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Japanese Electronic Study Data Submission in CDISC Formats

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ABSTRACT

Pharmaceuticals and Medical Devices Agency (PMDA) has announced that an electronic study data (e-study data) submission will be possible starting from October 2016 with a 3.5 years transitional period. The requirement of PMDA is similar to that of Food and Drug Administration (FDA) e-study data submission. However, there will be some differences which sponsors should understand precisely and also consider efficient processes for e-study data submission of a new drug application (NDA) to meet both PMDA and FDA requirements by collaborating globally. The goal of this paper is to facilitate global statistical programmers as well as statisticians to comprehend new requirements of PMDA to ensure efficient and successful Japanese e-study data submission in a timely manner.

INTRODUCTION

This paper describes a comprehensive process for the e-study data submission, mainly focusing on the differences between PMDA and FDA requirements, and also provides tips based on recent communication with PMDA. In addition, to provide a further understanding of Japanese e-study data submission, comparison with current process of NDA in Japan is summarized.

OVERVIEW OF JAPANESE E-STUDY DATA SUBMISSION

The initiation date of e-study data submission is October 1, 2016. There is a transitional period of 3.5 years from October 1, 2016 to March 31, 2020. Submission of standardized e-study data will be mandatory beginning April 1, 2020. On the other hand FDA will request standardized e-study data for studies which start after December 17, 2016. The difference is not only for target date but also for the status whether it is a study initiation for FDA or submission for PMDA.

Before starting preparation of e-study data submission, sponsors should refer below notifications and guidance published by Ministry of Health, Labor and Welfare (MHLW) / PMDA.

- "Basic Principles on Electronic Submission of Study Data for New Drug Applications", published on June 20, 2014, by MHLW.

  The first official announcement that MHLW / PMDA will require e-study data for NDA.

- "Notification on Practical Operations of Electronic Study Data Submissions", published on April 27, 2015, by MHLW.

  This document mainly describes practical issues and announces start date of e-study data submission for NDA.

- "Technical Conformance Guide on Electronic Study Data Submissions", published on April 27, 2015, by PMDA. Amendment version published on July 2016.

- Other related document / guidance such as Data Standard Catalog, Validation rules, FAQ document and web page and PMDA gateway manual. (in Japanese only)

In principle, clinical study data must be compliant to Clinical Data Interchange Standards Consortium (CDISC) standard format. No other data formats will be accepted by PMDA. Conformity of the e-study data submission data to the CDISC standards must be ensured under the responsibility of sponsors. The main targeted studies in e-study data submission are listed below.

- Data on results from all phase 2 and phase 3 studies (including long-term studies) that are generally regarded as major evidence for evaluation of efficacy, safety, and dosage and administration.

- For study results from phase 1 studies and clinical pharmacology studies, results from studies listed below are required to be electronically submitted.
    - Phase I studies of oncology drugs
    - Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g. in case of a strategy of global clinical trials and bridging studies)
    - QT/QTc studies based on ICH E14 guideline

Phase 1 and clinical pharmacology studies other than listed above are requested only if PMDA deems necessary. Further detail of targeted studies and e-study data are summarized in "Question and Answer Guide Regarding Notification on Practical Operations of Electronic Study Data Submissions", published by MHLW on April 2015, with relevant data format for clinical study data and analysis data.

PMDA TRANSITIONAL PERIOD

As mentioned above, from October 1, 2016 to March 31, 2020 will be transitional period. During this period, e-study data submission is not mandatory and sponsors can submit e-study data per study level, not submission level. i.e., only one study can be submitted electronically in clinical data package. Note that for such a partial e-study data submission, an application will be reviewed using the conventional review process.

E-STUDY DATA TO BE SUBMITTED TO PMDA

Here is the list of required CDISC compliant study data and related documents.

- Study Data Tabulation Model (SDTM) dataset
- Analysis Data Model (ADaM) dataset
- Define-XML for SDTM dataset
- Define-XML for ADaM dataset with Analysis Results Metadata (ARM)
- Annotated Case Report Form (aCRF)
- Study Data Reviewer's Guide (SDRG)
- Analysis Data Reviewer's Guide (ADRG)
- Statistical Analysis System (SAS®) programs for creating ADaM dataset and analyses

The point of emphasis here is that sponsors need not to submit all of ADaM datasets. The targeted ADaM dataset are for primary efficacy analysis and secondary efficacy analyses (secondary analyses of primary variable and analyses of key secondary variables), primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety. The scope of SAS programs to be submitted is the same, not all of programs for entire e-study data submission are required. Sponsors need not to adjust programs to be executed in the PMDA environment.

KEY DIFFERENCES BETWEEN PMDA AND FDA FOR E-STUDY DATA SUBMISSION

The important differences for Japanese e-study data submission compared to FDA are listed in the below table. Sponsors must be especially careful about CDISC compliance checks defined by PMDA. Although both PMDA and FDA use Pinnacle 21 validation tool, acceptance level is different. PMDA has its own specific "Reject" rules for SDTM, ADaM datasets and Define-XML. Because of that, PMDA's requirements of e-study data submission will make impact to e-study data submission preparation process which is suitable for only FDA.

Table 1. Key differences between PMDA and FDA

Differences	PMDA	FDA
Initiation date of e-study data submission in NDA	For studies that make a new drug application after October 1, 2016 with a 3.5 years transitional period. To be mandatory after April 1, 2020.	For studies that start after December 17, 2016
CDISC compliance check by Pinnacle 21 with specific criteria	SDTM, ADaM, Define-XML with specific "Reject" criteria.	SDTM, Standard for Exchange of Nonclinical Data (SEND)
Communication with health authorities	Consultation on data format of submission of electronic study data	Communicate by using Study data standardization Plan (SDSP)
Legacy data conversion	Non-CDISC compliant data won't be accepted. Requirements for e-study data are same as other CDISC compliant study.	"Legacy data conversion plan and report" should be specified in reviewers' guidance.
ARM	Define-XML should preferably include ARM but it is not mandatory.	Not required (as of September, 2016).
Clinical pharmacology (CP) studies	Specific documents are required in addition to e-study data.	Not clearly described in Study Data Technical Conformance Guide.

PMDA GATEWAY AND CDISC COMPLIANCE CHECK BY USING PINNACE 21 VALIDATOR TOOL

One of the biggest points of PMDA specific requirements in e-study data submission is to use gateway for NDA. Application form, electronic Common Technical Document (eCTD), e-study data and other relevant files will be submitted via the gateway. As user manual of gateway and instruction video have been provided by PMDA web site in Japanese, here an overview is provided.

First, sponsors create an advance notice which notifies planned date and time of an application and each e-study data about 1 - 5 weeks before NDA filing. Then "study data profile" needs to be entered on the gateway portal site, after that sponsors submit e-study data via gateway. Information of this study data profile is listed as below.

- List of Folders / Files
- Study ID
- Study Data ID (UUID)
- Operation (new, replace, and delete)
- Study Data Category (Single study that contains CDISC conformant data, Integrated study that contains CDISC compliant data, and study that does not contain CDISC data)
- Analysis type
    - "STS" for Standard Two Stage Approach
    - "POP" for Population Analysis
    - "PBPK" for Physiologically Pharmacokinetic Model Analysis
    - "Other" for CP study other than STS, POP and PBPK
    - "Non-CP" for non-CP study
- Description for CP study
- Version of SDTM / ADaM controlled terminology
- Japanese character code if applicable

Note that total size of e-study data will be different between PMDA and FDA. FDA describes that the maximum size of an individual dataset size is 5 gigabytes and it needs to be split if it is greater than 5 gigabytes. On the other hand PMDA doesn't specify maximum individual dataset size but total size of e-study data per one operation in gateway is 40 gigabytes. If individual dataset size is greater than 5 gigabytes, sponsors should notify PMDA of actual data size before submission. Other maximum data size is also described in PMDA FAQ page.

If PMDA identifies major errors in e-study data, then an application review will not be initiated until those errors are corrected. Validation for e-study data in CDISC formats is executed once PMDA received them via gateway, and PMDA checks e-study data by the Pinnacle 21 validator (enterprise version) with PMDA specific validation rule as below. That rule applies to SDTM, ADaM dataset and Define-XML and it has already been published on the PMDA website.

Table 2. PMDA validation criteria

Validation criteria	Rule
Reject	Rules which, if violated, will cause the review to be suspended until corrections have been made. Very basic rules such as the presence/absence of necessary datasets for each clinical study.
Error	Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made. In many cases, these rules are clearly stated in each standard and implementation guide, and if violated, sponsors should consult to the PMDA before the application about a reason for the violation and a reason why it is not possible to correct it. These rules must also be explained in the data guide.
Warning	Rules which, even when violated, will not necessarily require any explanation.

It is the most important to avoid errors of 'Reject' because if any of those errors are detected, an application review doesn't start until these errors are corrected.

COMMUNICATION WITH PMDA

There will be several meetings with PMDA for e-study data submission. The "consultation on data format of the submission of electronic study data" is newly settled to discuss about e-study data "formats". During this consultation, it depends on study situation though, sponsors can discuss on,

- Pinnacle 21 validation issues which can't be fixed.

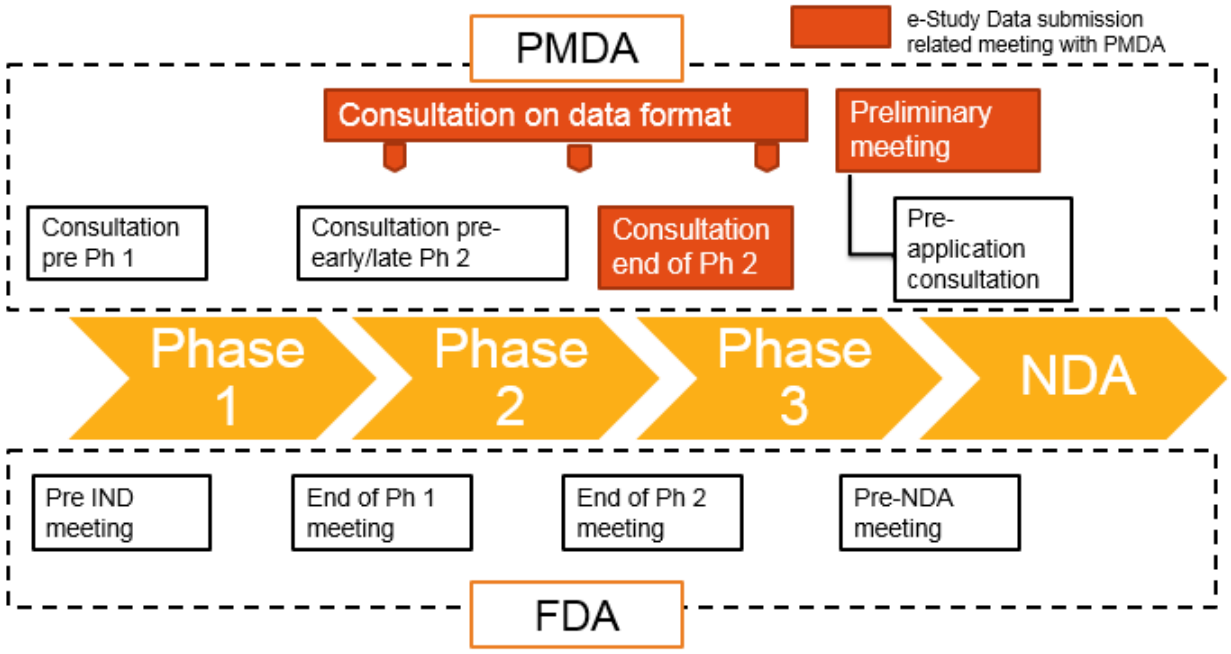
- Mapping issues from collected data formats to CDISC standards format, controlled terminology.
- Notify e-study data information such as
  - Custom SDTM domain to be submitted.
  - ADaM to be submitted.
  - SAS programs for ADaM and TFLs to be submitted.
  - TFLs to be implemented to ARM.
- Etc.

Note that discussion such as

- A scope of evaluation data in a clinical data package (Which clinical study is submitted electronically)
- What type of analyses to be submitted electronically as ADaM datasets, ARM
- What e-study data to be submitted for clinical pharmacology studies

is not in a scope of this consultation. Otherwise sponsors should use other existing clinical consultation such as End of Phase 2 consultation or other PMDA formal meetings.

Figure 1. PMDA consultation in NDA



In Figure 1, here you can see the general process for PMDA consultation in NDA. The most important thing here is to explain any validation issues categorized in “Error” on e-study data at this consultation. PMDA requests a meeting to share validation issues before NDA preliminary meeting.
At consultation on data format, sponsors have to provide e-study data information to be submitted to PMDA with the specific template, “Form 8” of implementation guideline for consultation. Form 8 is required to submit to PMDA prior to consultation to inform a summary of e-study data. It includes not only discussion point but also project/study information shown in below table. If sponsors decide to submit e-study data, final version of Form 8 has to be submitted at NDA preliminary meeting at the latest.

Table 3. Overview of Form 8

Contents of Form 8	Description
Basic information	Compound, product name, general name, drug form, dose regimen, ...

Contents of Form 8		Description
Clinical data package and overview of each clinical trial	Planned clinical study to be included in clinical submission package.	Describe all planned studies (both evaluation and reference data) regardless of the presence of electronic data.
	Detail information of clinical study submitting electronic study data	Study information (Protocol ID, target population, treatment group, efficacy and safety endpoint, number of patients per arm, ...)
Information of submitted clinical study, Integrated Summary of Efficacy (ISE) / Integrated Summary of Safety (ISS), CP study in CDISC format		• CDISC compliant status for SDTM and ADaM. E.g.) "Data collection was performed in CDASH format?", "Is ADaM created from SDTM?" • Data standards to be used. • File format • Total size of e-study data. • List of SDTM and ADaM dataset to be submitted and individual dataset description. • Pinnacle 21 validation result summary. • Etc.

LEGACY DATA CONVERSION

Legacy data conversion is one of major concerns to sponsors. How can sponsors overcome this time consuming and costly challenges? As of September 2016, PMDA provides no clear guideline for legacy data conversion whereas FDA suggests sponsors to provide legacy data conversion plan and report. However, PMDA requires that e-study data to be submitted must be formatted with CDISC standards in 'Basic Principles on Electronic Submission of Study Data for New Drug Applications' published in June, 2014. No simplified e-study data is referred by PMDA.

This means when sponsors decide to submit non CDISC compliant study data to PMDA,

1. Convert original source and analysis dataset to SDTM and ADaM dataset respectively. Because submission of SAS programs for ADaM dataset will be required, creating ADaM from SDTM dataset is more efficient than creating from original analysis dataset in terms of traceability.
2. Prepare aCRF, Define-XML, SDRG and ADRG.
3. Create SAS programs for analyses which can reproduce primary/key secondary efficacy analysis and key safety analysis in Clinical Summary Report (CSR).

One big challenge here is to draft new programs using converted data. If CSR has already been created by legacy data, programs need to be updated to use converted CDISC compliant data. As described previous section, not all of the programs will be required, therefore it is recommended to have an agreement on the scope of analyses for submission with PMDA at clinical consultation.

Furthermore, if discrepancies are found in results between converted data and legacy data, clarification should be explained in SDRG or ADRG as conversion issues.

ANALYSIS RESULTS METADATA (ARM)

ARM makes it possible for reviewers to trace a relationship efficiently among documentation, ADaM dataset and given analysis results. In the release of FDA study data technical conformance guide in March 2016, no clear requirements for ARM was provided by FDA. On the other hand, PMDA technical conformance guidance mentions 'the definition documents of the ADaM datasets should preferably include Analysis Results Metadata'. Even though ARM is not a mandatory requirement as of September 2016, PMDA strongly recommends to submit ARM. Although ARM is generally included as a part of Define-XML for ADaM datasets, PMDA allows sponsors to submit ARM in PDF format because PMDA considers content is more important than a format of ARM (i.e. PDF, XML, etc.).

For targeted analysis results defined in PMDA technical conformance guide are below.

- Main results of efficacy and safety
- Other results that provide rationales for setting of the dosage and administration.

CLINICAL PHARMACOLOGY (CP) STUDY

Electronic data of CP study or analysis needs to be submitted if it is important in clinical data package. Targeted CP study and analysis are listed in the below table.

Table 4. Target CP study and analysis

Content	Individual clinical study data	Efficacy and safety analysis	Pharmacokinetics (PK) or PK/PD analysis
Clinical studies where standard pharmacokinetic (PK) analysis was performed	SDTM	ADaM	ADaM is preferable, but other formats are acceptable
Population analysis (PPK)	May be submitted in formats other than CDISC standards		
Physiologically-based pharmacokinetic model analysis (PBPK)			

To submit non-CDISC compliant analysis dataset (i.e. non-ADaM dataset) for those PK/PD analysis, sponsors need to use the electronic data depending on software to be used for PK analysis. For example,

- Phoenix Projects (*.phxproj), WinNonlin file (*.pmo, *.pwo) for standard CP study
- Control and output files of NONMEM dataset for PPK
- Simcyp PE input and output files (XML formats) for PBPK

As other e-study data for CP study, firstly dataset definition file of non-CDISC compliant analysis dataset also needs to be submitted. It includes at least the variable names and the explanation of the variables to be submitted. This document is created in PDF format. Secondary, sponsors should submit 1) either analysis programs or programming specification which can specify analysis algorithm for PK parameter for standard PK analysis, 2) either programs for simulation or programming specification and procedure document for program execution (See example in PMDA technical guide appendix) for PPK. Those files also need to be part of electronic data.

In addition, to be created “Explanation of electronic data package on clinical pharmacology” by PMDA, sponsors need to provide study data profile to gateway as described in previous section.

SUGGESTION FOR SUCCESSFUL JAPANESE E-STUDY DATA SUBMISSION

EARLY COMMUNICATION WITH HEALTH AUTHORITIES AND CONSOLIDATE DATA STANDARDS INFORMATION WITHIN COMPOUND

One of the most important things in e-study data submission preparation is to define clinical data package for NDA as early as possible. For example, in Japanese e-study data submission, it is usually discussed on clinical data package in an end of phase 2 clinical consultation. Sometimes, clinical data package to PMDA is different from package to other health authorities. From that point of view, sponsors can estimate overall cost and resource for e-study data submission to cover all NDAs to various health authorities. Especially when legacy data is possibly to be included, we should consider conversion issues. Therefore PMDA consultation on data format should be taken place soon after clinical data package is decided.

Consolidating data standards is another important point because both FDA and PMDA keep updating data standard catalogs. It is essential for sponsors to be aware of accurate information of data standards for long term drug development. PMDA does not request SDSP but if sponsors consider a submission to both FDA and PMDA, SDSP will facilitate management of data standards within compound. However SDSP is currently specific document for FDA communication, thus it would be better to prepare other file which can specify each data standards, coding dictionary for data tracking purpose.

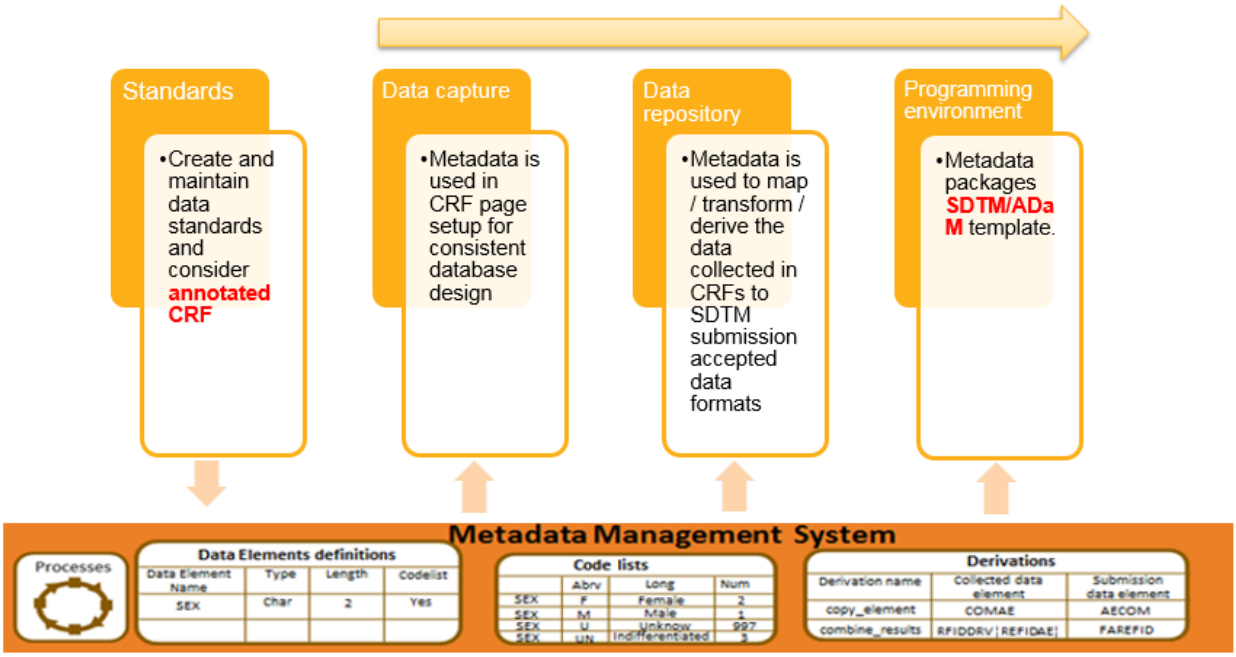
CREATING ONE CRT FOR PMDA AND FDA

Submission deliverables of e-study data are not so different between PMDA and FDA most likely. Therefore sponsors could consider creating only one CRT for both PMDA and FDA with meeting requirements of both health authorities.

What makes process simple? Standardization is one of the answers. In Novartis, Metadata Management System (MMS) helps to create standards. It will also support data traceability, consistency and quality within submission data package especially aCRF, SDTM and ADaM dataset. When a new standard is required for your study, several steps will be followed. Generally,

1. Generate example for a standard page by standard team.
2. Setup page model for SDTM annotation and reviewed.
3. Pages are endorsed by standard governance.
4. Prepare metadata for data repository considering new elements and standard derivations.
5. Generate standard templated programs from metadata.

Figure 2. Metadata Management System



For other CRT such as SDRG/ADRG and ARM, in Novartis those template, QC checklist and training material are available for end users to prepare e-study data submission efficiently. Especially when sponsors develop common SDRG/ADRG to simaltanious e-study data submission, it is recommended to describe both validation results for PMDA and FDA in conformance section because PMDA has different criteria of validation rule from FDA. Since Pinnacle 21 community version 2.0.1 (as of September, 2016, version 2.1.3 is the latest), sponsors can choose configuration either FDA or PMDA. In addition ARM is good communication tool for programmers in creating a complicated analyses, it is better to be included in programming process.

However if time lag is expected for PMDA e-study data submission from FDA submission, then sponsors need to use a latest version of validation tool and check if data is created in appropriate CDISC standards.

Therefore before NDA to PMDA, sponsors must check,

- Conformance checks against SDTM, ADaM and Define-XML by using latest validation tool.
- Conformance issues being described based on PMDA validation criteria and update SDRG and ADRG as needed.

If you have concerns about your data, you should be consulted by PMDA because PMDA doesn't plan to do test loading.

COLLABORATION BETWEEN JAPANESE AND GLOBAL TEAMS

The first step is to understand Japan specific requirements especially for global team who will support Japanese e-study data submission. Since majority of requirements are the same, it is better if global/Japanese teams have only one set of SDTM and ADaM datasets and their define-XML and SDRG/ADRG which meet both PMDA and FDA requirements including validation criteria if sponsors aim to submit them in PMDA and FDA simultaneously.

Second step is to discuss on roles and responsibilities globally who will check PMDA validation criteria or who will draft ARM for PMDA e-study data submission in addition to who will create SDTM/ADaM, Define-XML, and SDRG/ADRG to optimize resources globally. It is a key to have this discussion and make decision in advance at high level to avoid big discussions in the busiest time of e-study data submission preparation. It is recommended that sponsors have consistent policy not to spend much time for discussing in each e-study data submission. In order to have successful PMDA e-study data submission, global collaboration is essential. Global team needs to involve Japanese team from the beginning to get input, and Japanese team is also responsible to explain and input clearly what the PMDA specific requirements are.

CONCLUSION

E-study data submission can be beneficial for sponsors for potential reduction of data inquiries and data review time for NDA review by health authorities. However, it is a big challenge and time consuming for statistical programmers and statisticians to prepare deliverables which are suitable for e-study data submission. Currently PMDA and FDA request e-study data submissions. Both requests to comply CDISC format, but there are some differences between requirements of PMDA and FDA. Recent clinical development is more global development, and same clinical data package can be used for submission to PMDA and FDA. In order to work effectively, global and Japan team need to work together, share the knowledge of FDA and PMDA requirements each other, and incorporate Japan specific requirements into global submission package under standard process.

GROSSARY

ARM	Analysis Results Metadata
CP	Clinical Pharmacology
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
PBPK	Physiologically Pharmacokinetic Model Analysis
PPK	Population Analysis
STS	Standard Two Stage approach
TFL	Table, Figure and Listing

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