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Lessons Learned for Successful e-Study Data Submission to PMDA toward the End of Transitional Period

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ABSTRACT

Electronic study data submission (e-study data submission) to the Pharmaceuticals and Medical Devices Agency (PMDA) has started in October 2016 with 3.5-year transitional period, and will become mandatory starting from April 2020. Based on their experiences, several sponsors have already accumulated the know-how for the e-study data submissions to the PMDA during the transitional period.

Electronic study data submission greatly affects timeline and cost for the New Drug Application (NDA). Therefore, in terms of the global drug development, it is more efficient if the sponsors implement streamlined process for e-study data submission that would meet different requirements between the Food and Drug Administration (FDA) and the PMDA in order to achieve simultaneous submission to both health authorities. It is important that our knowledge are shared interactively as well as internationally to achieve a successful e-study data submission.

Therefore, ADaM team within CDISC Japan User Group (CJUG) is preparing a document (written in Japanese) to summarize useful tips for e-study data submission to the PMDA based on our experiences. In this paper, lessons learned, major considerations, and the key factors for successful e-study data submission to the PMDA will be discussed.

INTRODUCTION

This paper first outlines the e-study data submission. Then it will be described lessons learned, major considerations, and the key factors for successful e-study data submission to the PMDA, such as identifying which e-study data should be submitted, Consultation on data format of submission of e-study data (Consultation on data format), and consideration for the e-study data submission on global development.

SEVERAL ACTIVITIES OF CJUG ADAM TEAM IN 2018

The CJUG ADaM team's current activities are shown in the list below. There are seven ongoing projects and they are going to be completed by the end of September in 2018. All authors in this paper belong to project for the tips pf e-study data submission to the PMDA on practical experiences.

- Tips of e-study data submission to the PMDA on practical experiences
- How to write better statistical analysis plan to create ADaM specification efficiently
- Utility tools for ADaM and analysis
- Quality management for ADaM
- ADaM and analysis for clinical pharmacology
- Document for ADaM beginners/Translation of official ADaM-related documents
- Suggestion for ADSL to be easy to use for analysis

OVERVIEW OF E-STUDY DATA SUBMISSION TO THE PMDA

Electronic study data submission to the PMDA has started on October 1, 2016 with 3.5-year transitional period and will become mandatory starting from April 1, 2020. According to the information provided by the PMDA, as of May 1, 2018, 41 products (26 companies) have submitted e-study data to the PMDA during the transitional period. These products include submissions for domestic and global companies, as well as for NDA or supplemental NDA.

MAJOR CHANGE FOR PHARMACEUTICAL INDUSTRY IN JAPAN

Electronic study data submission has become a big impact for those who are part of the data science-related departments such as Data Managers, Statisticians, Clinical Pharmacologists and Statistical Programmers. They are affected in two different ways.

First, they have to implement streamlined process for the e-study data submission because it greatly affects the timeline and the cost for the NDA. Especially, in terms of the global drug development, it is more efficient if they implement the process for the e-study data submission that would meets different requirements between the FDA and the PMDA to achieve simultaneous submission to both health authorities. Therefore, all who are involved need to acquire higher level of technical skills and knowledge (e.g. CDISC, Programming, Statistics and Clinical Pharmacology).

Secondly, they have to now lead e-study data submission process and collaborate/discuss with stakeholders such as other departments (e.g. regulatory affairs) and the PMDA. Therefore, they need to manage, with competent soft skills, the entire e-study data submission process to meet the timeline and to negotiate with internal project members and the PMDA.

In addition to these, organizational changes within a company may be necessary in order to manage the entire process and promote good governance for the e-study data submission (e.g. PMDA consultation, timeline, budget etc.). In fact, in each of the sponsors that underwent e-study data submission process, the framework/organization of e-study data submission were changed as indicated below.

- Assign a CDISC expert in each Common Technical Document (CTD) team
- Establish an e-study data submission committee, which is organized by data science department and regulatory affairs in order to provide input for not only the compound-specific issues, but also for the general topics
- Create new department which will specialize in e-study data submission.

GENERAL MILESTONE AND TIMELINE

There are three types of consultations with the PMDA related to the e-study data submission. It is very important to understand the purposes of these consultations because they affect submission milestones and timelines. Please note that Clinical consultation and Consultation on data format have differences in purposes.

Table 1-1. Several consultations related to e-study data submission to the PMDA

Consultation	Purpose related to e-study data submission to the PMDA	Timing (recommendation)
Clinical consultation (e.g. End of Phase II meeting)	• To agree with the PMDA about target data/studies and analyses of e-study data submission	A couple of years to 6 months before NDA
Consultation on data format	• To discuss technical issues/concerns for data format • To share validation issues on Pinnacle 21	Several months before NDA to before Pre-consultation meeting on review schedule
Pre-consultation meeting on review schedule	• To confirm finalized submission package and application date • (Should send finalized Exhibit 8 to the PMDA beforehand)	6 weeks before NDA

Figure 1-2 shows the general milestones and the timelines for consultations with the PMDA related to the e-study data submission.

There are some important points to keep in mind.

- Electronic study data can be submitted via gateway system from five weeks prior to NDA.
- Test upload can be conducted via gateway system from eight weeks to two days prior to NDA. It does not conduct data validation check on Pinnacle 21 (P21) but conduct a virus check.
- Consultation on data format can be held more than once.
- In principle, Pre-consultation meeting on review schedule should be held after last Consultation on data format because final version of Exhibit 8 which is used at the Consultation on data format should be submitted before the Pre-consultation meeting on review schedule.

These points should be considered in order to achieve each milestone and meet the timeline.

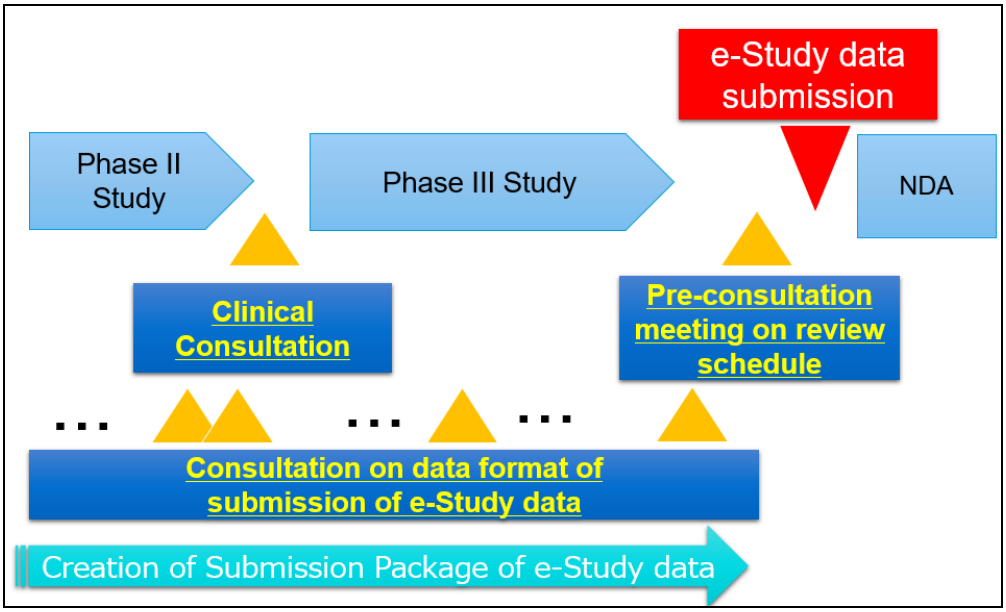

Figure 1-1. General milestone and timeline

GUIDANCE UPDATES AND FAQ RELEASES

There have been many updates to the guidance as well as FAQ releases as of Jul 2018 by the PMDA. Since these include important and practical updates about e-study data submission, it is imperative that the sponsors read and understand the latest updates and incorporate them into their preparation for that e-study data submission process. Some of the most important updates include:

1. The requirement begin date for the new CDISC standard and the end date support for the old CDISC standard indicated on FAQ releases;
2. The addition of the requirement for clinical pharmacology data submission on the guidance and FAQ;
3. The updated version number for the acceptable CDISC Controlled Terminology.

For the latest version of the guidance and all FAQ releases, please refer the PMDA website and references section on this paper.

IDENTIFICATION OF E-STUDY DATA TO BE SUBMITTED

In this section, the processes to identify the data/studies and analyses on the basis of our practical experiences are described.

GENERAL POINT OF VIEW

First of all, the sponsor should decide which evaluation and reference data/studies will be used as clinical data package for the NDA. This step is not specifically related to the e-study data submission, but it is important because it will determine target data/studies for the e-study data submission. Secondly, target data/studies to be submitted in the clinical data package should be identified based on the aforementioned PMDA guidance and FAQ releases. After that, target analyses such as ADaM dataset, programs used to create the ADaM datasets, and programs used for analyses should be identified for each data/study.

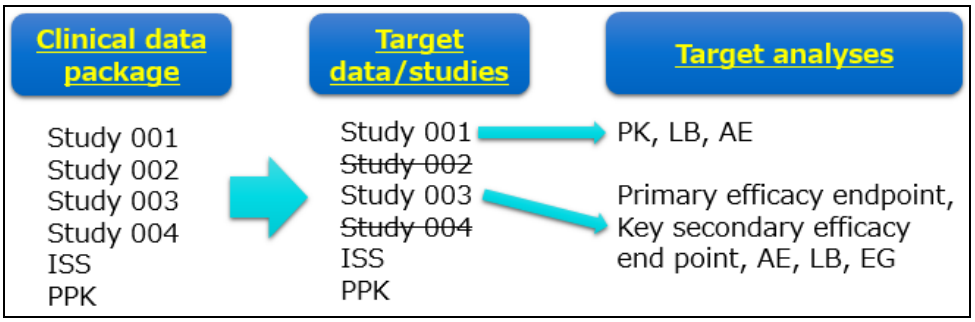

Figure 2-1. Overview of identification of target data/studies/analyses

The agreement with the PMDA on target data/studies and analyses should be reached at Clinical consultation such as at the End of phase II meeting.

Data science department would be heavily involved in the preparation of e-study data submission section in Briefing Book for the consultation as well as in the discussion with the PMDA at the consultation.

PROCESS TO IDENTIFY TARGET DATA/STUDIES AND ANALYSES

Step1. Confirm evaluation or reference data/studies in clinical data package,

Target data/studies will be chosen from clinical data package for the NDA. Classification of evaluation/reference is important to identify target data/studies because these two classifications are basic information to decide target data/studies. More detail will be described in Step 2.

- Evaluation data/study is a data/study used for main evaluation of drug.
- Reference data/study is a data/study which is positioned as supplement of evaluation studies.

Step 2. Identify target data/studies according to the PMDA requirements

The following table is the list of target data/studies for the e-study data submission outlined in Q&A regarding Notification on practical operations [4].

Table 2-1. Types of e-study data submission to the PMDA

a. Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration	
b. Study data from phase I studies and clinical pharmacology (CP) studies listed right	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 I and CP studies other than a and b, which were deemed necessary by PMDA	Clinical studies where standard pharmacokinetic analysis was Performed(Standard CP study)
	Population analyses (PPK)
	Physiologically based pharmacokinetic sufficient model analyses (PBPK)
References other than a and b, which were deemed necessary by PMDA	
Integrated summary of safety and efficacy (ISS/ISE)	

Categories ‘a’ and ‘b’ in the above table are most probably for evaluation data/studies and their e-study data that are required to be submitted. Regarding “phase I and CP studies other than category ‘a’ and ‘b’”, these e-study data (including datasets used in PPK and so on) are not necessarily required, but they may become required if the PMDA deems them necessary.

Please note that special considerations are needed for CP study as described in FAQ releases[7]. These considerations are very important to decide target data/studies even if a data/study is reference. Based on these conditions, sponsor needs to decide whether to submit a study data or not after they know the result of the study.

Q5-6. When a sponsor conducts clinical trials to evaluate the effect of intrinsic or extrinsic factors such as age, sex, weight, genetic factors, severity of disease, disease complications, or dietary, alcohol or smoking habits on the pharmacokinetics of an investigational drug, are these study data subject to submission even if the study result indicates negative effect of these factors on the pharmacokinetics of the drug?

Answer. It is not necessary to submit study data in that case. The 0.8 - 1.25 range on the geometric mean ratio of pharmacokinetic parameters (when pharmacokinetic parameters are log-normally distributed) can be used as one of the criteria for assessing a 'negative effect' in deciding whether the study data need to be submitted. In some cases, study data might not need to be submitted even though the ratio is not within the range of 0.8 - 1.25. To ensure the necessity of submission of study data evaluating the effect of intrinsic or extrinsic factors, we recommend using a clinical trial consultation if necessary.

In addition, regarding ISS/ISE, there is an important condition for e-study data submission on FAQ releases [7] as well.

Q4-4. When is it necessary to submit electronic datasets of integrated analyses (ISS/ISE)? What is the scope of electronic data on ISS/ISE that must be submitted?

Answer. ..., submission of electronic data for ISS/ISE will be requested when integrated analyses of multiple clinical studies were performed for the assessment of specific efficacy or safety, such as assessments in special populations or of rare adverse events, and when the results are considered to be relevant to the assessment of efficacy, safety, and dosage and administration of the product. In order to confer with the PMDA on the scope of the submission of electronic data of integrated analyses, applicants must use the clinical trial consultation, not the "consultation on data format of submission of electronic study data", because a decision on the scope of the submission accompanies scientific evaluations.
At the submission of data, ...

Step 3. Identify target analyses define in the PMDA requirements
The following passage is based on the target analyses point of view in Technical conformance guide [5].

It is not necessary to submit ADaM datasets for all analyses described in the statistical analysis plan. However, ADaM datasets should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as 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 applicant should preferably consult the PMDA beforehand on the sufficiency of the datasets to be submitted.

With respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration

In summary, it is NOT necessary to submit all ADaM datasets created. However, ADaM datasets related to more important analyses should be submitted. They are primary efficacy analysis, secondary efficacy analyses and primary safety analyses. The programs used to create the ADaM datasets and the analyses as well as Analysis Results Metadata (ARM) are the same requirement as ADaM datasets. Please note that the PMDA strongly recommends sponsors to submit ARM. Therefore, although submission of ARM is not required, sponsor should internally discuss the feasibility of the submission and submit them as often as possible. For more detail of ARM, please refer to Creation ARM section.

Step 4. Create Briefing Book for Clinical consultation
It is recommended to summarize the target data/studies before creating the Briefing Book for Clinical consultation. The following table is the example of a summary table for target data/studies and analyses described in Step 1 to 3. This table would become helpful in creating the Briefing Book.
Please note that sponsor needs to describe in more details the reasons why data or a study is subject to e-study data submission. This should be considered once target data/studies is decided in Step2. Examples of the reasoning are provided in the following table (Notes column).

Table 2-1. Example of summary of target data/studies and analyses

Step 1			*Step 2*		*Step 3*
Protocol No.	Phase	Evaluation/ Reference	e-study data submission	Notes	Target analyses
001	I	Evaluation	Yes	To meet condition to be submitted e-study data for CP study on FAQ (e.g. TQT study, BE study)	PK, AE, LB
002	I	Evaluation	Yes		PK, AE, LB
003	I	Reference	Yes		PK, AE
004	I	Reference	No	Not to meet condition to be submitted e-study data for CP study on FAQ (e.g. Within the 0.8 - 1.25 range on the geometric mean ratio in Food Effect and DDI studies)	-
005	I	Reference	No		-
006	II	Evaluation	Yes	Studies that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration	Key efficacy endpoint, AE, LB, Biomarker
007	II	Evaluation	Yes		Key efficacy endpoint, AE, LB, EG
008	III	Evaluation	Yes		Key efficacy endpoint, AE, LB
009	III	Evaluation	Yes		Key efficacy endpoint, AE, LB, EG
ISS	-	Evaluation	Yes	Analyses were performed to assess rare adverse events	AE

CLINICAL CONSULTATION

Sponsor needs to confirm the scope of evaluation or reference data/studies which are subject to e-study data submission by utilizing the existing framework of Clinical consultations provided by the PMDA [3].

Sponsor usually holds the End of phase II meeting with the PMDA in order to agree on the clinical data package as well as the target data/studies and analyses with the PMDA. There are some important points which need to be carefully considered when sponsor receives the consultation with the PMDA.

- Sponsor may have additional consultation with the PMDA if they did not to discuss the target data/studies and analyses at planned Clinical consultations.
- Follow-up meeting after the Clinical consultation may be held to discuss the target data/studies and analyses.
- Data science department leads the discussion of the contents of e-study data submission during the PMDA consultation.
- The PMDA will NOT answer any general questions related to other products.
- It is recommended to confirm at a Preliminary consultation when the sponsor is uncertain at which consultation any questions should be discussed. Preliminary consultation can be held to clarify the items which need consultation.

CONSULTATION ON DATA FORMAT

The purpose of the Consultation on data format is to agree with the PMDA on detailed contents of e-study data to be submitted in order to allow the PMDA to smoothly review them after the NDA. Some advice about contents of e-study data such as data format, data validation, version of standards, and so on could be obtained during this consultation. The data science department should lead the entire process for this consultation, such as preparation of supporting documents and discussion at the consultation meeting.

THE TOPICS THAT SPONSOR CAN CONSULT WITH THE PMDA

There is a restriction on which topics could be discussed at the Consultation on data format. Sponsor must choose appropriate type of meeting depending on the type of topics to consult, otherwise they will not get any advice.

Topics which sponsor can consult with the PMDA during the Consultation on data format, as well as the differences from those in clinical consultation are described in Notification on practical operations [3] and in Appendix 11 of the "Implementation guidelines for clinical trial consultation and confirmation of certification, etc., conducted by the Pharmaceuticals and Medical Devices Agency (PMDA Notification No. 0302070 of the Chief Executive, dated March 2, 2012)"(written in Japanese). In addition, some specific examples of topics which can be discussed in each type of meeting are given in FAQ releases. They can be summarized as follows:

(1) Topics related to data format of specific domains, data validation, version of standards, content of each document, method and timeline of data submission are to be discussed in Consultation on data format.
(2) Topics related to target studies/analyses of e-study data submission and the scope of whole submission package (not driven by e-study data specific things) are to be discussed in Clinical consultation or Pre-consultation meeting on review schedule.

The specific examples mentioned in Q&A Regarding Notification on practical operations [4], Technical conformance guide [5], and FAQ releases [7], regarding which sponsor should consult with the PMDA in Consultation on data format are :

- Scope of the submission of e-study data (Q&A Regarding Notification on Practical Operation: Q11)
- In case it is difficult to submit data in the SDTM/ADaM format (Q&A Regarding Notification on Practical Operation: Q11)
- Timing of submitting data in special case (Q&A Regarding Notification on Practical Operation: Q13)
- Medium which sponsor wishes to use to submit electronic study data (Technical Conformance Guide: Section 2.4)
- In case file size of any dataset is 5 gigabytes or greater (Technical Conformance Guide: Section 3.4)
- Folder structure to store and submit e-study data (Technical Conformance Guide: Section 3.4)
- Methods of implementation of SDTM/ADaM standards (Technical Conformance Guide: Section 4.1.1.1)
- In case sponsor would like to store variables for main analyses in SUPPQUAL (Technical Conformance Guide: Section 4.1.1.2)
- In case sponsor would like to use custom domain (Technical Conformance Guide: Section 4.1.1.2)
- In case e-study data contains Japanese text (Technical Conformance Guide: Section 4.1.5, FAQ: Q4-10)
- In case sponsor would like to submit e-study data only upon Electronic Common Technical Document (eCTD) revision (Technical Conformance Guide: Section 5.5)
- Methods of the submission of additional e-study data after the time of the NDA (FAQ: Q4-25, Q4-31)

There are 2 types of consultation of data format. One is a fee-charged meeting in which the PMDA will provide meeting minutes, and the other is a charge-free meeting without meeting minutes. Sponsor may select either type of the meeting. With respect to the topics that sponsor can consult with, we assume practically there is no difference between the 2 types because there is no description of difference in the guidance, and we have never observed differences in our past experiences.

EXHIBIT 8, "SUPPORTING DOCUMENT ON CONSULTATION ON DATA FORMAT OF SUBMISSION OF ELECTRONIC STUDY DATA"

The Exhibit 8 contains basic information of compound, content of consultation, summary of clinical study and e-study data submission package, and detailed information of e-study data to be submitted such as data format and data validation. As the Exhibit 8 is a Japanese form, some companies choose to translate it into English to share the information with global members, and ask them to review it, especially for the global study.

The explanation of data validation, which is the same as Issues Summary in the Reviewer's Guide (RG), is required. The explanation should be detailed enough so that it tells the PMDA how the actual data looks like. If sponsor is to claim that the error doesn't have any adverse impact on analyses performed by them, its explanation should be provided. The reason why the error can't be resolved should also be included. If the PMDA requests further explanation(s) for the error message on the P21 report, the Exhibit 8 needs to be updated and resubmitted to the PMDA after the consultation meeting. The RG may be attached to the Exhibit 8. Some examples for explanation of validation error are shown in the Table 3-1.

Table 3-1. Example for explanation of validation errors

Inappropriate explanations	Appropriate explanations based on our experience
Data stored according to CRF	Data stored according to CRF. If actual amount of dose of concomitant medication was unknown, "UNK" is entered in Dose Description (CMDOSTXT) field and Dose Units (CMDOSU) is not provided.
Not modified because analyses are not affected	There are some records where PARAMCD/PARAM are empty. Alternatively, there are equivalent variables EGTESTCD/EGTEST. Statistical analyses and data summary were performed using them.
Implemented as per company standards	In addition to variables of IDVAR and IDVARVAL, COGRPID and COSPID were also populated per company standard. COGRPID provides the traceability of where the comment came from, while COSPID is the sequence order within each

Inappropriate explanations	Appropriate explanations based on our experience
	subject.
NA (In case validation errors are detected in PMDA validation)	In this trial, subjects were expected to receive multiple treatments. Therefore, period start date time (i.e. TRxxSDT & TRxxSDTM where xx=01, 02 …etc.) were used in place of TRTSDT/TRTSDTM to avoid confusion.
NA (In case validation errors are detected in PMDA validation)	All records of "LBSTRESN does not equal LBSTRESC" are subjective tests. Subjective results reported in LBORRES and also in LBSTRESC values, but LBSTRESN is set to null. So LBSTRESN does not equal LBSTRESC.

CONSIDERATIONS FOR E-STUDY DATA SUBMISSION TO THE PMDA ON GLOBAL DEVELOPMENT

In case of global development, where the global e-study data are submitted not only to the FDA but also to the PMDA, the important success factors for e-study data submission to the PMDA are 1) to fully understand the differences in the requirements between the FDA and the PMDA, and 2) to improve the awareness of global colleagues of these difference. Table 4-1 shows the main requirements for the FDA and the PMDA for CDISC related deliverables as of July 2018.

Table 4-1. Requirements of the FDA and the PMDA for CDISC related deliverables

Item	FDA	PMDA	Notes
Decision criteria for e-study data submission	**Study** which started on or after 17Dec2016	Mandatory: **NDA** submission on or after 1Apr2020 (Transition period: **NDA** submission between 1Oct2016 to 31Mar2020)	PMDA: **Date of NDA** is used as decision criteria of e-study data submission. This may need legacy data conversion to CDISC format for some studies data not in FDA submission package.
SEND	v3.0, v3.1	-	
Nonclinical Study Data Reviewer's Guide (nSDRG)	Need to be submitted	-	
SDTM IG	v3.1.2, v3.1.3, v3.2	v3.1.2, v3.1.3, v3.2	PMDA: It is required to set SI units as Standard unit for Finding domains (excluding a part of items)
Clinical Study Data Reviewer's Guide (cSDRG)	Need to be submitted	Need to be submitted	
ADaM IG	v1.0, v1.1	v1.0	FDA: Only v1.1 will be acceptable for studies which will start on or after 15Mar2019.
ADRG	Need to be submitted	Need to be submitted	
Define-XML	v2.0	v1.0, v2.0	
P21 Validation Ver.	P21 Enterprise latest ver.	P21 Enterprise v3.0.5	Validation rule is different between the FDA and the PMDA. Therefore, validation check based on each rule is needed. Pinnacle21 Community version 2.1.3 can be used as compatible version for P21 Enterprise v3.0.5.
Analysis Results Metadata (ARM)	Recommended to submit	Highly recommended to submit	FDA: not mandatory but recommended in current situation PMDA: not mandatory but strongly recommended for their review
ADaM / Key analyses programs	Need to be submitted	Need to be submitted	

Item	FDA	PMDA	Notes
WHO Drug Dictionary	**Study** which started on or after 15Mar2018	Need to be applied	FDA: WHODrug Global B3 format will be acceptable for studies which will start on or after 15Mar2019.

CONSIDERATIONS FOR THE CASE OF E-STUDY DATA SUBMISSION TO PMDA AFTER FDA SUBMISSION

If there are some studies' data which were not included in FDA submission but are included in PMDA submission, data conversion to CDISC format from legacy study data may need for PMDA submission. This situation will need additional resource. And as an another situation, if there are some studies' data which were included in FDA submission but didn't meet PMDA requirements, the studies data will need to be updated so that they meet the requirements of PMDA regulations. Typically, the cases such as conversion to SI units in Finding domains, re-validation based on PMDA rules (including RG modification in most cases) and creation of ARM etc., are expected.

Conversion to SI units in Finding domains:

Sponsor needs to confirm whether sponsor's standard unit is SI unit or not for each item (except for some items such as blood pressure (mmHg vs. Pa)) in SDTM Finding domains and needs to convert it to SI unit if some of them are not SI unit. It is required by the PMDA to store SI unit in Standard Unit variable (--STRESU) and sponsor's standard unit in supplemental domain if it is used for analysis. In addition, it is necessary to describe the detail of conversion in SDRG. See Table 4.2 below.

Table 4-2. Data storage for SI unit conversion

Variable to store data	BEFORE conversion	AFTER conversion
Parent Domain Original Unit (--ORRESU)	Collected Original Unit	Collected Original Unit
Parent Domain Standard Unit (--STRESU)	Sponsor's Standard Unit	**Converted SI Unit**
Supplemental Domain	-	Sponsor's Standard Unit

Re-validation based on PMDA rules and modification of RG:

It should be noted that business rules for validation between the FDA and the PMDA are different. Even if sponsor tries to submit the e-study data for FDA submission to the PMDA as is, they will need to re-validate them unless validation based on PMDA rules is performed. Furthermore, it is recommended that the validation is performed by using the same version as used by the PMDA, i.e. Pinnacle21 Enterprise (P21E) v3.0.5. However, P21E version is updated automatically and users cannot perform the validation by setting a specific version as of July 2018. In reality, there have been many case examples reported where sponsors alternatively used the compatible version, i.e. Pinnacle21 Community (P21C) v2.1.3 so far. This will cause the use of different versions across regions.

It should also be noted that if any "Reject" issues were detected in validation report on PMDA rules, sponsor must fix the issue by correcting e-study data. Also, if some "Error" issues were detected, sponsor needs to consider whether they will need to fix the e-study data or not, and If the sponsor decides not to fix them, they must explain in detail the cause of the issue and the reason why sponsor didn't fix them at the Consultation on data format with the PMDA.

In addition to the re-validation, it should be noted that the conformance summary section in RG for SDTM and/or ADaM (SDRG and/or ADRG) will also need to be updated accordingly.

Table 4-3. Actions for validation results based on FDA and PMDA rules

Issue category	FDA (P21E latest ver.)	PMDA (P21E v3.0.5 / P21C 2.1.3)
Reject	-	Electronic study data MUST be corrected (it should be noted that the PMDA won't proceed with evaluation without correcting)
Error	Need to explain in RG	Need to explain in RG and explain to the PMDA at Consultation on data format (it should be noted that the PMDA won't proceed with evaluation without agreement)

Issue category	FDA (P21E latest ver.)	PMDA (P21E v3.0.5 / P21C 2.1.3)
Warning	Need to explain in RG	NOT necessarily need to explain in RG and explain to the PMDA at Consultation on data format. However, PMDA may request separately from the perspective of the quality of the clinical study data.

Creation of ARM:
The PMDA strongly recommends sponsors to submit ARM although it is not mandatory material. Sponsor can include ARM in Define.xml or submit ARM in PDF format. However, if sponsor tries to incorporate it into Define.xml, they will need to modify the file which was once finalized. In this case, it will be hard to prepare the ARM if in-house standard process and system are not applied to ARM preparation. The scope of submission for ARM will be decided based on the target analyses, in which sponsor should include primary/key secondary efficacy and important safety measurements, and it will be also related to the analysis programs to be submitted. Therefore, it is recommended to reach an agreement with the PMDA in advance which ADaM dataset/programs and analysis programs will be submitted at an existing Clinical consultation.

IMPORTANT CONSIDERATIONS FOR THE SIMULTANEOUS E-STUDY DATA SUBMISSION TO THE FDA AND THE PMDA

If sponsor tries to submit e-study data to both the FDA and the PMDA simultaneously, i.e. within a few months, it should be noted that the sponsor must prepare e-study data in a timely manner to meet the requirements for both the FDA and the PMDA. This includes the preparation for the last study in scope for the e-study data submission before the NDA.

For example, if the last study before the NDA submission is a global study, in order to prepare the e-study data effectively based on the requirements which were mentioned in the previous sections, it is recommended to consider the process for e-study data preparation well between Japan and global team members prior to the start of the study, and to incorporate both the FDA and the PMDA requirements into standard process/template for e-study data appropriately.

It is also expected that the personnel(s) responsible for e-study data preparation need(s) to understand the difference between the FDA and the PMDA requirements properly and to confirm the level of quality of deliverables in advance. For example, the sponsor needs to explain “Error” from P21 validation rule in SDRG and/or ADRG including the cause of the issue and the reason why sponsor didn’t fix it, so that the PMDA can accept the explanations at Consultation on data format. Therefore, it is recommended that Japan team members provide the instruction with global colleagues and review the deliverables, and so on. The PMDA accepts RGs written in English.

Table 4-4. Example: Template to summarize validation results based on both FDA and PMDA rules in RG

Dataset	Rule ID	Diagnostic Message	**FDA Severity**	**PMDA Severity**	Explanation
LB	SD1122	Missing value for LBSTRESN	Warning	Error	The conversion of lab value to standard value cannot be performed for those records with missing original unit (LBORRESU) or original unit cannot be converted to standard unit (LBSTRESU).

As mentioned so far, the explanation for the validation results before e-study data submission is required for the PMDA, but not required for the FDA. This means that sponsor needs to complete the preparation of e-study data prior to the Consultation on data format with the PMDA. Thus, simultaneous NDA submission will proceed under a tight schedule because e-study data and Exhibit 8 for Consultation on data format also need to be finalized in parallel with the creation of the clinical study report (CSR) and the CTD after the database lock of the last study prior to the NDA submission. Therefore, it is so vital to prepare the deliverables in collaboration with all relevant functions while seeing the entire picture.

In addition, for e-study data submission to the PMDA, sponsor can submit the e-study data five weeks before the NDA, but sponsor must finish the Consultation on data format and Pre-consultation meeting on review schedule before e-study data can be submitted. Furthermore, sponsor must submit the Exhibit 8 including validation results and explanations of “Error” to the PMDA by Monday of two weeks prior to the Consultation on data format. In order to

achieve a simultaneous submission in the short term after database lock of the last study, sponsor will need to consider the procedure and timeline carefully while remembering these restrictions. Sponsor should consult with the PMDA about timings of Consultation on data format and/or e-study data submission, if deemed necessary.

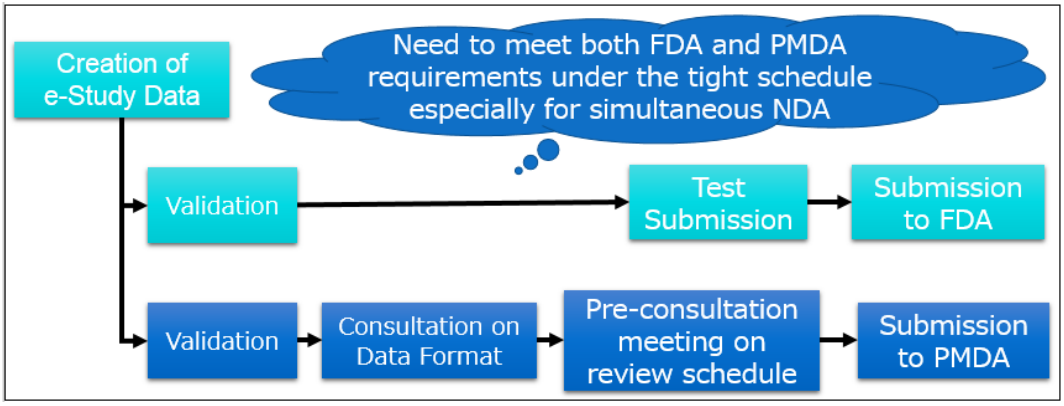

Figure 4-1. Example: Timeline of simultaneous NDA submission

IMPORTANT POINTS FOR THE REQUIREMENT FOR CP STUDY DATA SUBMISSION

The PMDA has a very specific requirement for the e-study data for the CP study. As mentioned in the process to identify target/studies and analyses section, there are very important requirements to be met for the CP studies. In this section, important points for the requirement for the CP studies will be described.

DATA NEEDED TO BE SUBMITTED IN CDISC FORMAT FOR CP STUDY

If a CP study data is positioned to be submitted, SDTM PC and PP need to be submitted with requirements described below:

Table 5-1. Conditions of creating SDTM domains for targeted CP Studies

Domain	Conditions
PC	In the case that serum/plasma/urine concentration data is collected, need to be submitted. Note that 1) sparse sampling for PPK is also needed to be submitted; 2) even if PPK results are not reported in the CSR for the study, the concentration data collected in the study are also needed to be submitted.
PP	In the case that PK parameters are derived, need to be submitted

THE REQUIREMENT OF THE DATA SUBMISSION FOR CP STUDIES THAT EVALUATE INTERNAL OR EXTERNAL FACTORS

Sponsors need to submit CP studies that evaluate internal or external factors if the results of 90% CI of geometric mean for PK parameters are out of the range 0.8 to 1.25 (Refer to Step 2 in process to identify target/studies and analyses section.) Therefore, the sponsor needs to decide whether to submit the CP study's data or not after they know the results of the study. Here is the table that shows the pros/cons of each approach that sponsors can take.

Table 5-2. Approaches to the preparation of e-study data submission for CP studies

Approach	Pros	Cons
Prepare e-study data of all possible studies in advance	If a study is decided to be submitted, sponsor can reduce a risk that they can't prepare it due to a short period of time.	Sponsors need to take a cost to prepare for all studies.
Prepare e-study data of a study after the result is available	If a study is decided not to be submitted, sponsors can save the time to prepare it.	If a study is decided to be submitted shortly before NDA, sponsors may have a trouble with preparing it.

CONCLUSION

For successful e-study data submission, it is essential to collaborate across companies and share knowledge and experience toward the fast-approaching mandatory phase because e-study data submission greatly affects timeline and cost for an NDA. If a sponsor works on e-study data submission on their own, they may be faced with a lot of difficulty. In such case, lessons learned such as items described in this paper would be helpful.

The data science department needs to take up on a new role and lead the whole e-study data submission. Especially, they have to get deeply involved in the discussions with stakeholders for the clinical consultation and the Consultation on data format. Therefore, they should improve technical skills and knowledge as well as soft skills for e-study data submission.

Regarding global development, it is very important to understand the differences between regions and meet both the FDA and the PMDA requirements on e-study data submission. By comprehending the requirements well, the sponsor would be able to implement a more streamlined process for e-study data submission in the future, which will allow for smooth simultaneous submissions to both health authorities.

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