

FDA and PMDA Study Data Submission Distinctions

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Abstract

The US Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) require standardized study data for certain regulatory submissions. Industry approaches to meeting these requirements vary across sponsors and between regulatory review divisions. Within the PHUSE 'Optimizing the Use of Data Standards' working group, the 'Industry Experiences Submitting Standardized Study Data' to Regulatory Authorities' subteam established a project to recommend best submission strategies and planning practices.

In the end-to-end process of drug development, it is essential to be aware of agency distinctions between the respective regulatory submission requirements. This poster addresses the similarities and differences in standards between the FDA and the PMDA covering mandates, data packages, dictionaries, validation rules, meetings, and timelines. Additionally, questions to help sponsors plan for submitting to both agencies based on industry experiences are included.

OVERVIEW

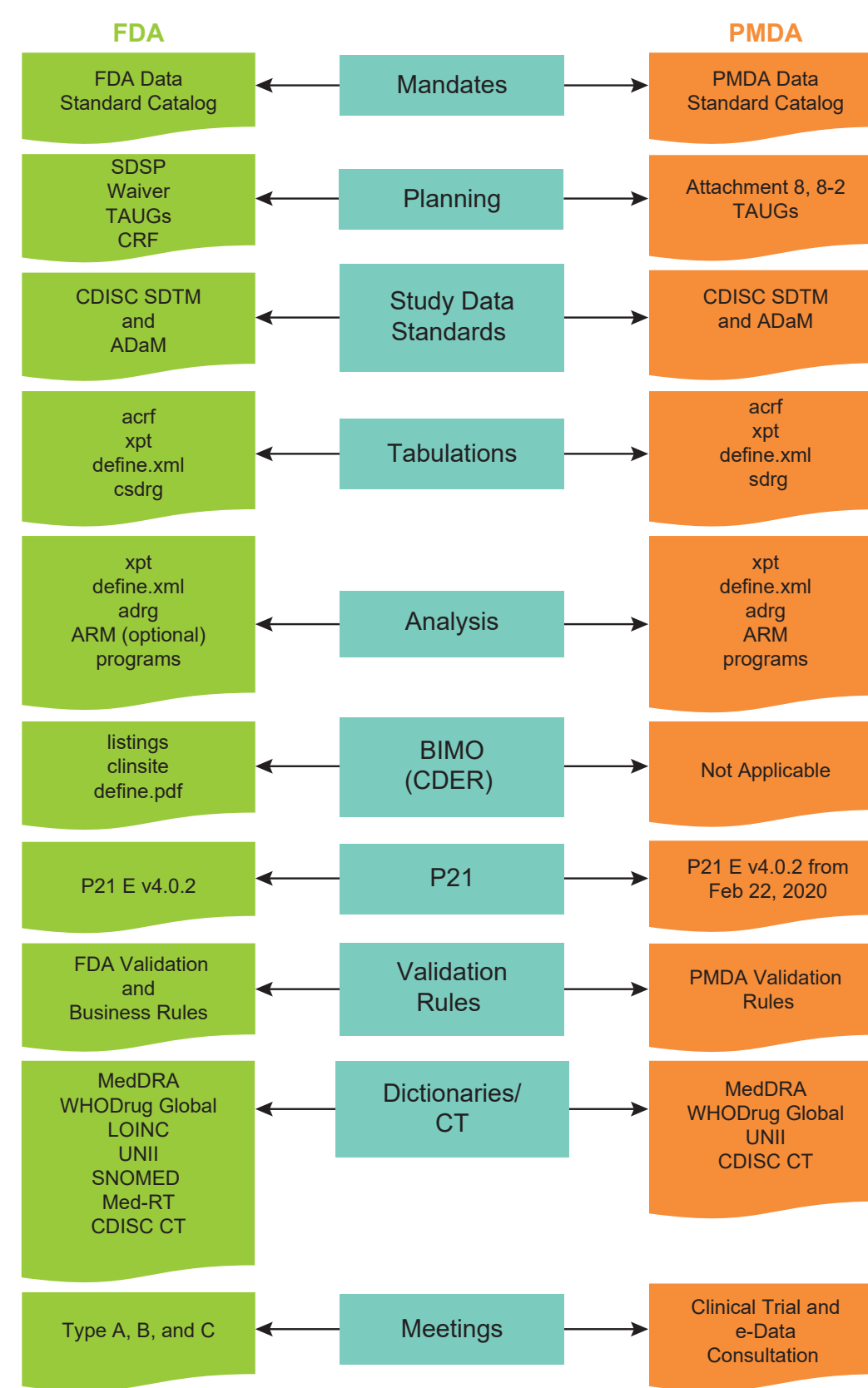
The requirement to adhere to electronic submission guidance from the FDA and PMDA and submit data in a standardized CDISC format is becoming critically important. The mandate, to submit data using the SDTM and the ADaM formats to the FDA, became effective as of 16-Dec-2016 for all study starts after this date. The mandate for submitting standardized data to the PMDA will become effective as of 01-Apr-2020, regardless of when the study commenced.

In the end-to-end process of drug development best strategy, planning, and communication practices, it is essential to be aware of the regulatory requirements to plan, develop, and submit the study data submission deliverables.

Although both health agencies require submission in CDISC SDTM and ADaM formats, there are some underlying differences in the data standards requirements that are to be addressed prior to submission. At present, it would be very difficult to submit the exact electronic submission data package to both agencies.

Figure 1. Chart Comparison of FDA and PMDA Study Data Submission Distinctions

The diagram below shows the comparison of documents, standards, and tools between both agencies.



FDA AND PMDA STUDY DATA DISTINCTIONS

The distinctions are classified into the following categories for ease of comparing mandates, standards, data packages, dictionaries, rules, and requirements between FDA and PMDA.

Table 1. Mandates Across FDA and PMDA Agencies

FDA		PMDA	
Mandates Across Agencies			
Reference: 4		References: 17, 22	
New Drug Application (NDA) Abbreviated New Drug Application (ANDA) Biologics License Application (BLA)	17-Dec-2016	NDA	01-Apr-2020
Investigational New Drug (IND) Application	17-Dec-2017	Transition Period	01-Oct-2016 to 31-Mar-2020
• Studies starting on or after 17-Dec-2016 are to adhere to CDISC format for NDAs, ANDAs, and certain BLAs and subsequent submissions to these types of applications • Studies starting on or after 17-Dec-2017 are to adhere to CDISC format for certain INDs • All electronic submissions are to be compliant to the FDA 'Data Standard Catalog' requirements • Waivers are possible for studies that started before 17-Dec-2016		• Irrespective of study start date, study data is to adhere to the CDISC format as of 01-Apr-2020. Refer to the PMDA Data Standard Catalog for the supported CDISC standards • Waiver/Exemptions are allowed under certain conditions based on the PMDA guidance updated on 24-Jan-2019. Such as: – Sponsors need to consult with PMDA for requesting a waiver/exemption	

Table 2. Comparison of Similarities and Differences in Study Data Submissions

FDA	PMDA
Study Data Planning	
References: 3, 11, 26 Study Data Standardization Plan (SDSP)	References: 18, 21, 24, 25 • Attachment 8 ('Consultation on Data Format of Submission of Electronic Study Data') • Attachment 8-2 ('Consultation on Exemption of Submission of Electronic Study Data') is also available
The SDSP is a living document. It is recommended to initiate and submit at pre-IND but no later than the end of Phase 2. Update and submit throughout development. For CBER submission, include CBER appendix within SDSP (template found in PHUSE website, SDSP Template with optional CBER appendix).	Attachment 8 is a living document. Submit prior to the eData Consultation as a preliminary meeting document. The finalized updated document is required for 'Pre-consultation meeting on review data format' that is planned 1 to 3 months prior to the application being submitted
Therapeutic Area User Guides (TAUGs)	
Reference: 4 TAUGs are expected to be followed if they are listed in the FDA TCG (Technical Conformance Guide - Section 5.2 Supported Therapeutic Areas). TA standards that have been approved by the FDA are considered part of the CDISC foundational standards. Also refer to 'Technical Guides – Therapeutic Area Information and Specifications' for additional information on the study data submissions to CBER and CBER (eg, Next Generations Sequencing, QT Studies, BMV, HIV, Vaccines, and Comparative Clinical Endpoint BE Studies).	Reference: 18 All Therapeutic Area Standards that have been published by CDISC may be used for submission and must be referenced in Attachment 8 and the Analysis Data Reviewers Guide. Sponsors need to consult with PMDA on Therapeutic Area Standards.
Case Report Forms (CRFs)	
CRF/TOC (The CRF TOC is a list of subjects for four standard AE categories of interest required for a submission (death, discontinuation from AE, discontinuation due to any other reason, and serious AE). Additional AE categories may exist depending on protocol-specific details (ie, AEs of Interest).	Not included in initial e-sub data package but may be requested later.
Individual eCRFs (The eCRFs of the subjects from CRF/TOC listing).	Not included in initial e-sub data package but may be requested later.
CRF/TOC and individual eCRFs are not part of dataset folder but part of m5 eCTD folder.	Not applicable
Tabulations	
Reference: 3 SDTM Annotated blank CRF saved as acrf.pdf SDTM datasets are to use transport format (.xpt) version 5.0. Study Data Reviewer's Guide is to be saved as csdrg.pdf (Include 'Legacy Data Conversion Plan' if applicable).	Reference: 18 Identical requirement Identical requirement Study Data Reviewer's Guide is to be saved as 'study-data-reviewers-guide.pdf' Discuss with PMDA alignment using csdrg.pdf
• Use define.xml v1.0 and define.pdf prior to 15-Mar-2018 • Use define.xml v2.0 on or after 15-Mar-2018 • A define.pdf is not required with v2.0, but recommend checking with the reviewer	Both define.xml v1.0 and v2.0 are permissible to use. The define.pdf is not necessary.
Supplement Data Definition (optional) is provided for describing the complex computation algorithm. It is not recommended to describe the complex and lengthy derivation in the define.xml due to the style limitation of define.xml.	Identical requirement
Analysis	
Reference: 3 • Use define.xml v1.0 and define.pdf prior to 15-Mar-2018 • Use define.xml v2.0 on or after 15-Mar-2018 • A define.pdf is not required but recommend checking with the reviewer ADaM datasets are to use transport format (.xpt) version 5.0 and prefix 'ad' for the dataset name (example: adxxx.xpt).	Reference: 18 Identical requirement Identical requirement
Analysis Data Reviewer's Guide is to be saved as adrg.pdf.	Analysis Data Reviewer's Guide is to be saved as 'analysis-data-reviewers-guide.pdf'. Discuss with PMDA alignment using adrg.pdf.
Submit programs in .txt format (provide the software programs and macros used to create all ADaM datasets and tables and figures associated with primary and secondary efficacy analyses). Label: If applicable, submit data and programs for any additional analysis to support the Prescribing Information.	The file name should include the extension of the analysis software used (ie, sas). If the file name does not contain an extension, an explanation about the file format should be included in the ADaM data guide. • Programs in txt format or pdf format have been allowed. Discuss this with the PMDA • No specific information on label requirements but PMDA recommends providing rationale for the setting of dosage and administration, which covers the label requirements
Analysis-Results-Metadata (optional).	Analysis-Results-Metadata (as part of define.xml v2.0 or as a separate PDF file).
Integrated Summary Safety (ISS)/Integrated Summary Efficacy (ISE)	
References: 3, 4 The same requirements of Analysis package stated in the above section applies to respective agencies.	References: 23, 24 Identical requirement
Software Programs	
Reference: 3 File names should only contain letters, numbers or hyphens, and no underscores or spaces.	Reference: 18 File names should only contain letters, numbers or hyphens, underscores, and no spaces.
All file names should be in lowercase.	All file names should be in lowercase.
Does not require any specific software for statistical analyses. Sponsor should consult with agency to confirm the choice of software and document this in the ADaM Data Reviewer's Guide.	Does not require any specific software for statistical analyses. Sponsor to document what software was used in both Attachment 8 and ADaM Data Reviewer's Guide.
Does not expect sponsor to submit executable programs, unless specifically requested by the agency.	Does not expect sponsor to submit executable programs.
No specific requirements for submitting standard company macros. Helpful in submitting analysis macros.	Prefers that macros be submitted when macros are used in programs submitted. If it is difficult to submit macros, specifications that describe algorithms can be documented in the ADaM Data Reviewer's Guide.
Files Types Accepted	
Reference: 14 CSV, XLS, XLSX for non-patient data	Reference: 18 CSV, XLS, XLSX acceptable (no specific rule defined in regulatory documents)
PDF	Identical requirement
XPT	Identical requirement
XML, XSL	Identical requirement
Programs in txt (ASCII)	Programs in .sas or software extension The following files can be submitted in the cp folder in the eCTD backbone: • ASCII Format Data Files • Phoenix Projects (*.phxproj) • WinNonlin Files (*.pmo, *.pwo)
Regulatory Documents	
Providing Regulatory Submissions in Electronic Format – Standardized Study Data ² Study Data Technical Conformance Guide ³	Basic Principles on Electronic Submission of Study Data for New Drug Applications ¹⁷ Technical Conformance Guide on Electronic Study Data Submissions ¹⁸
FDA Data Standards Catalog ⁴	PMDA Data Standards Catalog ¹⁹
Business Rules ⁵	No Business Rules
Validator Rules ⁶	Study Data Validation Rules ²⁰
FDA Technical Rejection Criteria for Study Data ⁶	Study Data Validation Rules ²⁰
Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions ⁷ Bioresearch Monitoring Technical Conformance Guide ⁸	No information
No information	Notification on Practical Operations of Electronic Study Data Submissions ²¹
No information	Question and Answer Guide Regarding 'Basic Principles on Electronic Submission of Study Data for New Drug Applications' ²² Question and Answer Guide Regarding 'Notification on Practical Operations of Electronic Study Data Submissions' ²³
No information	FAQs on Electronic Study Data Submission (Excerpt) ²⁴
Portable Document Format (PDF) Specifications ¹⁴	Electronic Common Technical Document Specification ²⁷

Table 3. Dataset and Variable Requirement Differences

FDA	PMDA
References: 3	Reference: 18
Datasets must be submitted using the SAS Transport Files v5 format.	Identical requirement
Dataset names (maximum 8 characters) should only contain lowercase letters, numbers, and must start with a letter.	Identical requirement
No other symbols or special characters should be included in variable and dataset names.	Special characters can only use low line '_'
For legacy studies on/before 17-Dec-2016, it is permissible to use the underscore character '_' in variable names and dataset names.	Special characters can only use low line '_'
Variable names (maximum 8 characters) should only contain uppercase letters, numbers, and must start with a letter.	Identical requirement
Variable names require use of ASCII text codes.	ASCII alphanumeric text codes
The allotted length for each variable containing text is to be set to the maximum length needed by that variable.	SDTM datasets should be optimized for length due to the PMDA validation rule.
Variable labels (maximum 40 characters) and dataset labels (maximum 40 characters) can include ASCII text codes and punctuation characters but avoid: • Unbalanced apostrophe • Unbalanced single and double quotation marks • Unbalanced parentheses, braces, or brackets ('', '(', and '[') • '<' less-than sign and '>' greater-than sign	Submission of data in the SAS v5 transport file format is required for data submission on the PMDA. Therefore, the limitations of SAS v5 transport file format is applicable. The limitations are as follows: • Variable name: max 8 characters • Variable label, dataset label: max 40 characters • Variable length: max 200 characters
Dataset >5 GB must be split and both the split and the non-split versions of the datasets must be submitted. Non-split dataset remains in the main dataset folder and split dataset goes to the sub folder (/split) within the main folder.	Consult the PMDA beforehand if the size of a dataset file is 5 GB or greater.
Not applicable	If variables had been collected in Japanese text, then refer to PMDA TCG section 4.1.5, 'Handling of data written in Japanese text' for guidance.
Technical Conformance Guides	
Screen failures, when provided, should be included as a record in DM with the ARM, ARMCD, ACTARM, and ACTARMCD fields left blank. This convention is inconsistent with the SDTMIG v3.2 and earlier versions.	No such specific requirements for PMDA. However, P21 PMDA Rule has a note for this inconsistent (violation): Violation of SD002 (Required variables cannot be NULL, for any records) will be considered part of Rejection criteria, except for the following variables in DM domain that will be considered Errors: -ARMCD, ARM, ACTARMCD, and ACTARM.
For subjects who are randomized in a treatment group but not treated, the planned arm variables (ARM and ARMCD) should be populated, but actual treatment arm variables (ACTARM and ACTARMCD) should be left blank per TCG v4.2. This convention is inconsistent with SDTMIG.	No such specific recommendation. Refer to the above information from P21 PMDA Rule.

Table 4. Validation Rules

FDA	PMDA
References: 5, 6 Four rejection rules based on FDA technical rejection criteria. (Refer to FDA Technical Rejection Criteria.)	References: 20, 20a • Based on PMDA new validation rules: • 9 SDTM Rejects • 13 ADaM Rejects • 14 Define-XML Rejects
FDA uses and accepts latest P21 Enterprise version available.	P21 PMDA uses P21 Enterprise v3.0.5 to check compliance, which has compatibility with P21 community v2.1.3. PMDA to update to v4.0.2 from Feb 22, 2020. PMDA announced the dates of new validation rules and P21 Enterprise version: • Validation rules 1.0 support ends 31-Mar-2021 • Validation rules 2.0 requirement begins 01-Apr-2020 • Transition period for validation rule: 01-Apr-2020 to 31-Mar-2021 • PMDA to use P21 Enterprise 4.0.2 from 22-Feb-2020
REJECT	
• Rejects are reported as Errors in P21 tool. • The technical rejection criteria should be met before submission (not yet turned on).	• Rejects will cause the review to be suspended until corrections have been made • All rejects must be resolved before submission
ERROR	
• Errors that CAN be fixed SHOULD be fixed. • Errors that cannot be fixed should be documented and explained in the Data Reviewer's Guide with a clear rationale.	• Errors that CAN be fixed SHOULD be fixed. • Errors that cannot be fixed should be documented and explained in both the Data Reviewer's Guide and Attachment 8 with a clear rationale and explain them at the 'Consultation on Data Format' meeting. • Errors without any prior explanation will cause the review to be suspended until corrections have been made.
WARNING	
• Warnings that CAN be fixed SHOULD be fixed. • Warnings that cannot be fixed should be documented and explained in the Data Reviewer's Guide with a clear rationale.	• Warnings that CAN be fixed SHOULD be fixed. • PMDA does not require the explanation for warnings. • The reason for the violation may be requested separately from the perspective of the quality of the clinical study data.

Table 5. Formal Meetings During Drug Development Life Cycle

FDA	PMDA
Reference: 13 There are four different types of formal meetings (Type A, Type B, Type B [end of phase (EOP)], and Type C).	Reference: 24 Consultation on data format meeting is divided into two meetings: • Clinical trial consultation (eg, Pre-P1, Pre-P2, End of Phase 2, and Pre-NDA) • e-Data consultation meetings
• Technical questions as part of Type C meeting • Could also be part of Type B and Type B (EOP) meetings (eg, Pre-IND, End of Phase 2, Pre-NDA/Pre-BLA meeting)	Clinical trial consultation: • Sponsor needs to consult which study data/analysis will be submitted as part of the clinical trial consultation meeting. (Sponsors cannot consult this at e-data consultation meetings.) Three types of e-Data consultation meetings: • Consultation on preparation of submission of electronic study data for methods of storing data and/or submission • Consultation on data format of submission of electronic study data for validation results • Consultation on exemption of submission of electronic study data The Clinical trial and submission of electronic study data consultations meetings can be requested multiple times at any time during the drug development. Please refer to the FAQ1-5 for the details on consultation meetings at 'FAQs on Electronic Study Data Submission (Apr 2019)' document.

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References

All references are in the poster paper and in handouts.