress the bone marrow production of these bad antibodies. I finally reached a safe zone - remission in late 2005. During this time, I lost my job due to this illness.
In 2007, I was diagnosed with another autoimmune disease, celiac's disease - a gastrointestinal disease where the lining of the bowel is broken down by exposure to gluten in foods.
In 2008 I was finally able to go back to work when all of my blood work and lab values returned to normal. I was starting to feel like I was getting my life and body back when in early 2009, my fifth autoimmune disease was discovered when I was falling frequently and I was unusually fatigued and weak. This disease was the worst - myasthenia gravis. As the disease progressed, I began to lose control over my ability to chew and swallow. I was scheduled for a thymectomy in February, 2010. This is a serious surgery, but gave me a real chance at the remission I needed. If myasthenia progresses, the lungs can become too weak to work, resulting in death by myasthenia crisis. I went into a very short remission that lasted until early 2013 and spent this last year in chemotherapy attempting to abolish the bad antibodies attacking my neuromuscular system.
I am still praying and hoping for remission, but I truly feel that there will only be one way to assure myself of some sort of healthy future. I need to rid my body of the essure coils. I have spoken with all of my doctors, all of which are supportive and feel that this is probably NOT a coincidence. Even Dr. Galen, when I recently tracked him down in retirement, could not argue the facts. The deterioration of my health are all due to autoimmune disease which can be triggered from the foreign bodies in my fallopian tubes. I have an appointment with a surgeon later this month and am hoping to move forward with a real recovery, the recovery of this wife, mother, and nurse to have the healthy life I so deserve.
Again, I ask you to listen to this group of women who all have a story. Their lives were changed by a device that was not adequately monitored during clinical trials, by physicians who were not adequately trained and by a company that has not adequately listened to their patients.

Amanda Dykeman

Good morning, and thank you for allowing me the opportunity to speak with the FDA on behalf of women with Essure Problems. I would like to point out that as women, we deserve to know EXACTLY what is being placed into our bodies. This is particularly important when it is an elective procedure that implants a device permanently into a very sensitive part of a woman. Very simply put, this is NOT the case with essure. Yes, there is a basic material list, but several elements are missing.
For example, there are steps that need to be taken with the fibers and nitinol to ensure its safety. Our research shows that there are chemicals and or proteins used during manufacturing of the essure system. Studies show they can be toxic, carcinogenic, and thrombogenic. Why are we not made aware of these residues that could be left not only on the device itself, but also on the catheter!?

It's sad that the only way women are informed of this information is through our own research. We demand answers as we continue our medical journeys even after removal of the essure device. What Mrs Avina has described is becoming the norm among the essure problems community. Women with cancers, blood clotting disorders, autoimmune disorders and the like.
You can't say these aren't related to essure based on what you've seen with the clinical trials anymore. We have more women in our group with these problems than the pivotal and phase 2 trials, probably even phase 3. So it's time to listen and provide us with the facts and answers we desperately seek and deserve! Thank you!

Kim Meyers

Hello my name is Kim Myers. First I would like to say that all of the women involved with the efforts to bring awareness to the problems with the Essure Procedure are just ordinary women who trusted the system to protect us from harmful products. None of us ever thought that we could not trust the information that we were receiving from our doctors or that any product approved by the FDA would have the potential to do great harm especially since this procedure is not a life saving device. Our experiences were so horrible & when we turned to our doctors for help we discovered that they didn't seem to have that much knowledge about the product. That brought up the question in our minds what is this product? Why do the doctors know so little?
We weren't able to get answers from the people who we thought should know so we began to search for the answers on our own. For me personally it really frightened me the more I learned. When I really thought about the procedure it seemed to me that so many conditions had to be met in order for this to be successful. There are so many IF's. 1st there is the big question of whether they can even be placed. 2nd are they placed correctly, 3rd if the tubes occlude, 4th if they stay in place & worst of all if you have problems then you will have a hard time finding a doctor who even knows what to do in the event of a problem. Most likely it will take major surgery & in many cases a hysterectomy. As I learned more about how the PET fibers are designed to cause a chronic inflammatory reaction in the body. Based on what The company stated in the PMA minutes that the PET fibers would cause this non stop inflammation in the fallopian tubes the rest of my life or other women's lives. I wondered what happens if microscopic particles of the Pet fiber were carried to other parts of the body via the blood stream. There seems to be no studies as to what happens when that occurs. I faced major surgery & with no assurances that all that stuff could ever be completely removed my body. Let me assure you had any of this information been made available to me, I would not have ever allowed something like that to be placed in my body.
Those are some huge concerns that we have & others will address those issues further. I would like to talk some about the HSG test. The HSG test is a required part of the procedure but yet so many women are not informed that their insurance will not pay for it or they will lose coverage before they can have the test. Since Essure all hinges on the so called successful HSG test does the FDA feel any responsibility in making sure that this test is covered. Shouldn't Bayer/Conceptus have to include that test in the cost of the Essure procedure because if a woman does not have that test for any reason then Bayer/Conceptus has been allowed to exclude those women from any stats regarding their product. If Bayer/Conceptus is allowed to continually disregard adverse event reports because the woman didn't have the hsg test, the doctor or radiologist didn't read the results correctly this does not make sense. The product has failed because a woman has gone thru the process & yet no matter what is claimed it didn't work. How can the FDA sit back & not take action. There also seems to be no real way to know if devices are correctly placed unless patient undergoes surgery. We have many instances of women having numerous tests & being told that the devices are in place but yet it is found during surgery that they are not. Sometimes the devices can be seen with ultrasounds, sometimes they can't. Women are put thru MRI's which we've been told will not show the devices. Let me make this real personal, I hurt for 3 years. I had many visits to the doctors, the ER. I had many transvaginal ultrasounds, CT scans was prescribed all sorts of medications to control chronic pelvic pain. I was seen at different facilities. I saw different doctors. No one detected a device that was plainly embedded in my uterus. If no one can find a device with the amount of tests I had performed then how can they ever claim that they can determine placement. We have other women & I believe there are a few case studies about missing devices. This is a birth control device. This is not some risky life saving device No one seems concerned about what these devices do to a woman's body or where the devices end up. . It seems to me that everyone is only concerned with how many women can we sterilize quickly. I'm not sure how effective it really is in preventing pregnancy because as was stated earlier if a woman doesn't have the HSG test then it doesn't count as a product failure should a woman become pregnant.
We have started trying to collect information that demonstrates the kind of problems that are occurring with Essure. As I stated earlier we are just a group of ordinary women who have been harmed by a product. We did not think about keeping stats or having a questionnaire until recently. This may account for the small of amount of participants in the info we are collecting. We will provide some of the information that we have collected. We realize that the FDA is accustomed to polished speakers & presentations put forth by the corporations but we have lived the consequences of this procedure. We've actually had these things in our bodies so even though we may not have all the fancy words & terms I believe that we are in a better position to tell the FDA about this product.
There also is great confusion as to just what all Bayer/Conceptus is entitled to as far as medical records. Women are scared. They do not want Bayer/Conceptus to have access to their records until their healthcare needs are met. Some women have been told that by filing an adverse event report with the FDA that the report entitles Bayer/Conceptus the right to their medical records. These women are afraid that if Bayer/Conceptus has access that they might influence the care they are given regarding removal of the essure devices. They feel that Bayer/Conceptus has way too much influence

on the doctors for them to be heard. This is based on their own personal experience with doctors who refuse to admit that Essure can cause a problem even when there were problems immediately. At one time FDA had on the FDA website that they estimated that less than 1% of all adverse events are reported. I believe that statement has since been removed. Most consumers do not even know that such a thing exists where you can report a problem with a product & the ones that do have found it intimidating. At one point they had to check the box that they were dead in order to file a report.
We've spoken with a few doctors & they seem to think the reason for the low numbers in reporting & the unwillingness by other doctors to admit to a patient there might be a problem is out of fear. Most surgeries being performed due to Essure Problems are coded as chronic pelvic pain or other reasons for insurance purposes because removal of essure is considered by most insurance companys as a reversal so that is another factor in the small number of reports. Bottom line is how many people have to be harmed before any action is taken. I think we all know that the Essure procedure has some major problems & it's time for the FDA to do the right thing. At the very least a black box warning should be put on the product. This black box warning should strongly warn physcians to make sure that a woman will have the resources needed to have the HSG test performed. Put a black box warning on it to make sure that doctors & patients are aware that performing ablations concomittently can cause the HSG tests to be unreliable. Put a Black Box warning on the product about how to safely remove the devices.
Peper Long Contraindications can be narrow or broad but it is ultimately up to the physician to abide by labeling. This is called Practice of Medicine where doctors are given broad leave to use according to the doctors judgement. Includes off-label uses and required doctor patient communication that the FDA does not regulate.
Kim Meyers Isnt that why a black box warning could help in protecting people from harmful products.
Peper Long FDA can issue but the company should be informing doctors and doctors informing patients
Michelle Garcia discussed statistics 55% miscarriage compared to 10-15% in the normal population and the 6 cases of a rare form of Auto immune disease and questioned how the safety was assessed prior to approval.
According to the FDA website and the Code of Federal Regulations, the FDA is charged with assuring that devices intended for human use are safe and effective. A review of the seven studies on Essure states the end points are (1) bilateral micro-insert placement rate, (2) identification of factors predictive of micro-insert placement failure, (3) evaluation of aspects of the ESS305 design that may impact bilateral placement rate; and (4) hysteroscopy time to perform the procedure. None of these endpoints refer to the devices safety? What data was used by the FDA to provide assurances that the device is 'safe?'
Under section 814 of the CFR, PMA can be suspended or withdrawn if O)Newly acquired information means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA.
Questioned how safety was assessed when the 7 FDA mandated studies never mention safety in the protocol.
Peper Long Safety data was given to the FDA and all published literature was reviewed. We are interested in seeing additional data from all sources to continually assess the benefit/risk profile.
Carrie Hirmer
Last year, the age of 38, I had Essure placed. I had Essure in for a much shorter time than most of the women on the call, only 4 weeks. In that four weeks, I had numerous visits to my doctor and ended up in the ER after Essure had caused an infection in one of my fallopian tubes, which resulted in a 4 day hospital stay that I spent on 3 different IV antibiotics and pain meds. When I went back to my doctor, we decided that a hysterectomy was my only option because of all the damage that Essure had caused. When my doctor opened me up during surgery, he discovered that the infection had turned into a softball sized abscess and was leaking infection into my abdomen. Had we waiting any longer to do surgery, the results could have been fatal. The entire time I had Essure in, I could not function – could not work, could not drive, could not eat, could not take care of my daughter and my household. Had I known that Essure contained nickel, I would never have had it done as I have a nickel allergy. When I asked my doctor why he didn't disclose that to me, he said it was because the FDA didn't require him to. So, had the FDA not lifted the nickel contraindication warning on Essure, he would've been obligated to disclose that information to me, and I would never had Essure done and would still have my reproductive organs. Now, almost one year later, I am still dealing with the after effects of Essure and the hysterectomy it caused me to have. No woman should have to go through this.
Amanda Dykeman Asked about the ablation study which is late. This study is important because many women are getting ablations after essure. Concerned about an increased risk of Post Ablation Syndrome
Peper Long I will look into the Ablation study. No information. The FDA will look at information collected from all sources. A doctor can review a product and submit an Investigational Device ????. Send it to me and I will make sure it gets to appropriate staff.
Melanie Goshgarian asked if the 17 doctors treating her can talk to the professional scientific staff at the FDA for guidance on treating her allergies since essure.
Peper Long No, you should consult with your doctors, but will be happy to look at whatever you send me.

Kim Meyers This is an important issue and I find it odd that so few people from the FDA were willing to sit in on this call.
Peper Long This is standard for these types of calls to only have one or two people. I will make sure the minutes will get to the appropriate staff. Highlighted the importance of women filing Adverse Events
Kim Meyers Discussed the uneasiness of women to file because they are scare doctors might cancel care or Bayer might start asking for Medical Records.
Peper Long Assured us that the FDA would not request our medical records or share confidential information to Bayer.
Some discussion about it happening amonst the participants.
Gabriella Avina Has PMA ever been lifted?
Peper Long Enforcement with companies is voluntary. I don't know that we ever have. If we have it would be rare. We recommend recalls but the company would be the one to issue it. Compared a recall to a software fix. A withdrawal would pull a product off the market.
Dolly Pena Asked about nickel exposure to her baby in the womb or through breastmilk
Peper Long Discuss any concerns about the risks and benefits wih your doctors.
Dolly Pena My doctors do not have any answers or guidance for me and I can not find it on my own either.
Peper Long You have to get guidance from your Doctor We have gone 10 minutes over and need to end the call. I appreciate everyones input.