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Effective Approach for ADaM Submission to FDA and PMDA

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ABSTRACT

Regulatory Authorities are continuously updating their submission requirements, like Food and Drug Administration (FDA) released the Study Data Technical Conformance Guide V4.6 in November 2020 and Pharmaceuticals and Medical Devices Agency (PMDA) revised the Technical Conformance Guide on Electronic Study (e-Study) Data Submissions in January 2019. Accordingly, CDISC Analysis Data Model Implementation Guide (ADaMIG) versions are being continuously evolved. Currently FDA is accepting the Analysis Data Model (ADaM) datasets as per ADaMIG V1.1 whereas PMDA requires as per V1.0. Hence, it is a challenge to adhere to the differences between the guidelines of these two agencies.

If any Sponsor needs to get approval for a Drug in both the US and Japan, then the Study data must be in compliance with both the regulatory requirements and CDISC standards. Currently, for clinical studies starting on or after Mar 15, 2019, the ADaM datasets are expected in compliance to ADaMIG V1.1 for e-submission to FDA. On the other hand, ADaM datasets are required in compliance to ADaMIG V1.0 to PMDA for applications being submitted on or after Apr 1, 2020. Here, the suggested approach is to analyze the difference between two regulators and accommodate requirements in such a way that creates one ADaM that is optimum for both agencies.

This paper provides some examples of ADaM Submission Package requirements such as w.r.t., the Standard catalog/Control Terminology/Required Documents like Analysis Results Metadata (ARM)/ Analysis Data Reviewer's Guide (ADRG) and Define file, and also the handling of Pinnacle 21 issues (Reject/Error/Warning).

INTRODUCTION

CDISC Compliance electronic data submission is mandatory in PMDA for applications being submitted on or after Apr 1, 2020. On the other hand, the FDA has requested e-data submission in CDISC format earlier for studies starting after Dec 17, 2016.

Currently, PMDA is using the CDISC Data Validation Rules V1.0 which is acceptable for application dates from Oct 1, 2016 to Mar 31, 2021, and version 2.0 will be acceptable for application dates from Apr 1, 2020.

The software that PMDA is using is Pinnacle 21 Enterprise 4.0.2, and the engine corresponding to the validation rules are as 1511.6 (Validation Rule Version 1.0) and 1810.3 (Validation Rule Version 2.0).

The PMDA Severity for ADaM Rules is classified as "Reject", "Error", and "Warning" which are defined as following:

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.

As per the Current PMDA Data Standards Catalog dated Nov 1, 2019, the clinical study ADaM datasets are expected to be in compliance to ADaMIG V1.0 starting from Oct 1, 2016. Hence, ADaM datasets must be validated by Pinnacle 21 tool against the validation check which are in line with ADaMIG V1.0 and any unavoidable errors should be well explained in the ADRG section 6 and discuss at e-data consultation meetings.

FDA released the Study Data Technical Conformance Guide V4.6 in November 2020 which provides the detailed instruction on Study Data Validation Traceability under Section 8.

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There are three kind of Validation Rules applied:

1. Standard Development Organizations (e.g., CDISC) provides rules that assess conformance to its published standards ADaMIG V1.1.
2. FDA Electronic Common Technical Document (eCTD) Technical Rejection Criteria for Study Data that assess conformance to the standards listed in the catalog.
3. FDA Business and Validator Rules to assess that the data support regulatory review and analysis.

As per the Current FDA Data Standards Catalog dated Mar 15, 2021, the clinical study ADaM datasets are expected to be in compliance to ADaMIG V1.1 starting from Mar 15, 2019. Hence, ADaM datasets must be validated by Pinnacle 21 tool against the validation check which are in line with ADaMIG V1.1 and any unavoidable errors/warnings should be well explained in the ADRG section 6.

The FDA Severity for ADaM Rules are also classified as “Reject”, “Error”, and “Warning”.

Reject: Based on FDA technical rejection criteria and must be fixed prior to submission.

Error & Warning: Should be documented and explained in Analysis Dataset Reviewers Guide Section 6.

ADAMIG VERSION 1.1 VS 1.0

Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Team developed the ADaMIG Version 1.0 in year 2009, and then in year 2016 released the version 1.1. The ADaMIG document specifies ADaM standard dataset structures and variables, including naming conventions. The FDA and PMDA made it mandatory to submit the clinical analysis datasets in compliance to ADaMIG. If a study data need to be submitted to FDA and PMDA both, then rather than creating two set of separate ADaM datasets in compliance to ADaMIG V1.1 and V1.0 respectively, it’s suggested to create one set of ADaM datasets which fulfills both the regulatory agency requirement. This approach should save time to get the study data submitted to both the agencies and hence in turn should shorten the drug review and approval process time.

KEY DIFFERENCES AND SUGGESTED APPROACH TO HANDLE

Below are the main differences between the two ADaMIG versions 1.1 and 1.0, and the suggested approach to handle those differences in such a way which should be acceptable by both the agencies.

1.Index Variable Names - ADaMIG version 1.0 allows the index 'y' to be replaced with integers from 1-9. This was expanded in ADaMIG version 1.1 to allow integers from 1-99. As this does not violate any rules/naming conventions for version 1.0, integers up to 99 can be used in both the IG versions.

Currently, Pinnacle 21 PMDA validation will flag this as an “Error” with message “Illegal variable name: y is not in [1-9] for SITEGRy(N)” against the Validation Rule ID AD0213.

Hence, an explanation should be added in ADRG for PMDA that mentions the IG differences, and should be consulted with PMDA.

2.One-to-One Codelist - PMDA has defined 1:1 as within a study. All AVISITN values must be the same for each unique value group of [PARAMCD, AVISIT] when PARAMCD and primary variable AVISIT are populated. For example, the code and decode of AVISIT/AVISITN must be the same throughout the study. This was clarified in ADaMIG version 1.1 that it must only be 1:1 within a parameter i.e. dataset level instead of within a study.

This is classified as an Error in PMDA validation, and as per IG V1.1 best practice would dictate that the mapping would be on-to-one within a study, but this is not an ADaM requirement.

Hence, should be kept one-to-one within a study.

3. Analysis Flag (ANLzzFL) Label - In ADaMIG version 1.0 label is 'Analysis Record Flag zz'. This was changed in ADaMIG version 1.1 to 'Analysis Flag zz'. There is no such validation rule for the ANLzzFL

label check in Pinnacle, hence it is suggested to use the label as per later version of IG, because there is separate variable for Record label flag e.g., ITTRFL Intent-To-Treat Record Level Flag. Also, Parameter and record level Numeric flags have been removed in ADaMIG v1.1 Table 3.3.8.2, but are still allowed to be used if required.

4. Analysis Range y Upper Limit - In ADaMIG version 1.0, AyHI was incorrectly classified as a text variable. It was corrected in ADaMIG version 1.1. All version must use numeric for this variable. As this variable is being used in deriving the R2AyHI which is equal to AVAL / AyHI. Likewise, for the Analysis Range y Lower Limit AyLI variable. There is no such validation rule to check this in Pinnacle.

5. Completers Record/Parameter-Level Flag - In ADaMIG version 1.0, this variable was COMPRFL/ COMPPFL. It should have matched the naming of the ADSL population flag variable which is COMPLFL. It was corrected to COMPLRFL/COMPLPFL in ADaMIG version 1.1 to make consistent with the subject-level population flag COMPLFL. Suggest to use the name defined in later IG version as there is no such validation rule to check this in Pinnacle.

6. PARAMN Data Type - In ADaMIG version 1.0, PARAMN is required to be an integer. In ADaMIG version 1.1, it is allowed to be integers and decimals. Suggest to keep it as integer which should meet both the agency requirements.

7. PARAMTYPE Parameter Type - PARAMTYP is permissible in both ADaMIG version 1.0 and 1.1 but is retired in ADaMIG version 1.2. Hence, suggest not be use this variable in any version of IG being used.

8.TRTP Planned Treatment's Core value - This is required in ADaMIG version 1.0 and must be equal to one of the values in TRTxxP. In ADaMIG version 1.1, TRTP is conditional and must match at least one of the character planned treatment variable in ADSL (e.g., TRTxxP, TRTSEQP, TRTxxPGy). But at least one treatment variable is required in BDS dataset, it may be subject-level or record-level treatment variables (e.g., TRTxxP, TRTP, TRTA).

Currently, Pinnacle 21 PMDA validation will flag this as an "Error" with message "Required Variable value is null" against the Validation Rule ID AD0196. Hence, suggest to keep the TRTP in BDS datasets.

9.Datapoint Traceability Variables SRCDOM - In ADaMIG version 1.0, the label is "Source Domain" and the values were the 2 letter SDTM dataset name. In ADaMIG version 1.1, the label was changed to "Source Data" and in addition to SDTM names, ADaM dataset names, value of RDOMAIN in SUPP—or SUPPQUAL may also be used. We recommend using the name defined in later IG version as there is no such validation rule to check this in Pinnacle.

10. New Variables Added in ADaMIG version 1.1 – There are 46 variables added in version 1.1, as they do not violate any rules/naming conventions for version 1.0, hence these variables can be used in all IG versions for the purpose defined in the ADaMIG if needed for analysis.

Range Related: ANRHIC, ANRLOC, AyHIC, AyIND, AyLOC, ByIND;

Category Related: AVALCAyN, BASECAyN, CHGCATyN; Sub period Related: ASPER, ASPERC, ASPREDT, ASPREDTF, ASPREDTM, ASPRETM, ASPRETMF, ASPRSDT, ASPRSDTF, ASPRSDTM, ASPRSTM, ASPRSTMF; Dose Related: DOSCUMA, DOSCUMP, DOSEA, DOSEP, DOSEU; Criterion Related: MCRITy, MCRITyML, MCRITyMN, PCHGCAyN; Phase Related: PHEDT, PHEDTF, PHEDTM, PHETM, PHETMF, PHSDT, PHSDTF, PHSDTM, PHSTM, PHSTMF; Date Related: STARTDTF, STARTDTM, STARTTMF; Others: CNSDTDSC, EVNTDESC and ASEQ.

In general, it is advised to follow the later ADaMIG version 1.1 if it fits the requirement of both the regulatory agencies but in case of any discrepancy the priority should be given to the severity of P21 issue as shown in below examples. As per PMDA conformance, check against IG V1.0 the severity of P21 issue is higher than FDA conformance check against IG V1.1; hence, PMDA validation rule should be given preference which should be okay from FDA perspective because these issues are found in FDA checks as well but with missing Severity.

Pinnacle 21 ID	Machine-Testable Failure Criteria	PMDA Severity	FDA Severity	Recommendation
AD0005	A variable with a suffix of FL has a value that is not Y, N or null	Reject	NA	Follow as per PMDA
AD0176	ABLFL value is not Y or null	Reject	NA	Follow as per PMDA
CT2001	Variable value not found in non-extensible codelist, e.g., AESER, COUNTRY,SEX etc.	Reject	NA	Follow as per PMDA
AD0109	Within a study, for given value of PARAMCD, there is more than one value of AVISITN for a given value of AVISIT	Error	NA	Follow as per PMDA

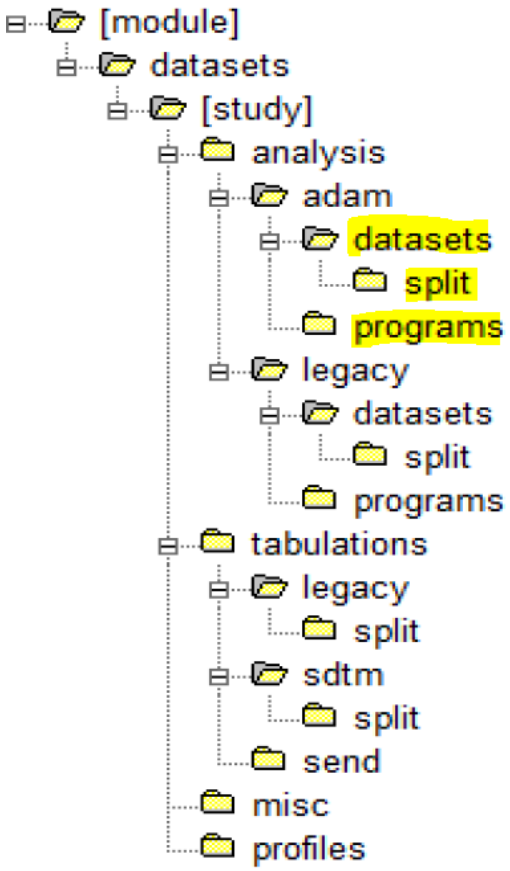
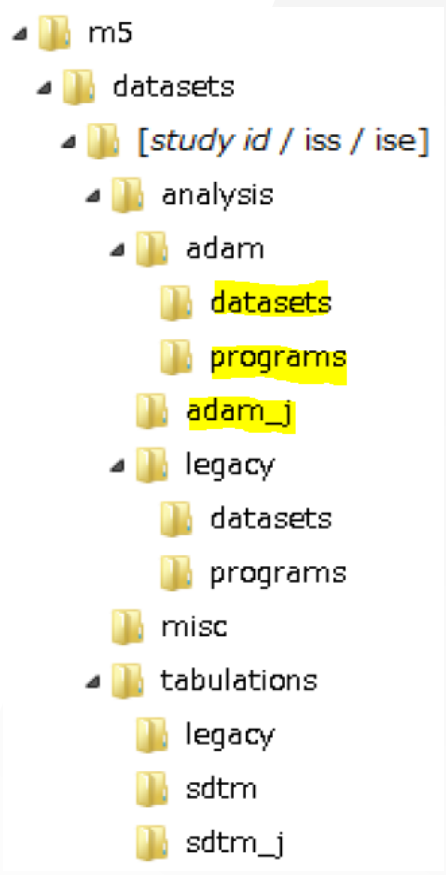
KEY POINTS TO CONSIDER

There are specific Guidance Documents provided by regulatory agencies like Data Standards Catalog, Study Data Technical Conformance Guide, Validation Rules etc. which are listed below and must be followed by Pharma Companies for successful e-submission of study data.

There is one Form 4061 provided by FDA, which is a Self-check worksheet for Study Data Preparation. This form is designed to help prepare newly submitted study data to FDA, i.e., studies for which no files have been previously submitted and is not required for submissions.

Likewise, there is one document “FAQs on Electronic Study Data Submission (Excerpt)” provided by PMDA in Apr 2019, which provides guidance on new drug review and consultation and relationship between electronic submission data and eCTD. Also, there is one supporting document Attachment 8 for consultation on Data Format of Submission of Electronic Study Data, which contains details of planned should be shared with PMDA prior to the meeting.

FDA	PMDA
Standards for clinical analysis datasets	
• Data Standards Catalog v.7.0 (15-Mar-2021) • Study Data Technical Conformance Guide V 4.6 (Nov-2020) • Technical Rejection Criteria for Study Data (Revised 22-Jan-2019) • CDISC: ADaM v2.1, ADaMIG v1.1 • Sample eCTD Submission Validation Process	• Data Standards Catalog (01-Nov-2019) • Technical Conformance Guide on e-Study Data Submissions (24-Jan-2019) • Study Data Validation Rules (27-Sep-2019) • CDISC: ADaM v2.1, ADaMIG v1.0 • Consultation Meeting - Study Data Submission, Supporting Document Attachment 8 (Optional)
ADaM Submission Package	
• Datasets in .xpt files • Programs and macros in ASCII text format, executable extension not to be used • Define.xml v2.0/2.1 and/or pdf files (optional) • ADRG (filename: adrg.pdf) • ARM (optional)	• Datasets in .xpt files • Programs and macros in .sas files • Define.xml v1.0/v2.0 and/or pdf files (optional) • ADRG (analysis-data-reviewers-guide.pdf) • ARM Specification v1.0 for Define-XML v2.0 is required to support key efficacy and safety
Datasets Specific Requirements	
• Name - Maximum up to 8 characters • Name - Contain lowercase letters, numbers, Start with a letter	• Name - Maximum up to 32 characters • Name - Contain lowercase letters and numbers • Name - underscore and hyphen is permitted

• Name - underscore allowed for legacy studies • Size - Dataset > 5 Gigabyte (GB) to be split • Both split/non-split datasets must be submitted • Define.xml must link to the non-split datasets • Legacy datasets should be submitted if analyzed	• Size - Dataset > 5 GB - to be consulted • No requirement to split datasets • Notice the PMDA Gateway throws errors for xpt files with hyphens • Legacy datasets should be submitted if analyzed
eCTD Folder Structure for Study Datasets	
	

As per eCTD folder structure shown above, the Folder [Module] should be named as “m5” for clinical study data submission, and Folder [study] should be named with study identifier or analysis being performed (e.g., study123, iss, ise). Other folders like “datasets”, “analysis”, “adam” at level 2,4, and 5 respectively should not contain any file at this level. The highlighted folder “datasets” at level 6 should contain the ADaM datasets as .xpt files and place the split ADaM datasets if any under the highlighted subfolder “split” at level 7. The Programs for ADaM datasets, tables, figures should be kept under the highlighted folder “programs” at level 6. In case data is collected in Japanese then Japanese datasets should be kept under the highlighted folder “adam_j” at level 5. The documents like define.xml, adrg.pdf should be kept at level 6 under the “datasets” folder. Likewise, the “tabulation” folder is keep SDTM datasets and “profiles” folder for patient profiles, and the “misc” folder at level 4 is to keep miscellaneous datasets that don’t qualify as analysis, profile or tabulation datasets.

There is a Sample eCTD submission process set by FDA to assist sponsors and applicants who have not previously submitted an eCTD study data and have New Drug Application (NDA), Investigational New

Drug (IND), Biologics License Application (BLA) or Abbreviated New Drug Application (ANDA) number and plan to submit an actual submission to FDA within 12 months of sample request, where as in PMDA there is a provision to set up pre-consultation meetings.

For a common submission package, the Dataset names should be up to 8 Characters and contains only lowercase letters, and numbers. If any dataset size > 5 GB, then split datasets should be created and rules splitting the dataset should be noted in ADRG. The ARM document should be created for both the agencies with different IG and P21 tool versions used, split dataset details if created should be noted in ADRG for FDA. Split datasets should be submitted under the "split" folder in eCTD folder structure.
In case the data is collected in Japanese, then Japanese dataset and a corresponding alphanumeric dataset containing the ASCII characters should be created, and the Japanese datasets should have submitted under "adam_j" folder designated in eCTD folder structure.

CONCLUSION

Based on the key requirements from regulatory agencies, and CDISC standards as stated above, the aim is to create the one common ADaM datasets which meets the requirements for both FDA and PMDA as much as possible to reduce overall submission time. In order to achieve this the Pinnacle 21 should be run as early as possible, and the severity of P21 conformance rule should be given priority in order as Reject, Error and Warning.

Issues resulting in P21 findings as Reject must be fixed, whereas unavoidable Errors if any should be noted in ADRG for FDA and noted in Appendix 8 and discussed with PMDA in consultation meetings, and unavoidable Warnings if any should be noted in ADRG for FDA and PMDA both though it's not required for PMDA. In case if anything is unclear then it should be discussed with regulatory agency during the consultation/regular meeting prior to submission.

REFERENCES

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