PhUSE US Connect 2018

Paper SP03

Ready, Set, Go: Planning and Preparing a CDISC Submission

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ABSTRACT

Preparing regulatory submissions in the pharmaceutical industry can be a very stressful experience due to the large amount of work and the need to research and understand regulatory and CDISC submission requirements. This paper aims to help clinical programmers and statisticians by providing information and advice for planning and preparing a CDISC submission. The paper focuses on the delivery of CDISC data packages, since these are typically the responsibility of clinical programmers and statisticians. The paper will cover the topics:

- Regulatory requirements for CDISC submissions
- Components of CDISC submission data packages
- Planning a CDISC data submission
- Best practices for preparing CDISC submission data packages
- Resources for more information about CDISC submissions

INTRODUCTION

This paper provides information to clinical programmers and statisticians to help them better plan and prepare CDISC submissions. The paper will first give a high-level overview of regulatory requirements and components of CDISC submission data packages. The paper will then focus on strategies and best practices for planning and preparing CDISC submissions.

REGULATORY REQUIREMENTS FOR CDISC SUBMISSIONS

This section provides a high-level overview of regulatory requirements for CDISC submissions. This section is not exhaustive, and it does not provide implementation details – that is beyond the scope of this paper. This section is intended to ensure readers have general knowledge about submission requirements, so that they will later be able to better understand the section on *Planning a CDISC Data Submission*.

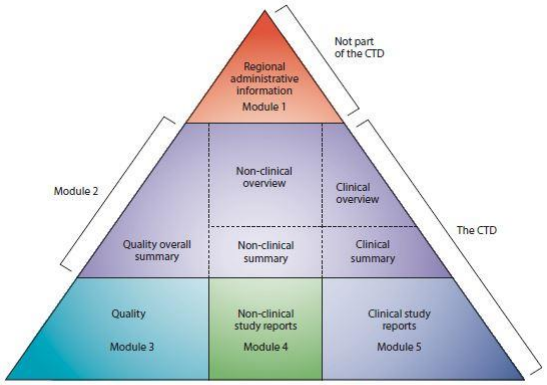
COMMON TECHNICAL DOCUMENT

One of the most important regulatory requirements is compliance with the Common Technical Document (CTD) standard. The CTD is a set of specifications for submissions to regulatory agencies. The CTD standard was created by the International Conference on Harmonisation (ICH), an organization launched in 1990 with the goal of harmonizing pharmaceutical regulatory requirements across different countries.[1] The CTD standard specifies:[2, 3]

- What documents should be included in regulatory filings (e.g. Protocols, Clinical Study Reports, Risk Management Plans, etc.)
- Specifications on the content and format of many documents (from DIA presentation)
- Associated document type-definitions (DTDs) and stylesheets
- The folder structure for storing files and the naming conventions for folders and files
- Technical specifications for an XML backbone file providing metadata about content files

The following diagrams provide a graphical view of some of the requirements for the organization of files and documents within the Common Technical Document.

General High-Level Organization of the Common Technical Document from ICH [2]

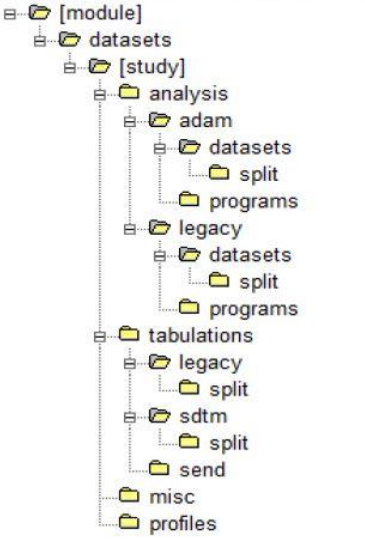


The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Clinical Study Reports and Clinical data packages (also known as CRT packages) are stored in Module 5.

eCTD Module 5 Folder Structure for Study Data (i.e. CRT packages). [3]

Figure 1: Folder Structure for Study Datasets



The Food and Drug Administration (FDA), European Medicines Agency (EMA), and Pharmaceuticals and Medical Devices Agency (PMDA) require compliance to CTD standards for electronic submissions, and other regulatory agencies are in various states of readiness for accepting CTD-compliant submissions. However, agencies may have additions to the ICH's CTD specifications.[4, 5] Thus, it is very important to consult with individual regulatory agencies to understand the specific CTD requirements of each agency.

Some sources for additional information about eCTD requirements are listed below.

- **FDA eCTD Information**
- **eStandards: Global Use of Electronic Submissions**

CDISC AND DATA PACKAGE REQUIREMENTS BY COUNTRY/REGION

CDISC is now the predominant industry data standard for pre-clinical and clinical data included in regulatory submissions. Thus, knowledge of the CDISC data standard and the global requirements for CDISC is an important part of preparing a CDISC submissions.

The table below gives a summary of the current CDISC and Data Package Requirements by Country/Region.

Country/Region	CDISC Data Package Requirements
United States [6, 7, 8]	• Data Packages required • CDISC required for studies starting after December 17, 2016 • SDTM Trial Summary domain required for all studies. For non-CDISC studies, TS must contain at least one record where Study Start Date = earliest informed consent date for all subjects in a study.
European Union	• Under review
Japan [8, 9]	• Data packages currently not required • CDISC data packages required for submissions on/after April 1, 2020 • Currently in transitional period
China [8]	• Data packages currently not required • Has endorsed CDISC • Has requested CDISC data packages for some submissions
Canada	• Data packages currently not required • No CDISC requirement yet • Has requested CDISC data packages for some submissions

As you can see in the table above, CDISC is now a requirement for the FDA, and it will soon be required by the PMDA and other regulatory agencies. Even if a regulatory agency does not formally require CDISC or data packages, it is still possible that they will request these for a particular submission. Therefore, it is imperative that submissions teams consult with regulatory agencies prior to submissions to confirm the exact requirements for their submission.

FDA REQUIREMENTS

This section gives a high-level overview of FDA requirements for regulatory submissions. For full information about FDA requirements for CDISC submissions data packages, please refer to the FDA Study Data Standards Resources website https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm. The following key FDA documents are available at this website.

FDA Data Standards Catalog	Contains specifications for the data standards and versions that the FDA supports. For each data standard version, it contains dates when support for the version begins and ends and dates when the requirement for the version begins and ends. The Data Standards catalog contains separate tabs for Data Exchange standards and Terminology standards.
FDA Study Data Technical Conformance Guide	Contains technical specifications for submission of electronic study data. Examples of the technical specifications in this document are: • Dataset / File sizes • eCTD directory structure • Use of Controlled Terminology • Reviewer's Guides • Validation of CDISC data • Submission of software programs • Data Standards for integrated analyses
FDA Business Rules	FDA Business Rules describe the business requirements for regulatory review. These business requirements help ensure that study data is compliant and useful and supports meaningful review and analysis. The FDA Business Rules are English-language descriptions of the FDA's business requirements.
FDA Validator Rules	The business rules are accompanied with validator rules which provide detail regarding FDA's assessment of study data for purposes of review and analysis. The FDA Validator Rules are programmatic checks of the FDA business rules. There is not a one-to-one correspondence between the FDA Business Rules and Validator Rules because it may not be possible to programmatically validate all business rules.

To ensure compliance with its requirements and specifications, the FDA validates study data included in submissions. According to the FDA *Study Data Technical Conformance Guide*, there are three types of study data validation rules that the FDA uses:

"1. Standards Development Organizations (e.g., CDISC) provide rules that assess conformance to its published standards (See www.CDISC.org).
2. FDA eCTD Technical Rejection Criteria for Study Data that assess conformance to the standards listed in the Catalog (See above).
3. FDA Business and Validator rules to assess that the data support regulatory review and analysis." [3]

The FDA *Study Data Technical Conformance Guide* and the FDA Technical Rejection Criteria documentation gives information about the timings of the FDA's Study Data validation checks. [3, 10]

- Upon receipt of a submission, the FDA has announced that it will follow a Technical Rejection Process. With this process, the FDA will run high-level checks for eCTD and data standards conformance. If the submission package fails these checks, it will be rejected. The FDA Technical Rejection Criteria are listed on the FDA website at: **FDA Technical Rejection Criteria**. The proposal for the FDA Technical Rejection process was rolled out in late 2016. The FDA will give the industry 30 days' notice on the FDA eCTD website prior to the criteria becoming effective. [10]

- During review of a submission, the FDA will perform additional validation, such as CDISC Conformance checks and checks for compliance to FDA Business Rules and FDA Validator Rules.

There are a few instances where the FDA rules for CDISC compliance differ from the CDISC Implementation Guide requirements. Fortunately, these are small in number, but one must be aware of these differences. This is an important reason why one should be familiar with the FDA Business Rules. Examples of these instances is listed below:

- FDA *Study Data Technical Conformance Guide* states that FDA wants all applicable SDTM domains to include EPOCH, but EPOCH is a permissible variable in CDISC SDTM model. [3, 11, 12]
- SDTM LB.LBLOINC variable is permissible according to CDISC, but the FDA lists LOINC under Terminology Standards in the FDA Data Standards Catalog and expects to receive it. [6, 11]
- SDTM Implementation Guide 3.2 states "Data for screen failure subjects, if submitted, should be included in the Demographics dataset, with ARMCD = "SCRNFAIL" and ARM = "Screen Failure". However the FDA *Study Data Technical Conformance Guide* states "Screen Failures, when provided, should be included as a record in DM with the ARM field left blank." [3, 11]

PMDA REQUIREMENTS

As noted in the section *CDISC and Data Package Requirements by Country/Region*, the PMDA will require CDISC data packages for all submissions on or after April 1, 2020. The PMDA is currently in a transitional period before this requirement takes effect. During this transitional period, the PMDA will accept legacy data packages as well as hybrid CDISC and legacy data packages. For all submissions during the transition period, the specific requirements for a particular submission must be agreed upon with the PMDA. The PMDA recommends that sponsors have a consultation meeting about the data format for submission of electronic data with the PMDA at least one year before the submission. [13, 14, 15, 16]

The following table provides a summary of the key differences between FDA and PMDA requirements, as of the time of the writing of this paper. Note that this summary is not exhaustive – there are additional differences between FDA and PMDA requirements that are not listed here. This table contains key differences only. For all submissions (both to the FDA and PMDA), the sponsor must consult with the regulatory agency prior to the submission to confirm the specific requirements for the submission.

Requirement	**FDA** [3, 6, 7, 10]	**PMDA** [9, 13, 14, 15, 16]
Studies in scope of Data Standards Requirements	All studies in submission	Studies which provide the major evidence for efficacy, safety, & dosage/administration, i.e. all Phase II and III and some Phase 1 studies (Oncology, QT/QTc, and comparative PK studies for Japanese population)
Data standards versions	Version on the FDA Standards Catalog at the time of study start. Individual studies in submission may have different data standards versions.	Refer to the PMDA's website (http://www.pmda.go.jp/) for versions of the CDISC standards, controlled terminologies, and dictionaries that are accepted by the PMDA. It is sufficient to use different versions within the same application, but the same version must be used within the same clinical study. From Technical Conformance Guide on Electronic Study Data Submissions,24-Aug-2016
Integrated Analyses	Sponsors must provide at least ADaM, with terminology aligned to a single version.	May be asked to provide ADaM (no specific requirements articulated about terminology).
Study Data Standardisation Plan	Initial: Expected at IND Updated: at least 1) no later than End of Phase 2 and 2) at pre-NDA Final: required with NDA	Called the "Form 8" document. Draft Document: Well in advance of submission preferred Final Document: required with NDA

Pinnacle 21 checks	Categorizes severity as Error and Warning	PMDA-specific versions of some checks. Categorizes severity as Reject, Error, and Warning.
System International (SI) Units	Does not yet require SI units for all parameters	Requires SI units in SDTM. ADaM should include unit used for analysis.
Submission of Software Programs	Should submit: • Programs used to ADaM datasets, tables and figures for primary and secondary efficacy analyses • Programs used to generate analyses that are included in the drug label	Requires submission of programs used to create the ADaM datasets and programs used for analyses
Analysis Results Metadata	No stated preference for Analysis Results Metadata	Prefers to receive Analysis Results Metadata
File Names of Reviewer's Guides	• SDRG file name*: csdrg.pdf • ADRG file name*: adrg.pdf * For clinical data	• SDRG file name: study-data-reviewers-guide.pdf • ADRG file name: analysis-data-reviewers-guide.pdf

The following key PMDA documents contain data standards requirements and technical specifications for CDISC submissions:

Advanced Review with Electronic Data Promotion Group	PMDA web page containing links to many useful documents and guidances for CDISC data submissions
Data Standards Catalog (2017-03-03)	Contains specifications for the data standards and versions that the PMDA supports. For each data standard version, contains dates when support for the version begins and ends. Contains separate tabs for Data Exchange standards and Terminology standards.
Technical Conformance Guide on Electronic Study Data Submissions (Revised in Nov 2016)	Contains technical specifications for submission of electronic study data.
Study Data Validation Rules (2015-11-18)	PMDA's validation rules for study data. Document has separate tabs for SDTM Rules, ADaM Rules, and DEFINE-XML Rules. PMDA assigns a Severity to each rule with the following possible values: • Reject: Rules which, if violated, will cause the review to be suspended until corrections have been made. • Error: Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made. • Warning: Rules which, even when violated, will not necessarily require any explanation.
Basic Principles on Electronic Submission of Study Data for New Drug Applications **Q/A for Basic Principles**	Document and Q&A about basic principles for electronic submissions of study data to PMDA. Topics covered include: • Types of data that must be submitted electronically • Data standards requirement • Submission of analysis programs • eCTD requirement • MedDRA coding
Notification on Practical Operations of Electronic Study Data Submissions **Q/A for Notification on Practical Operation**	Additional information about the electronic submission of study data to PMDA. Includes topics such as the following: • Electronic submission of integrated analyses (ISS/ISE) data • Validation for the acceptance of electronic data • Submission of programs • Controlled Terminology and Dictionary requirements

FAQs on Electronic Study Data Submission (Excerpt)	Frequently Asked Questions about electronic submission of study data to PMDA

COMPONENTS OF CDISC SUBMISSION DATA PACKAGES

This section describes the components of a CDISC submission data package. This section does not provide technical details for the components. Instead, it is intended to give the reader a high-level overview of the scope and number of deliverables in a CDISC submission data package.

STUDY DATA STANDARDIZATION PLAN

The Study Data Standardization Plan (SDSP) is an important document for submissions to the FDA. The *FDA Study Data Technical Conformance Guide* states "For clinical and non-clinical studies, sponsors should include a plan (e.g. in the IND) describing the submission of standardized study data to FDA. The Study Data Standardization Plan (SDSP) assists FDA in identifying potential data standardization issues early in the development program."[3] The Conformance guide also specifies the timings of when the SDSP should be submitted to the FDA. The initial document should be included in the IND application. For CBER, submit SDSP no later than end-of-Phase 2 meeting. The conformance guide also states "The SDSP should be updated in subsequent communications with the FDA as the development program expands and additional studies are planned."[3]

The SDSP describes the data standardization approach for studies in a submission. It should contain:

- List of the planned studies with information such as phase and study design
- Planned data standards, formats, and terminologies and their versions or a justification of studies that may not conform to the currently supported standards.[17]

A PhUSE working group for the Study Data Standardization Plan has collaborated with the FDA to develop SDSP templates and a Completion Guidance document, available at: https://www.phuse.eu/css-deliverables.

SDTM CASE REPORT TABULATIONS (FOR EACH STUDY AND FOR EACH INTEGRATED ANALYSIS)

Each study or integrated analysis in a submission should ideally have an SDTM Case Report Tabulation (CRT) package. An SDTM CRT package will consist of SDTM datasets in XPT format, a Data Definition table (i.e. DEFINE file) in XML and optionally PDF format along with style sheets, a Reviewers Guide, and an Annotated CRF.[3, 5]

Note that integrated analyses do not always have to provide an SDTM CRT packages. It can be acceptable to integrate data at the ADaM level and submit only an ADaM CRT package. However, the decision about whether to integrate data at the SDTM and ADaM level must be discussed and agreed with the regulatory agency. In all cases, the integration of the data must follow the guideline listed in the FDA *Study Data Technical Conformance Guide*: "Regardless of the specific versions used for individual studies, pooled analyses (e.g., for an integrated summary of safety) should be conducted using a single version of a terminology. The current version should be used at the time that data across studies are pooled. This will ensure a consistent and coherent comparison of clinical and scientific concepts across multiple studies. Sponsors should specify the terminologies and versions used in the study in the SDRG."[3]

ADAM CASE REPORT TABULATIONS (FOR EACH STUDY AND FOR EACH INTEGRATED ANALYSIS)

Each study or integrated analysis in a submission should have an ADaM Case Report Tabulation (CRT) package. An ADaM CRT package will consist of ADaM datasets in XPT format, a Data Definition table (i.e. DEFINE file) in XML and optionally PDF format along with style sheets, and a Reviewers Guide. The ADaM CRT package may also contain Analysis Results Metadata.[3]

CLINICAL SITE DATA FOR CDER'S INSPECTION PLANNING

As part of the regulatory review process, the FDA conducts site inspections to ensure that clinical investigators, sponsors, and Institutional Review Boards (IRBs) comply with FDA regulations. To facilitate their site inspections, the FDA requests that pharmaceutical companies voluntarily submit data that describes the characteristics and outcomes of clinical investigations at the site level. [18]

There are two components to the clinical site data to be provided to the FDA: [18, 19]

1. Listings of clinical data by site
2. A summary level clinical site dataset in a standardized electronic format.

Submission teams will need to consult with their FDA review team during pre-NDA or pre-BLA meetings to determine what clinical site data to provide. For some submissions, listings of clinical data by site may be

sufficient. In other cases, the FDA may request the summary level clinical site dataset. If a clinical site dataset is needed, the FDA and sponsor will need to discuss and decide what studies to include in the dataset and also agree on details about the content. The clinical site data to be provided to the FDA will come from several sources, such as clinical databases (e.g. SDTM and ADaM data), the Clinical Trial Management System (for investigator information), Financial systems (for info on financial payments to sites and investigators), and Regulatory (for NDA and BLA numbers).

On 16 February 2018, FDA published the draft guidance entitled *"Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions" along with the "Bioresearch Monitoring Technical Conformance Guide"*. The notice of this draft guidance is available at https://www.federalregister.gov/documents/2018/02/16/2018-03236/submission-of-content-necessary-for-bioresearch-monitoring-inspection-planning-for-the-center-of. [18]

SOFTWARE PROGRAMS

Both the FDA and PMDA request submission of software programs. The FDA *Study Data Technical Conformance Guide* states: *"Software Programs Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information (PI) if applicable. The specific software utilized should be specified in the ADRG. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Sponsors should not submit software programs with executable file extensions, and these programs should be Sponsors should submit software programs in ASCII text format; however, executable file extensions should not be used."* [3]

In other words, sponsors should submit the following software programs to the FDA:

- Primary and secondary efficacy analyses (programs for ADaM datasets and Tables and Figures)
- Analyses of clinical data included in drug label (new)

Software programs should be submitted in ASCII format with non-executable file extensions.

The PMDA Technical Conformance Guide on Electronic Study Data Submissions states: "*Programs to be submitted with respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted. The main purposes of requesting the submission of these programs are to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment."* Sponsors should confirm the requirements for submission of software programs with the PMDA during the submission consultation meeting.[15]

When submitting software programs to a regulatory agency, it is good practice to provide documentation for the submitted software programs. The template ADaM Data Reviewers Guide developed by PhUSE contains a section (Section 7) for Submission of Programs. This section should contain the following information:[20]

- Description of which programs are being submitted
- Table of Contents for the programs
- Software Version and Environment

An example of a completed Section 7 of an ADaM Data Reviewers Guide is available on the PhUSE Wiki at ADRG.

POPULATION PK PACKAGE (IF APPLICABLE TO THE SUBMISSION)

Some submissions will include a Population PK data package. CDISC data standards currently do not exist for Population PK data packages.[21]

PLANNING AND PREPARING A CDISC DATA SUBMISSION

The most important step to take when preparing a CDISC data submission is to start early. Here are specific steps you should start well in advance of your submission filing date.

1. Start the Study Data Standardization Plan early. When a new drug project appears to have submission potential, create a Study Data Standardization Plan with info on all studies in the project with their data standards, formats, and terminologies and their versions. Keep this document up-to-date as new studies are started.

2. Review and understand relevant regulatory requirements (e.g. FDA Business Rules, FDA requirement to submit Trial Summary for all studies).

   Take the time to educate yourself on regulatory requirements. At a minimum, review the FDA and PMDA sources listed in this paper. These sources are not lengthy, and they contain specific technical specifications for submissions that sponsors must comply with to avoid Technical Rejections or Refuse to File issues.

3. Plan resource and timelines for all components

   Sponsors generally develop project management plans for submissions, but these plans sometimes do not include all components of submissions. A robust project management plan must include time and resource for all tasks including the Study Data Standardization Plan, integration of data, Clinical Site Data for CDER's Inspection Planning, preparing SAS programs for delivery, SDTM and ADaM Reviewer's Guides, creating Trial Summary datasets for non-CDISC studies, and QC of eCTD.

   As a warning: depending on the specific requirements for a submission, the task of providing Clinical Site Data to the FDA may require a lot of time and resources.

4. Discuss and plan well in advance the strategy for the following items:

   Handling of Non-CRF Data in Submissions
   All data sources should be included in the CRT packages, including non-CRF data, such as Excel spreadsheets. Decide as early as possible whether you will convert these data sources to SDTM, provide them in ADaM datasets, or deliver them as XPT files in the misc folder of Module 5 of the eCTD.[22]

   Filing to Both the FDA and PMDA
   If filing to both FDA and PMDA, plan a strategy for meeting requirements for both agencies. As noted earlier in the paper, there are many differences between the FDA and PMDA requirements for CDISC data packages. If sponsors do not plan for these differences, this could cause sponsors to have to create separate CRT packages for the FDA and PMDA, which is more work for the submission team.

   Strategy for the ISS/ISE data package [3,15,23]
   Both the FDA and PMDA have been clear that they expect integrated analyses to be produced using data which has been aligned to a single CDISC version and a common terminology. Also, the FDA expects the latest versions of dictionaries to be used for integrated data. CDISC standards do not yet cover integration of multiple studies. So, sponsors will need to decide how they will integrate datasets and align them to a common terminology. This can be done at the ADaM level, but integrating at the SDTM level will give better traceability. Consult with the regulatory agency well in advance about your ISS/ISE data integration strategy and obtain their agreement to avoid last minute surprises and re-work.

   If your submission team decides to integrate data at the ADaM level, then you will need to harmonize CDISC version, terminology, and dictionary versions in the ADaM datasets. In addition, you will need to consider harmonizing additional items, such as baseline values, analysis flags, and PARAMCD/PARAM values.

   Test Submissions to FDA
   The FDA allows companies to submit a sample or test submission prior to an actual submission to help sponsor or applicants who have not previously submitted an eCTD and/or standardized study data. The FDA will validate the sample eCTD submission using standard FDA CDISC validation checks. The sample submissions are not reviewed by FDA reviewers at any time.
   It is important to have realistic expectations about the utility of a test submission to the FDA. The FDA validation will only yield information about the compliance of the data package to the standard FDA checks. The FDA will not review the content of the test submission including the Reviewers Guides. So, it is possible that the FDA

review team that reviews the actual submission may later raise concerns or ask questions about issues that were not identified during the review of the test submission.

Information about the FDA Sample Submission Validation Process is available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm .

Analysis Results Metadata in ADaM CRTs

Analysis Results Metadata is a very helpful tool for clearly explaining the algorithms of analyses. Also, the PMDA has stated that it prefers to receive Analysis Results Metadata. Therefore, it is a good practice to create Analysis Results Metadata for key analyses to improve the readability and traceability of your submission package. The Clinical Statistics and Programming functions should discuss and plan in advance which analyses are good candidates for Analysis Results Metadata.

5. Work closely with Regulatory Affairs and Regulatory Operations throughout the submission planning and preparation process.

   In most pharmaceutical companies, it is the Regulatory Affairs department that works directly with the regulatory agencies. Therefore, it is helpful to develop a close relationship with this group, so that they can clearly communicate questions and proposals about data packages to the regulatory agencies. In addition, the Regulatory Affairs and Regulatory Operations groups may have information about regulatory feedback on other recent submissions that will be helpful to know.

6. Seek agreement with regulatory agencies during Pre-NDA/Pre-BLA meetings and communications

   As stated several times already, it is essential to communicate with the regulatory agencies to confirm the specific requirements and preferences for a particular submission. Different agencies and even different divisions within the same agency may have different requirements and preferences. Clear communication and agreement is critical for avoiding last minute surprises. At a minimum, try to reach agreement on the following data package components:
   - ISS/ISE Integration at SDTM or ADaM level
   - Clinical Site Data for FDA's Site Inspection Planning – confirm details of CLINSITE dataset
   - Software Programs - confirm which programs will be provided
   - Any data standard or eCRT question

   Companies can submit questions to the FDA CDER eData team using their email address: edata@fda.hhs.gov

7. Build in quality from the beginning.

   Here are some ways to build in quality from the beginning.

   Sometimes clinical programmers wait until all Clinical Study Report analyses are complete before they begin the work of writing ADaM metadata specifications. A better process is to write ADaM metadata specifications prior to programming of the ADaM datasets. With this approach, the ADaM metadata specifications can be QCed in parallel with the ADaM datasets, thereby making sure they are correct and consistent with the ADaM datasets. It is also best practice to run Pinnacle21 checks on ADaM datasets prior to completion of CSR analyses. This will allow you to find any structural problems with the ADaM datasets prior to release of the CSR analyses. If structural problems are found after the release of CSR analyses, then the ADaM datasets and Tables, Listings and Figures will need to be corrected, rerun, and re-QCed – which is obviously a lot of work.

   When addressing Pinnacle 21 messages, be sure to correct any Reject errors for a PMDA submission. It is allowable to explain some messages in the Reviewer's Guides, but It is also best practice to correct other error and warning messages, whenever possible.

   Also, remember that software programs are a deliverable to regulatory agencies. Reviewers will read your software programs, so you need to make sure they are readable, well-commented, and comply with Good Programming Practices. Information about Good Programming Practices is available at the PhUSE Wiki at http://www.phusewiki.org/wiki/index.php?title=Good_Programming_Practice. Ensure that programs are well-written and well-commented during their development. It would be much more difficult to comment and restructure programs later in the submission process.

Lastly, keep in mind that reviewers at the regulatory agencies will be reading all of your documentation for your data packages. Write clear and consistent documentation in your ADaM metadata specifications and ADaM Reviewers Guide, and avoid company-specific jargon.

RESOURCES FOR MORE INFORMATION ABOUT CDISC SUBMISSIONS

The PhUSE Data Submissions (SDTM and ADaM) Team answers questions about CDISC submissions. Submit questions to this team at the web site https://www.phuse.eu/wiki-feedback.

Responses to question are posted at :
http://www.phusewiki.org/wiki/index.php?title=SDTM_FAQ_Team_Responses#Topic:_Data_Submissions_.28DSUB_Sub-Team.29 .

CONCLUSION

Preparing CDISC submission data packages is hard work. Submissions require a large number of analyses, datasets, programs, and documents. A deliberate and proactive approach is key to avoiding last-minute scrambles to meet deadlines or to make changes to meet previously unknown requirements. Best practices for a smooth CDISC submission include:

- Start planning early
- Educate yourself on regulations and components of CDISC submissions
- Work closely with Regulatory Affairs to proactively seek early agreement with regulatory agencies
- Create a robust project management plan that includes all components
- Build in quality from the beginning

CDISC submissions are an area where an early investment of time, education, and planning will pay off with time and resource savings in the long run.

REFERENCES

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ACKNOWLEDGMENTS

I would like to thank and acknowledge Warwick Benger and Miho Hashio at GSK who answered questions and provided me with invaluable information. I am very grateful for their kind support and guidance.

I would also like to thank and acknowledge the members of the PhUSE CDISC Data Submissions working group for the advice and support they provide to members of the PhUSE community.

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