Paper SA02

The Misery of the Miscellaneous Folder in Module 5

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ABSTRACT

Preparing regulatory submissions packages in the pharmaceutical industry can be very challenging due to the large amount of work and the need to research and understand regulatory and CDISC submission requirements. This paper aims to help those involved in placing the submission documents in the appropriate Module 5 folders by providing information and recommendation based on experience with the Misc folder within this Module. The paper will cover the following topics with regards to the Misc folder in Module 5:

- Regulatory requirements for CDISC submissions
- Best practices for preparing CDISC submission data packages
- Use Cases
- Frequently Asked Questions
- Resources for more information

INTRODUCTION

This paper provides information to clinical programmers and statisticians to help them better plan and prepare CDISC submissions. First it gives a high-level overview of regulatory requirements and components of CDISC submission data packages then focus on strategies and best practices for the use of the Misc folder in Module 5 for submission.

REGULATORY REQUIREMENT 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 the Miscellaneous folder in Module 5.

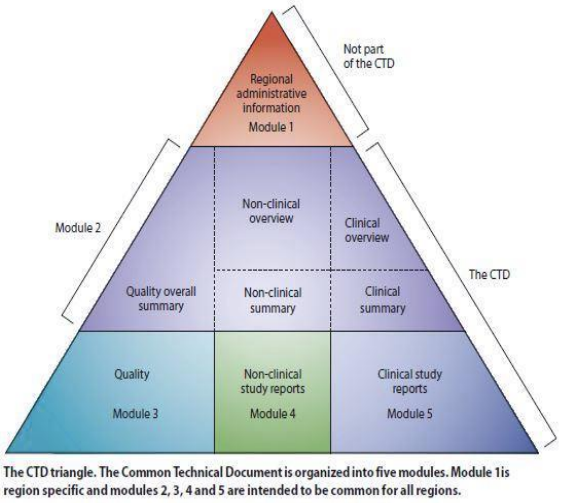
COMMON TECHNICAL DOCUMENT

One of the most important regulatory requirements is compliance with the Common Technical Document (CTD) standard. The CTD is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. 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
- 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.

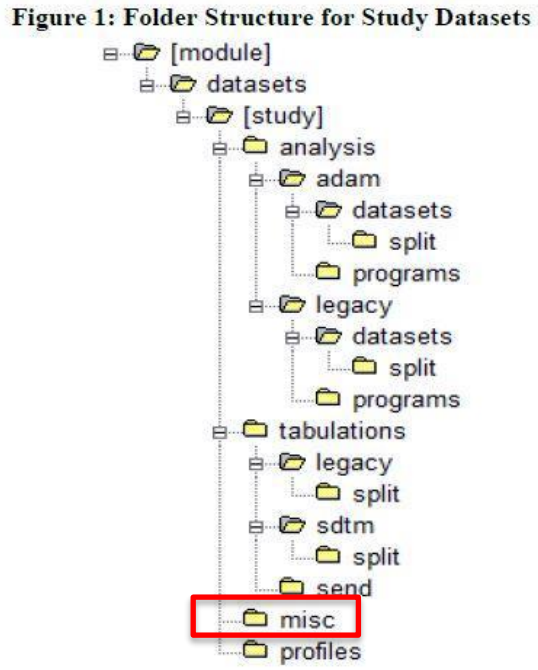
General High-Level Organization of the Common Technical Document from ICH [2]



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]



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 Required • Has endorsed CDISC
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 submission. Therefore, it is imperative that submission 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 on CDISC submissions data packages, please refer to the FDA Study Data Standards Resources website https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources. The following key 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, 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 the 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 90 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, there are only a few of these 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 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. Different versions may be used 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 (2019-11-01)	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 Jan 2019)	Contains technical specifications for submission of electronic study data.
Study Data Validation Rules Version 1.0 (2015-11-18) Acceptable from Oct 1, 2016 to Mar 31, 2021 (application date) **Study Data Validation Rules Version 2.0 (2019-09-27) Acceptable from Apr 1, 2020 (application date)**	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

ECDT MODULE 5 STRUCTURE

Study datasets and their supportive files should be organized into a specific file directory structure when submitted in the eCTD[2] format as per the eCTD Module 5 Folder Structure for Study Data figure above. The submission of files within the appropriate folders allows automated systems to detect and prepare datasets for review and minimizes the need for manual processing by the reviewer.

THE MISCELLANEOUS FOLDER

The FDA Study Data Technical Conformance Guide (SDTCG) v3.2 specifies that miscellaneous datasets, those that do not qualify as analysis, profile, or tabulation datasets, should be put in the misc folder, which was formally known as the listings folder. Although the SDTCG does not specifically mention what a miscellaneous dataset would include, it is believed to consist of any data not captured in SDTM but used in the creation of ADaM datasets or TLGs within the submission. Look-up tables, such as a list of prohibited concomitant medications, AEs of special interest, CTC Toxicity grades and deviations collected somewhere other than on the CRF are examples of this miscellaneous data.

Requirement	FDA	PMDA
Misc folder	Folder to contain non-SDTM datasets used in the ADaM creation, e.g. look-up tables, metadata datasets	Folder for storing data which is not appropriate for storage in the analysis or tabulations folder

It is important to note that the referenced look-up tables should be documented as well in the Analysis Data Reviewer's Guide (ADRG). The actual look-up table can be included in the appendix of the ADRG and referenced in the section of the document

that uses it. This also assists in the traceability of the data used in the analysis to the source.

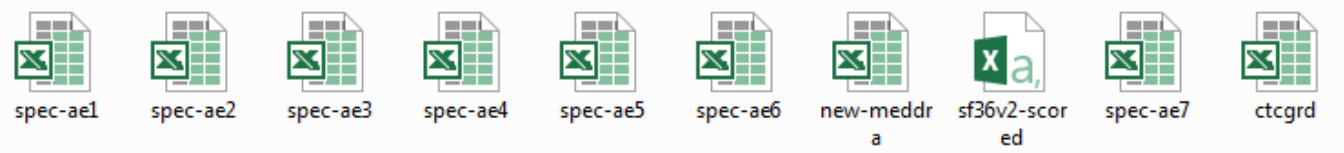
At Janssen the programming group is the only group to utilize the misc folder for files relevant to the analysis data submissions.

USE CASES

Below are examples of what Janssen has included in the misc folder for several of our recent submissions.

EXAMPLE 1

../m5/datasets/CNTO####/analysis/misc



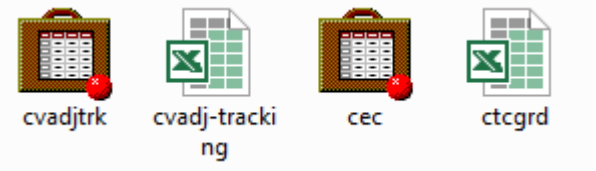
In this example you see files for the CTC Toxicity Grade (ctcgrd), several files for AEs of special interest, a file of new MedDRA terms and the Short Form 36 Health Survey (SF-36) question score information.

The toxicity grade spreadsheet is used in deriving the toxicity grades for laboratory data in the analysis datasets.

The files for the AEs of Special Interest were used in the creation of several of the AE related tables and listings.

EXAMPLE 2

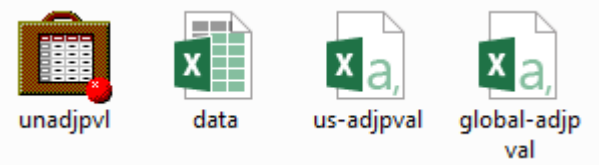
../m5/datasets/CNTO####/analysis/misc



In this example we again see the file for the CTC Toxicity Grade (ctcgrd) but in this study we also see files for the Cardiovascular Adjudication. The cec.xpt file contains data transferred from the adjudication committee, cvadjtrk.xpt is the tracking file containing records from the locked database and cvadj-tracking.xls is the tracking file used by clinical and contains the dossier number for each case to be adjudicated. These files were all used in the creation of the analysis dataset for Cardiac Adjudication.

EXAMPLE 3

../m5/datasets/SCE###/analysis/misc



This example is from a Summary of Clinical Efficacy submission that combined the efficacy data from several studies with files containing the adjusted and unadjusted p-values for the specific multiplicity adjusted testing procedure which were used in the creation of tables in the submission.

BEST PRACTICES

Be sure to review and understand the relevant regulatory requirements such as the FDA Business Rules, the FDA and PMDA eCTD guidelines, etc. Take time to educate yourself on the different regulatory requirements. At a minimum, review the FDA and PMDA sources listed in this paper. These sources are not long, and they contain specific technical specifications for submission.

Discuss and plan well in advance the strategy that you will use for items such as the handling of non-CRF data within the submission. All data sources should be included in the CRT package, including non-CRF data, such as Excel spreadsheets that are used as look-up tables. Decide as early as possible whether you will convert these data sources to SDTM, provide

them in ADaM datasets, or deliver them as XPT or XLS files in the misc folder of Module 5 of the eCTD.

Work closely with your companies Regulatory Affairs and/or Regulatory Operations department throughout the submission planning and preparation process. Develop a close relationship with these groups. As they generally work directly with the agencies, they can be used to communicate your questions and proposals about data packages to the regulatory agencies. They may also have useful information from the agencies on recent submissions that may be helpful in planning your submission.

During the Pre-NDA/Pre-BLA meetings and communications seek agreement with the regulatory agencies to confirm the specific requirements and preferences for a submission. Different agencies and even different divisions within the same agency may have different requirements and preferences. Clear communications and agreements are critical for avoiding last minute surprises during a submission. Companies can submit questions to the FDA CDER eData team using their email address: edata@fda.hhs.gov

Lastly, keep in mind that reviewers at the regulatory agencies will be reading all your documentation for your data packages. Ensure that your documentation is clear and consistent across the submission.

FAQS

Q: Since it is at the same folder level in Module 5, can the misc folder be used for both Tabulations and Analysis files?
A: Yes, the misc folder can be used for both. A naming convention should be in place to ensure that the files can easily be identified as tabulation or analysis related.

CONCLUSION

Preparing regulatory submissions packages in the pharmaceutical industry can be very challenging due to the large amount of work, the need to research and understand regulatory and CDISC submission requirements and with the large amount of documentation that goes into a submission. Understanding the data, the analysis that is required and the documents needed to support the analysis early in the study will assist you in determining how and where you will place this documentation in the Module 5 folders and whether you will need to utilize the misc folder.

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