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Single Day Event

Looking back 2 years of PHUSE Japan e-Data sub team

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Disclaimer

- The contents of this presentation represent the opinions of the individual presenters and do not represent the opinions or positions of the organization to which they belong.

- The contents of this announcement are omitted for convenience of explanation, and may not always contain accurate information.

Today’s Agenda

- COVID-19’s impact to e-Data submission in Japan
- White Paper about e-Data submission to PMDA
- e-Data sub team’s Progress

COVID-19’s impact to e-Data submission in Japan

e-Data in Urgent Situation

- March 18, 2020, Notification “Basic Principles on Electronic Submission of Study Data” was revised and the sentence below was added.
  - The submission of electronic data may not be required for drugs that will be urgently used to prevent the occurrence or spread of health hazards, even for new drugs that fall under the above conditions.

Our Team Members' Experiences in COVID-19 Vaccines & Treatments

- There were both experiences, submitting and not submitting e-Data to PMDA.
- When submitting, e-Data was not submitted in the standard timeline and not compliant to PMDA's requirements.

White Paper about e-Data submission to PMDA

Progress of white paper for PMDA Electronic Data submission

- Title

  PMDA Electronic Data Submission Deep Dive

  -How to reach for Japanese regulatory requirements-

- Disclaimer

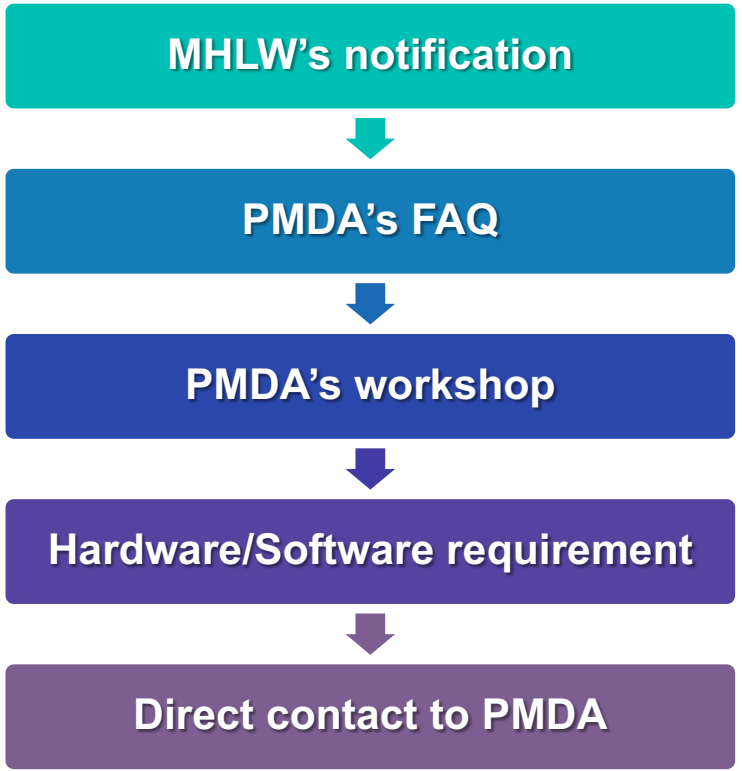
  This white paper is based on the views of the PHUSE Japan e-Data submission team and is not approved by PMDA.

Objectives

- We asked PHUSE members about the problems they had when submitting electronic data in Japan, which involved overseas personnel.
  - For overseas personnel, it takes time to understand the difference between FDA and PMDA, and the knowledge of PMDA requirements varies due to frequent personnel changes.
  - Because FDA does not require CDISC compliance for older studies, overseas personnel are reluctant to comply with CDISC.
- We are preparing the white paper focusing on the solutions and explaining the practical aspects.

Contents

- Our white paper will explain 5 steps for the solutions.
- It also contains selectively translated FAQs of the April 2021 FAQs on Electronic Data Submission.



Notifications from Japanese regulatory agency

- Major example resolved by the notifications.
  - Case Study : m5 folder structure
    - Since PMDA has its specific regulations on the folder structure, the character limit of the folder name and file name, the characters that can be used, etc., when submitting e-Data used in the submission to FDA before, it is necessary to confirm that there are no violations from PMDA's regulations.

PMDA's FAQ

- The below case is the example of the FAQs regarding application electronic data.
  - Analysis Results Metadata in the field of clinical pharmacology
    - Q5-30 in the FAQs has the description about ARM in the clinical pharmacology area.
    - According to Q5-30, in the studies with the standard pharmacokinetic analysis, the applicants are asked to submit ARM for the statistical analyses using PK/PD parameters. However, if the applicants submit the analysis datasets in formats other than ADaM, the applicants don't have to submit ARM.

PMDA's workshop

- Some topics in the workshops have no descriptions in the notifications or FAQs.
  - Explanation of additional data errors after the submission for cutoff analysis
    - For the long-term study, the sponsors often do the cutoff analyses for the applications and the final analyses after the applications.
    - On February 28, 2017, PMDA stated that "when additional data are submitted after application, if a new violation against the validation rule corresponding to an Error, which has not been explained before the application, is detected, it is necessary for the applicants to explain the reason before the submission of the data".

Hardware / Software requirement

- The applicants must refer to the system requirements.
  - Gateway System
    - If the file size of one electronic file exceeds 10 GB and the file size of all electronic files exceeds 100 GB, you need to contact PMDA.
    - When applying for e-Data at Gateway System, make sure that the file name and folder name do not use prohibited characters. In particular, make sure that the file name does not use the uppercase letters.

Direct contact to PMDA

- There are 5 frameworks for consultation with PMDA regarding electronic data submission.
  - Although consultation materials can be prepared in English, Q&A are usually conducted in Japanese.

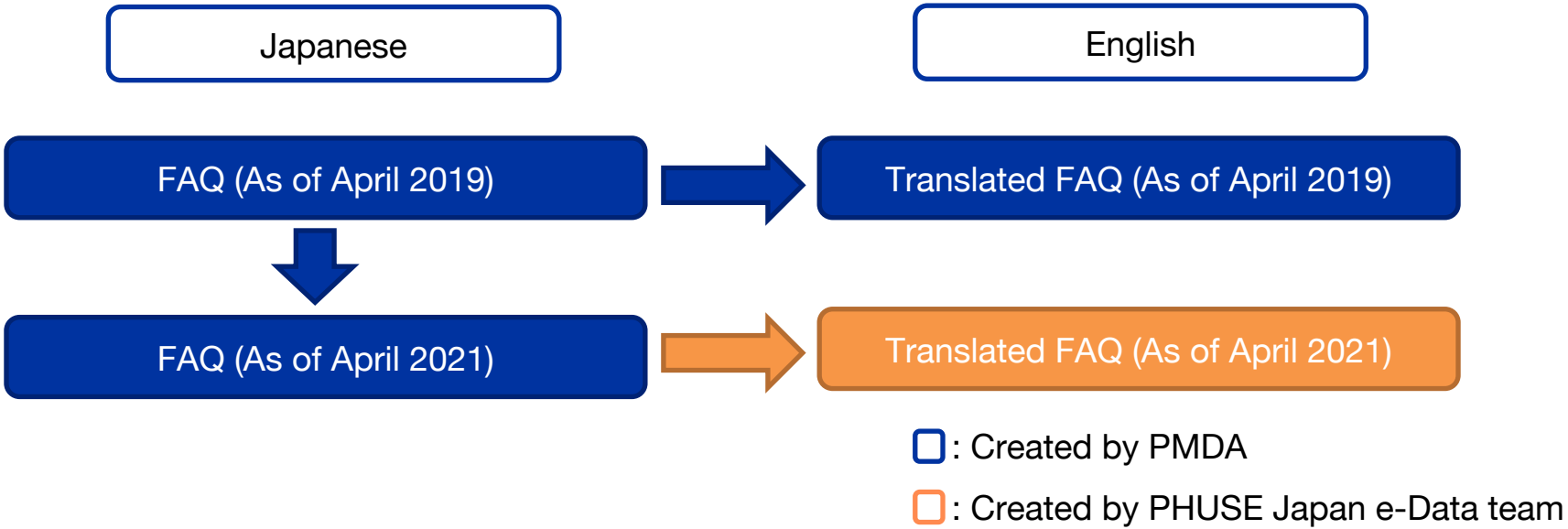
Direct contact to PMDA

- The working group for e-Data submission with PMDA that serves as the contact for 4 industry groups of JPMA, PhRMA, EFPIA, and JCROA. If your company belongs to any of these organizations, you can make inquiries to PMDA through this industry group, regarding e-Data and Gateway System.
  - However, the questions are limited to the general topics and the topics specific to a company or project are not allowed. Inquiries are free, but Q&A are basically conducted in Japanese.

Direct contact to PMDA

- In addition, PMDA has an e-mail address for inquiries regarding the next-generation examination/consultation system. Inquiries about the homepage for general electronic data applications can be made in English.
  - But inquiries about the Gateway System are said to be made in Japanese.

Appendix: FAQ



- We selectively translated FAQs of April 2021. On the other hand, FAQs translated by PMDA into English are based on the excerpt of April 2019.
- If the FAQ is updated and translations by PMDA are added, please refer to them.

Appendix: FAQ (newly added question)

- Q.1-6-3: For reasons such as a large number of studies in the data package, please explain how to receive check results early after the Attachment 8 “Explanatory document on electronic study data (Form A)” is submitted.
  - A: Form A submitted at the time of applying for the pre-NDA meeting will be reviewed in about 2 weeks after its submission . As long as the review is completed by PMDA, the validation results can be shared regardless of the timing of the pre-NDA meeting. Please consult with PMDA if the you wish to know the validation results early.

Future plans (tentative)

- Public review
  - January 2022
- Release
  - February 2022

e-Data sub team’s Progress

e-Data sub team's Progress

We are working in three groups this year.

1. Issue Summary Writing Guide
2. System to Collect Issue Summary Explanations
3. Optimal use of Consultation on preparation of submission of electronic study data with PMDA

e-Data sub team’s Progress
-Issue Summary Writing Guide-

Background

- Last year, PHUSE Japan e-data submission task team and CJUG SDTM/ADaM have collected the Issue Summary explanations which were shared at PMDA Consultation meeting. This year's task is the next step of this.

Background

- 2.2.1 Validation_Error_Justification.xlsx↵

  エクセルファイル Validation_Error_Justification.xlsx は PMDA が公開しているバリデーションルールバージョン 2.0 のファイルを元に作成されており (SDTM Rules は A 列から H 列、ADaM Rules と Define.xml は A 列から G 列)、Pinnacle21 で実際に検出されたが修正できず、申請電子データ提出確認相談(以下、確認相談)で PMDA に共有した Error の説明内容をエクセルファイルにまとめている。(尚、バージョン 1.0 を利用した場合もこのファイルにまとめている。どのバージョンを利用したかは、ファイルの O 列に記載している。) ファイルは Datasets 欄、Description/Explanation 欄に過去に FORM A (様式 8) に記載した内容を転記している。その他参考情報として、申請時期、領域、使用した Pinnacle21 のバージョン情報等を記載している。シートはバリデーションの対象ファイルごとに、"SDTM Rules"、"ADaM Rules"、"Define-XML Rules"と分かれ、その他の経験の共有用として、"その他"シートに分かれている。↓

RULE ID	MESSAGE	DESCRIPTION	PMDA Severity	Datasets	Description\Explanation
CT2001	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	Reject / Error	CM, PR	IG and CT were set based on STENRF, but Pinnacle 21 only enabled BEFORE, COIN considered a Pinnalce bug. Pinnacle Forum (posted on November 19, 2018) https://www.pinnacle21.com/forum/ relation-reference-period-strtpt-non-extensible-codelist

Goal & Objective

- **Goal**
  - Make it easy for everyone to write Issue summary section in SDRG and ADRG
- **Objective**
  - Create the guidance/metadata of explanation with simple and clear explanation
  - Improve the quality of the explanation

Goal & Objective

RULE ID	MESSAGE	DESCRIPTION	PMDA Severity	Datasets	Description\Explanation
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RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	Example Sentences
CT2001	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible	ALL	Reject / Error	Because of the 'false positive'

Activities in 2021

- **Schedule**
  - 2021 Jul: Discuss the deliverables
  - 2021 Aug: Read and Understand all Explanations
  - 2021 Sep-Oct: Discuss how to simplify/standardise the Explanations
  - 2021 Nov-Dec: Create the writing guide for the Explanation
  - 2022 Jan – tbd : Review and update the file

e-Data sub team’s Progress

-System to Collect Issue Summary Explanations-

Collection of Issue Summary Explanations

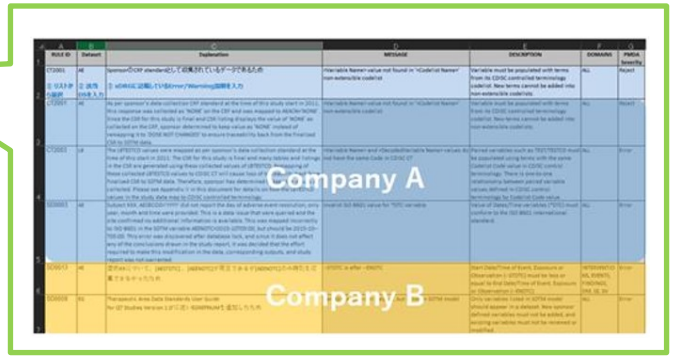
- The purpose of questionnaire is to continuously collect the explanations.
- However, the collection method is to enter manually by user last year.
  → In order to reduce the burden on the respondents,
  1) the input form was improved.
  2) a program to automatically collect issue summaries from XDRG is currently under development.
- Everyone who cooperated for this questionnaire will be provided with the latest Masterfile.

Win-Win cooperation

Cooperative company

If kindly gave a case PHUSE Japan,

then PHUSE Japan returns the latest Masterfile.



1st step: Improvement of input form

Fill in the required information in the ‘Input form’

< Input form [excel sheet] >

Rule ID	Dataset	Explanation	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity
[e.g.] CT2001	AE	SponsorのCRF standardとして収集されているデータであるため	<Variable Name> value not found in <Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL	Reject

CT2001
CT2002
CT2003
CT2004
CT2005
CT2006
SD0001
SD0002

Must be filled

Rule ID : Select the ‘Rule ID’ from the drop-down menu
Dataset : Enter the dataset name
Explanation : Enter the explanation of this error (or warning)

★ MESSAGE, DESCRIPTION, DOMAINS and Severity automatically displays once ‘Rule ID’ is selected.

2nd step: Approach to Automation

xDRG

Masterfile of
P21 Error and Explanation

*Umm, it's time consuming to make reports **manually.** It should be left for later…*

If automated,

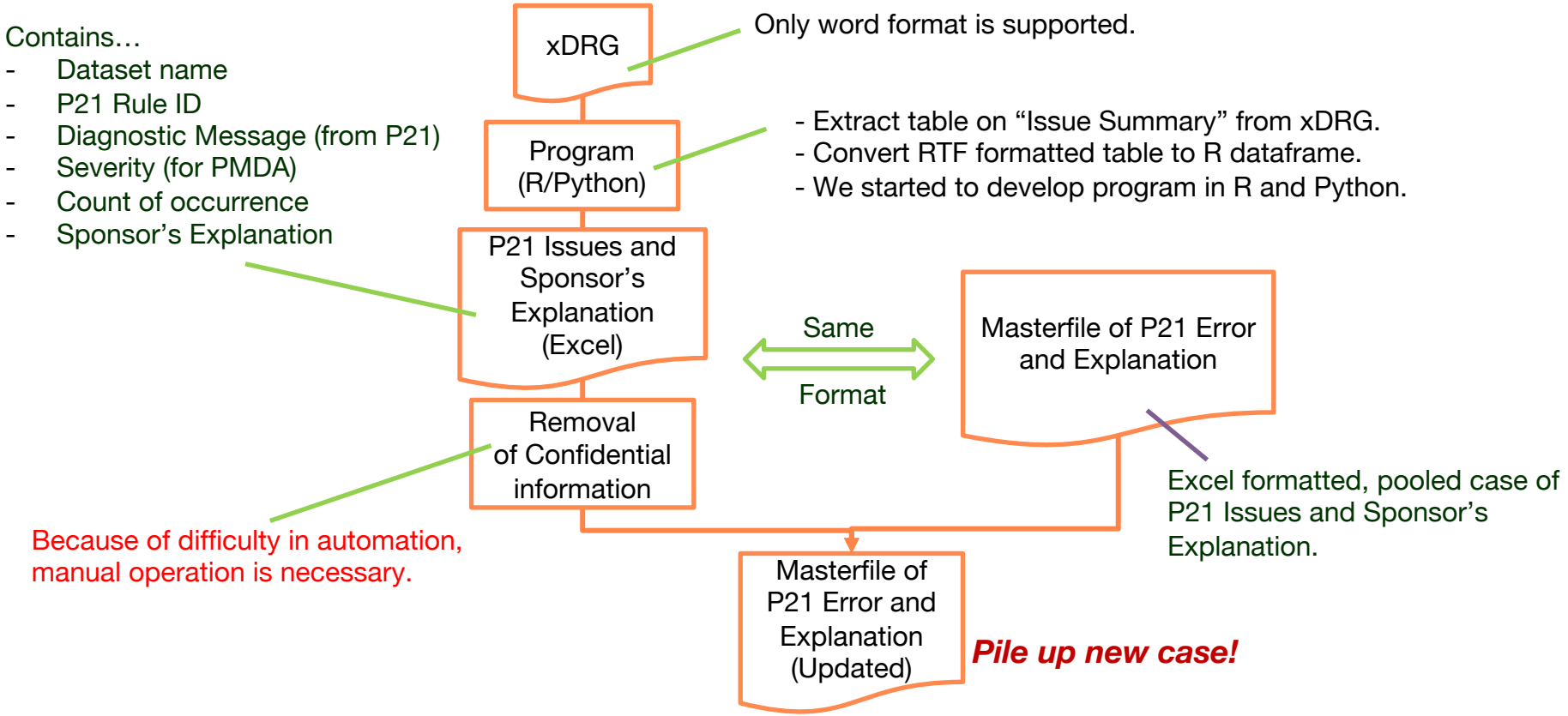
xDRG

Programs

Masterfile of
P21 Error and Explanation

*Just running **programs**? It's easy to make reports.*

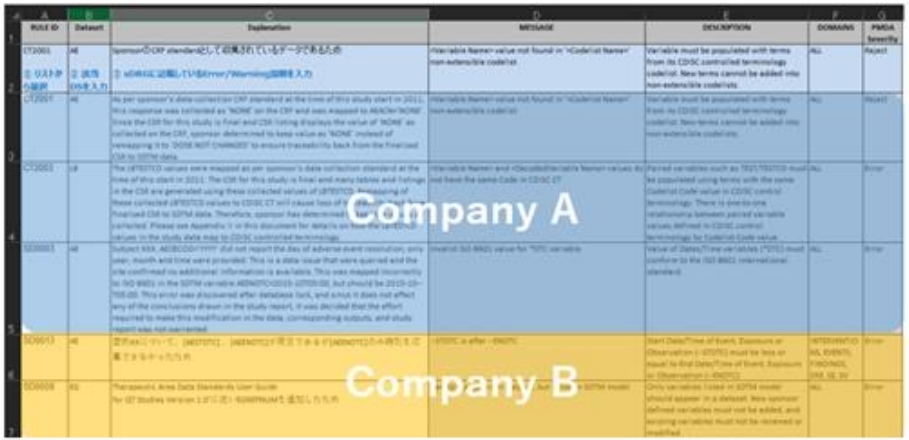
Automation Flowchart



Showing draft

xDRG

Dataset	P21 Rule ID	Diagnostic Message	Severity (PMDA)	Count	Explanation
ADIMMU	AD0150	Inconsistent value for AVAL	Warning	1	Numeric Representation of value has large number of decimal places.
ADLBTOX	AD0127A	ABLFL BASE or BASEC is present but ABLFL is not present	Error	1	Only on treatment values are included in the dataset. So, there is no records marked as baseline record.



Masterfile of
P21 Error and Explanation

e-Data sub team’s Progress

-Optimal use of Consultation on preparation of submission of electronic study data with PMDA-

Optimal use of Consultation on preparation of submission of electronic study data with PMDA

- Our team collected cases of the consultation.
- Content of the questionnaire
  - Background of consultation
  - Consultation content
  - Explanatory material for consultation (PPT, DRGs, SAS datasets, Excel file, etc.)
  - Regulatory response

Results

No.	Background	Consultation content	Explanatory material	Regulatory response
1	How to handle Reject issue in an old study	MedDRA coding was not done in some events.	Word document	The events which MedDRA coding was not done, populated a statement such as "Not coded".
2	Traceability of ADaM datasets	The source of the PK data included in ADaM is an external file, not SDTM. SDTM and ADaM were created separately using same external file as the source.	It was explained using tables in the consultation content document. The document was created in Word, converted to PDF and submitted.	Submit an external file that is the source data for the ADaM dataset. Describe in the data guide.

Results

No.	Background	Consultation content	Explanatory material	Regulatory response
3	The difference of MedDRA version between SDTM and ADaM, or ADaMs	Acceptability of different MedDRA versions within a study	Word document with oral suggestions from sponsor	PMDA did not accept the difference of MedDRA version within a study
4	The difference of MedDRA version between SDTM domains	Since the version of MedDRA is different between MH and AE of SDTM, we checked the version described in define.xml.	It was explained using tables and figures in the consultation content document. The document was created in Word, converted to PDF and submitted.	As for the dictionaries to be used, it is necessary to use a unified version within the same clinical trial as described in 4.1.3 attached to "Revision of Technical Conformance Guide on Electronic Study Data Submissions".

Results

No.	Background	Consultation content	Explanatory material	Regulatory response
5	There are two different ADaM packages in one study and the applicant would like to ask advice from PMDA about how to store them in the m5 folder.	The analysis method was changed during the study. PMDA asked to submit the ADaM datasets before and after the change, so the applicant asked about how to store it in the study folder.	Briefing document and Form A	One should be stored under the adam folder which is a regular folder to be stored, and the other should be stored in the misc folder.

Results

No.	Background	Consultation content	Explanatory material	Regulatory response
6	There are two CRT packages with different dates of data cutoff (DCO) within one study, and the applicant would like to ask advice from PMDA about how to store them in the m5 folder.	There are two CRT packages with different dates of data cutoff (DCO) within one study, and PMDA asked to submit both of them, so the applicant asked about how to store them.	Briefing document and Form A	The study folder should be divided into two, and the CRT package should be stored in each. (Example) Create xyz-dco1 and xyz-dco2 under m5\datasets where xyz is a study id.

Results

No.	Background	Consultation content	Explanatory material	Regulatory response
7	To check if a certain file is required to be submitted as a file for simulation.	Whether the files and its stored folder to be submitted are appropriate.	The proposed cp folder structure, program procedures, and consultation instructions. These documents were created in Word.	Any files related to the model or simulation should be submitted.

Summary

- There were two consultation patterns:
  1. Obtained instructions from PMDA: 5 cases (#1, 2, 5-7)
  2. Rejected by PMDA: 2 cases (#3, 4)

- Sponsors' preference is to avoid converting the FDA compliant study data to meet PMDA requirements. However, PMDA does not always accept FDA compliant study data as is.

Conclusion

- We would like to request PMDA to update FAQs on Electronic Study Data Submission frequently to avoid having consultations for similar cases.
- We suggest sponsors to arrange a consultation on preparation if it is difficult to determine whether the data meet PMDA requirements or not, and/or if anything from PMDA's official notices or FAQs is unclear.
- We suggest sponsors to plan the consultation on preparation ahead in case where a major CRT package revisions are needed.

Member list

Company	Name （mention）
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Eli Lilly	Tomohiko Funai （船井友彦）
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If you are interested in our team…

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