Objective Assessment of Manufacturing Technology Investments

by

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SUBMITTED TO THE MIT SLOAN SCHOOL OF MANAGEMENT AND THE
DEPARTMENT OF CHEMICAL ENGINEERING
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREES OF

MASTER OF BUSINESS ADMINISTRATION
AND
MASTER OF SCIENCE IN CHEMICAL ENGINEERING

ARCHIVES

IN CONJUNCTION WITH THE LEADERS FOR GLOBAL OPERATIONS PROGRAM AT
THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
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Craig Jeremy Rothman

Submitted to the MIT Sloan School of Management and the Department of Chemical Engineering
on May 11, 2012, in partial fulfillment of the
requirements for the degrees of

Master of Business Administration
and
Master of Science in Chemical Engineering

Abstract

Amgen is a biotechnology company with manufacturing plants throughout the world. New manufacturing technologies are constantly being developed and implemented in order to address cost, quality, regulation, and competitive forces. However, deciding on the technologies to implement is difficult because there is much uncertainty and the regulatory constraints of old products need to be balanced with the need of manufacturing flexibility for new products.

Interviews were conducted with executives at Amgen and other biotechnology companies to understand their current decision-making processes and no gold-standard decision-making process emerged. The current process at Amgen is a business case along with net present value (NPV). However, the process has been found to be somewhat biased and decisions are often made on gut-instinct and excitement. In addition, the business case often fails to capture some of the more subjective, intangible elements of new technologies. Therefore, a technology decision-making framework based on the Analytic Hierarchy Process (AHP) is introduced.

The AHP is an objective, group decision-making approach. For usability and sustainability, commercial software from Expert Choice was used in case studies to validate AHP as a decision-making approach within Amgen. One case study looked at options to upgrade a clinical manufacturing facility. An AHP model was analyzed simultaneously with a typical business case and NPV analysis. The AHP model allowed management to understand the more subjective areas where the options differed and therefore was a suitable approach that added value. Another case study was performed looking at choosing a standardized drug substance container where five previous analyses had been performed, but no decision made. The AHP model allowed the different criteria to be combined in one model with cross-functional input so that management could make a holistic decision. The AHP approach had many benefits and using commercial software made the process easier for users and allowed for a more sustainaible process within Amgen.

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Acknowledgments

I would like to thank Amgen for sponsoring my internship and my company supervisors Thomas Seewoester and Jerod Price who provided support for my project. In addition, I would like to thank the numerous people at Amgen who supported me by introducing me to others, answering questions, and helping with my project. Specifically, I would like to acknowledge Aaron Contreras, Tom Monica, Shane Kurowski, Dave Czerwonka, Ed Sanderson, and Carrier Li without whom I would not have been able to complete the project case studies. I would also like to thank LGO alumni Leigh Hunnicutt and Eric Dolak who provided guidance on Amgen and the project.

I would also like to sincerely thank the Leaders for Global Operations (LGO) program for its support along with my thesis supervisors Roy Welsch and Charles Cooney. They provided invaluable advice for the direction of this thesis. I also want to thank my classmates who were always there to support each other and provide a distraction from the large amount of work and tasks. The experience was greatly enhanced by my fellow classmates at Amgen in California — Daniel Bolgren, Chris Garvin, Marnix Hollander, Patrick Riechel, and Sally Smith. The camaraderie we experienced living together in Malibu and sharing times on the beach, at Yogurtland, surfing, swinging on the trapeze, and walking around Santa Monica left me with countless memories.

And last, but certainly not least, I would like to thank my fiancé Robert and my parents, sister, and brother-in-law who were always there to encourage me through all the work and late nights. You always believed in me and supported me through my many years of education, for which I am eternally grateful.

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Chapter 1. Introduction

The pharmaceutical industry generally produces two kinds of pharmaceuticals: small molecules and macromolecules, which are also known as biologics. Small molecule pharmaceuticals, such as penicillin, are typically produced through defined chemical processes or purified from microbes and are typically delivered orally in pill or tablet form. Macromolecule pharmaceuticals are more complicated to produce because their production involves the generation of the active pharmaceutical ingredient (API) from bacteria, fungal, insect, or mammalian cells, and must be purified from the rest of the cellular material through several chromatography steps. The API is typically a liquid, known as bulk drug substance, which is then formulated into a drug product in order to be delivered non-orally. There are many technologies used throughout the production of biologics. This thesis will focus on the issues around investing in biologic manufacturing technologies and how using the Analytic Hierarchy Process can improve the decision-making process.

Amgen, Inc. is a biotechnology company headquartered in Thousand Oaks, CA that discovers, develops, manufactures, and markets drugs for the treatment of various diseases. These drugs are mostly biologics. It has one clinical manufacturing facility located in Thousand Oaks, CA and several commercial manufacturing sites located in the United States, Europe, and South America. As with other healthcare companies, Amgen has to constantly make decisions on which technologies it will invest in, which place it should introduce new technologies, which products it will advance out of research, and which new technologies may be required for each new product.

This thesis describes a tool to make more objective assessments and decisions around new technology introduction in order to help management make the right decisions in a timely manner.

1.1 Problem Statement

The biologics manufacturing process is complex. Recently, several factors have caused the biotechnology industry to undertake numerous changes to how it produces these drugs. These reasons include regulatory requirement changes, improvements in manufacturing technology, new types of active pharmaceutical ingredients, patient safety, and the need to decrease costs in order to improve margins. In addition, to maintain good standing with regulatory agencies, pharmaceutical companies must ensure they are maintaining current good manufacturing processes (cGMP). Since what is defined as "current" changes over time, companies must continually evaluate their processes and add technologies and equipment where needed. This often involves retrofitting existing technology and/or facilities and can even involve the need to build a new manufacturing plant.

New technology usually follows a pre-defined path through an organization from research to commercial implementation (or from small-scale to large-scale) as shown in Figure 1. A new technology typically begins in research where it is characterized and tested. It then progresses through process development and a pilot plant, which is a very scaled-down manufacturing plant. Technology then progresses to the clinical manufacturing facility, which produces bulk drug substance and drug product for clinical trials around the world and also supports the lifecycle needs of commercialized products. Finally, once a technology is well understood, it can be introduced into commercial manufacturing facilities. It usually follows this path because of increasing regulatory burdens as a technology progresses into clinical and commercial operations and the cost is greater the larger the scale of the technology. However, this pathway is not always taken and the realizable value of new technology coming out of research is not always clear due to high complexity and long implementation schedules.

Several questions arise from the need to implement new technologies:

- What technologies will be needed for future products?
- Which of several technologies to choose?
- Where to introduce the new technologies?
- When to introduce the new technologies?
- How does implementation affect current processes?
- Balancing the cost of new technologies with the benefits?

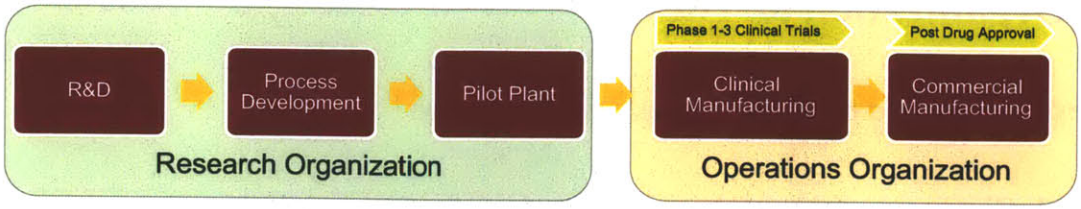


Figure 1: Typical progression of technology through a pharmaceutical company. *Technology usually progresses through five stages of the research and operations departments. Research and development, process development, and the pilot plant are the first three steps in research while clinical manufacturing and commercial manufacturing are the two steps in operations.*

Amgen realizes that in the past they have not always answered the above questions using a robust set of factors or impacts. This occurs at many companies and can be the result of an inadequate decision-making process. Decisions can be biased when the decision-making process involves people from different groups throughout an organization. In addition, depending on who sponsors an assessment, the analysts may propose the option that they feel their boss wants. Furthermore, sometimes the decision-maker has a "feeling" about what they want the outcome of the analysis to be and therefore they may overly influence the process so that what they want is selected. Finally, sometimes the person who is excited about a certain technology or has a "gut instinct" about the right answer pushes it through the decision-making process without a truly objective assessment. Thus, Amgen is looking for an unbiased decision-making process that can be both comprehensive and sustainable.

1.2 Hypothesis

This thesis proposes a strategic framework that can evaluate many aspects of new manufacturing technology in an objective manner. The decision-making process to answer the above questions needs to be robust while being simple, quick, easy-to-understand, and easy-to-use so that the right decision is made in a timely manner. If management can analyze both subjective and objective criteria that can be tangible or intangible, then they can make better decisions with greater understanding. The project focused on evaluating technologies for implementation in Amgen's clinical bulk drug substance manufacturing and clinical formulate / fill / finish drug product manufacturing.

1.3 Organization of Thesis

This thesis is organized into 6 chapters as described below:

Chapter 1 Gives an overview of the problem and briefly discusses the hypothesis that was tested at Amgen, Inc.

Chapter 2 Discusses the biotechnology industry and Amgen

Chapter 3 Explores the current processes used for decision-making at Amgen and other companies and discusses issues with innovating, specifically with regards to decision-making and implementation

Chapter 4 Explains the framework used to make objective decisions and the commercial software used during the project that implements the framework

Chapter 5 Discusses the results of three case studies performed using the new framework

Chapter 6 Concludes the thesis and makes recommendations for future applications

Chapter 2. Background and Context

The biopharmaceutical industry is generally composed of two industries — the pharmaceutical industry and biotechnology industry. The industry is highly competitive as can be seen in Table 1, which lists the market share and sales of the top 15 global companies in the biopharmaceutical industry.

Table 1: Global Sales of Top Biopharmaceutical Corporations. *Sales are in US$ with quarterly exchange rates and cover direct and indirect pharmaceutical channel wholesalers and manufactures. The figures include prescription and certain over the counter data and represent manufacturer prices. Adapted from IMS Health Midas, December 2010 [1]*

Top Corporations	2010 Market Share (%)	2010 Sales (US$ MN)	2009 Sales (US$ MN)
Global Market	100	791,449	752,022
Pfizer	7.0	55,602	57,024
Novartis	5.9	46,806	38,460
Merck & Co	4.9	38,468	38,963
Sanofi-Aventis	4.5	35,875	35,524
Astrazeneca	4.5	35,535	34,434
GlaxoSmithKline	4.3	33,664	34,973
Roche	4.1	32,693	32,763
Johnson & Johnson	3.4	26,773	26,783
Abbott	3.0	23,833	19,840
Lilly	2.8	22,113	20,310
Teva	2.7	21,064	15,947
Bayer	2.0	15,656	15,711
Amgen	2.0	15,531	15,038
Bristol-Myers Squibb	1.9	14,977	14,110
Boehringer Ingelheim	1.9	14,591	15,275

The pharmaceutical industry has existed for centuries and includes companies that generally manufacture and market small molecule pharmaceuticals. Small molecule pharmaceuticals are produced through defined chemical processes. The small molecule API is then typically combined with other inactive chemicals in pill or tablet form to be delivered orally to a patient; however, sometimes they are delivered intravenously as is done for some chemotherapy agents. Small molecule pharmaceuticals are typically marketed as either brand name or generic drugs. Brand name drugs are those marketed and manufactured by the drug's original patent holder. After the patent for a small molecule pharmaceutical expires, other companies typically manufacture and sell the drug as a generic at a reduced price since they did not have to bear the research and development costs of the drug. Therefore, the majority of revenue received for a small molecule pharmaceutical occurs between when the product is first introduced to the market and the patent expires. Generic drugs are attractive for companies to produce because no regulatory clinical trials are required since the manufacturing process is chemically defined.

The biotechnology industry is much younger than the pharmaceutical industry as it has developed over the last century since the discovery of the central dogma of molecular biology. Biotechnology companies generally manufacture and market macromolecule pharmaceuticals, also known as biologics, which are produced from bacterial, fungal, insect, or mammalian cells. The API from the cells is purified from the rest of the cellular material through several chromatography steps as described in Section 2.1.1. During these steps, several enzymatic modifications may be performed on the molecule such as adding or removing functional groups from its carbohydrate structure. The result of the purification process is a liquid product, known as bulk drug substance, which must then be formulated into a drug product that is typically delivered by injection. Since the biologic manufacturing process is not chemically defined, other companies cannot identically replicate the product after a molecule's patent expires; therefore, there are no generic biologics, but companies are interested in creating near-identical molecules called biosimilars. However, because of the high cost of biologics for patients, there has been growing support for a regulatory pathway to approve biosimilars.

There are significant differences between the two industries other than the molecular size of the product. Over the last decade, the biopharmaceutical industry has seen increased global yearly revenue as shown in Figure 2; however, over the same time period the growth rate year-over-year has declined [2]. This is largely due to expiring small molecule patents, pricing pressures, increased generic competition, and fewer new drug discoveries and regulatory approvals in the pharmaceutical industry [3, 4]. Thus, pharmaceutical industry revenue growth was only 1% in 2010 whereas the biotechnology industry revenue growth was 10% in 2010 [5, 6]. Therefore, the older, larger pharmaceutical industry has increasingly sought to merge and acquire biotechnology companies as shown in Figure 3 or develop their own biotechnology ventures. Thus, an increasing number of companies are involved in both the pharmaceutical and biotechnology markets. The factors affecting the overall industry and its increasing focus on biotechnology are described in more detail in Section 2.2.

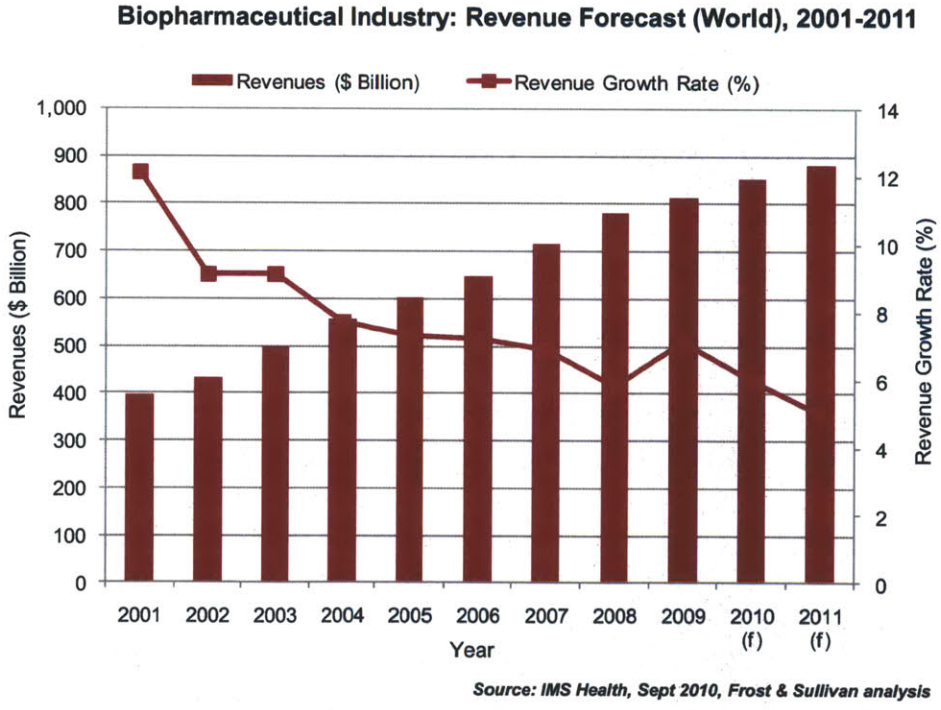


Figure 2: Biopharmaceutical Industry Revenue from 2001-2011. *The revenue from selling biopharmaceuticals has been increasing from about $400B to about $890B while the yearly revenue growth rate has decreased from about 12% to about 5%. [2]*

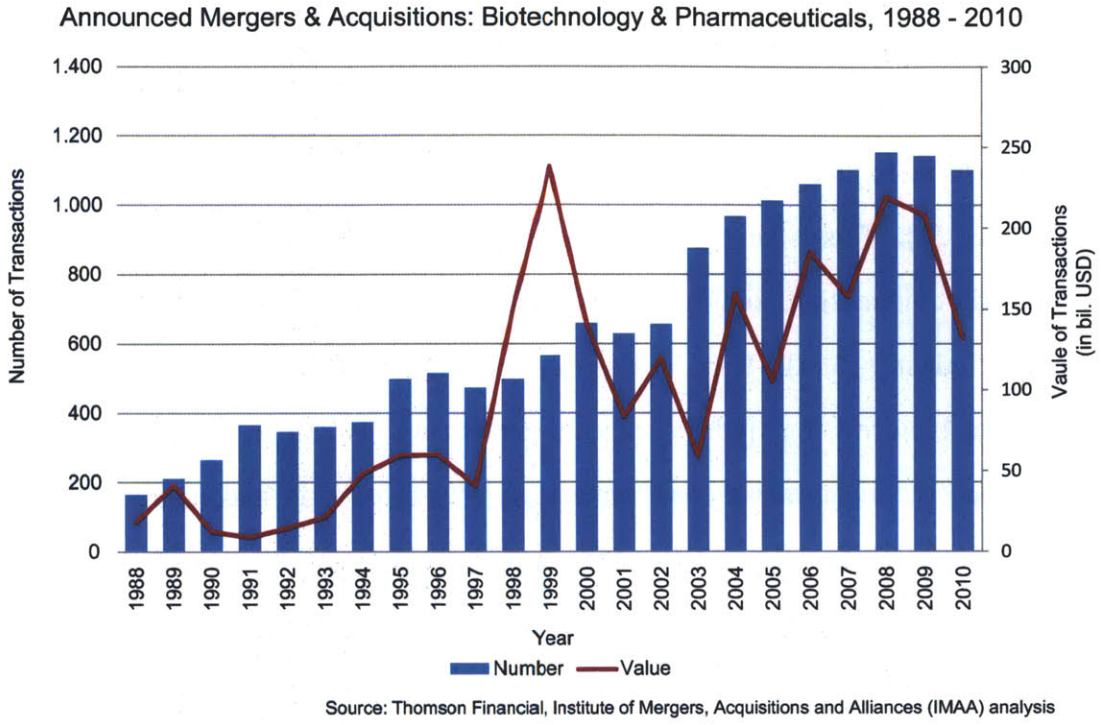


Figure 3: Announced Mergers & Acquisitions: Biotechnology & Pharmaceuticals, 1988-2010. *The number of mergers and acquisitions in the biotechnology and pharmaceutical industry has steadily increased [7]*

2.1 Biotechnology Industry Overview

The biotechnology industry is relatively young and is primarily composed of companies working on human health technologies, such as biologic drugs, as shown in Figure 4. However, the industry also includes companies using biotechnology in other applications like energy and agriculture. Nevertheless, this thesis focuses purely on the medical biotechnology industry.

As shown in Figure 4, the two largest biotech companies are Roche and Amgen, Inc. Over the last decade, revenue growth has been positive (except for the recession period of 2008-2009), and it is forecased to increase over the next decade. Employment in the industry has been relatively constant while the dollars spent on research and development has increased slightly year-over-year except for the 2008-2009 period [5].

The industry is complex and undergoing many changes. Key market drivers are an increased use of specialty pharmaceutical products, the expansion of emerging country markets, blockbuster

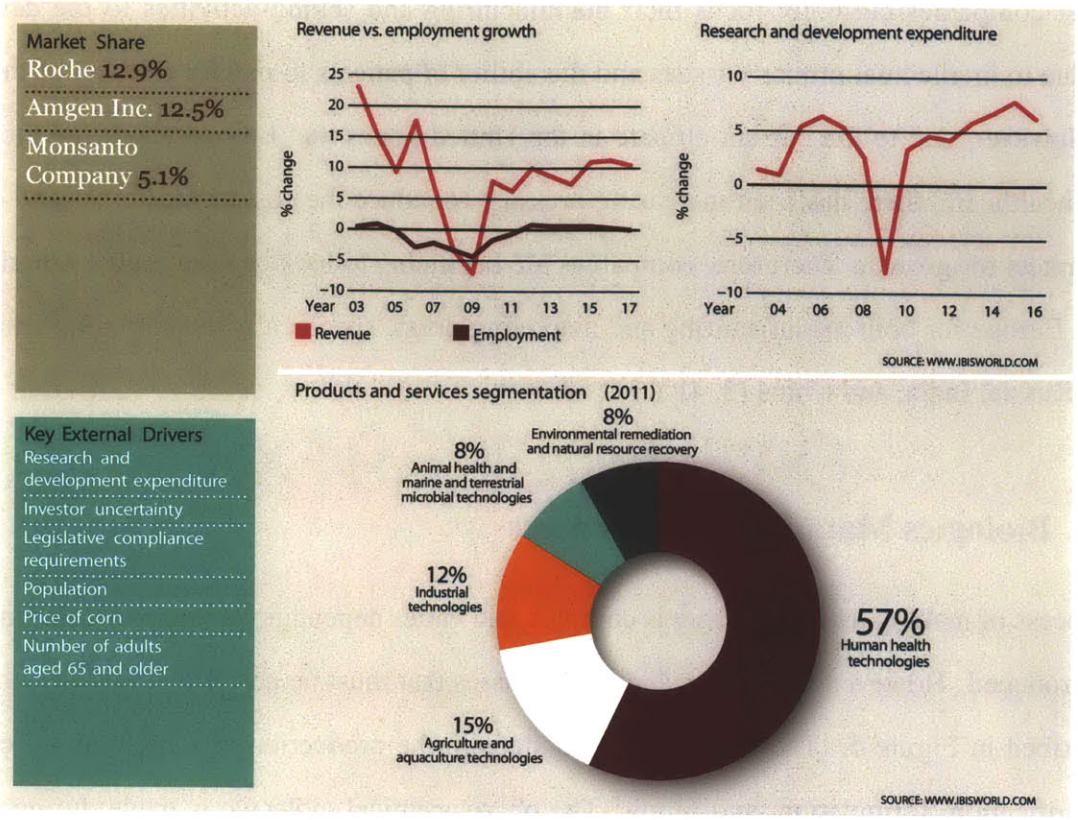


Figure 4: *Biotechnology Industry Overview [5]*

revenue performance, and population factors such as an increasing proportion of people over age 65 and a better understanding of patient subsets through diagnostic tests. On the other hand, markets are restrained by maturation of developed countries to slow/low growth at the macro level, biosimilar/biogeneric emergence on the global stage, and increased scrutiny and impact from payers and health technology economic assessments [3].

As mentioned above, there have been numerous mergers and acquisitions within the biotechnology industry due to the promising nature of future medical treatments from biotechnology. This includes advances to treating current diseases and also the prospect for discovering medicines with new technologies such as stem cells, gene therapy, and personalized medicine. Biotechnology companies are looking to use these new technologies to treat diseases such as cancer by finding specific biomarkers to more specifically target treatment. Other major disease target areas are HIV/AIDS, Hepatitis C, drug-resistant infections, diabetes, Alzheimer's disease, and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [4].

Most companies currently focus their manufacturing and selling activities to the developed world due to intellectual property issues and the ability of patients to pay for the cost of the drugs sold. However, due to the current climate in the United States and Europe about the increasing cost of healthcare, there has been increasing pressure to reduce the cost of medicines and explore new markets for growth. Therefore, companies are beginning to look to Asia, Latin America, and Eastern Europe for both manufacturing and marketing drugs, specifically the emerging markets of Brazil, Russia, India, and China [3, 4].

2.1.1 Biologics Manufacturing Process

The process of making a biologic drug is complex and varies depending on the particular molecule being produced. However, there are standard processes that must be performed for every biologic as described in Figure 5. There are four main steps to the production of a biologic — cell culture, purification, formulation, and filling. The pharmaceutical molecule is made during the cell culture process by growing bacterial, fungal, or mammalian cells in a bioreactor. Depending on the process, the pharmaceutical may be contained within the cells or it may be secreted into the media in which the cells grew. There are two typical production methods for growing the cells in a bioreactor — batch and perfusion. The batch method involves growing cells for a certain period of time in the bioreactor and then taking all the cells out of the reactor for the next step of the process, purification. The perfusion method involves growing the cells for a longer period of time in the bioreactor while continuously extracting cells and adding growth media at steady state. Once the pharmaceutical ingredient has been produced by the cells in either a perfusion or batch bioreactor, several purification steps are performed in a batch manner.

The purification process occurs after the cells and/or supernatant liquid are taken from the bioreactor. The cells and/or liquid are then put through different types of chromatography columns in order to separate the actual pharmaceutical from the rest of the cellular material and liquid. These chromatography columns usually work on principles of size exclusion, anion exchange, affinity, or pH balance. Numerous support operations are required to keep the cell culture and

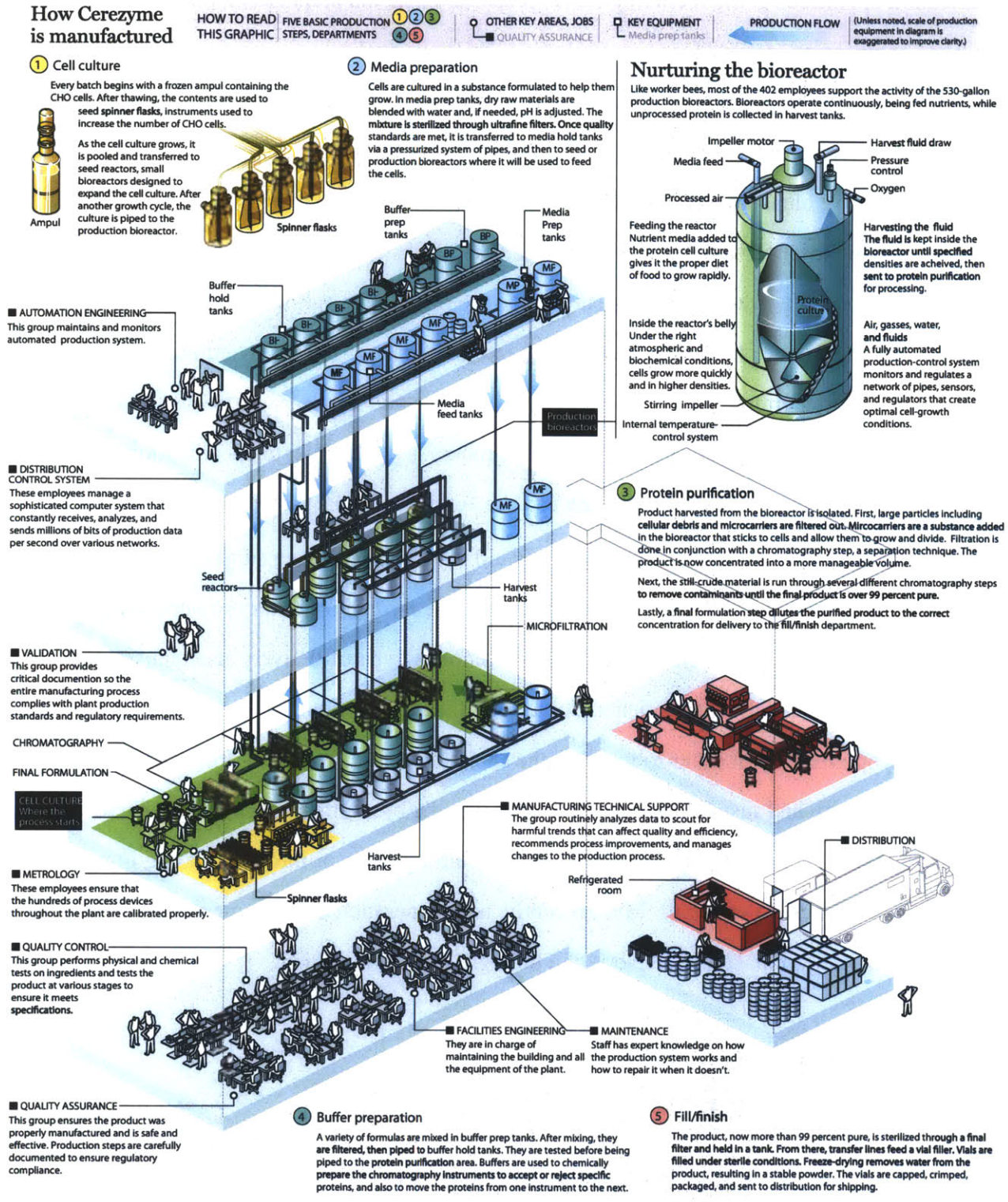


Figure 5: Making a Biotech Drug. *The basic steps for the production of Genzyme's Cerezyme biologic are shown: cell culture, media preparation, protein purification, buffer preparation, and fill/finish. Other support functions include automation engineering, metrology, validation, quality control, quality assurance, maintenance, facilities engineering, manufacturing technical support. Adapted from [8].*

purification operations going including buffer preparation, media preparation, cleaning operations, facilities engineering, maintenance, metrology, validation, quality assurance, quality control, and automation engineering. Buffer and media preparation involve mixing large amounts of chemicals with water in tanks and then storing them for use during the production process. The cleaning operations involve cleaning using caustic chemicals or steaming and in commercial manufacturing is typically done through running clean-in-place (CIP) and steam-in-place (SIP) skids. Metrology involves calibrating the various equipment used in the plant while validation ensures processes are standard and repeatable. Facilities engineering and maintenance repair any equipment issues and keep the building operating efficiently. Quality assurance and quality control ensure all standard operating procedures are performed and that the process is performing to specifications. Automation engineering programs and controls the various automated tasks that run in the plant.

Once the molecule is purified it exists as a liquid known as bulk drug substance. The bulk drug substance must then be formulated to the correct dosage through dilution or concentration of the solution. Finally, the liquid is filled into vials or another type of delivery mechanism such as a syringe for doctors to deliver to patients. Sometimes the liquid product is freeze-dried in a process known as lyophilization in order to increase the shelf-life of the product. Large molecules cannot be delivered orally and instead must be delivered into the bloodstream or muscle. Therefore, the typical administration of a biologic is through a needle injection or intravenous bag in a doctor's office or hospital rather than a pill. More recently, next-generation delivery mechanisms have been researched in order to make the delivery of a biologic to patients easier.

2.2 Factors Influencing Industry Change

There are numerous forces causing the industry to change how it manufactures its biologics. The forces can be summarized into regulatory, economic, safety, efficiency, and environmental factors. These forces have spurred the research and development of new manufacturing technologies that companies need to decide between and how to implement.

2.2.1 Regulatory Factors

The biopharmaceutical industry is heavily regulated to ensure patient safety. Each country has their own regulatory process that oversees pharmaceutical and biotechnology drug approvals. Regulatory agencies are tasked with approving new drugs and ensuring that companies have current good manufacturing practices (cGMPs). For this reason, companies must continually evaluate and invest in manufacturing technology in order to satisfy regulations. The most prominent drug regulatory agencies are the Food and Drug Administration (FDA) of the United States of America, the London-based European Medicines Agency (EMEA) of the European Union, and the Ministry of Health, Labor, and Welfare of Japan [9].

The drug approval process requires at least three phases of human clinical testing. In phase I, a small number of healthy individuals are given the drug to test safety and dosing. In phase II, a larger number of people who have the disease are tested to identify efficacy, safety issues, and optimal dosing. Finally, in phase III, an even larger number of patients with the disease are used to test the drug in placebo-controlled trials to statistically show that the drug is efficacious and safe [9]. The whole process of moving a drug from phase I to the end of phase III could take 10-15 years and sometimes post-approval studies are required as well.

Most clinical trials are placebo-controlled in order to ensure any measured effect of the drug is actually due to the drug and not some other factor. Placebo-controlled trials involve giving one set of patients a placebo or inert substance while the other set of patients receives the drug being tested. The patients who receive the drug and those who receive the placebo are often randomly assigned. Frequently, the trials are performed double-blind, which means neither the patient nor the doctor knows who is receiving the drug and who is receiving the placebo, in order to remove any possibility for bias. The manufacturing process for a drug typically must be finalized once a drug reaches phase III clinical trials because there is no other regulatory approval step between phase III trials and marketing a drug to patients. If a part of the process must be changed after the phase III clinical trials, companies must show that the change does not materially affect the drug produced, which can be both costly and time-consuming.

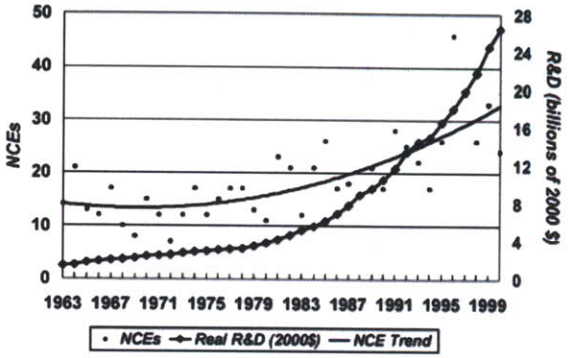
The FDA and other regulatory agencies frequently inspect manufacturing plants in order to ensure that drugs are manufactured in the safest manner for patients. Over the last few years, these agencies have given warning letters to pharmaceutical and biotech manufacturers after they inspect and find deficiencies in their operations. Companies that receive a warning letter are given a certain amount of time to correct the deficiencies. If the deficiencies remain, then the FDA can give a company a consent decree, which means the government takes over the operations of the manufacturing facility for a specified time. The purpose is to ensure patient safety while jointly implementing a plan to remediate the manufacturing plant and return it to company control. A prominent case occurred in 2008 when the FDA gave Genzyme Corporation a warning letter followed by a consent decree for various reasons after the site was contaminated with a virus and had to be shut down for several months [10, 11]. One significant concern was their maintenance of equipment, but it also related to Genzyme not keeping up with the newest manufacturing processes. At the end of 2009, Genzyme had to send a letter to doctors warning them of foreign particles in their filled vials [12]. The foreign particles could have been prevented or reduced with a new technology called isolators, which is the subject of the case study in Section 5.2. This is just one example for why companies need to constantly evaluate their manufacturing technology in order to ensure they are following *current* good manufacturing practices, and not just good manufacturing practices, so that they remain in good standing with regulatory agencies.

2.2.2 Economic Factors

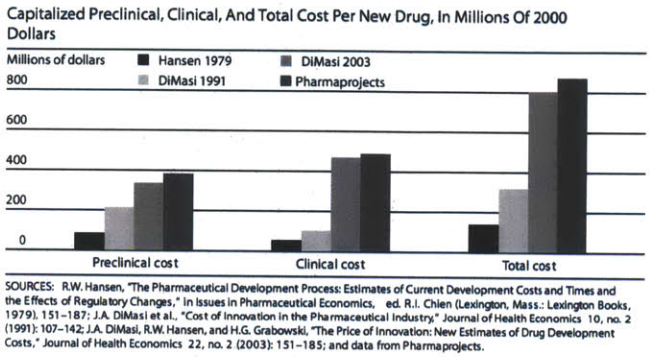
There are two economic motivating factors for the need to implement new manufacturing technologies — rising costs and decreasing revenue. While pharmaceuticals and biologics enjoy healthy margins while the drug is under patent protection, these margins are being threatened.

The average cost to research and develop a new drug and bring it through clinical trials to market has risen exponentially over time as shown with inflation-adjusted dollars in Figure 6a [13]. In addition, Adams and Bratner have compiled several studies looking at the cost of new drug development showing that the cost has increased over time as shown in Figure 6b [14]. The cost of

a drug is high because relatively few drugs make it from research through clinical trials and thus the cost of one approved drug also includes the cost to develop the ones that failed. Companies need to invest in new technologies in order to achieve better research and manufacturing efficiencies to decrease the cost of bringing a drug to market.



(a) Industry R&D Expenditures(2000 dollars) and US new chemical entity (NCE) approvals from 1963 to 2000. *Source of data: PhRMA(2001) and Tufts CSDD Approved NCE Database. Image and caption from [13].*



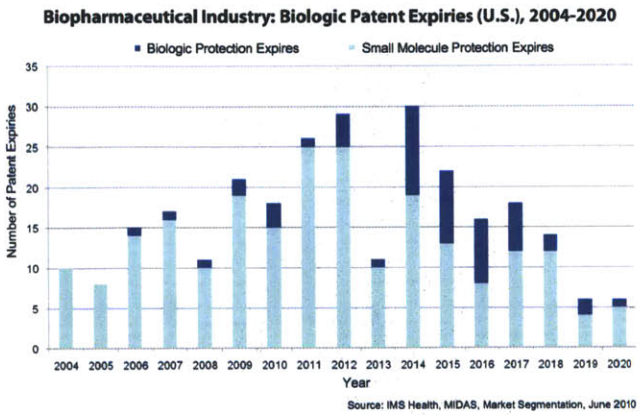
(b) Increasing cost to market a drug. *The inflation-adjusted cost to develop and market a new drug has increased from about $175M in 1979 to about $800M in 2003. [14]*

Figure 6: Increasing costs to research, develop, and market a new drug.

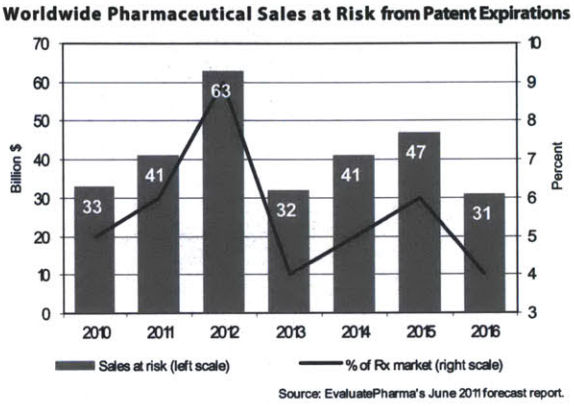
The amount of revenue that companies can achieve for every drug is being pressured due to patents expiring, increased competition, and fewer approvals. Companies have relied on blockbuster drugs that provide billions in revenue per year while under patent protection to fund future research. However, the patents for many of these blockbuster drugs are nearing expiration as shown in Figure 7. Once a patent expires and generic competition begins, the typical margin of 80-90% drops to about 5%. Since there is no regulatory framework for biosimilars, this does not occur as much in the biotechnology industry. However, because biologics can cost tens or hundreds of thousands of dollars per year per patient and the cost of healthcare is rising, the FDA and other regulatory agencies are looking at mechanisms to implement biosimilars as described in Section 2.2.3 in order to introduce competition and reduce the amount patients have to pay and which in turn will reduce revenues.

In addition, while Figure 6a shows that up to the year 2000 the number of molecules approved by the FDA has increased slightly over time, this trend has decreased in the last decade as shown

in Figure 8, because the FDA has started to require more from companies looking for a new drug approval. Rather than just allow a follow-on molecule that treats a disease in a similar way, the FDA is beginning to require new drugs to be either more efficacious or safer in order to be approved.



(a) Patent Expiries from 2004-2020. *A large number of biologic and small molecule patents are expiring in the first half of the 2010s. [2]*



(b) Worldwide Pharmaceutical Sales Patent Expirations. *Billions of dollars in sales are at risk due to patent expiries in the first half of the 2010s, which ranges from 4-9 percent of sales. [4]*

Figure 7: Patent Expiries and effect on Worldwide Pharmaceutical Sales. *A large number of patents are expiring in the first half of 2010s that puts 4-10 percent of drug sales at risk.*

2.2.3 Other Factors

There are several other factors influencing the need for new manufacturing technology such as environmental concerns, capacity, efficiency, personalized medicine, and biosimilars. Current production processes as described in Section 2.1.1 utilize equipment that must be cleaned and sterilized using thousands of gallons of water per day. The large amount of operations performed per day requires several hours to clean and sterilize equipment that results in production downtime. The cleaning and other peripheral equipment also takes up much space. Thus, the industry is looking at moving towards single-use equipment instead of stainless steel equipment that is widely used today. The single-use equipment could be recycled and could have numerous benefits such as less water usage, less downtime between operations, less storage space, and greater flexibility to make changes.

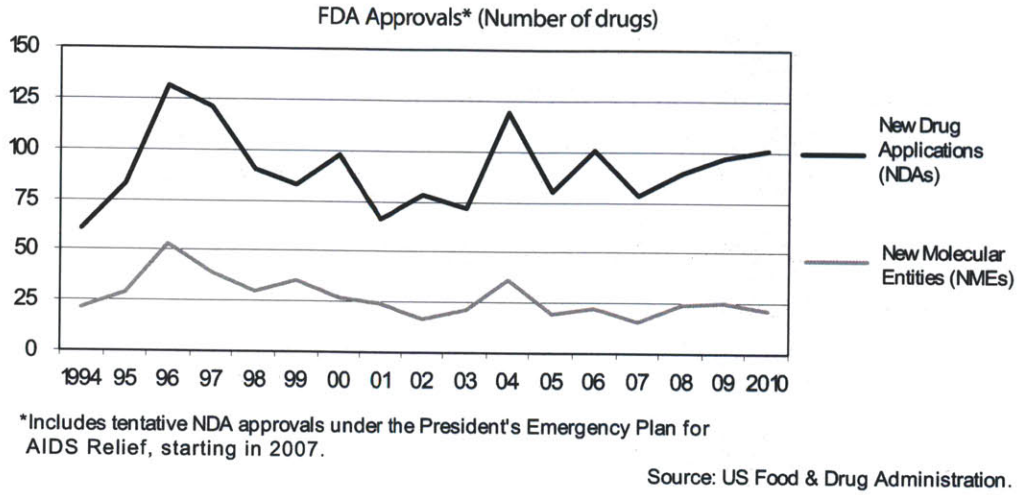


Figure 8: FDA Drug Approvals from 1994-2010. *The black line represents the number of new drug applications (NDAs) each year and the gray line represents the number of new drugs approved each year. The number of new drugs approved each year has trended downward. [9]*

The human genome project, which was completed around 2001, mapped the nucleotide sequence of human DNA and it has spurred innovation in technology that allows for quick, cost-effective genetic testing of human diseases. This is beneficial because more and more diseases, such as cancers, are found to be caused by DNA mutations. Thus, cancer is thought of not as one disease, but as many different diseases caused by many different mutations. Thus, as the cost and time to sequence DNA decreases, doctors will be able to personalize medicine and companies can create drugs that are tailored for specific genetic causes. These personalized medicines would probably have to be manufactured cost-effectively since they would be produced in smaller quantities. Therefore, new technologies such as smaller, single-use equipment will need to be implemented in order to more economically produce smaller quantities of a drug.

The growing support for regulatory agencies to create a pathway for biosimilars, which will result in competition for biologics and lower margins, will require more efficient manufacturing methods. Thus, manufacturers are beginning to look into methods to continuously manufacture biologics by making the drug purification process as continuous as the perfusion bioreactor process. Novartis and the Massachusetts Institute of Technology have created a 10-year research collaboration called the Novartis-MIT Center for Continuous Manufacturing in order to study how to enable continuous manufacturing for biologics. They state that the benefits of continuous manufacturing

are [15]:

- Accelerating the introduction of new drugs through efficient production processes
- Requiring the use of smaller production facilities with lower building and capital costs
- Minimizing waste, energy consumption, and raw material use
- Monitoring drug quality on a continuous basis rather than through post-production, batch-based testing
- Enhancing process reliability and flexibility to respond to market needs

Much research beyond this initiative is taking place across the industry in order to achieve continuous manufacturing and other technological advances to pharmaceutical manufacturing to achieve the above results.

2.3 Amgen

Amgen, Inc. is a biotechnology company headquartered in Thousand Oaks, CA that discovers, develops, manufactures, and markets drugs (mostly biologics) for the treatment of various diseases. Founded in 1980, it has grown to approximately 17,000 employees with 2010 revenues of $15.1 billion, 2010 product sales of $14.7 billion, and 2010 R&D expense of $2.9 billion. Amgen's main research facilities are located throughout the United States, Canada, United Kingdom, and Germany. Through research and acquisitions Amgen's principal products are the following: Aranesp® (darbepoetin alfa), Enbrel® (etanercept), EPOGEN® (Epoetin alfa), Neulasta® (pegfilgrastim), NEUPOGEN® (Filgrastim), Nplate® (romiplostim), Prolia® (denosumab), Sensipar® (cinacalcet), Vectibix® (panitumumab), and XGEVA® (denosumab) [16].

Amgen supports the therapeutics it develops and markets through activities that include the following: process development, clinical manufacturing, bulk protein manufacturing, formulation / fill / finish, distribution, and quality and regulatory compliance. It has one clinical manufacturing facility located in Thousand Oaks, CA and several commercial manufacturing sites located in the United States, Europe, and South America [17].

Chapter 3. Innovation – Decision-Making and Implementation

Due to the factors discussed in Section 2.2, companies need to constantly innovate and therefore introduce new technologies into their production methods to stay competitive. This often requires numerous decision makers within the company. In order to suggest improvements to Amgen's decision-making processes, we interviewed Amgen stakeholders to understand its current decision-making methods and interviewed executives at similarly situated companies to benchmark current practices. Then, various decision-making methods were researched for implementation in order to alleviate issues with and improve the outcome of Amgen's current decision-making processes. Once a technology is selected for implementation, the implementation process needs to be robust enough such that the implementation is successful. This thesis focuses solely on the decision-making process and some thoughts on implementation are discussed in the conclusion.

3.1 Benchmarking Current Practices

Stakeholders in Amgen's process and product engineering, process and product development, clinical operations, corporate manufacturing, and finance departments were interviewed to understand Amgen's current processes for making technology implementation decisions. Typically a successful technology starts in research and makes its way to process development, the pilot plant, clinical manufacturing, and finally commercial manufacturing. At each step along the way, executives or a committee decides whether to keep investing in the technology. They usually evaluate the technology with a business case and net present value (NPV) financial analysis. The business case describes the objective of the technology and presents the pros and cons of implementation while the financial analysis takes a discounted cash flow using a standard discount rate. Some Amgen executives feel that a NPV analysis is easily biased by the analyzer's assumptions to support any

desired outcome. In the early 2000s, Amgen explored using decision analysis, which includes a real options financial model to understand the expected value of a new technology. However, after using decision analysis for a few years, they found the process to be too cumbersome; therefore, they reverted to using net present value since it was simple and well understood by executives.

In addition, when groups have had to select one out of various technologies, they have sometimes used Kepner-Tregoe (KT) analysis. KT analysis involves a group meeting with a facilitator to select the criteria around which to evaluate options, assigning weights to the criteria, and then ranking the options for each criterion. The sum-product of the weights with the rankings gives a ranking of the best option to select. However, this process is not well-suited to many of the decisions that Amgen needs to make for the following reasons:

- It is incapable of handling both subjective and objective criteria in a simple manner.
- It is subject to bias from the entire group picking the weights together in the same room.
- The "boss" may influence choices as stakeholders try to please him/her.
- Group dynamics such as an "800-lb gorilla" and shy participants affect the outcome.
- It requires a facilitator and the decision-makers to meet together at the same time.

Three executives from other large biotechnology or pharmaceutical companies were also interviewed to understand their company's processes for innovating and implementing new technology. They mentioned that new technology often gets propagated bottom-up from scientists. Scientists may get excited about a certain technology that they discover at a conference or read in a scientific journal article and then they propagate it through their organization. In addition, sometimes new technologies are developed based on scientific grass-roots idea generation. Finally, there are also top-down technology initiatives from executives who are looking at reducing risk or improving another measure.

Since there is much business pressure to develop new products quickly, one company develops new technologies as part of their process development due to limited resources. However, they think this is risky and increases the timeline to introduce a new technology. Another company said they used to use real options in order to analyze technology improvement options, but it was controversial so they abandoned that method and instead now use return on investment (ROI) to make decisions. The financial analysis for return on an investment was not very rigorous and

they felt they were good at estimating costs. The third company said that they have a technology council that meets monthly to go over new technology options along with opinions from various departments. The council acts as an advocate for new technologies with management.

No matter what method each company uses to discuss, evaluate, or introduce technologies, each felt that it was important to connect research and development, operations, strategy, and finance when making decisions. One company believed that technology development should be independent from process development for producing a new biologic or pharmaceutical drug, thereby taking technology development out of the critical path of producing new molecules. The result from interviewing the executives was the realization that there is not currently a gold standard for technology assessment and implementation.

3.2 Decision-Making

Decision-making is a complex process as there are often various inputs into the process and the outcome is usually of critical importance. Yet, decision-making is difficult because much uncertainty usually exists around the inputs into the process and there are numerous ways to look at a single problem. Many types of decision-making and technology assessment methods and tools exist as shown in Table 2. These tools typically fall into the areas of economics, decision analysis, group decision support systems, systems engineering/systems analysis, technological forecasting, information monitoring, technical performance assessment, risk assessment, market analysis, and externalities/impact analysis.

Christensen et al. discuss in [19] how three typical financial analysis tools can hurt innovation in companies. These tools are the discounted cash flow and net present value, fixed and sunk cost considerations, and emphasis on earnings per share and looking only at the impact to short-term financials. In regards to discounted cash flow and NPV, they say that innovators commonly make two errors that promote anti-innovation. First, that the base case against which a project is compared is the current health of the company and the belief that it will extend indefinitely into

Table 2: Technology assessment toolkit for managing technology in the globally competitive enterprise. *Taken from [18].*

- Economic Analysis
  - Cost/Benefit Analysis
  - Cost-Effectiveness Analysis
  - Lifecycle Cost Assessment (LCA)
  - Return on Investment (ROI)
  - Net Present Value (NPV)
  - Internal Rate of Return (IRR)
  - Breakeven Point Analysis
  - Payback Period Analysis
  - Residual income
  - Total Savings
  - Increasing Returns Analysis
- Decision Analysis
  - MultiCriteria Decision Making
  - Multiattribute Utility Theory
  - Scoring
- Group Decision Support Systems (GDSS)
  - Delphi/Group Delphi
  - Analytic Hierarchy Process (AHP)
  - Q-sort
- Decision Trees
- Fuzzy Logic
- Systems Engineering/Systems Analysis
  - Technology System Studies
  - System Dynamics
  - Simulation Modelling and Analysis
  - Project Management Techniques
  - System Optimization Techniques
    - Linear, Integer, and Non-linear Programming
  - Technology Portfolio Analysis
- Technological Forecasting
  - S-Curve Analysis
  - Delphi/AHP/Q-Sort
  - R&D Researcher Hazard Rate Analysis
  - Trend Extrapolation
  - Correlation and Causal Methods
  - Probabilistic Methods
- Information Monitoring
  - Electronic Databases
  - Internet
  - Technical/Scientific Literature Reviews
  - Patent Searches
- Technical Performance Assessment
  - Statistical Analysis
  - Bayesian Confidence Profile Analysis
  - Surveys/Questionnaires
  - Trial Use Periods
  - Beta Testing
  - Technology Decomposition Theory
  - S-Curve Analysis
  - Human Factors Analysis
    - Ergonomics Studies
    - Ease-of-Use Studies
  - Outcomes Research
- Risk Assessment
  - Simulation Modeling and Analysis
  - Probabilistic Risk Assessment
  - Environment, Health, and Safety Studies
  - Risk-based Decision Trees
  - Litigation Risk Assessment
- Market Analysis
  - Fusion Method
  - Market Push/Pull Analysis
  - Surveys/Questionnaires
  - S-Curve Analysis
- Externalities/Impact Analysis
  - Externalities Analysis
  - Social Impact Analysis
  - Political Impact Analysis
  - Environmental Impact Analysis
  - Ethical issues Analysis
  - Cultural impact Analysis

the future. Instead, it is more probable that there will be a nonlinear decline in performance. They reference that this is typically called Parmenides' Fallacy. Second, they discuss how discounted cash flows can suffer from estimation errors because the impact of future investments are hard to predict beyond a few years out. In regards to fixed and sunk costs, they argue that the idea of having to choose between full-cost and marginal-cost options does not allow a company to make the same decisions that a new entrant might make and thus the company does not make a decision for the future. Finally, they note that many executives are incentivized to think about the short-term financial costs rather than looking at the long-term picture, which may cause innovation projects to not be implemented that in fact should be for the long-term benefit of the company. The paper also discusses how the stage-gate approval process for technology focuses too much on the numbers that are based on many assumptions and they instead suggest using a discovery-driven planning process [19].

Once a technology assessment has finished and a technology option is selected, then the technology must actually be implemented. Klein and Knight discuss several issues with technology implementation and suggest ways to improve technology implementation success [20]. They cite that there are six major reasons for difficult technology implementation [20]:

- Many innovations are unreliable and imperfectly designed.
- Many innovations require would-be users to acquire new technical knowledge and skills.
- The decision to adopt and implement an innovation is typically made by those higher in the hierarchy than the innovation's targeted users.
- Many team and organizational innovations require individuals to change their roles, routines, and norms.
- Implementation is time consuming and expensive.
- Organizations are a stabilizing force.

This results in "observers estimat[ing] that nearly 50% or more of attempts to implement major technological and administrative changes end in failure [20]."

Based on the literature above, I believe Amgen should augment its net present value financial approach with more holistic measures that will not let it fall into the traps that Christensen discusses. Meyers et al. say that "as reasoned by experts, some innovations do not result in desired benefits because of a mismatch between the buyer's strategic goals and the innovation's implemen-

tation and results...however, when the supplier keeps an eye on the full range of factors—technical and otherwise—successful implementation is more likely [21]." In addition, the technology innovation that Amgen implements often impacts numerous areas and therefore its decision-making tools should handle information from many people so that those whom the technology affects are involved in the decision-making process. Therefore, out of the above decision-making methods, the Analytic Hierarchy Process was selected for its robust behavior and is discussed in Section 4.1.

Chapter 4. Framework

As discussed earlier, Amgen typically utilizes a business case and NPV analysis or Kepner-Tregoe analysis in order to make technology decisions. Yet, an objective, standard decision-making process would be highly beneficial for implementing new technologies. There are numerous decision-making approaches as discussed in Section 3.2 and Amgen needed a new approach that was objective, robust, simple, easy-to-use, easy-to-understand, quick, and that easily allowed global, group collaboration. Due to these factors, the Analytic Hierarchy Process was selected as the decision-making method in a simple framework shown in Figure 9.

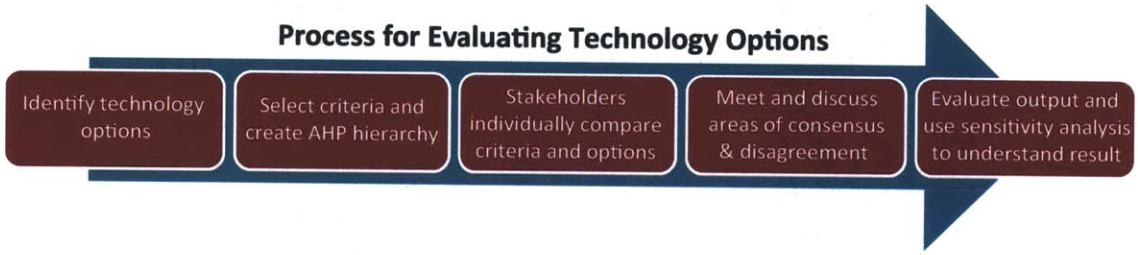


Figure 9: Assessment Process for Technology Decisions. *The process starts with identifying the options amongst which the decision needs to be made. Then the criteria are selected in order to create the AHP hierarchy. Pair-wise comparisons are performed on the criteria and options. Finally, the group meets to discuss the results and evaluate the output with sensitivity analysis.*

4.1 The Analytic Hierarchy Process (AHP)

The Analytic Hierarchy Process (AHP) was developed by Thomas Saaty in the 1970s as a novel group decision-making method [22]. There are many literature citations where it has been used for technology implementation decisions [23, 24, 25, 26, 27, 28, 29, 30]. The process involves participants making pair-wise comparisons amongst criteria in order to determine the correct weighting of various factors. First, the stakeholders must identify the various options that need to be prioritized or selected against. Next, the criteria must be selected in which to evaluate the various options against. These criteria are setup in a hierarchy from basic to specific as shown in Figure 10.

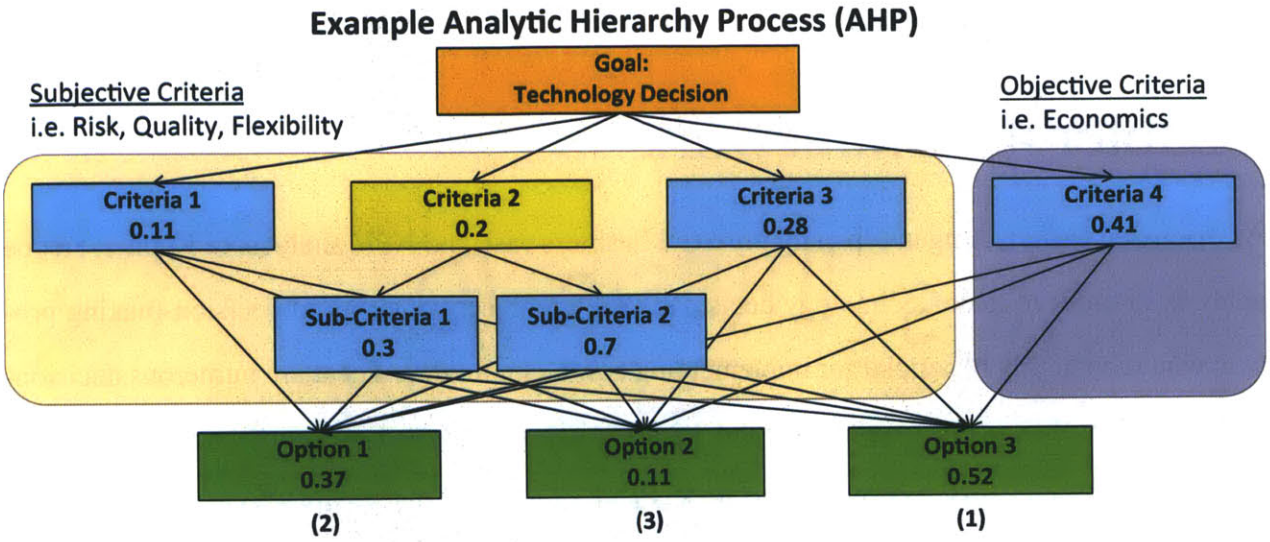


Figure 10: Example Analytic Hierarchy Process. *At the top of the hierarchy is the decision — select a technology option. Beneath the decision are various criteria, subjective criteria are denoted on the left and objective criteria are denoted on the right. The criteria in the yellow boxes are criteria with sub-criteria and these are not evaluated against the options. The criteria in blue boxes represent covering criteria and these are evaluated against the options. At the bottom of the hierarchy in the green boxes are the options. Beneath each criteria box is the local weight of the given criteria (each row of the hierarchy sums to 1). Beneath each option box is the result of the sum product of the criteria weights and option weights. This value gives the ranking of the options. In this example, the ranking is Option 3, Option 1, Option 2.*

The hierarchy is composed of both covering criteria and regular criteria. The covering criteria are the criteria without any sub-criteria and the criteria against which the options are evaluated. The regular criteria are all criteria that are not covering criteria and they are used to determine the overall weighting of the covering criteria. The AHP process involves stakeholders individually making pair-wise comparisons amongst criteria on the same row and then comparisons of the options against the covering criteria. Weights are assigned based on the comparisons and then the output, a ranking, is based on the sum-product of the criteria weights and the comparisons between the options and covering criteria. Typically, the fundamental scale for pairwise comparisons as shown in Table 3 is utilized for the comparisons. However, it is also possible to use words such as "equal," "moderate," "strong," "very strong," and "extreme." Another option is to use a graphic representation such as area or volume of an object to compare two items.

Table 3: The Fundamental Scale for Pairwise Comparisons. *The scale commonly used for pairwise comparisons in AHP. Adapted from [22, 31].*

Intensity of Importance	Definition	Explanation
1	Equal Importance	Two elements contribute equally to the objective
3	Moderate Importance	Experience and judgment moderately favor one element over another
5	Strong Importance	Experience and judgment strongly favor one element over another
7	Very Strong Importance	One element is favored very strongly over another; its dominance is demonstrated in practice
9	Extreme Importance	The evidence favoring one element over another is of the highest possible order of affirmation
Intensities of 2, 4, 6, and 8 can be used to express intermediate values. Intensities of 1.1, 1.2, 1.3, etc. can be used for elements that are very close in importance.		

The weights for the criteria or options are derived from the comparisons by entering them on a matrix as shown below. When the equation $Aw = nw$ is solved, the value for n represents the principal eigenvalue for the matrix A with w being the eigenvector for matrix A. The values in the eigenvector represent the weights for the respective criteria [22].

$$\begin{array}{c} \\ A_1 \\ A_2 \\ \vdots \\ A_n \end{array} \begin{array}{c} \begin{array}{cccc} A_1 & A_2 & \cdots & A_n \end{array} \\ \begin{pmatrix} w_1/w_1 & w_1/w_2 & \cdots & w_1/w_n \\ w_2/w_1 & w_2/w_2 & \cdots & w_2/w_n \\ \vdots & \vdots & \ddots & \vdots \\ w_n/w_1 & w_n/w_2 & \cdots & w_n/w_n \end{pmatrix} \end{array} \begin{pmatrix} w_1 \\ w_2 \\ \vdots \\ w_n \end{pmatrix} = n \begin{pmatrix} w_1 \\ w_2 \\ \vdots \\ w_n \end{pmatrix}$$

For example, we can take a 3x3 matrix as shown below and calculate the eigenvector. First, the product of the values in each row is calculated giving 0.5, 0.125, and 16 from top to bottom of the matrix. Then the nth root of these values is determined. Since this is third order matrix, the third root of the product of each row is taken giving 0.7937, 0.5, and 2.5198 from top to bottom of the matrix. Finally, the eigenvector is determined by taking the third root terms and dividing them by

the sum of the third root values, which equals $0.7937 + 0.5 + 2.5198 = 3.8135$. So the eigenvector is 0.2081, 0.1311, 0.6607 from top to bottom of the matrix. Thus, the A_1 factor has a weight of 20.81%, the A_2 factor has a weight of 13.11%, and the A_3 factor has a weight of 66.07%.

$$\begin{array}{c} \\ A_1 \\ A_2 \\ A_3 \end{array} \begin{array}{c} \begin{array}{ccc} A_1 & A_2 & A_3 \end{array} \\ \begin{pmatrix} 1 & 2 & 0.25 \\ 0.5 & 1 & 0.25 \\ 4 & 4 & 1 \end{pmatrix} \end{array}$$

Only those individuals that have specific knowledge about a given branch of the criteria or the options in the hierarchy need to do comparisons. Thus, AHP is flexible such that only subject matter experts determine the weightings of criteria and options. Once the weights are derived for each individual's comparisons, the weights can be combined to determine the overall group's ranking of the options. Therefore, it is possible to combine different subsets of individuals participating in an AHP analysis to determine how a certain department or group of individuals would make the decision if they were the sole deciders. It is also possible to weight certain individuals more strongly than others, for example, to give the decision-maker two or three times the weight of other individuals when combining the scores.

4.1.1 Consistency

Since participants make multiple pair-wise comparisons amongst the criteria on a given branch and level of the hierarchy, it is important to ensure that the participant makes the comparisons in a consistent manner. For example, it is not logical to say that A is better than B, B is better than C, and then C is better than A. Instead, to be consistent, A should be better than C. Therefore, it is necessary to calculate a consistency score that the participants and project manager can use to ensure both that the participant is thinking about their comparisons and that it is done in a logical manner.

Since the participants do not just make a binary comparison (participants can say A is much

better than B or A is slightly better than B), then the process needs to allow for some inconsistency. The method proposed by Saaty involves determining a consistency index (CI) that equals $(\lambda_{max} - n) / (n - 1)$, where n represents the principal eigenvalue of the matrix A above. The consistency index is then "compared with the same index obtained as an average over a large number of reciprocal matrices of the same order whose entries are random. If the ratio (called the consistency ratio CR) of CI to that from random matrices is significantly small (carefully specified to be about 10% or less), we accept the estimate of w. Otherwise, we attempt to improve consistency [22]." If a set of comparisons are completely consistent then $\lambda_{max} = n$.

4.1.2 Criteria

One of the major benefits of the analytic hierarchy process is that it can include both subjective and objective criteria for the options to be compared against. AHP is good for subjective criteria because someone can usually easily make a comparison of one item against another on a scale. However, AHP is also good for objective criteria because an objective item can easily be mapped to the fundamental scale for pairwise comparisons. For example, if we were comparing two cars against cost, one could take the ratio of the costs in order to select how much better one car is over the other. Another method with a budget could be to compare the cost to the budget and rank based on the ratio of how much the cost deviates from the budget. This method can be adapted for many situations involving objective data.

4.1.3 Adaptations

Numerous adaptations have been suggested and implemented since AHP was first described and introduced. These include methods to introduce fuzzy logic around the comparisons such that greater uncertainty can be taken into account [29]. A similar process called the Analytic Hierarchy Network (ANP) builds on AHP by allowing feedback loops instead of a simple hierarchy [29]. Advancements have been suggested for calculating a consistency score and the cut-off for when a matrix is consistent enough to be accepted [32]. Finally, improvements have been suggested for the

calculation of weights for the criteria, especially for incomplete matrices, which are comparison matrices where the participant does not make every pair-wise comparison possible [33].

4.1.4 Criticisms

The major negative aspect of AHP is that it can suffer from rank reversal. Rank reversal can occur if an option is added to the hierarchy after an analysis is performed. The addition of the extra option could cause some of the rankings from the previous analysis to reverse instead of the new option just being inserted into the same ordered ranking. This can be a slight issue in prioritization where the objective is to prioritize many projects or options for importance. However, in the case where a single option is being chosen for implementation, rank reversal will have little impact.

4.2 Commercial Software Implementation

Several previous theses discussed creating and implementing decision-making tools in Microsoft Excel at various companies [34, 35, 36]. However, some of these companies have noted that adoption and maintenance of such tools was difficult after the project period. Therefore, in order to improve the usability and sustainability of a new decision-making process for Amgen, several commercial decision-making tools that implement AHP were investigated. The software researched were EC11.5 and Comparion™ Suite by Expert Choice® (http://www.expertchoice.com), Decision Lens 3 by Decision Lens, Inc. (http://www.decisionlens.com), and MindDecider Team by MindDecider (http://www.minddecider.com).

The software by Expert Choice® was chosen after examining the various features, availability, support, price, and implementation offered by the three companies. Decision Lens only offered a consulting model that required a consulting contract along with the software. MindDecider lacks the usability and support I sought as it is based outside the United States and did not offer a web-based solution. In addition, it has a unique user interface that has no menus and requires a lot of mouse right-clicks to select options. The software made by Expert Choice® has a typical

user interface, has excellent documentation and support, and is provided in two versions that were well-suited for the project period and then for implementation throughout Amgen after the project period. Expert Choice only implemented the base version of AHP without any adaptations. Since this was the first implementation of AHP throughout Amgen, the goal was to use the simplest method that met the objective, which the base version of AHP does.

The two versions of software made by Expert Choice are a desktop version called EC11.5 as shown in Figure 11 and a web-based version called Comparion^{TM} as shown in Figure 12. We used the desktop version of the software during the project due to the short time duration of the project and the time required to install the web-based version on internal Amgen servers. However, because the web-based version has greater usability for projects that involve many people in multiple locations, that is the version recommended for use at Amgen beyond the project period. Because of the limitations in the desktop version for use with people in multiple locations, I created a Microsft Excel worksheet survey with slider bars that I sent around to participants in order to record their feedback to the AHP comparisons as shown in Figure 13. The survey results were then inputted into the Expert Choice desktop software.

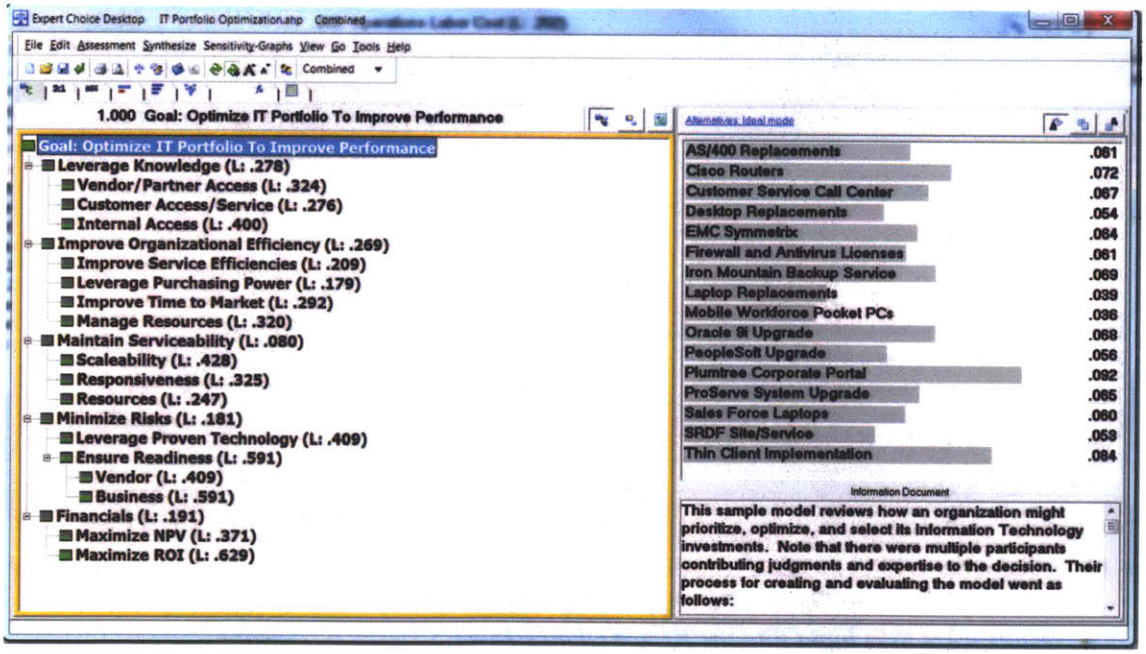


Figure 11: Screenshot of Expert Choice EC11.5 Desktop software.

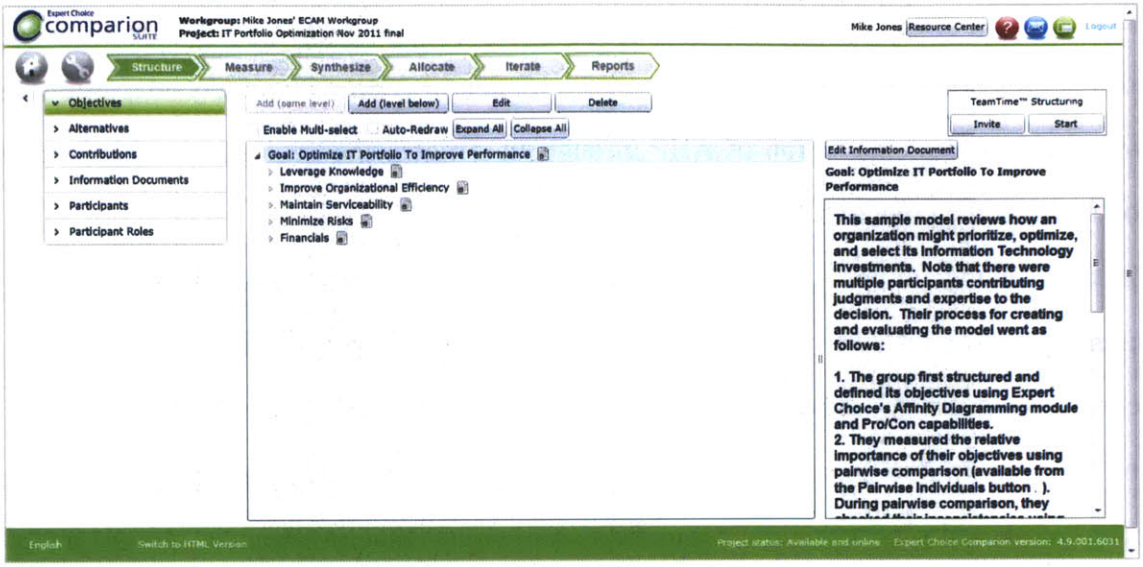


Figure 12: Screenshot of Expert Choice Comparion™ web-based Software.

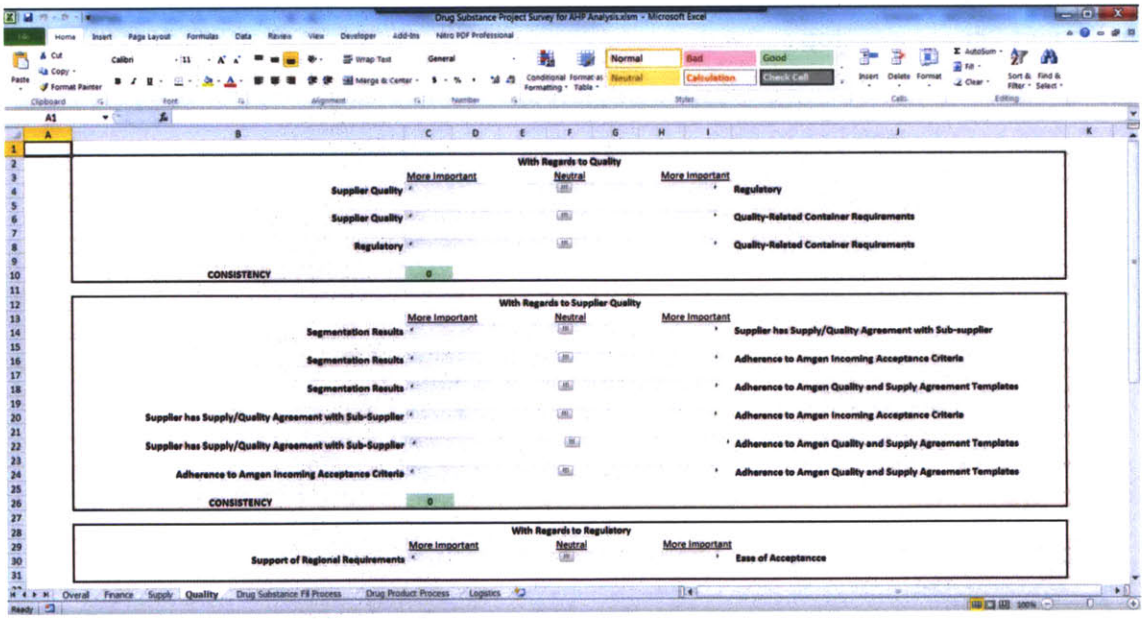


Figure 13: Screenshot of Microsoft Excel Survey for AHP Analysis. *A Microsoft Excel spreadsheet was created for stakeholders to input their pair-wise comparisons of criteria and alternatives. The results were then input into the Expert Choice EC11.5 Desktop software.*

Chapter 5. Case Studies

Several case studies were undertaken in order to test out the framework and decsion-making process. The first case study investigated the use of Expert Choice software for AHP analysis as compared to a Microsoft Excel-based AHP implementation performed two years prior with the eData Infrastructure Technology (EDIT) Forum. The second case study looked at using AHP for a project selection decision as compared to the typical method of using a business case and net present value financial analysis. We modeled the project in AHP concurrently with the typical analysis in order to compare the outcome. Finally, the third case study used AHP to make a decision on an issue *de novo* that had had five previous analyses performed without an actual decision being made and implemented.

5.1 eData Infrastructure Technology Project Prioritization

At the end of 2010, Amgen's eDIT Forum tried to prioritize projects that they had on their agenda for the following year. In order to prioritize the projects, they built a home-grown implementation of AHP in Microsoft Excel. The 12 stakeholders on the forum analyzed the criteria in the analytic hierarchy as shown in Figure 14 and the 14 projects against the criteria. The project manager implemented AHP in Excel by having participants make pair-wise comparisons in a long list that required the participant to select A or B along with a number for the relative strength of the comparison for each row. The scale used was the typical AHP scale as shown in Table 3 in Section 4.1. Once the spreadsheet with the relevant criteria was created, the project manager and participants e-mailed it back and forth. The Excel spreadsheets used in the initial project had to be revised several times due to programming errors that can arise in a home-grown project. A survey of the participants was performed at the end of the analysis; they found the process with Excel to be too laborious and time-consuming.

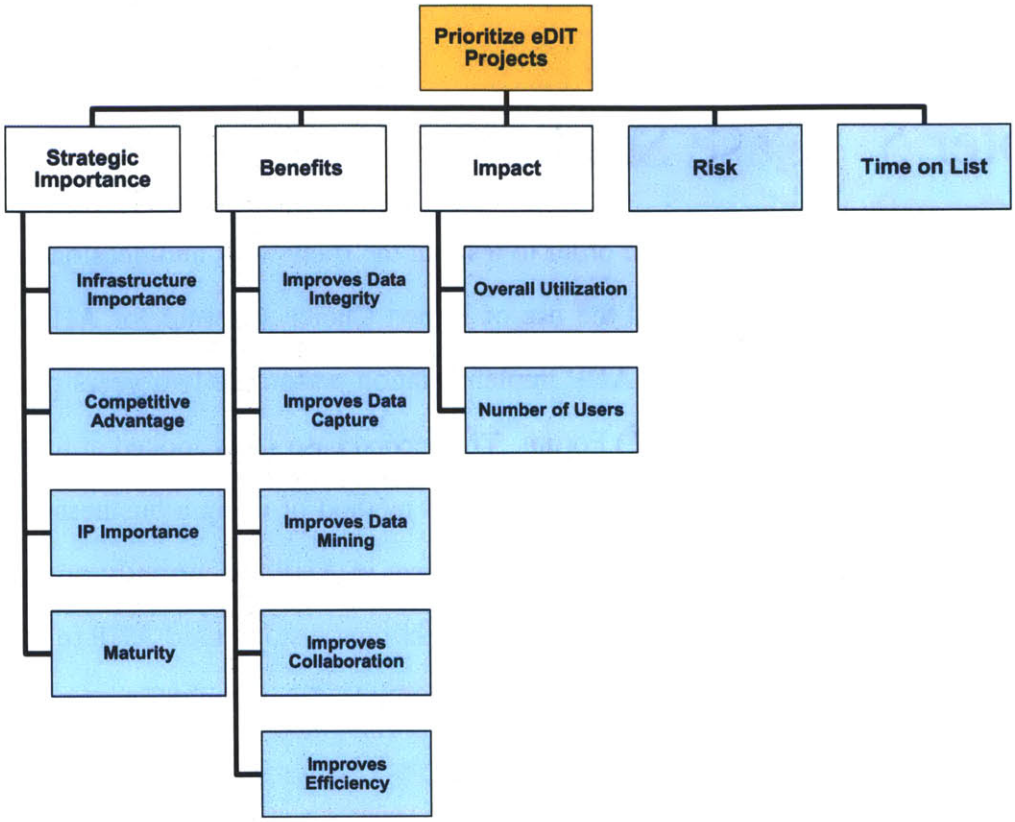


Figure 14: AHP Hierarchy for eDIT Project Prioritization. *The yellow box denotes the objective of the hierarchy criteria. The grey boxes represent general criteria whose weightings are derived from the weighting of the more specific covering criteria shown in the blue boxes.*

We took the data from the Excel analysis and input it into Expert Choice Desktop 11.5 in order to compare factors such as time, management, multiple user support, data, and others between the two software packages. As the data was input into Expert Choice, we noticed some minor mistakes in calculations that had not been caught and fixed in the final Excel analysis performed the previous year. While the desktop version of Expert Choice was used for the analysis due to time and money constraints, the benefits would be extendable to the web-based version of Expert Choice that Amgen would use in the future. The differences between Excel and Expert Choice were then discussed with the project manager.

The Expert Choice software was deemed superior to Excel based on five categories as summarized in Table 4. Expert Choice allows a user to easily create any new hierarchy with a few clicks of the mouse compared to the required manual setup of many cells with complex calculations within

Excel for each new decision hierarchy. Expert Choice also eliminates any possible errors from typos or wrong cell references that can occur in the manual setup process in Excel. The desktop and web-based version of Expert Choice stores everyone's responses in one place without the need to consolidate individual responses as is required with Excel. With Excel, the project manager needs to e-mail spreadsheets back and forth with participants and keep track of each person's spreadsheet responses. The web-based version of Expert Choice handles multiple users in an easy manner by sending e-mails to participants allowing them to go to a website to make their pair-wise comparisons rather than the project manager sending unique instances of spreadsheets to users requiring them to go row-by-row to record their responses with Excel. The Expert Choice software has numerous built-in tools to analyze the results including several different sensitivity analysis graphs on the weights of the criteria, checks on the consistency of people's responses, and the ability to compare each person's response with each other. The Microsoft Excel version has no sensitivity analysis or other methods to compare the responses of individuals to each other. Since Expert Choice is commercial software designed for AHP analysis, it comes with detailed documentation on how to use the software and perform analyses. It also includes professional technical support. A user-created Excel version has no such documentation and requires the programmer who made the spreadsheets to manually comment and provide on-going support. Finally, the only category in which Excel is better than Expert Choice for AHP analysis is the availability of the software. Every user within Amgen has Microsoft Excel on their computers for numerous tasks and is therefore considered free. However, the web-based version of Expert Choice requires a yearly license that is on the order of tens of thousands of dollars.

In addition to comparing the identical processes with different software packages, we also analyzed features that Expert Choice contains that the Excel-programmed AHP did not. In the eDIT analysis the stakeholders were required to make every possible comparison among pairs of criteria. This resulted in the complaint from participants that the process was too time-consuming. However, Expert Choice has several options that can reduce the number of comparisons necessary in order to save time when there are either a large number of criteria, a large number of options, or

both. Furthermore, Expert Choice has built-in functions that allow a utility, maximum, or minimum function to be used when comparing objective values. Expert Choice also contains several built-in sensitivity analyses that allow for the dynamic adjustment of criteria weights that can be used to identify weighting cutoffs to shift a certain project's ranking. Finally, Expert Choice has an add-on called Resource Aligner that allows a cost-benefit selection of projects to take place for cases where AHP is being used for project prioritization.

Table 4: Excel vs. Expert Choice Comparison for AHP. *The italicized areas were deemed better for the given software approach. Expert Choice is better in every category except availability.*

	Microsoft Excel®	**Expert Choice®**
Time	intensive setup and administration, error-prone	*easy setup, built-in calculations reduces errors*
Management	spreadsheets, e-mail, time intensive	*web-based, time-saving*
Multiple User Support	tedious	*built-in* (web-based version only)
Data	manually processed	*built-in synthesis and sensitivity analysis*
Documentation	none	*provided*
Availability	*free*	yearly license

Based on the comparison between Excel and Expert Choice, management made the decision to use Expert Choice for future decision-making processes involving AHP. While Expert Choice requires a yearly fee compared to Excel, its use will allow for easy setup of analyses that does not require a programmer and it will be more sustainable due to its documentation and technical support availability.

5.2 Clinical Manufacturing Building Upgrade Selection

Amgen needed to update its master plan for its formulate / fill / finish clinical manufacturing facility in Thousand Oaks, CA. The goal of the project was to select a facility upgrade plan that would bring clinical manufacturing into technology alignment with commercial manufacturing, allow for the testing of future technologies, reduce costs and improve economics, enable more rapid response to clinical demands, mitigate risks, and ensure lifecycle support for Amgen's products. Many of

drivers reasons overlap with the factors for change in the industry discussed in Section 2.2. The main method to accomplish the goal involved selecting a plan to upgrade the technology used to formulate the clinical drug substance and fill vials and syringes. With the help of an engineering consulting firm, plant management identified the three options listed in Table 5 of which they needed to select the best one.

Table 5: Clinical Manufacturing Upgrade Options. *Three options were evaluated in order to determine the best path forward for Amgen's clinical manufacturing facility. The description details have been left out to protect confidential information.*

	Description	**Location**
Do Nothing	Current State	Current Building
Option 1	Adds Catch-up Technology, Maintains Legacy Capabilities, Prepares for Future	Minor Building Renovation Expansion into Adjacent Building
Option 2	Future Capabilities, Maintains Legacy Capabilities	Expansion into Adjacent Building

The main technologies suggested for implementation in option 1 and option 2 were restricted access barrier systems (RABS), isolators, and automated inspection. Until recently, the current standard for filling vials and syringes was to do so in a class 100 / ISO 5 cleanroom (a maximum of 100 particles of size 0.5 μm or larger per cubic foot of air) with restrictions around the movement of operators. However, newer technology such as RABS and isolators can be more aseptic as they are more contained. An isolator is a large machine with a pressurized, aseptic environment within it that allows for the filling of vials and syringes without any human interaction. In addition, the machine can be fully sterilized with vaporous hydrogen peroxide (VHP). RABS are more exposed to the air in a room and generally require manual cleaning. These newer technologies provide numerous benefits over a standard cleanroom and the FDA and other regulatory agencies are starting to expect pharmaceutical companies to upgrade their facilities.

Along with newer filling equipment, regulatory agencies want to ensure that all vials and syringes are particle free so that only product is injected into patients. Currently, the clinical manufacturing facility uses manual inspections to ensure product reaches patients particle-free while commercial manufacturing facilities use a combination of manual and automated inspection. Au-

tomated inspection allows for an extra inspection step and ensures that no product is delivered to patients with any glass fragments, protein aggregates, or other issues.

The project team of 12 stakeholders came from a wide array of departments such as finance, project management, facilities engineering, quality, clinical manufacturing, corporate manufacturing, process and product development, and process and product engineering. The group met to develop the AHP first and second level criteria hierarchy as shown in Figure 15 based on the project description and goals.

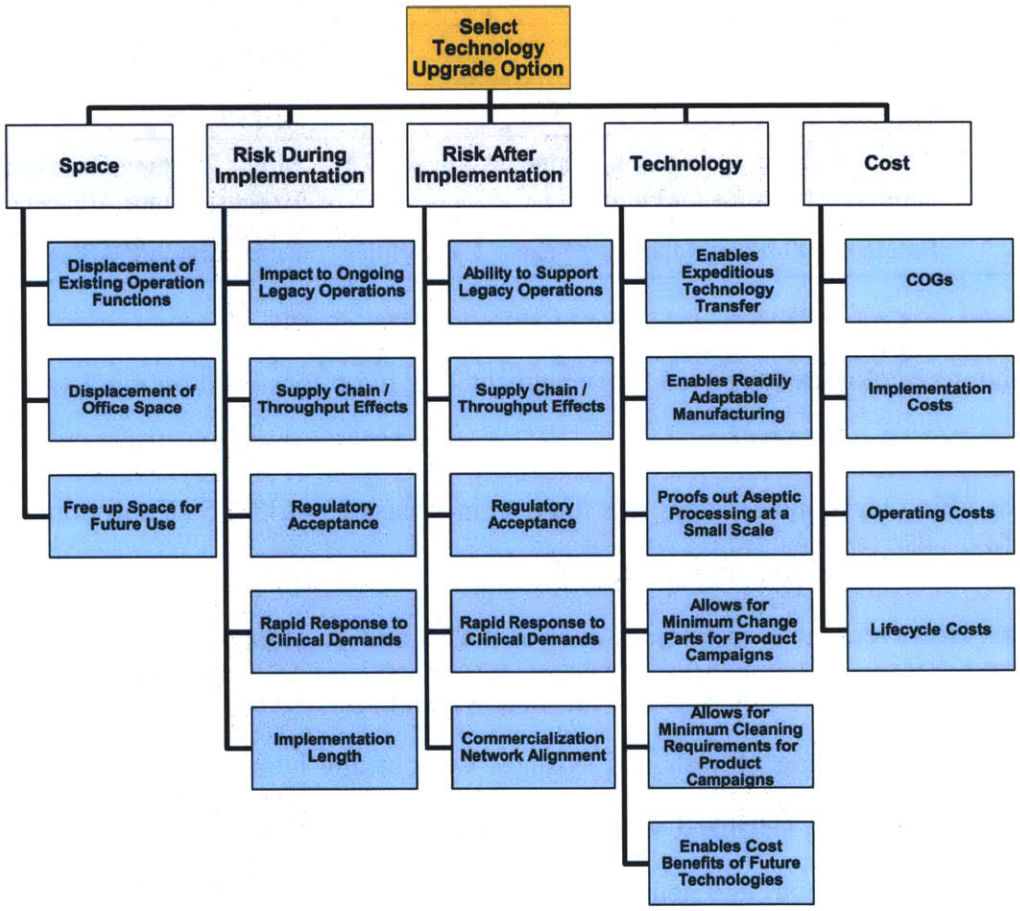


Figure 15: AHP Hierarchy for Clinical Manufacturing Upgrade Selection. *The yellow box denotes the objective of the hierarchy criteria. The grey boxes represent general criteria whose weightings are derived from the weighting of the more specific covering criteria shown in the blue boxes.*

A survey was sent to each of the 12 stakeholders for them to make pair-wise comparisons amongst the criteria in order to obtain the weighting for each criteria. Participants were instructed to only compare the criteria in which they felt knowledgeable and they did so using the funda-

mental scale for pairwise comparisons. The results from the survey were compiled and input into the Expert Choice software. Then the stakeholders who had the most detailed knowledge about each of the options met to compare the options against the covering criteria. This included the plant manager / executive director, plant director, project engineer, and project manager. As there is much uncertainty about the future, many of the comparisons, except for cost, required the stakeholders to make subjective comparisons. All the comparison results were input into Expert Choice with the results shown in Figure 16.

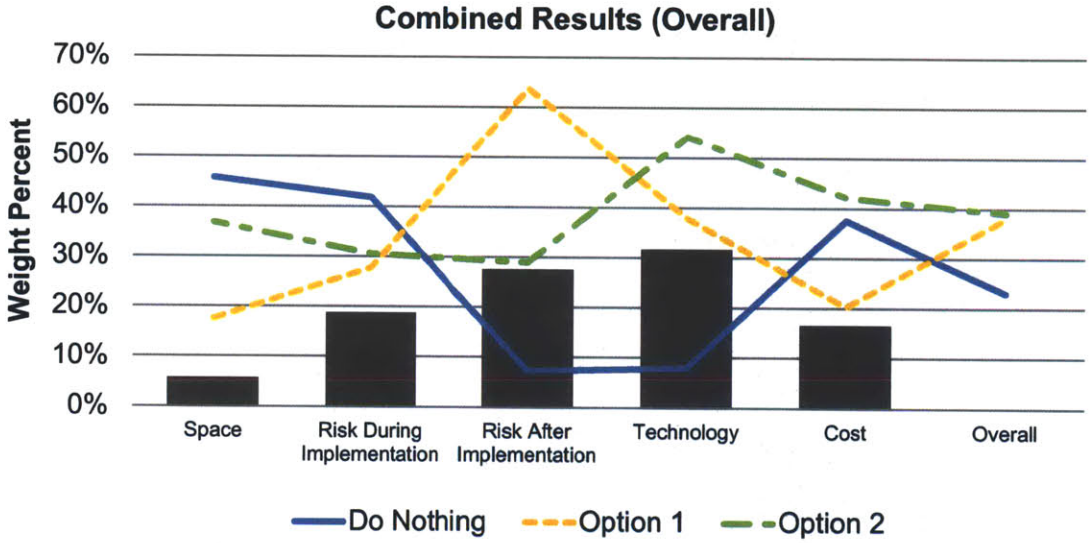
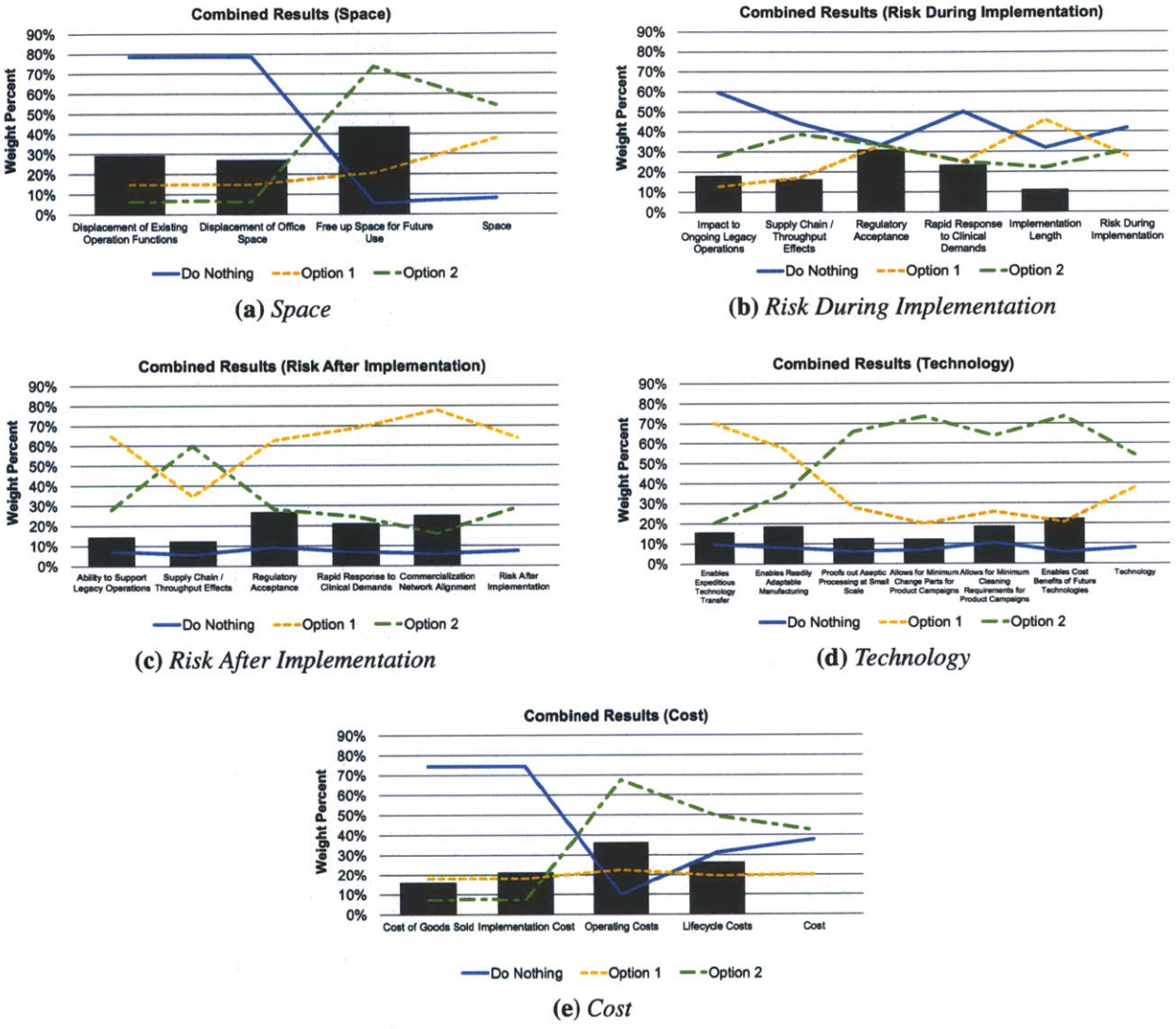


Figure 16: Overall Results from Clinical Manufacturing Upgrade Selection AHP Analysis. *The criteria weights (grey bars) resulted from the combined pair-wise comparisons of 12 stakeholders. The option weights (lines) for each criteria category were derived from the combined pair-wise comparisons of the four stakeholders with the most knowledge of the options.*

The pair-wise comparisons of the criteria resulted in technology having the highest impact, followed by risk after implementation, risk during implementation, cost, and space. The pair-wise comparisons resulted in "do nothing" being the highest rated option for space and risk during implementation. Option 1 was the highest rated for risk after implementation while option 2 was highest rated for technology and cost. The overall combination of the criteria weights and option weights resulted in option 2 being ranked slightly higher than option 1 with "do nothing" ranked last. Since the overall results between option 1 and option 2 were so close, it may help to look deeper into each criteria category to understand how each option was weighed in regards to the

covering criteria. Graphs representing the criteria weights and option weights for the second level criteria are shown in Figure 17.



(a) *Space*

(b) *Risk During Implementation*

(c) *Risk After Implementation*

(d) *Technology*

(e) *Cost*

Figure 17: Clinical Manufacturing Upgrade Selection Level 2 Criteria Weights from AHP Analysis. *The criteria weights (grey bars) resulted from the combined pair-wise comparisons of 12 stakeholders. The option weights (lines) for each criteria category were derived from the combined pair-wise comparisons of the four stakeholders with the most knowledge of the options.*

Beyond being able to see the combined results of all the stakeholders, one of the advantages of AHP is that the project manager and decision makers can analyze the responses from the individual participants. The results from four of the individuals that took part in the clinical manufacturing upgrade selection analysis are shown in Figure 18. The decision-makers can thus take the back-

ground of an individual into account to see what the outcome would have been if they were the sole decision-maker based on their department, geography, or some other trait. If a true outlier is observed, that person can be removed from the overall analysis to see how the overall results would change. Thus, the decision-maker can ensure the right decision is made between two very close options.

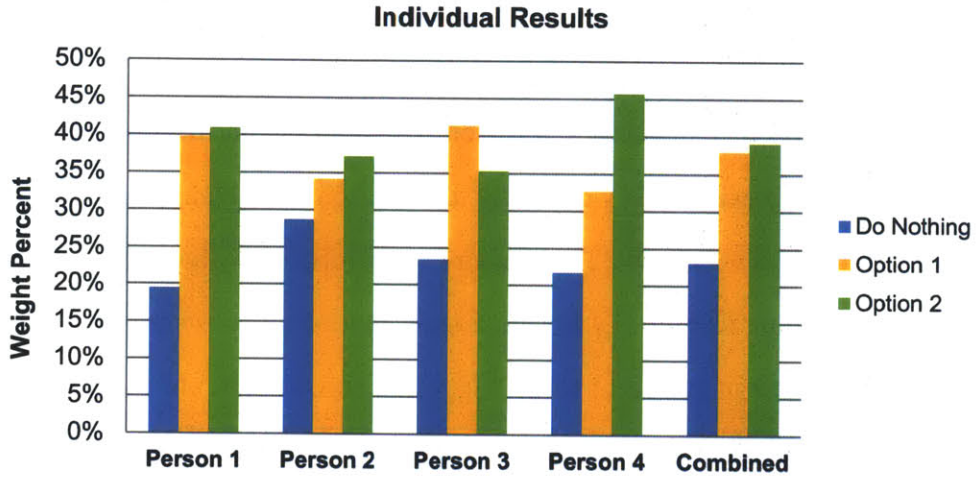


Figure 18: Example Individual Results from Clinical Manufacturing Upgrade Selection AHP Analysis. *The outcome of the analysis for person 1, person 2, and person 4 ranked option 2 as the best alternative. The outcome of the analysis for person 3 ranked option 1 as the best alternative. The relative difference between the three options was less for person 2 than for the other individuals.*

The typical decision process (business case and NPV) was performed simultaneously with the AHP analysis. The typical analysis identified option 1 as the best plan for the future. As is the case with traditional decision-making, the plant manager had identified option 1 as the best plan before the analysis was complete based on his "gut instinct." Therefore, management initially proposed option 1 to senior management as the best option. However, the AHP analysis showed that overall option 1 and option 2 are very similar and that perhaps option 2 would be best depending on the priorities of senior management and basically the tradeoff of future technology and risk after implementation.

The clinical manufacturing upgrade project was an excellent case to test the AHP decision-making process. The stakeholders had an idea of what they wanted to accomplish along with several options that would satisfy their goals to varying degrees. AHP allowed the stakeholders to

clearly define and objectively assess the correct weightings of the objective and subjective criteria while taking into account the opinions of many individuals. The outcome showed the typical analysis was correct, but that either option 1 or option 2 could be justified depending on the preference of one criterion over another. This helped ensure management made the right decision.

5.3 Drug Substance Storage Container Technology Selection

Amgen stores its drug substance material in a frozen state after the purification process but before the formulate / fill / finish process. They currently use two container technologies, plastic carboys and steel cryovessels as shown in Figure 19. Amgen had performed five studies since 2005 in order to select a standard container technology in which to store its drug substance. Four of the studies suggested carboys while the most recent study suggested cryovessels; each study only looked at a single aspect of the technologies such as their impact on costs, supply chain risk, freeze/thaw rate, or throughput. Since each analysis focused on a narrow effect of the technology, the leader of each study could not achieve buy-in from management on the correct container technology and thus another study was requested. In 2011, management wanted a holistic look at the technologies so it could finally make a decision and standardize its processes. AHP is a perfect tool for such an analysis.

(a) *Carboy* **(b)** *CryoVessel*

Figure 19: *Carboy and Cryovessel*

The project manager requested stakeholders from diverse departments such as finance, supply chain, global strategic sourcing, quality, clinical manufacturing, corporate manufacturing, process and product development, and process and product engineering. The stakeholders also represented the various manufacturing locations such as Rhode Island, Puerto Rico, California, Colorado, Ireland, and contract manufacturing sites. The group was composed of 14 individuals and it met over several weeks to develop the first and second level criteria hierarchy shown in Figure 20 and the third level criteria as listed in Tables 6-11 in Appendix A. A pipeline biologic drug was used as a model molecule for the mathematical analysis of throughput effects.

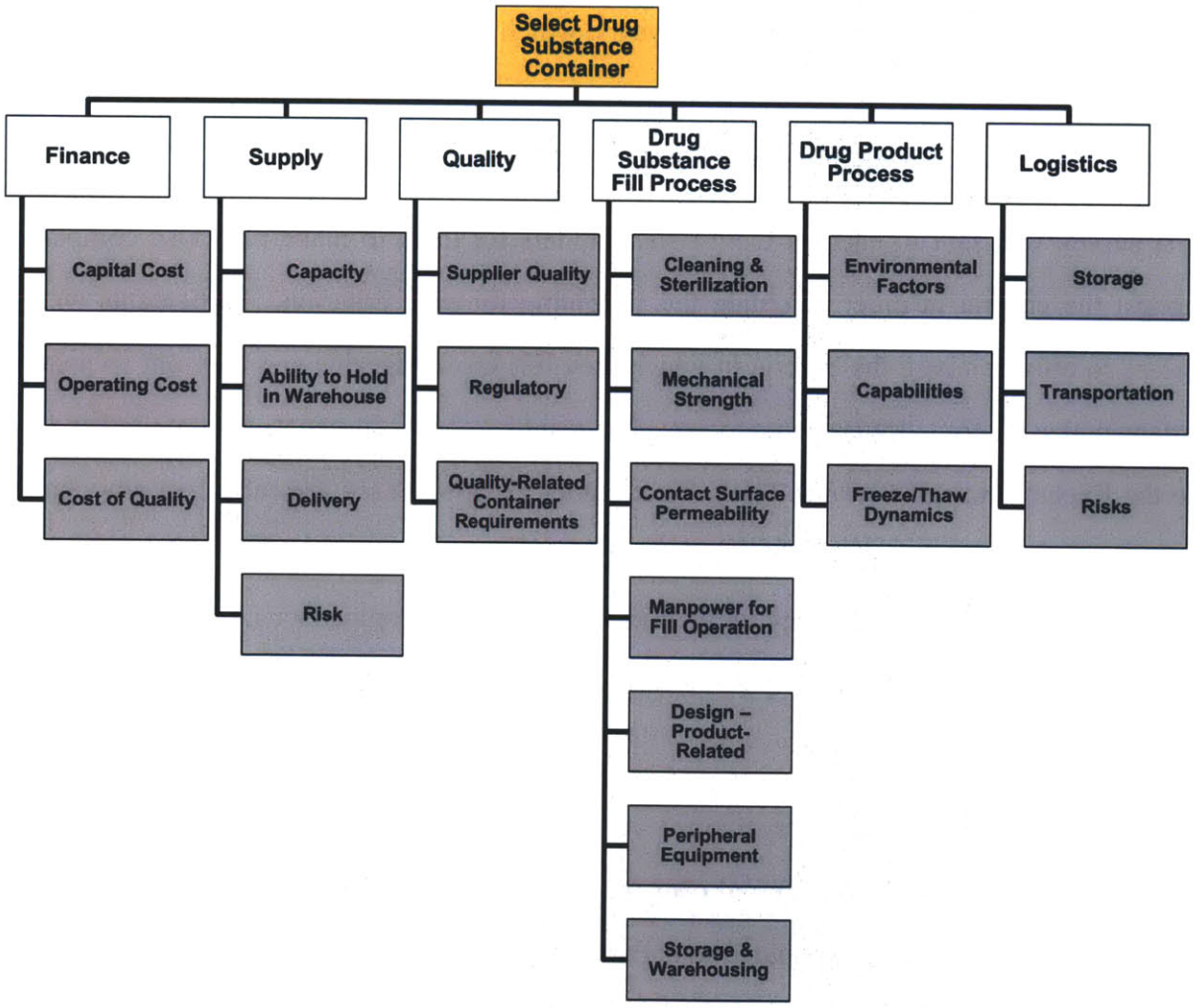


Figure 20: AHP Hierarchy for Drug Substance Container Selection. *The yellow box denotes the objective of the hierarchy criteria. The grey boxes represent general criteria whose weightings are derived from the weighting of the more specific covering criteria, which are shown in Tables 6-11 in Appendix A.*

There are many characteristics of a drug substance container that differ between the plastic carboys and stainless steel cryovessels as shown in the hierarchy. The plastic carboys are made from resins that need to be tested for leachable and extractable data to ensure that the plastic material does not affect the biologic product. In addition, the plastic material needs to be checked to ensure that there are no particles leftover from the vessel production process. The stainless steel cryovessels do not have these issues since the material is inert and does not shed. In addition, the vessels are available from manufacturers in different range of volumes. Carboys are smaller (typically 10-20 liters) and thus more would be needed for a large production volume whereas cryovessels are larger (typically 200 liters). Carboys are relatively cheap and single-use whereas cryovessels are expensive to procure and last about ten years, which requires cleaning and maintenance. The various characteristics of the vessels also impact the supply chain and logistics through differences in how they affect transportation, storage, capacity, delivery, and risk.

A survey was sent to each of the 14 stakeholders for them to make pair-wise comparisons amongst the criteria in order to obtain the weighting for each criterion. Participants were instructed to only compare the criteria in which they felt knowledgeable and they did so using the fundamental scale for pairwise comparisons. The results from the survey were compiled and input into the Expert Choice software. The subject matter experts in each area acquired any objective data that could be used in the analysis. The objective data was then compiled and sent out to the 14 stakeholders along with a survey for them to make pair-wise comparisons of the options against the covering criteria. All the comparison results were input into Expert Choice with the results shown in Figure 21.

The results showed that in every major level criteria category except logistics that the stainless steel cryovessels are strongly preferred over the plastic carboys. This resulted in the overall preference of the cryovessels as compared to carboys in the ratio of two to one. However, when this recommendation was presented to senior management, they did not necessarily believe the result. Since various analyses for this decision have been on-going for over five years, many managers had preconceived notions or "gut instinct" on which container technology should be selected as

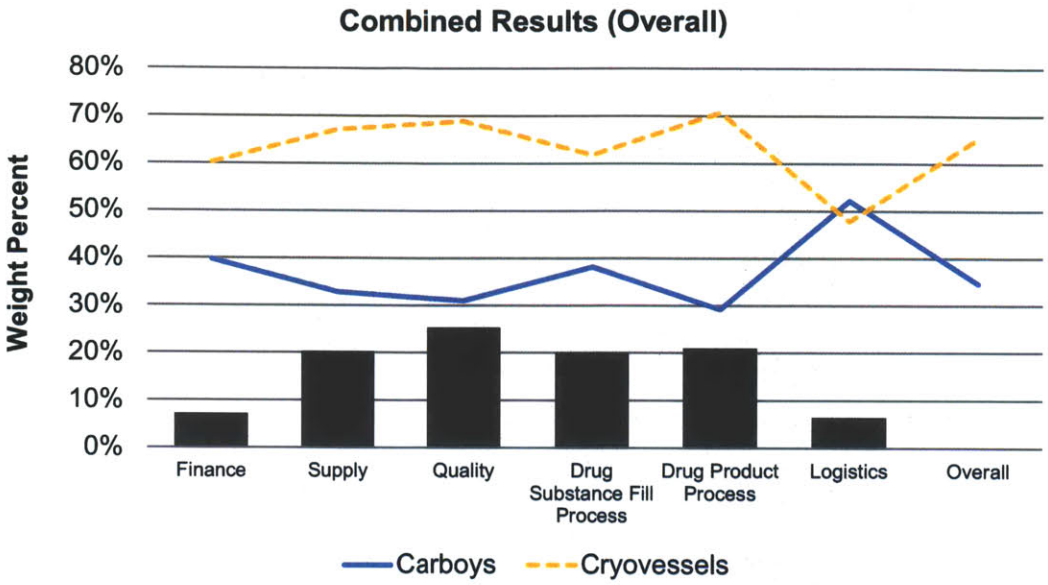


Figure 21: Overall Results from Drug Substance Container AHP Analysis. *The criteria weights (grey bars) resulted from the combined pair-wise comparisons of 14 stakeholders. The option weights (lines) for each criteria category were derived from the combined pair-wise comparisons of the four stakeholders with the most knowledge of the options.*

the standard. Since AHP analysis was new to senior management, there did not exist much trust in the process and therefore management requested that a typical business case and NPV analysis be performed that included all the criteria included in the AHP analysis. This analysis is currently on-going as of spring 2012.

Since AHP is a new decision-making tool, there will be barriers that need to be overcome in order to achieve buy-in from management. Performing an AHP analysis along with a typical analysis, as was done with the Clinical Manufacturing Upgrade Project, will allow management to compare a process they are familiar with against a new process. Thus, over time they can learn to trust the result of the AHP method and see the value that it provides. Now, there will always be the issue where a key decision-maker already has in mind a result and that person just wants any analysis to confirm and match the pre-determined result. While a decision-maker may have significant experience in a certain area, it is important to step back and look at a scenario in an objective manner. That is one of the purposes of the AHP process. Thus, incentives may be required for managers to use the AHP process for more informed decision-making.

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Chapter 6. Conclusion and Recommendations

6.1 Conclusion

Economic, regulatory, and other factors are spurring innovation in pharmaceutical manufacturing technologies. Changes in both small and macromolecule pharmaceutical manufacturing requires companies to make decisions about which technologies to implement and when and where to implement them. An objective decision-making approach can help ensure the correct decisions are made, but the process is difficult because decision-makers prefer quick, simple analyses and there is often a lot of uncertainty in predicting the long-term benefits and risks of new technology.

Therefore, in this thesis the Analytic Hierarchy Process was described as a method that allows both objective and subjective factors to be taken into account in decision-making. The process eliminates many of issues with traditional decision-making approaches and allows a manager to understand the input from many individuals on a decision-making team. A case study was performed to test the benefits of commercial software and two case studies were performed to assess AHP as a decision-making process. The results from the case studies showed that using Expert Choice® is a sustainable approach to decision-making for large teams across different geographies from different departments. The AHP analysis allowed managers to understand why a certain decision is preferable over another and perform sensitivity analysis to further understand the results.

Making decisions is difficult and it is likely that no method is applicable for every decision that needs to be made. However, using the Analytic Hierarchy Process is one step in the right direction towards making better, more objective decisions. Therefore, companies need to frequently evaluate their decision-making approaches and adapt their methods to the right situation in order to ensure all voices are heard and the right information is taken into account.

6.2 Recommendations

Amgen should continue to use the AHP decision-making method with Expert Choice® for their future technology decisions. In order to do so, Amgen may want to socialize the approach and continue getting buy-in from further case studies with other departments, including those outside of manufacturing. In addition, Amgen may want to implement AHP as a standard decision-making platform while advertising its benefits throughout its departments. AHP is a robust decision-making process that can help managers make objective decisions on any topic. For the case studies in this thesis, the desktop version of Expert Choice was utilized in order to complete the studies in the time allotted. However, for ease of use and access across the company, Amgen should install the web-based version of Expert Choice called Comparion™.

As discussed in Section 3.2, the sole use of net present value to analyze the financials of a project may prevent beneficial innovations from being implemented. Therefore, Amgen should try to re-implement a real options model that can take into account the great amount of uncertainty in technology projects and can also sometimes better capture the potential long-term upsides of a given technology. The financial analysis from a real options model can easily replace the net present value analysis used in the case studies in this thesis.

Concurrent with the decision-making process described in this thesis, Amgen has also sought to overhaul its technology advancement process. They have organized a Technology Advancement team composed of senior managers that will meet quarterly to discuss upcoming technology projects with the goal to prioritize, select, and facilitate the projects that should be advanced. The AHP decision-making process is very apt for these choices and should be utilized by this body in order to make their decisions.

Appendix A. Drug Substance Container 3rd Level Hierarchy Criteria

Table 6: Drug Substance Container — Finance Sub-criteria.

Capital Cost	Operating Cost	Cost of Quality
Drug Substance Container Cost	Maintenance Cost	Validation
Associated Equipment Cost	Cleaning & Sterilization Cost	Investigations
Facility Modification Cost	Disposal Cost	Raw Material Risks
	Operations Labor Cost	
	Transportation Cost	
	Impact to Plant Capacity	

Table 7: Drug Substance Container — Supply Sub-criteria.

Capacity	Ability to Hold in Warehouse	Delivery	Risk
Meet Current Annual Demand	Safety Stock <= 3 Years	Ability to Supply Globally	Business Continuity Plan
Meet Future Demand	Safety Stock > 3 Years	On-time, Correct, Complete	Transparency / Risk of Total Supply Chain
		Ship Under Stipulated Conditions	Low Risk of Insolvency or Market Exit

Table 8: Drug Substance Container — Quality Sub-criteria.

Supplier Quality	Regulatory	Quality-Related Container Requirements
Segmentation Results	Support of Regional Requirements	Container Version Available for Small-Scale Experimental Work
Supplier has Supply/Quality Agreement with Sub-Supplier	Ease of Acceptance	Leachable / Extractable Profile
Adherence to Incoming Acceptance Criteria		Functionality
Adherence to Quality and Supply Agreement Templates		Supply Chain Security
		Stability

Table 9: Drug Substance Container — Drug Product Process Sub-criteria.

Environmental Factors	Capabilities	Freeze / Thaw Dynamics
Re-usable Containers	Scale-down Model of Freeze / Thaw Behavior	Freeze Time
Resistant to Cleaning Agents	Range of Fill Volumes that can be Validated	Thaw Time
Biodegradable Container	Ability to Sample from Drug Substance Container	
	Closed Processing	
	Ability to Aseptically Aliquot from Container	
	Easy to Dispense with High Yield	
	Ability to Mix in Container After Thawing	
	Accommodate Static or Dynamic Thawing	
	Easy to Thaw Dug Substance	

Table 10: Drug Substance Container — Logistics Sub-criteria.

Storage	Transportation	Risks
Protect Product from Light Exposure	Tamper Proofing	Shipping Quanitities (Amount at Risk)
Maintenance of Container Closure	Ergonomically Friendly	Inspection from Customs Opening the Container
Amgen Business Continuity Plan	Air Shipments Dry Ice Requirements	Training of Handling the Vessels
Labelling / Re-labelling	Import / Export Documentation	
Capacity for Long-term Storage/Weight of the Vessel		
Empty or Full Tanks (Warehouse or Return to Warehouse)		
Ergonomically Friendly		
Ease of Inventory Reconciliation		

Table 11: Drug Substance Container — Drug Substance Fill Process Sub-criteria.

Cleaning & Sterilization	**Mechanical Strength**	**Contact Surface Compatability**	**Manpower for Fill Operation**	**Design – Product-Related**	**Peripheral Equipment**	**Storage & Warehousing**
Ease of Cleaning	Able to Withstand Handling During Cleaning	Inert to Product Excipients	Number of Staff Required to Perform Fill	Shaped to Allow Quick and Uniform Freeze to the Center	Maintenance of Equipment	Staging Space
Ease of Sterilization	Able to Withstand Sterilization / Autoclaving	Acceptable Levels of Leachables / Extractables	Ergonomic Concerns	Controllable Freeze/Thaw rate for Sensitive Proteins	Space Requirement for Peripheral Equipment	Storage Space
Low Particle Count Prior to Cleaning	Resistant to Crack, Chip, Abrasion, and Drop Fracture	Low Protein Binding	Training Complexity	Self-standing		Storage Configuration
Maintains Sterility for Prolonged Period	Resistant to Stress from Freezing	Low Gas Permeability		Lifetime		Protection from Light
	Resistant to Shock and Stress from Transport	Low PS-20 Binding		Allows Closed Processing		
		No Particle Shedding		Allows Aseptic Handling		
		Surface Finish		Allows Easy Transfer in Case of Refiltration		
				Allows Sampling		
				Ease of Validating Container Integrity		
				Allows Accurate Measurement of Weight		
				Light Exposure Control		
				Anti-static Property		
				Ability to Perform Visual Inspection		
				Compatability with Existing Cleaning and Sterilization Equipment		
				Container Size Meets Drug Product Fill Requirements		
				Process Cycle Time		
				Prep Time for Containers		

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