Paper PP11

Does One Size Fit All?

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ABSTRACT

Submitting data to the Health Authorities is a critical part of our business to obtain approval for our medicines. Currently, three agencies, namely FDA (USA), PMDA (Japan), and NMPA (China), require clinical trial data for filing. Preparing one set of data packages will not satisfy all agencies' needs. i.e., Variations **DO** exist. Hence, understanding the agency-specific requirements could help us to submit quality data packages to facilitate efficient review to get our medicines approved faster and get them to the patients sooner. This poster demonstrates these variations across these agencies with respect to the submission requirements and recommendations. This is based on our interpretation of the data requirements across the agencies. It also highlights the importance of being aware of these variations to help adequately plan time, resources, and contents when considering filing to multiple agencies in parallel.

INTRODUCTION

The three agencies – **FDA** (United States Food and Drug Administration), **PMDA** (Pharmaceuticals and Medical Devices Agency), and **NMPA** (National Medical Products Administration) require submission of clinical trial data as a part of the New Drug Application (NDA), Biologics License Application (BLA) or label extension of a marketed products. Can we create one eSubmission (eSub) data package and submit it to the different agencies **without making any modifications?** Ask yourself, "**Does One Size Fit All?"**

This paper attempts to help show the submission requirements and highlights the variations across the agencies compared to the FDA requirements. It also shares Roche-Genentech's internal approach while submitting data to different agencies.

HIGH-LEVEL OVERVIEW

The table below provides high-level similarities and distinctions between the FDA, PMDA, and NMPA.

 **FDA (USA)** **CDISC Mandate:** **All studies started after December 17, 2016**	 **PMDA (Japan)** **CDISC Mandate:** **All studies submitted after April 1, 2020**	 **NMPA (China)** **CDISC Recommended+:** **All studies submitted after October 1, 2020**
Tabulation / SDTM data	**Tabulation / SDTM data**	**Tabulation / SDTM data**
SDTM annotated Case Report Form (acrf.pdf)	**SDTM annotated Case Report Form (acrf.pdf)**	**SDTM annotated Case Report Form (acrf.pdf)** • Chinese version of CRF, current practice is to have SDTM dataset/variable names remain in English
SDTM Define file (define.xml)	**SDTM Define file (define.xml)**	**SDTM Define file (define.xml) or PDF (definel.pdf)** • Translation required : dataset label, variable label, codelists & derivations
SDTM SAS xpt's (*.xpt, split if >5GB) • Conformance to **FDA validation rules**	**SDTM SAS xpt's (*.xpt, No split criteria for file size but should consult with PMDA if datasets are >10GB)** • Conformance to **PMDA validation rules** • **WHODrug must be used** for drug coding • **SI units should be used to standardized results of laboratory test (e.g. g/L → mol/L)**	**SDTM SAS xpt's (*.xpt, split if >4GB for eCTD)** • Conformance to **NMPA (same as FDA) validation rules** • **Translation required – dataset & variable labels, text within variables, e.g. WHODrug, MedDRA terms** • **UTF8, and Chinese character encoding**
SDTM Reviewers Guide (csdrg.pdf) • Explanation of the validation results against **FDA validation rules (Errors only)** • **No Rejects acceptable**	**SDTM Reviewers Guide (csdrg.pdf or study-data-reviewers-guide.pdf)** • Explanation of the validation results against **PMDA validation rules (Errors only)** • **No Rejects acceptable** • **Coefficients required for conversion from original units to SI units**	**SDTM Reviewers Guide (csdrg.pdf)** • Explanation of the validation results against **NMPA validation rules [Errors only]** • **Translation required: whole document**
Analysis / ADaM data	**Analysis / ADaM data**	**Analysis / ADaM data**
ADaM Define file (define.xml)	**ADaM Define file (define.xml)**	**ADaM Define file (define.xml) or PDF (definea.pdf)** • **Translation required : dataset label, variable label, codelists & derivations**
ADaM SAS xpt's (*.xpt, split if >5GB) • Conformance to **FDA validation rules**	**ADaM SAS xpt's (*.xpt, No split criteria for file size but should consult with PMDA if datasets are >10GB)** • Conformance to **PMDA validation rules**	**ADaM SAS xpt's (*.xpt, split if >4GB for eCTD)** • **Conformance to NMPA (same as FDA) validation rules.** • **Translation required - dataset/variable labels, text within variables (WHODrug & MedDRA terms) codelists and derivations**
Software (i.e., SAS, R) programs [*.txt] • Readable format, executable not necessary **Note:** At Roche-Genentech we use **pkglite** R package	**Software (i.e., SAS, R) programs (*.txt, *.sas)** • (e.g. SAS, R) - Readable format, executable not necessary	**Software (i.e., SAS, R) programs (*.txt)** • Readable format, **(and Executable R code preferred)** **Note**: At Roche-Genentech we **pkglite** R package
ADaM Reviewers Guide (adrg.pdf) • Explanation of the validation results against **FDA validation rules (Errors only)** • **No Rejects acceptable**	**ADaM Reviewers Guide (adrg.pdf or analysis-data-reviewers-guide.pdf)** • Explanation of the validation results against **PMDA validation rules (Errors only)** • **No Rejects acceptable**	**ADaM Reviewers Guide (adrg.pdf)** • Explanation of the validation results against **NMPA validation rules (Errors only)** • **No Rejects acceptable** • **Translation required: whole document**
Analysis Results Metadata (ARM) - Not required	**Analysis Results Metadata (ARM) - Strongly recommended**	**Analysis Results Metadata (ARM) - Not required**
		Blue and Green text indicates variations ***+ Roche-Genentech's current approach***

CDISC FORMAT MANDATE FOR REGULATORY SUBMISSION

The FDA requires any study that started* after 17-DEC-2016 to be submitted in CDISC complaint format. **[** Study start is being the earliest informed consent date***]**.**

The PMDA requires CDISC complaint submission for any study submitted after 01-APR-2020, regardless of when the study started.

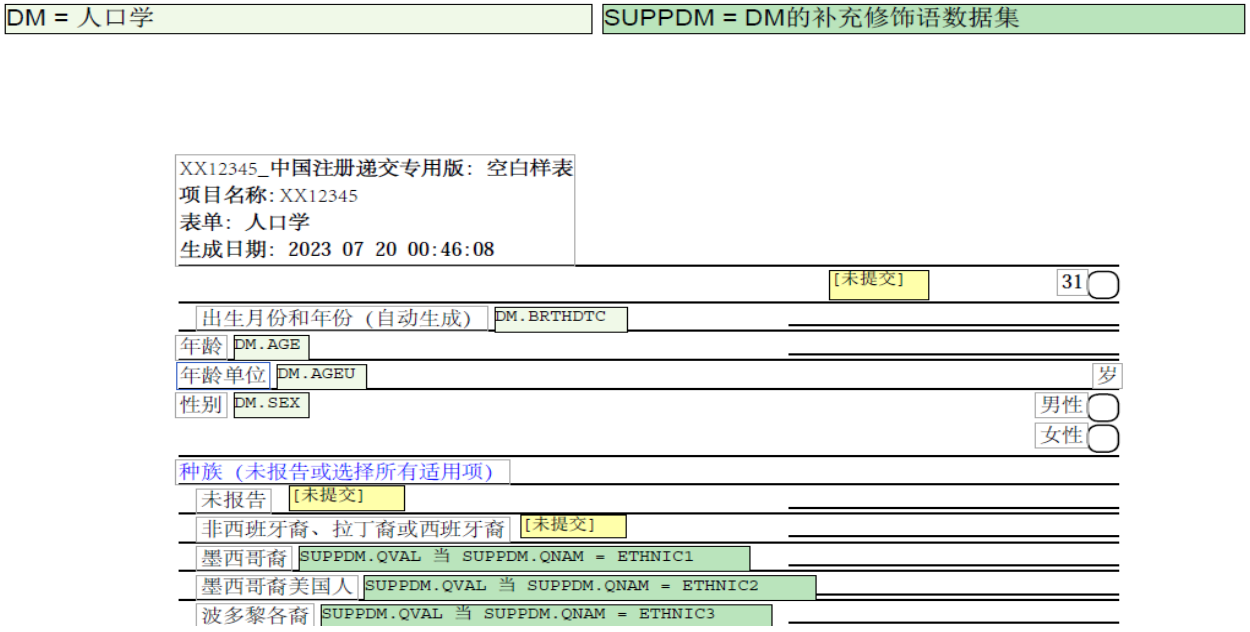
The NMPA has not mandated the use of CDISC standards but strongly recommends it. The NMPA requires submission in electronic format and translation to Chinese for the studies filled after 01-OCT-2020.

SUBMISSION COMPONENTS / DELIVERABLES

CDISC deliverables consist of the SDTM and ADaM packages. The SDTM package includes aCRF, Define.xml, SDTM datasets in XPT format, and cSDRG. The ADaM deliverables contain Define.xml, ADaM XPTs, ADRG, and Readable code used to create ADaM datasets and primary and secondary analysis results. The similarities and the differences for each Agency are discussed under each subsection.

ANNOTATED CASE REPORT FORM (aCRF)

While the FDA and PMDA both require an English version of aCRF, the NMPA requires translation of all fields on the CRF except for dataset and variable names, as shown in the below screenshot.

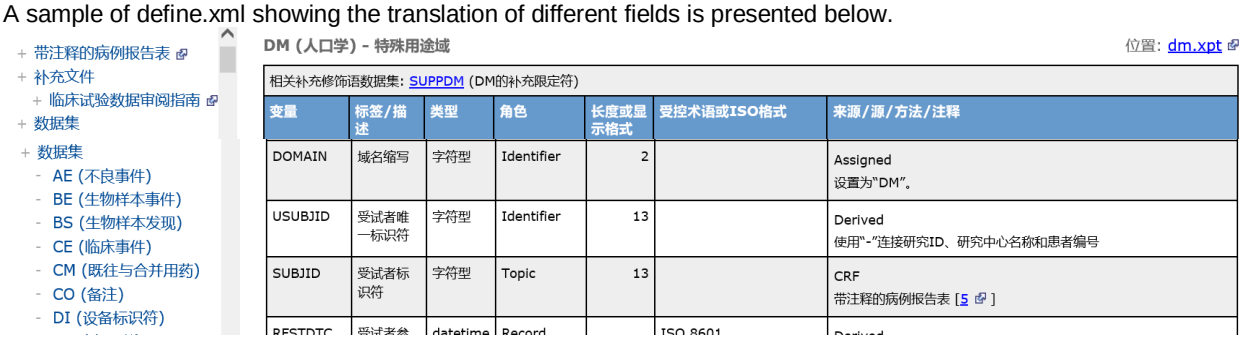


DEFINE FILE (DEFINE.XML)

Both the **FDA** and the **PMDA** require define.xml explaining the derivation rules for variables within datasets that are included in a submission.

The **NMPA** accepts 'define' files in both **'.xml'** (define.**xml**) and **'.pdf'** (definel.**pdf**) formats but requires translation of dataset and variable labels, code lists, and derivations.

A sample of define.xml showing the translation of different fields is presented below.



SAS DATASETS (.XPT)

All Agencies require SDTM and ADaM datasets to be submitted in SAS Transport **(.XPT)** format. While the FDA and PMDA require **V5,** the NMPA accepts **V5** or higher versions. Nevertheless, some variations exist, and the agency-specific dataset requirements in a submission are described below.

FDA: SDTM.DM and ADaM.ADSL must be included in the CDISC submission. In addition, the SDTM.TS domain must be submitted to the FDA regardless of the study start date. If the dataset(s) size is **>5 GB**, they need to be **split**, and both split and unsplit datasets need to be submitted.

PMDA: Similar to the FDA, SDTM.DM and ADaM.ADSL must be included in the submission. The PMDA has not rolled out explicit **split** criteria; however, it is recommended to consult with the PMDA if the dataset(s) is **>10 GB**. In addition, WHODrug must be used, and SI units should be used to represent standardized results for laboratory tests.

NMPA: SDTM.DM and ADaM.ADSL are required for NMPA submissions. At Roche-Genentech, we follow the FDA's requirements and submit the TS domain. The NMPA requires **splitting** dataset(s) if the size is **>4 GB** and submitting only split datasets.

REVIEWER'S GUIDE (RG)

The Reviewer's Guides for both SDTM and ADaM are required for all agencies.

Each Agency has its own rules and validation engine to check the data and submission compliance. The findings and severity of the issues identified could vary across the Agencies. Findings should be clearly documented within RGs. Moreover, if there is a split dataset in a submission, the detailed rules of splitting should be included in the Reviewer's guide to aid the reviewers in recreating a single dataset.

There is a slight variation in the file naming convention of RGs as follows:

Reviewer's Guide	FDA	PMDA	NMPA
SDTM Reviewer's Guide	csdrg.pdf	csdrg.pdf **or** study-data-reviewers-guide.pdf	csdrg.pdf
ADaM Reviewer's Guide	adrg.pdf	adrg.pdf **or** analysis-data-reviewers-guide.pdf	adrg.pdf

SOFTWARE PROGRAMS

FDA: The FDA requires readable code to be submitted in ASCII text **(.txt)** format for all programs used to create ADaM datasets and primary and secondary efficacy results. Hence, the **'.sas/. R'** extension files should be changed to **'.txt'** format. At Roche-Genentech, we use the ***pkglite*** package to convert R programs to **'.txt'** format and vice versa.

PMDA: It accepts both SAS and R programs; however, the file extensions of **'.sas/.R'** should not be changed.

NMPA: The NMPA requires readable SAS code in **'.txt'** format. If the sponsor chooses to submit R programs, executable R codes are preferred.

At Roche-Genentech, if we plan to submit the R programs, our approach is to have a prior discussion and agreement with the appropriate Agency.

ANALYSIS RESULT METADATA (ARM)

ARM is optional for both the FDA and the NMPA, whereas the PMDA strongly recommends submitting ARM for primary and secondary efficacy analyses and key safety analyses.

CONCLUSION

CDISC data standard is mandated by both the FDA and PMDA. The mandate is applied based on the study **start date** for the FDA (after **17-DEC-2016**) and the **submission date** for PMDA (submitted after **01-APR-2020**).

For the NMPA, CDISC standard is not yet mandated but recommended. It requires submission in electronic format and translation to Chinese for the studies submitted after **01-OCT-2020**. At Roche-Genentech, we follow the FDA approach for the NMPA submissions.

Each of the three agencies adheres to distinct conformance rules and validation engines, with variations in the severity of compliance issues. What may be considered an **'Error'** for one Agency could be deemed a **'Reject'** by others.

While the FDA and PMDA submission packages are in English, the NMPA has additional translation requirements.

Given all of the above-described variations, one data package without modification does not satisfy all the Agencies' requirements. While the FDA package can be used as a starting point, Agency-specific updates need to be made. Having an understanding of the similarities and differences across the agencies could help in the early planning of time and resources and setting priorities.

ACRONYMS

aCRF	Annotated Case Report Form
ADaM	Analysis Data Module
ADRG	Analysis Data Reviewer's Guide
ADSL	Subject-Level Analysis Dataset
ARM	Analysis Result Metadata
BLA	Biologics License Application
CDISC	Clinical Data Interchange Standard Consortium
cSDRG	Clinical Study Data Reviewer's Guide
DM	Demographics
eCTD	Electronic Common Technical Document
eSub	eSubmission
FDA	U.S. Food and Drug Administration
GB	Giga Bite
NDA	New Drug Application
NMPA	National Medical Products Administration
PMDA	Pharmaceuticals and Medical Devices Agency
RG	Reviewer's Guide
SDTM	Study Data Tabulation Module
TS	Trial Summary
V	Version

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