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# BIMO Package: Challenges and Perspectives While Keeping Up with the Upgrades in the BIMO Technical Conformance Guide and the BDRG Guidelines

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## ABSTRACT

The Food and Drug Administration (FDA) released an updated version (v3.0) of the Bioresearch Monitoring (BIMO) Technical Conformance Guide (TCG) in August 2022. Coincidentally during this time, PHUSE Working Group made its first release of the BIMO Data Reviewer's Guide (BDRG) draft package that included a well evolved BDRG template. As a part of an NDA submission, we prepared the BIMO Package in line with these latest BIMO guidance documents. In this paper, we highlight the updates from the latest version of BIMO TCG and their implications in our efforts in adapting to these upgrades while preparing the BIMO package. While BDRG is still an optional document, we also generated this document based on the BDRG template. In particular, the BDRG template included ten required sections, and we share our perspectives and describe the elements needed for completing these required components. Finally, as required in the BDRG, we also prepared a conformance report for the CLINSITE data using Pinnacle 21 Enterprise (P21E), and we highlight the technical challenges that we encountered while generating the P21E report.

## INTRODUCTION

The submission processes of the clinical study data to Food and Drug Administration (FDA) for New Drug Application (NDA) and Biologics License Applications (BLA) packages have been well established and are currently practiced in both pharmaceutical companies and Contract Research Organizations (CRO). As a part of the review processes, the FDA carries out site-level inspections to ensure the integrity of the data submitted, and to verify that the rights, health, and welfare of those who participated in the studies were protected, and importantly to confirm that the clinical study investigators, CROs, sponsors and their review committees comply with necessary regulations.

Since the current format of the clinical data packages are focusing on the subject-level data and generating outputs accordingly, these data packages are not readily providing the details about the site-level information that can enable FDA to conduct site-level inspections. To efficiently audit the sites, a wealth of information is needed at every site; this includes, for example, subject data, informed consent, treatment group assigned, and name and contact specifics of investigators at each site. To facilitate the site level inspections and collect a spectrum of details at the site level, the FDA established a program, namely the Bioresearch Monitoring (BIMO) Program for the studies being submitted for their review process. The FDA Office of Scientific Investigations (OSI) manages the BIMO program for drugs, and the FDA's Division of Inspections and Surveillance (DIS) manages the BIMO program for Biologics. The FDA BIMO develops guidelines for inspections of clinical investigators, sponsors, and institutional review boards (IRBs) and updated versions are being released to cope up with the growing requirements that are being witnessed.

Standardized format for Electronic Submission of NDA and BLA content for the planning of BIMO Inspections for Center for Drug Evaluation and research (CDER) submissions draft guidance was published by the FDA and contained binding as well as non-binding recommendations. The FDA published an initial guidance in 2011 to lay out the expectations and formats for the data elements that reviewers need to carry out at the site level. These efforts finally led to the release of the more established draft guidance and a Technical Conformance Guide (TCG). The FDA published the very first version of the BIMO TCG in February 2018. This document contained technical specifications for clinical data submission by pharmaceutical companies used in the planning of FDA BIMO inspections. The second release (v2.0) of

the TCG was published in July 2020 and latest (current) release (v3.0) was made for the public review in August 2022.

The OSI requests the sponsors to submit three required components that are applicable for the BIMO audit and an optional element, BIMO Data Reviewer's Guide (BDRG) as specified below

1. Clinical Study-Level Information: Information in this section includes a comprehensive list of all clinical sites that participated in each pivotal study, list of external organizations which the sponsor has contracted for clinical research activities, and study specific documents such as protocol, protocol amendments and annotated case report forms.
2. Subject-Level Data Line Listings by Clinical site: For each site of each pivotal study, subject level data is required and by-site listings for the following categories: consented subjects, adverse events, important protocol deviations, efficacy endpoints, concomitant medications, and safety monitoring. These listings can be organized either by site, then by listing or by site, then by subject, then by listing.
3. Summary-Level Clinical Site Dataset. Sponsors are required to provide a single file that contains summary level clinical site data for all sites for all pivotal studies. This dataset is to be submitted in SAS Transport File Format and named as CLINSITE.XPT. The purpose of this dataset is to summarize the clinical investigator sites and their relevant administrative information, safety, and efficacy findings.
4. BIMO Data Reviewer's Guide. Though this is an optional part, this is highly helpful as it provides a very comprehensive view of the BIMO package. It includes well-organized sections encompassing all components of the BIMO package with the links to their locations. Each section provides an opportunity to the sponsors to provide any additional information that could not be accommodated in the above three components.

Currently the inclusion of the BIMO package has become a familiar and standard process as a part of the NDA and BLA submissions. Both CROs and sponsors have demonstrated their expertise in efficiently handling the generation of BIMO submissions. Especially in the light of site-specific subject data line listings, a good number of publications have disseminated the logistics and methods for the efficient generation of these listing outputs. Indeed, some of the sponsors have created an exclusive team to oversee the BIMO processes, and macros to generate these listings very efficiently. Despite being optional, still sponsors tend to submit BIMO Reviewer's Guide in their own format for the reasons described above. So far there was no specific template and one of the PHUSE working groups had initiated the efforts in generating a formal template for the BDRG; the first draft version of this template was released in late 2022.

Recently we prepared a BIMO package as a part of an NDA application for a sponsor based on the guidelines from the latest versions of the TCG (v3.0) and the BDRG draft template. In this paper we highlight the updates in the TCG and present our perspectives on preparing the BIMO package based on these two latest guideline documents.

## IMPORTANT CONSIDERATIONS PRIOR TO BIMO PROGRAMMING

1. It is noticeable in many instances that the sponsors start thinking about the BIMO package at the end of CSR programming activities especially when the sponsor team realizes the readiness of the data for its final submission. Consequently, the timeline for preparing the BIMO package becomes too short and the last-minute effort in this preparation creates a cumbersome situation. Hence it is highly advisable to initiate the BIMO related programming tasks in conjunction with the start of the programming activities pertinent to CSR submissions.
2. Since multiple stake holders (examples, Clinical Operations, Clinical Finance, Site Management, statistician, medical writing, clinical/statistical programming), especially in complex global trials, involved in the preparation of the BIMO preparation, the programming team lead could establish contacts well ahead to alert the teams for getting the inputs from the cross functional teams ready.

3. Discussion must take place well ahead about the versions of guidance documents to be followed, nature and number of the listings to be included and designing of specification file for the CLINSITE data. Though the FDA recommends the sponsors to follow the latest TCG, if sponsors chose to use the older version of TCG, then necessary communications are to happen with the FDA prior to the start of the BIMO package.
4. Regardless of the readiness of the programming team, in our experience, obtaining clean and user-ready details needed for the CLINSITE data from all the sites involved in the study has always been challenging. Based on our experience, to expedite this process, we proposed a template Microsoft Excel® sheet with column names identical to the variables needed for the CLINSITE data for the site and study level details so that information from the file can be extracted manually into a SAS data format without a need for re-work.
5. It is highly desirable to have conversation(s) with the regulatory unit that is facilitating in placing the BIMO Listings and other components in the eCTD especially about the specific options that the team wants to adopt. Appendix B in the TCG provides two options for the folder structure and it is important for the Programming team to know this plan upfront so that necessary logistics will be in place during the production of Listings.
6. Since there is no specific format for collecting all site-level contact details, these details do come in different files/formats from multiple sources. Eventually if all these site level details are mapped into any of the SDTM components (at least in a supplemental qualifier), then there is a high possibility that the information would be subjected through quality control processes at an early stage. When these details are captured in the SDTM data, they can be readily extracted during the preparation of CLINSITE data.
7. We frequently notice, in many instances with multiple sponsors, the use of email addresses related to the public domains (such as Gmail, Yahoo, Hotmail etc.) as the contact email addresses of the principal investigators. Is it a safe practice? Certainly, the investigators are affiliated to specific organizations that will have their own validated email networking. This suggests a need for efforts to get the validated work email addresses of the clinical investigators in the light of patient safety and privacy. Besides, can the FDA or any review committee communicate about any of sensitive information to the investigators in public email accounts?

## UPDATES IN THE BIMO TECHNICAL CONFORMANCE GUIDE

BIMO TCG is a guidance document that represents the current thinking of the FDA on preparation of the BIMO Package which is a part of the regulatory submission. However, the FDA clearly states that the Sponsors can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. In this situation, the sponsor needs to discuss with the FDA well ahead of the submission processes.

So far there have been three versions of TCG available with the release of the current version in August 2022. All these versions still adhere to the maintenance of the following three parts under which the BIMO package deliverables are distributed.

I. Clinical Study-Level Information
II. Subject-Level data line Listings by Clinical Site
    A. Organization of the Subject-Level Data Line Listings: Subject-level data line listings by clinical site, should include information under the following topics:
        1. Consented Subjects
        2. Treatment Assignment
        3. Discontinuations
        4. Study Population
        5. Inclusion and Exclusion Criteria
        6. Adverse Events
        7. Protocol Deviations
        8. Efficacy Endpoints
        9. Concomitant Medications
        10. Safety Monitoring

III. Summary-Level Clinical Site Dataset: Most of the updates pertaining to the current version, in comparison to the second version are being reflected in the third part of the package only, i.e. CLINSITE dataset.

**Updates under Part I**: In the current version of the TCG, there are no updates on the guidelines related to the first part of the package.

**Updates under Part II:** Under this part, noticeably there are two minor updates. The first one is subheading related; the heading of the section related to the protocol deviations was listed as "Important Protocol Violations" in the previous version of TCG; in the current TCG, it has been revised as "II.7. Protocol Violations" to reflect the fact that the sponsors are required to include the listings that should include a description of the deviation and identify whether the deviation is an important or non-important protocol deviation. The second update is under the heading, "II.A.8. Efficacy Endpoints" of the current TCG, additional clarity has been added as follows: "*For example, when efficacy endpoints are assessed based on a laboratory, imaging, components of a clinical outcome assessment(s), or other study procedures, the by-subject, by-clinical site listing should include all testing results that contribute to the derived efficacy endpoint*". Accordingly, we included listings containing specific tests results pertinent to the derivation of endpoints.

**Updates under Part III:** This part is all about the CLINSITE dataset. The updates in the current TCG focus on the variables related to the population selection and the presentation of efficacy results at the site level. At least 40 variables are defined for each study site and these variables cover the information ranging from administrative to specific site-specific safety and efficacy findings. Under the current TCG, the variables of this dataset can be grouped under the following five categories:

i. Study level and the Scope of the Application: Study Title, Sponsor details, Site, Application type (IND/NDA/BLA and relevant reference numbers)

ii. Study Conduct: Arm, Cohorts, Enrollments and Study Populations

iii. Safety: Subject Treatment, Study discontinuations, Important and Non-important Protocol deviations, SAEs, Non-SAEs, Death details

iv. Efficacy Details: Population wise Endpoints, Efficacy Results and Censor details

v. Site level Information: Contact information of Primary clinical investigators, Financial Disclosure and Site details.

The BIMO TCG provides detailed guidelines for each variable. Though there are not major differences between the previous and current versions of TCG in terms of overall structure of the CLINSITE dataset, a few variables from the previous version were removed, and some additional variables have been added in the current TCG. Here we focus on these changes and share our perspective as follows:

**Site Specific Population Variables - SAFPOP and EFFPOP:** The previous version of TCG included only the SAFPOP (Number of Subjects in Safety Population) to provide the data by the clinical site and the treatment arm for the safety population for each pivotal study. SAFPOP represents the total number of subjects in the safety population at a given site by treatment arm. However, all the BIMO packages still included the efficacy related variables to represent the efficacy results at the site level. To address this gap, a new variable, EFFPOP (Number of Subjects in Efficacy Population) has been added in the latest TCG version to identify the total number of subjects in the primary efficacy population, as defined in the clinical study report, at a given site by treatment arm to support the proposed indication in the application (Table 1). This is one of the noticeable and important updates in the current TCG. This bifurcation of the population reflects the basis and handling of values for the newly added additional variables, TRTEFFR1, TRTEFFR2, CENSOR1 and CENSOR2.

| Variable Index | Variable Name | Variable Label | Type | Controlled Terms or Format | Note or Description | BIMO TCG |
|---|---|---|---|---|---|---|
| 13 | SAFPOP | Number of Subjects in Safety Population | Num | Integer | Total number of subjects in safety population at a given site by treatment arm. | v2.0 & v3.0 |

| Variable Index | Variable Name | Variable Label | Type | Controlled Terms or Format | Note or Description | BIMO TCG |
|---|---|---|---|---|---|---|
| 14 | EFFPOP | Number of Subjects in Efficacy Population | Num | Integer | Total number of subjects in primary efficacy population as reported in the Clinical Study Report at a given site by treatment arm. | v3.0 |

**Table 1. Updates on the Site-specific population variables in TCG.**

It is to be noted that the 40 variables described in the TCG are mandatory and the sponsors are encouraged to add additional variables, depending on the study requirements and unique conditions reported in the study.

**Site-Specific Efficacy Result Variables:** As per the previous TCG, in the CLINSITE data, summary statistics for each primary efficacy endpoint were presented in the variable, TRTEFFR, though there used to be only one variable to represent population, called SAFPOP. TRTEFFR was associated with TRTEFFS that collects the standard deviation (STD) of the summary statistic (TRTEFFR) for each primary end point, by treatment arm.

In the current TCG version, both TRTEFFR and TRTEFFS have been subjected to change. The scope of the TRTEFFR has been bifurcated into two new variables, TRTEFFR1 (Treatment Efficacy Result for SAFPOP) and TRTEFFR2 (Treatment Efficacy Result for EFFPOP) to provide the data exclusively for SAFPOP and EFFPOP populations respectively (Table 2). Values reported in TRTEFFR1 and TRTEFFR2 reflect simple summary statistics for each primary efficacy endpoint(s), by treatment arm at a site, based subjects in the SAFPOP and EFFPOP populations respectively. The method used for deriving these two variables, including a description of which analysis datasets and associated variables are used to derive two efficacy result variables, should be described in the CLINSITE Define.XML.

Though we have added above TRTEFFR1 and TRTEFFR2 in the CLINSITE data in line with the current TCG version, we still kept TRTEFFR and TRTEFFS based on the previous version of TCG in the CLINSITE data. Because one of the studies from the same compound was submitted earlier based on the previous TCG and that study included these two variables. To have connectivity and comparison, we maintained these two previous version efficacy result variables.

| Variable Index | Variable Name | Variable Label | Type | Controlled Terms or Format | Note or Description | BIMO TCG |
|---|---|---|---|---|---|---|
| 20 | TRTEFFR1 | Treatment Efficacy Result for SAFPOP | Num | Floating Point | Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP | v3.0 |
| 21 | TRTEFFR1 | Treatment Efficacy Result for SAFPOP | Num | Floating Point | Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in EFFPOP | v3.0 |
| 22 | TRTEFFR | Treatment Efficacy Result | Num | Floating Point | Summary statistic for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP. | v2.0 |
| 23 | TRTEFFS | Treatment Efficacy Result STD | Num | Floating Point | Standard deviation (STD) of the efficacy result (TRTEFFR) for each primary efficacy endpoint by treatment arm at a given site for subjects in SAFPOP. If N=1, set to “0.” | v2.0 |

**Table 2. Updates on the Site-specific Efficacy results variables in TCG.**

**CENSOR Variables:** For the studies whose primary endpoint is a time-to-event endpoint, the sponsors are required to include a data element, CENSOR. In the previous TCG, there was only one CENSOR variable. The current TCG provides the two variables for the CENSOR (Number of Censored Observations) related data: CENSOR1 (Censored Observations in SAFPOP) and CENSOR2 (Censored Observations in EFFPOP). The number of censored observations for the given site and by treatment arm for the SAFPOP and EFFPOP are included under the variables, CENSOR1 and CENSOR2 respectively (Table 3). If a study does not contain a time-to-event endpoint, this data element should be recorded as a missing value.

| Variable Index | Variable Name | Variable Label | Type | Controlled Terms or Format | Note or Description | BIMO TCG |
|---|---|---|---|---|---|---|
| 24 | CENSOR1 | Censored Observations in SAFPOP | Num | Integer | Total number of censored observations in SAFPOP at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank | v3.0 |
| 25 | CENSOR2 | Censored Observations in EFFPOP | Num | Integer | Total number of censored observations in EFFPOP at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank. | v3.0 |
| 26 | CENSOR | Number of Censored Observations | Num | Integer | Total number of censored observations at a given site by treatment arm for primary endpoint (e.g., applicable to time-to-event). If not applicable, leave blank. | v2.0 |

**Table 3. Updates on the Site-specific Censor variables in TCG.**

**COUNTRY Variable:** In the previous version of TCG, the values for the COUNTRY variable are governed by the three letter ISO (International Organization for Standardization) 3166-1-alpha-3 format for representing the country in which the test site is located. In the current TCG, GENC (**G**eopolitical **E**ntities, **N**ames and **C**odes Terminology) format has been used. The decision to use the GENC format is line with the FDA's announcement per one of the FDA's publications dated, 07/19/2019 that states, "*The Food and Drug Administration (FDA or Agency) is announcing the adoption of the current version of the Geopolitical Entities, Names, and Codes (GENC) Standard on December 17, 2020. The GENC Standard is the U.S. Government profile of International Organization for Standardization (ISO) 3166 "Codes for the Representation of Names of Countries and Their Subdivisions." It specifies an authoritative set of country codes and names for use by the U.S. Government for information exchange, using ISO 3166 names and code elements wherever possible, with modifications only when necessary to comply with U.S. law and U.S. Government recognition policy. Adopting the GENC Standard will enable FDA to be in conformance with U.S. Government naming and recognition policies.*"

Though both GENC and ISO3166 codes use three letter values for representing countries of the test sites, we programmatically verified if there are any discrepancies between these two codes. In the Table 4., some examples are given that show a few countries from the ISO 3166 list are absent in the GENC and the vice versa. Regardless of any implications from these discrepancies, we would like to highlight here this fact so that when GENC is being adopted during any of the forthcoming updates in the validation engines for the CLINSITE data, necessary considerations would be given.

| Countries/Codes represented by ISO3166 and not by GENC | Code |
|---|---|
| Åland Islands (ALA) | ALA |
| State of Palestine (PSE) | PSE |
| Svalbard and Jan Mayen (SJM) | SJM |
| United States Minor Outlying Islands (UMI) | UMI |

| Countries/Codes represented by GENC and not by ISO3166 | Code |
|---|---|
| West Bank (XWB) | XWB |
| Wake Island (XWK) | XMK |
| Vatican City (VAT) | VAT |
| Tromelin Island (XTR) | XTR |
| Spratly Islands (XSP) | XSP |
| Paracel Islands (XPR) | XPR |
| Palmyra Atoll (XPL) | XPL |
| Navassa Island (XNV) | XNV |

**Table 4. Discrepancies between ISO3166 and GENC code lists.**

**Pinnacle 21 Enterprise and Define.XML generation for the CLINSITE data**: As outlined in the BIMO TCG, the CLINSITE data set should be accompanied by a data definition file. We created the data definition for the CLINSITE dataset using the Pinnacle 21 Enterprise tool (v5.2.0). The specification file for the CLINSITE data was used to generate the Define.XML and Define.pdf. Though we prepared the CLINSITE data based on the current version of TCG, at the time of our submission, the Pinnacle 21 Enterprise tool did not support the current version of TCG when generating the conformance report. In the P21E setting, only the first two versions of the TCG are available; we generated the report based on the TCG v2.0 setting, and the validation engine that was available was P21 2204.1 (Table 5). This is also one of the reasons for maintaining required variables that existed in the previous version and were deleted in the current TCG. While addressing the findings from the conformation report generated by P21E, the issues that we were not able to resolve can be grouped into in the following four categories:

i. Special characters in state names: Special characters in name of the states such as “São Paulo”, “Córdoba”, “Södermanland and Uppland”, “Ôsaka”, “Île-de-France”, created error in the Pinnacle report. These were original names as we received the Clinical department, and we mapped the same into the CLINSITE dataset.

ii. Special characters in the city names: Special characters in names of cities such as “Córdoba”, “Créteil”, “Ribeirão Preto”, “São Paulo”, created errors in the Pinnacle report. These are the original names as we received from the clinical trial operations team, and we mapped the same data into the CLINSITE dataset.

iii. Under the financial disclosure amount “>=$25,000”, “<$25,000” the symbols created the issues even though we had captured appropriately.

iv. A few of the postal codes from the non-US sites created issues. For example, a few postal codes from South Korea resulted in errors even though the postal codes corresponded to the correct cities.

| Dataset | Rule ID | Message | Affected | Changed | Impact | Type |
|---|---|---|---|---|---|---|
| CLINSITE | BM0011 | Invalid value for FINLDISC variable | Xxx | x | Medium | Error |
| CLINSITE | SD0037 | Value for CITY not found in (City) user-defined codelist | Xx | x | Medium | Error |
| CLINSITE | SD0037 | Value for POSTAL not found in (Postal Code) user-defined codelist | Xx | x | Medium | Error |
| CLINSITE | SD0037 | Value for STATE not found in (State) user-defined codelist | Xx | x | Medium | Error |

**Table 5. Portion of the P21E CLINSITE validation report.**

## BIMO DATA REVIEWER'S GUIDE

While there has been a great deal of knowledge and practices on the generation of the BIMO package in recent years, there was no industry defined guidance on the Reviewer's Guide for the BIMO package prior to the latest release of the first draft of the BIMO Reviewer's Guide from PHUSE in late 2022. Nevertheless, in recent years, sponsors have been including BIMO Reviewer's Guides in their own formats. To streamline the content and the naming convention for this reviewer's guide, it is to be noted that the current BIMO TCG specifically dictates that the BIMO Reviewer's Guide is to be called as "BIMO Data Reviewer's Guide". Per TCG, BDRG is an optional document, but it is highly recommended to be submitted.

In our practice, we encourage the sponsors to submit this document as a part of the BIMO packages due to the following reasons.

- BDRG can provide a clear overview of all the components of the BIMO package so that this can serve as the first place that reviewers can go to learn about the BIMO package.
- Sponsors can provide their explanations and any additional details that they cannot incorporate in the defined list of listings and the CLINSITE dataset.
- It is also a document where any potential deviations from the TCG can be recorded.
- Sponsors may come across unique situations in their clinical trial sites due to the length/complexity of the trials and certainly this is a document that can explain these situations.
- As the components of the BIMO package grow, industry standards/guidelines (TCGs) evolve due to the growing needs and the validation engines/tools are getting constantly updated. This becomes the document where the sponsors can provide the challenges and perspective on the technical issues or gaps that were being met across these elements during the preparation of the BIMO package.

There are 10 required sections in the BDRG. The first two sections, Introduction and Study Description, have general introductory information about the study, but from the section three, the details of study-level, subject-level, and site information can be captured. Here we present the section headings and their serial numbers as presented in the BDRG so that the readers can relate and refer to the original draft template published on the PHUSE site.

**1. Introduction** – This is a required section to provide information on the purpose, navigation, and the hyperlinks within the BDRG document, acronyms, BIMO clinical data standards and the study-related metadata used in the application. In the Section 1.3, sponsors should document the version and date of the following documents that were used for preparing the BIMO Package. In general, it is highly recommended by the FDA to use the most current BIMO TCG and in our case, we followed the current version, TCG, v3.0 as listed in Table 6.

| BIMO Guidance | Version and/or Date |
|---|---|
| Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry (DRAFT GUIDANCE) | February 2018 |
| Bioresearch Monitoring Technical Conformance Guide | August 11, 2022 |
| Summary-level Clinical Site Dataset Definition File (define.xml) | 2.0 |

**Table 6. BIMO Guidance Table.**

**2**. **Study Description** – This section provided the summary of the study details (Study Identifier, Study Title, Study Phase) for the study used to support safety and efficacy in the application.

**3. Part I - Request for Clinical Study-level Information** – provides information on the structure followed in the Part I (Items A and B) deliverables and supporting information for the Part I (Items A, B and C [C1

and C2]) deliverables for each of the major (i.e., pivotal) studies used to support safety and efficacy in the application.

**3.1. Part I (Item A)** – **List of All Clinical Sites** – This is a Listing consisting of detailed information regarding the sites participating in the clinical study. This information, in the form of Microsoft Excel® file has been provided by the Clinical Trial Operations team of the sponsor to include the following: the counts of the total number of sites and out of which the number of sites that have screened subjects with a signed informed consent, sites that have at least one subject randomized, sites with all subjects screened but are screen failure and sites without any subject enrolment. Also, there is another document containing the financial disclosure details for each site that has been used and provided by another cross functional team.

Being a global study, since the site level details were coming from several sites spanning across multiple countries, we faced many challenges in accessing and standardizing the site level data. Some of the notable challenges included the following: missing/incomplete data for the site ID and their names, insufficient contact specifics (phone, fax, email, contact addresses, incorrect postal codes) of Clinical investigators, lack of designations for the investigators whether Principal or Sub-Investigators where multiple investigators were assigned for site, incomplete/lack of financial details (dollar values) associated with the sites. The rule is that only Principal Clinical Investigators' details is to be included.

**3.2. Part I (Item B)** – **Entities Contact Information and Trial-related Files** – This outlines the nature and contact specifics of the entities that the sponsor contracted for the services performed for the study we submitted. Since the whole idea is to incorporate the appropriate and necessary entity information, in our case, we presented the details in the following format (Table 7) as PDF deliverable for the clinical study.

| Category of Services | Services to be performed (Refer to vendor contract and SOW for full specific details) | Vendor name and address(es) | Primary contact name and contact information |
|---|---|---|---|
| Data Management | Data transfer from database, edit checks, data review. | Firm Name, Address. | Name, Functional title, Email ID, Tel Number |
| Medical Writing | Documentation for the study | Firm Name, Address. | Name, Functional title, Email ID, Tel Number |

**Table 7. Site Specific Entities Contact Information.**

**3.3. Part I (Item C1)** – **Protocol and Amendments** – Being a global trial, this study included a few protocol versions that are specific to the countries that included the trial sites. Accordingly, we tabulated all the protocol versions that were used during this study (Table 8). Ideally Regulatory Operations stakeholders are responsible for creating hyperlinks and attachments for Module 5 once the BIMO package has been finalized. Programming team should work closely with the regulatory team to ensure that the hyperlinks are added appropriately.

| Study Identifier | List All Protocol/Local Amendment Version Numbers | If Local Amendment (List Country) | Date Effective | Location Reference (Items Included In) |
|---|---|---|---|---|
| ABC-123 | Original | | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 0.1 | Country 1 | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 1 | | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 1.1 | Country 2 | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 2 | | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 2.1 | Country 1 | xxxx-xx-xx | Refer in the Section 10 |

| Study Identifier | List All Protocol/Local Amendment Version Numbers | If Local Amendment (List Country) | Date Effective | Location Reference (Items Included In) |
|---|---|---|---|---|
| ABC-123 | Amendment 3 | | xxxx-xx-xx | Refer in the Section 10 |
| ABC-123 | Amendment 3.1 | Country 2 | xxxx-xx-xx | Refer in the Section 10 |

**Table 8. List of protocols being used in the study.**

**3.4 Part I (Item C2)** – **Annotated Case Report Form (aCRF)** – This table provides a comprehensive list of all aCRFs for each of the major studies used to support safety and efficacy in the application. Since the final version of the aCRF has already been submitted in the datasets folder of the study (tabulations\ SDTM), there is no need to include the final aCRF again in the BIMO package; hence the location of the file is being shared in this Table 9.

| Study | Annotated Case Report Form (aCRF) | Location Reference |
|---|---|---|
| ABC-123 | Final aCRF | It is located in the datasets folder (tabulations\SDTM) of the study |

**Table 9. Final version of the aCRF.**

**Section 4: Part II – Subject-level Data Line Listings by Clinical Site** – This section provides a high-level overview, structure and supporting information for the BIMO listings. Current TCG describes 11 listings as mandatory listings as listed in the sections below. However additional listings are allowed based on a need to split any of the listings based on specific parameters. It is to be noted that if a sponsor is not including any of the 11 mandatory listings, it is expected to have the text string such as “Not Submitted” for the specific listing in the table below, rather than deleting the same from the table itself (Table 10). This is important so that it would receive the attention of the reviewers for why a particular listing is not included in the package. In our practice, we adopted following steps: In the table of Listings, the listing has been marked whether they were added in addition to the mandatory ones with the text value “Additional Listing” under the “Comments” column. We maintained the serial numbers and the title of listings in line with the TCG, though we have noticed the usage of alphabets (as Listing A, Listing B and so on) in other studies.

**4.1. Subject-level Listings**: There are three options given in the guidance to submit the listings (By Study, By Site and By Listing), among which by site representation is more feasible.

| Study Identifier | Listing No. | Listing Title | Comments |
|---|---|---|---|
| ABC-123 | 1 | Listing 1: Listing of Consented Subjects | |
| ABC-123 | 2 | Listing 2: Listing for treatment assignments | |
| ABC-123 | 3a | Listing 3a: Listing of Discontinuation during run-in period | Split; Additional Listing |
| ABC-123 | 3b | Listing 3b: Listing of Discontinuation from the study Treatment | Split; Additional Listing |
| ABC-123 | 3c | Listing 3c: Listing of Discontinuation from the study | Split; Additional Listing |
| ABC-123 | 4 | Listing 4: Listing of Study Population | |
| ABC-123 | 5 | Listing 5: Listing of Inclusion and Exclusion criteria | |
| ABC-123 | 6a | Listing 6a: Listing of Adverse Events and dates | Split; Additional Listing |

| Study Identifier | Listing No. | Listing Title | Comments |
|---|---|---|---|
| ABC-123 | 6b | Listing 6b: Listing of Serious AEs and dates | Split; Additional Listing |
| ABC-123 | 6c | Listing 6c: Listing of Deaths | Split; Additional Listing |
| ABC-123 | 7 | Listing 7: Listing of All Protocol Deviations | |
| ABC-123 | 8a | Listing 8a: Listing of Primary Efficacy Parameters | Split; Additional Listing |
| ABC-123 | 8b | Listing 8b: Listing of Secondary Efficacy Parameters | Split; Additional Listing |
| ABC-123 | 9 | Listing 9: Listing of concomitant medications | |
| ABC-123 | 10 | Listing 10: Listing of Safety monitoring – Part 1 | Split; Additional Listing |
| ABC-123 | 10a | Listing 10a: Listing of Safety Endpoints collected as Clinical Events | Split; Additional Listing |
| ABC-123 | 10b | Listing 10b: Listing Safety monitoring – Part 2 | Split; Additional Listing |
| ABC-123 | 10c | Listing 10c: Listing Safety monitoring – Part 3 | Split; Additional Listing |

**Table 10. List of Listings submitted in the BIMO Package.**

While we maintained the serial numbers and their title names in line with the TCG, we split the listings wherever needed under specific requirements. For example, the discontinuation listings were split into three parts, based on dropouts and their period; adverse event listings were split into three parts (adverse events, serious adverse events, deaths); efficacy listings were split into two parts based on primary and secondary efficacy parameters; the labs and the clinical events related listings were split into four parts based on specific parameters and additional conditions. We added relevant notes under the “Comments” column against the listings that were split.

**4.2. Primary, Key Secondary Endpoints and Clinical Events** – The following table (Table 11) provides the information about the two listings related to Primary and Secondary Endpoints: one for the Primary Efficacy endpoint and the other one for the Secondary Efficacy Endpoint.

| Study Identifier | Endpoint Category or Clinical Events | Endpoint or Clinical Events Description | Criterion | Listing No. |
|---|---|---|---|---|
| ABC-123 | Primary Efficacy | Description for the Primary Efficacy Events | Description and logics for the criterion to be applied | 8a |
| ABC-123 | Secondary Efficacy | Description for the Secondary Efficacy Events | Description and logics for the criterion to be applied | 8b |

**Table 11. Site-specific Efficacy Endpoints.**

**4.3. Safety Monitoring and Clinical Events** – The following table (Table 12) provides information about safety monitoring in Part II listings. This contains the Labs and Immunogenicity related Clinical Events listings information.

| Study Identifier | Safety Monitoring or Clinical Events | Criterion | Listing No. |
|---|---|---|---|
| ABC-123 | Labs | Description and logics for selection based on specific parameters to be applied | 10 |
| ABC-123 | Labs | Description and logics for selection based on specific parameters to be applied | 10a |
| ABC-123 | Immunogenicity | Description and logics for selection based on specific parameters to be applied | 10b |
| ABC-123 | Immunogenicity | Description and logics for selection based on specific parameters to be applied | 10c |

**Table 12. Site-specific safety monitoring and clinical events.**

The subject-Level data line listings have been provided in PDF format. Appendix A in the TCG described two options for the folder structure for arranging the listings. Of the two, we followed the Option A which is the most reproductive process to generate the listings: By Site, by Listing Option A (Figure 1): As pointed out earlier, decision on the choice of folder options (based on Appendix B of TCG) influences the programming logistics and hence this decision was taken at the very beginning of the BIMO programming steps.

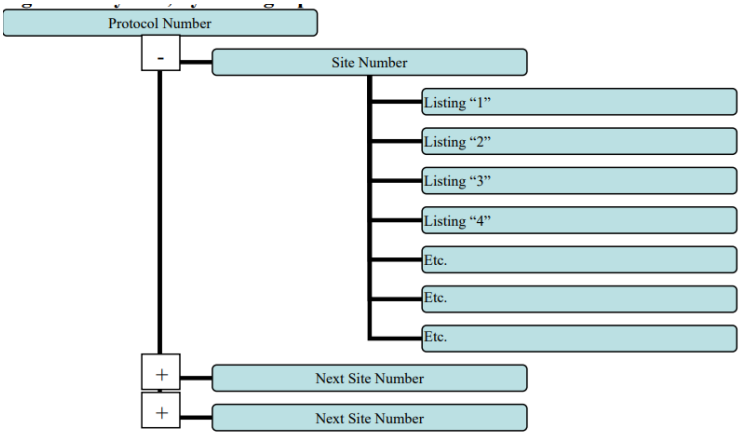


**Figure 1. By Site, by Listing Option A as given in the TCG's Appendix A.**

**Section 5: Part III Summary-level Clinical Site Dataset** – This dataset provides supporting information for the BIMO clinical data (summary-level clinical site dataset and a supporting Define-XML for the study), and should contain one record per study, clinical site, treatment arm, primary endpoint and secondary endpoint. As stated in the BIMO TCG section of this paper, there are 40 variables that are mandatory, ranging from administrative information to specific safety and efficacy findings. Data Definition files as well as the conformance report generated from the Pinnacle 21 tools must accompany this dataset and accordingly, we included in the submission.

**5.1. Treatment Variables** – In this section, we clarified the connection between the SDTM and ADaM treatment variables, and the use of planned and treatment variables in the CSR and BIMO analysis. BDRG provides specific questions in this regard, and we provided the answer in the same format.

**For: ABC-123**
**Use of ADaM Treatment Variables in the CSR Analysis**

ARM versus TRT01P

- Are the values of ARM equivalent in meaning to the values of TRT01P?

Yes, the values of ARM are equivalent in meaning to the values of TRT01P.

ACTARM versus TRT01A

- If TRT01A is used, then are the values of ACTARM equivalent in meaning to the values of TRT01A?
  Yes, the values of ACTARM are equivalent in meaning to the values of TRT01P.

Are both planned and actual treatment variables used in analyses?

Yes, the planned treatment arm is used in the efficacy analysis and the actual treatment arm is used in safety analysis.

**Use of ADaM Treatment variables in the BIMO analysis dataset (CLINSITE)**

- Are both planned and actual treatment variables used in BIMO analysis?
  Yes, both treatment variables were used in the CLINSITE dataset.

**5.2 Primary, Key Secondary Endpoints Summary** – This section provides information about the endpoints that are used in the Part III CLINSITE dataset (Table 13). It is to be noted that the BDRG template draft needs to be modified in line with the new efficacy variables present in the current TCG. Accordingly, we revised to accommodate the details needed for the newly added efficacy variables of SAFPOP and EFFPOP subjects while keeping the efficacy variables based on the previous version of TCG as explained on TCG section of this paper.

| **1** | **2** | **3 (TCG v2.0)** | **4 (TCG v3.0)** | **5 (TCG v3.0)** |
|---|---|---|---|---|
| **Study Identifier** | **Endpoint Category Endpoint Type [ENDTYPE] Endpoint Description [ENDPOINT]** | **Endpoint Criterion [TRTEFFR]** | **Endpoint Criterion for SAFPOP [TRTEFFR1]** | **Endpoint Criterion for EFFPOP [TRTEFFR2]** |
| ABC-123 | Example: Primary or Secondary Endpoint / Continuous / Discrete / Change | Summary statistic for the primary efficacy endpoint for subjects in SAFPOP | Summary statistic for the primary efficacy endpoint for subjects in SAFPOP | Summary statistic for the primary efficacy endpoint for subjects in EFFPOP |
| | **6 (TCG v2.0)** | **7 (TCG v2.0)** | **8 (TCG v3.0)** | **9 (TCG v3.0)** |
| **Study Identifier** | **Endpoint Result STD [TRTEFFS]** | **Censor Criterion [CENSOR]** | **Censor Criterion for SAFPOP [CENSOR1]** | **Censor Criterion for EFFPOP [CENSOR2]** |
| ABC-123 | Standard Deviation (STD) of the Efficacy results for subject in SAFPOP. If N=1, set to '0'. | Description and criterion for censoring for subjects in SAFPOP | Description and criterion for censoring for subjects in SAFPOP | Description and criterion for censoring for subjects in EFFPOP |

**Table 13. Site-specific endpoint summary results.**

**Section 6: External Datasets and Sources** – The Table 14 lists all external data sources that are used as an input for the BIMO clinical data. These files were also provided as PDF files and described in Part I (Item A) – List of All Clinical Sites section.

| External Data Sources | Description | Source | Comments |
|---|---|---|---|
| Screen Failure File | Consented screen failure subject information file | Sponsor / Clinical Trial Operations Team | Not collected on the CRF |
| Financial Disclosure Amount | Financial disclosure amount (US$) by site containing disclosures for the clinical investigators | Sponsor / Clinical Trial Operations Team | Not collected on the CRF |
| Clinical Investigator and Site Contact Information | Included full name, postal address, contact numbers (Phone & Fax), email addresses of both principal and sub-investigators | Sponsor / Clinical Trial Operations Team | Not collected on CRF |

**Table 14. External datasets and their sources.**

**Section 7: Site-specific Matters** – This section provides the site-specific information related to the site concerns, any additional site-specific details that are of interest to the readers that the sponsors want to communicate, subjects transferred between sites and identical site ID used in multiple studies for the sites used in the BIMO clinical data.

**7.1. Site Concerns** – The following table provides any site-related concerns and any site-specific additional information for the sites that may/may not be present in the BIMO clinical data for each study. Only the sites with concerns are listed. It will be helpful to report even when there is no concern to report, as shown in the Table 15.

| Study Identifier | Site # with Concerns (If any) <Grouped by Country Code> | Comments |
|---|---|---|
| ABC-123 | No Concerns to report for any site | N/A |

**Table 15. Site specific concerns.**

**7.2. Subjects Transferred Between Sites** – The Table 16 provides information related to only the subjects that transferred between sites.

| Study Identifier | Subject Identifier | Enrolled Site ID | Switch Site ID | Switch Date | Reason for Transfer | Comments |
|---|---|---|---|---|---|---|
| ABC-123 | 00001 | 201 | 205 | xxxx-xx-xx | Investigator moved from 201 to 205 | N/A |
| ABC-123 | 00006 | 242 | 261 | xxxx-xx-xx | Investigator dropped from the study | N/A |
| ABC-123 | 00003 | 281 | 292 | xxxx-xx-xx | Investigator moved from 281 to 292 | N/A |

**Table 16. Sites with transferred subjects.**

This section was indeed helpful to notice a wrong entry into the CSR listings and it was immediately corrected after cross checking between the BIMO listings and CSR outputs. Also, section 8 lists additional details in this regard.

**7.3. Identical Site ID Used in Multiple Studies –** In our case, there were no instances where identical site numbers used in multiple studies, we explicitly mentioned this fact in the Table 17 with a text string “No Identical Sites were used in multiple studies”.

| Site # | Study Identifiers | Comments |
|---|---|---|
| N/A | ABC-123 | No Identical Sites were used in multiple studies |

**Table 17. Identification of Site ID that is being used in multiple studies.**

**Section 8: Site Summary** – This section provides an overview on the site summary statistics (total number of sites, sites that have enrolled at least one subject with a signed informed consent, sites that have only screen failed subjects with a signed informed consent and additional information such as the sites having screen failed subjects with an informed consent and sites without any subject enrollments and so on) for the sites used in the BIMO clinical data for the study used to support safety and efficacy in the application (Table 18).

| Study Identifier | Site Summary | Comments |
|---|---|---|
| ABC-123 | xx sites that have enrolled at least one subject with a signed informed consent<br>xx sites that have only screen failure subjects with a signed informed consent<br>xx sites without any subjects screened | |

**Table 18. Sites summary.**

**Section 9: Conformance Summary for Part III Clinical Site Dataset** – This section provides an overview of validation checks and the inputs used to evaluate the conformance summary/findings on the CLINSITE dataset (Part III, Summary-level clinical site dataset) deliverable while using the BIMO TCG v2.0 or v3.0.

**9.1 Conformance Inputs** – Under this section, the following details were provided in the format laid out in the BDRG template: programming software name and version used to generate the CLINSITE data, version of the Pinnacle 21 tool and validation engine being adopted for generating the conformance report for the CLINSITE data, and finally the version of the TCG that was followed to prepare the BIMO Package. We used SAS® (v9.4) to generate the CLINSITE dataset and Pinnacle 21 Enterprise (v5.2.0) with the validation engine P21 2204.1 (Figure 2) and inputs that are listed in the Table 19. One of the challenges that we faced during validation in Pinnacle 21 tool is that we were not able to select TCG v3.0 option, because only TCG v2.0 option was available to generate the conformance report at the time our submission.

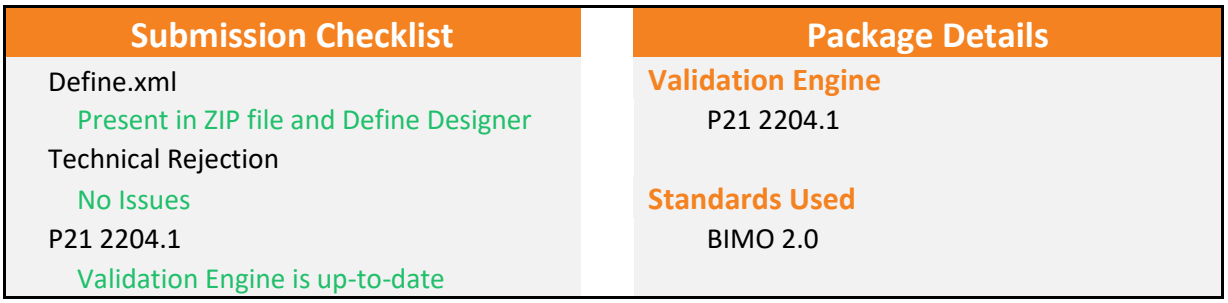


**Figure 2. Details on Pinnacle 21 and its validation engine.**

| | | | |
|---|---|---|---|
| Datasets | Description | Class | Source |
| CLINSITE | Clinical Site Data Elements Summary | SPECIAL PURPOSE | clinsite.xpt |
| DEFINE | Define.xml | | define.xml |
| GLOBAL | Global Metadata | | |

**Table 19. Conformance inputs.**

**9.2. Issues Summary** – During our preparation, after addressing all findings identified in P21 conformance report, only four groups of errors were existing as those 'errors' were not fixable (Table 20). The root cause of these errors were the special characters found in the original values of the CITY, POSTAL CODE and STATE variables that were reported from some of the non-US sites. Even though those values were accurate, Pinnacle 21 engine was not able to recognize them. Hence these error messages were categorized as "False Positive" under the "Explanation". In addition to the above address related values, presence of symbols in the financial disclosure values also resulted in errors though we did present the actual values as we received from the sites.

| Study Identifier | Dataset | Issue (Data /define.xml) | Diagnostic Message | Explanation |
|---|---|---|---|---|
| ABC-123 | CLINSITE | define.xml | Value for CITY not found in (City) user-defined code list | This is generated due to the encoding configuration used in the Aspera connectivity processes; Values are verified to be accurate. Hence False Positive. |
| ABC-123 | CLINSITE | define.xml | Value for POSTAL not found in (Postal Code) user-defined code list | Postal codes are verified to be accurate; error reporting may be due to a glitch in data collection on global postal codes; Hence False Positive. |
| ABC-123 | CLINSITE | define.xml | Value for STATE not found in (State) user-defined code list | This is generated due to the encoding configuration used in the Aspera connectivity processes; Values are verified to be accurate. Hence False Positive. |
| ABC-123 | CLINSITE | define.xml | Invalid value for FINLDISC variable | The values concur with the Standards; symbols in the value triggered the error; hence False positive. |

**Table 20. Issue Summary.**

**Section 10: eCTD Folder Structure Skeleton for BIMO Items in MODULE 5** – The TCG provides two options in Appendix A as stated earlier in this paper for having folder structure in eCTD under the MODULE 5, and we adopted the first option, Option A. The figure below (Figure 3) reflects the overview of the folder structure that we followed for the BIMO submission.

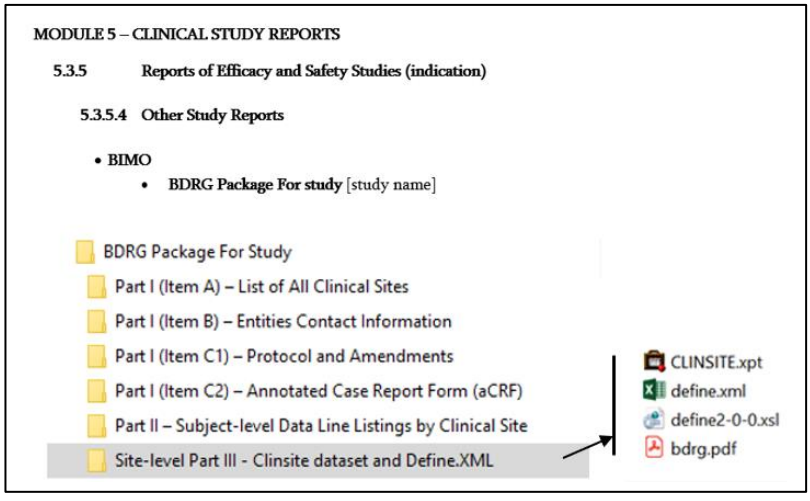


**Figure 3. Folder Structure under Module 5 for placing BIMO Package.**

The BDRG also has an optional section i.e., Section 11: Appendix (for other documentation/supplemental information that would be helpful to FDA reviewers). Under this section, we included all the additional files in the PDF format.

## CONCLUSION

The focus of this paper, from a broader perspective, is to highlight the updates in the current version of the TCG (v3.0), advantages from the latest release of more formalized BDRG template and to share our experiences and challenges that we faced in one of our recent efforts to prepare the BIMO package. We also highlighted the gap between the version of the Pinnacle 21 validation engine that we had while preparing our submission and its implications in generating the conformance report. We briefly discussed the differences between the previous and current versions of TCG. This paper also underlined how the contents in the subsequent TCGs have evolved in keeping up with the growing requirements for presenting the data in the context of emerging complexities and diverse nature of the trials, and, also the advantages of more streamlined format in the latest release of the BDRG. Especially the current version of TCG presented the updates that have reflected in presenting the site-specific data, importantly efficacy endpoints and censoring criteria based on specific populations (safety vs efficacy) in the CLINSITE data. It is the expectation of the FDA that the sponsors should adopt the current version of the TCG for preparing the BIMO package. However, sponsors have their flexibility to prefer to adopt the version of the TCG that they want for submitting their BIMO package.

As pointed out earlier in this paper, there was no specific industry recommended format and guidelines for the BDRG, though sponsors tend to submit the Reviewer's Guide to provide additional details to support their safety and efficacy data. Certainly, a well-defined format will be more helpful for the agency during the review of the applications from the sponsors. Recent release of the BDRG template added high level of clarity with the 10 required sections that allow sponsors to highlight all possible scenarios and technical details that were met at specific sites during the trial and that they were not able to be presented in the listings and CLINSITE dataset. To conclude, it is anticipated that the forthcoming releases and updates in the TCG, BDRG and validation engines in the Pinnacle 21 tool will be in sync with each other and result in a highly formalized complete BIMO Package that can efficiently facilitate the FDA to conduct site audits to ensure necessary site-related compliances pertinent to the NDA/CSR/BLA applications.

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