2021 US INTERCHANGE

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Conference | Trade Show

Hybrid Event | 20-21 October

PMDA Update
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Pharmaceuticals and Medical Devices Agency
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• *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC or PMDA.*

• *The author have no real or apparent conflicts of interest to report.*
Agenda

1. Introduction
2. Update of data submission
3. Update of consultation and change of the operation
4. Points to consider on data submission to PMDA
5. Other information
Accumulation and utilization of data

**NDA submission**
- Submission of data
  - Submission of electronic data from clinical and nonclinical studies
  - Storage of electronic data in the dedicated server and registration in the database

**Regulatory Review**
- Use of electronic data
  - Accessible, visualized electronic data for each reviewer
  - Easy to identify individual clinical case data, drilling down of data
  - Operation of various analyses - simple, subgroup analysis for the present

**Utilization of Accumulated Data**
- Integration of cross-products information
  - Utilization of exhaustive information by therapeutic category for review/consultation
  - Internal review on particular theme – e.g.) active utilization of M&S
    - Review on pediatric dosage
    - Preparation of disease model
    - Development of evaluation indicator
  - Utilization in preparation of guideline

Submission of electronic clinical study data has started since Oct 1st 2016!
One and a half years have passed since the transitional period ended…

- Since the transitional period of data submission was ended on March 31, 2020, now we have 1.5-year experiences of the full-scale operation of receiving and using study data at PMDA.

- We summarized the information based on the experiences and provided that to the sponsors at the workshop/conference held in Japan.

- We have changed the operation of the consultation meeting for e-data submission, particularly for the “consultation on data format” from April 1, 2021.

- We will continue to proceed the optimization of the operation, in order to improve the efficiency of the data preparation in industry.
Update of data submission
Data submitted with new drug applications

• 238 NDAs were submitted with electronic study data as of Mar 31, 2021.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of NDAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)</td>
<td>31</td>
</tr>
<tr>
<td>J-FY 2018 (Apr 1, 2018 – Mar 31, 2019)</td>
<td>33</td>
</tr>
<tr>
<td>J-FY 2019 (Apr 1, 2019 – Mar 31, 2020)</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
</tr>
</tbody>
</table>

Since the transitional period ended on March 31, 2020, this number got close to the average number of NDAs per year. The situation will be the same also in the future.
Requests based on the validation results

- We have sent letters of requesting data correction and/or additional explanation of the data at the initial submission of 76/238 NDAs (32%) as of Mar 31, 2021.

<table>
<thead>
<tr>
<th>Year</th>
<th>N of NDAs/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-FY 2016</td>
<td>7/10</td>
</tr>
<tr>
<td>J-FY 2017</td>
<td>13/31</td>
</tr>
<tr>
<td>J-FY 2018</td>
<td>10/33</td>
</tr>
<tr>
<td>J-FY 2019</td>
<td>10/42</td>
</tr>
<tr>
<td>J-FY 2020</td>
<td>36/122</td>
</tr>
<tr>
<td>Total</td>
<td>76/238</td>
</tr>
</tbody>
</table>
Reason of sending letters with requests

In most cases, the reasons of sending letters to applicants were detection of non-compliance with the PMDA Validation Rules categorized “Error” without pre-explanation.

Here are the major reasons, we think, why such situation happens.

• Lack of contents of validation performed by the sponsor in advance
  Please check FAQ1-24 and make sure that all the validations needed have been performed.
  • SDTM datasets and ADaM datasets
  • Consistency between SDTM and ADaM
  • Structure of XML in define.xml
  • Consistency between define.xml and each SDTM/ADaM dataset

• Change of the existence or name of the file which was referred in define.xml, after the validation performed by the sponsor.

• Incorrect description of the version of the standards or the validation rule in define.xml or electronic submission gateway.
To avoid the issues in the data submission process...

Most of the issues that submitted data are not accepted and request is sent to the sponsor can be prevented by confirming the following points in advance, by reference to FAQ.

• The contents and the settings of the CDISC data validation by the sponsor
• The versions of the data standards and the validation rules, included in define.xml or selected in the electronic submission gateway
• The location and the name of the files
Update of consultation and change of the operation
### Consultation related to study data submission

<table>
<thead>
<tr>
<th>Clinical trial consultations</th>
<th>FAQ1-5, as of Mar 31, 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>A sponsor and the PMDA identify which study data and/or analysis data are subject to be submitted electrically.</td>
<td></td>
</tr>
</tbody>
</table>

#### Consultation on preparation of submission of electronic study data

A sponsor and the PMDA discuss contents such as method of storing data, handling of variables, and strategy of storing data which cause the violations of CDISC conformity, regarding study data and/or analysis data planned to be submitted.

#### Consultation on data format of submission of electronic study data

PMDA confirms the validation results, i.e., the explanation of “Error” of violations and the reasons why they cannot be corrected.

#### Consultation on exemption of submission of electronic study data

A sponsor and the PMDA discuss contents such as,
- whether submission of a part of or whole of the study data could be exempted based on Q2 in “Q&A regarding Notification of Basic Principles”
- adequacy of the reason why study data would be submitted in another format than the CDISC standards and sufficiency of the contents based on Q10 in the “Q&A regarding Notification of Basic Principles”

#### Pre-NDA Meeting

The PMDA does a final confirmation of the contents of materials attached to approval application and scheduled submission date. The Sponsor should explain the contents of electronic study data submission using the Attachment 8/Form A.
Consultation related to study data submission

FAQ1-5, as of Mar 31, 2021

Clinical trial consultations
A sponsor and the PMDA identify which study data and/or analysis data are subject to be submitted electrically.

Consultation on preparation of submission of electronic study data
A sponsor and the PMDA discuss contents such as method of storing data, handling of variables, and strategy of storing data which cause the violations of CDISC conformity, regarding study data and/or analysis data planned to be submitted.

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Pre-NDA Meeting
The PMDA does a final confirmation of the contents of materials attached to approval application and scheduled submission date. The Sponsor should explain the contents of electronic study data using Attachment 8/Form A.
Consultation for clinical e-data submission

- 669 consultation meetings have been conducted as of Mar 31, 2021.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of consultations</th>
<th>Year</th>
<th>Number of consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consultation on preparation</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consultation on exemption</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>669</td>
<td></td>
</tr>
</tbody>
</table>
Cases PMDA requests correction of the data based on the validation results

- Datasets with violations categorized as “Reject”
  
  Please correct the data because we cannot receive them.

- Use of non-ASCII or 2-byte characters was detected as the results of the validation
  
  • Ref: Notification on Practical Operation 3(1) a (iii), Technical Conformance Guide 4.1.5

- Use of terminology that is not compliant to MedDRA or use of multiple versions of terminology
  
  • Ref: Notification on Practical Operation 3(1) c, Technical Conformance Guide 4.1.3

  Please consider the data correction first. If it is difficult, we suggest to come to “Consultation on preparation of submission of electronic study data”.

As noted above, there are few cases that PMDA requests correction of the data based on the results of the CDISC validation by sponsor. For other cases, we understand the reason of the violations and reason why they can not be corrected for the data submission.
Change of the operation of the consultation meeting for data submission

- Recently, contents of explanations of results of the CDISC validation performed by sponsors in advance has been improved and has included sufficient information.
- Then there have been no major issues in the conclusion of the “Consultation on data format” meeting in most cases.

From April 1, 2021, sponsors should report the results of the CDISC validation of all the clinical studies for submission at “Pre-NDA Meeting”, and do not need to apply “Consultation on data format of submission of electronic study data”

- Please refer the FAQ1-23 to include sufficient information in the explanation of the errors.
Consultation related to study data submission
From April 1, 2021

Clinical trial consultations
A sponsor and the PMDA identify which study data and/or analysis data are subject to be submitted electrically.

Consultation on preparation of submission of electronic study data
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Pre-NDA Meeting
The PMDA does a final confirmation of the contents of materials attached to approval application and scheduled submission date. The Sponsor should explain the contents of electronic study data submission using the Attachment 8/Form A.
Consultation for clinical e-data submission

After the change of the operation

- The implementation status of the consultation meetings after the change in the operation is as follows.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-FY 2021 (Apr 1, 2021 – Sep 30, 2021)</td>
<td>Consultation on data format</td>
</tr>
<tr>
<td></td>
<td>Consultation on preparation</td>
</tr>
<tr>
<td></td>
<td>Consultation on exemption</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

CDISC 2021 US Interchange | #CDISCUS #ClearDataClearImpact
Points to consider on data submission to PMDA
Selected points to consider on data submission to PMDA

There are some points to consider based on our experiences on receiving study data. Please review them when you submit the data to PMDA or help your Japanese colleagues to submit the data to PMDA.

• CDISC validation performed by sponsor
• Preparation of the materials for the explanation of the data
• The final check of the data to be submitted
• Data submission via Electronic Submission Gateway
CDISC validation performed by sponsor

CDISC validation which is necessary to be performed

Please check FAQ1-24 and make sure that all the validations sponsors need to perform have been performed.

- SDTM datasets and ADaM datasets
- Consistency between SDTM and ADaM
- Structure of XML in define.xml
- Consistency between define.xml and each SDTM/ADaM dataset
CDISC validation performed by sponsor

Version of the standards used in CDISC validation by sponsor

Please make sure that the CDISC validation in PMDA is performed with using the versions of the standards described in the define.xml. The sponsor should perform the validation with the same condition (version).

• Ref: FAQ4-27 (Related)
Explanation of the validation results

Please check the explanation of the violations categorized “Error” in the validation results.

- Rule ID
  - Ref: FAQ1-22

- Severity of the violation based on the PMDA Validation Rules
  - The severity in other region can also be described.

- Correct DOMAIN

- Relationship between rule ID, message, and explanation.
  - Please take care of similar messages/explanations.
CDISC validation performed by sponsor

Version of the PMDA Validation Rules

At the current moment, below will be the points to consider for the future update of the PMDA Validation Rules.

• For the validation by sponsors prior to the submission, a specific version of the PMDA Validation Rules should be used for the data of all clinical trials in the same submission.

• Now we only accept PMDA Validation Rules Ver2.0. Note that even during a term when we accept multiple versions of the validation rules, only one version can be selected and used for one application.

• Please be careful about the application date and the version of the PMDA Validation Rules that can be accepted.
Preparation of the materials for the explanation of the data

Development of Form A and Reviewer’s Guide

Please make sure the following and also avoid any discrepancy between the materials and the define.xml (if applicable).

• Correct combination of the versions of standards
  • e.g., SDTM and SDTM IG

• Correct version of CDISC controlled terminology
  • Version of the CT should be one posted on the NCI website

• The version of the validation tool used will be needed for the investigation when some problems arise in the data submission to PMDA. Please describe all the digits of the version exactly.
  • e.g., “4.0.2”, not like “4.0.0+”

• Particularly in Form A submitted to PMDA, please describe not only software-dependent information such as version of the validation engine, but also the version of the PMDA Validation Rules (2.0 at this moment).
Preparation of the materials for the explanation of the data

Development of Form A and Reviewer’s Guide

If the validation results by sponsor have been explained to PMDA with using Form A “Information about the conformity of electronic data to the CDISC standards”, please make sure that the necessary contents are reflected also in the Reviewer’s Guide.

There are cases that necessary contents were not reflected in the Reviewer’s Guide.

PMDA recommends organizing the necessary explanations in the Reviewer’s Guide and simply referring the Reviewer’s Guide in Form A.
The final check of the data to be submitted

Folder structure and folder name

- Please make sure that the folder structure and folder names follow the PMDA Technical Conformance Guide 3.5.
  - Particularly for the names of folder of SDTM and ADaM datasets, such as “tabulations”, “datasets”.

File name and storage

Please make sure the following.

- Whether the data to be submitted are stored
- The existence, location, name, and format of the file referred in define.xml
- The name of the definition file of the datasets must be “define.xml”.
The final check of the data to be submitted

Version of the standards in the define.xml

Please also make sure that the versions of the standards in the define.xml are acceptable versions by the PMDA Data Standards Catalog.

- Description of an unacceptable version will cause “irregular” validation states.
- Please be careful with the version of IG. ADaM IG v1.1 and SDTM IG 3.3 have not yet been accepted in Japan…
Other information
New and old versions of CDISC standards

- PMDA plans to include the new versions of CDISC standards in the PMDA Data Standards Catalog after the investigation of its impact and development of the validation rules. Also, PMDA plans to exclude the old versions based on the investigation on actual usage in the industry.

<table>
<thead>
<tr>
<th>Standards</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>Under review in PMDA</td>
</tr>
<tr>
<td>SDTM v1.7 &amp; SDTM IG v3.3</td>
<td>Final test for the implementation</td>
</tr>
<tr>
<td>ADaM IG v1.1</td>
<td>Will be reviewed after the implementation of v1.1</td>
</tr>
<tr>
<td>ADaM IG v1.2</td>
<td>Updated contents and impact on the Electronic Submission Gateway will be reviewed</td>
</tr>
<tr>
<td>Define-XML v2.1</td>
<td>Started to investigate the usage in the industry</td>
</tr>
<tr>
<td>Old</td>
<td>Started to investigate the usage in the industry</td>
</tr>
</tbody>
</table>
Submission of COVID-19 related data

- We understand the Therapeutic Area User Guide for COVID-19 related clinical studies and clinical studies impacted by COVID-19, and also the recommendation of storing the non-standard variables by FDA Technical Conformance Guide.

- At the moment, the study data based on these documents are basically accepted when sponsors submitted them to PMDA, but please make sure the following points.
  - Please explain the reference document in the reviewer’s guide.
  - Explanations will be needed when the violations categorized “Error” occur in the CDISC data validation.
  - Please consider to use “Consultation on preparation of submission of electronic study data” when there are any problems with storing the study data.
Submission of non-clinical study data

- Use of non-clinical study data in new drug review is still under discussion by a research group including PMDA toxicology reviewers.
- At this point, we are not able to show the plan and/or schedule.
Summary

• Advanced Review with Electronic Data Project is being executed on schedule and successfully, so far.
  • All data has been successfully received since Oct 1, 2016 and we smoothly shifted to post-transitional phase.

• PMDA will continue to provide consultation meeting according to each situation and information on the data submission for industry.

• 1.5-year full-scale operation of receiving study data, we will review the experiences and will optimize the operation, in order to improve the efficiency of the data preparation in industry.

• We appreciate your continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug, with preparation and submission of standardized study data.
Thank You!

New Drug Review with Electronic Data, PMDA

https://www.pmda.go.jp/english/review-services/reviews/0002.html (English)

https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0003.html (Japanese)