Best Practices for the Submission of Data in Japan

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Contents

Revision History

Version	Date	Summary
1.0	2022-Jul-09	Initial Version

1. Introduction

1.1. Background

Since 1 April 2020, Japanese drug approval applications have required the submission of electronic data. This has increased the need for global project members to understand Japanese regulatory requirements. However, it is not easy for global personnel to understand the notifications issued by the Japanese regulatory agency. In addition, some materials are not translated into English, which will be a barrier to understanding the requirements. The PHUSE Best Practices for the Submission of Data in Japan project was established as a sub-team of PHUSE Japan. One of the activities of the sub-team is to create materials that will help global personnel submit electronic data to the Pharmaceuticals and Medical Devices Agency (PMDA).

1.2. Problem statement

The PHUSE white papers Industry Experiences Submitting Standardized Study Data to Regulatory Authorities[1] and FDA and PMDA Study Data Submission Distinctions[2] discussed differences in preparing standardised data between the Food and Drug Administration (FDA) and the PMDA, and summarised the regulations for electronic data to the PMDA. In order to meet the requirements for electronic data submission to the PMDA, applicants must plan and decide on the best approach to address the Japanese notifications[3] and support deliverables. These methods are almost consistent for all companies and products, and knowing these methods is useful for global personnel communicating with Japanese regulatory authorities, mainly the PMDA. This paper will introduce these available methods.

1.3. Scope

The scope of this white paper is electronic data submission to the PMDA.

1.4. Abbreviations, acronyms and definitions

Term	Description
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ARM	Analysis Results Metadata
CDISC	Clinical Data Interchange Standards Consortium
DM	Demographics
eCTD	Electronic Common Technical Document
EFPIA	European Federation of Pharmaceutical Industries and Associations
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
Gateway system	Application electronic data system
GB	Gigabytes
GUI	Graphical User Interface
CROA	Japan CRO Association
JPMA	Japan Pharmaceutical Manufacturers Association
MHLW	Ministry of Health, Labour and Welfare
PhRMA	Pharmaceutical Research and Manufacturers of America
PK/PD	Pharmacokinetics/Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency
Q&A	Questions and Answers
SDTM	Study Data Tabulation Model

2. Overview

In order to submit electronic data that meet PMDA requirements, it is necessary to create appropriate electronic data based on several materials, including notifications. Figure 1 shows the order and the basis for making decisions when planning PMDA applications.

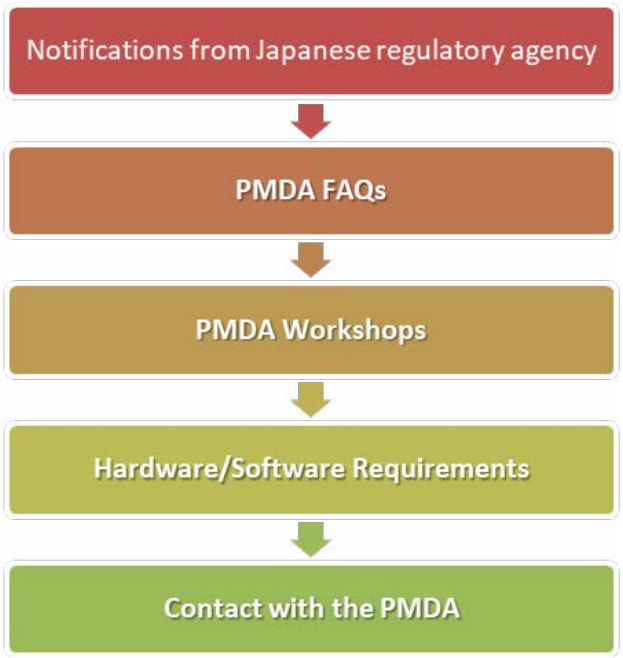

Figure 1 The order and basis for making decisions for PMDA applications

The applicants should refer to the Ministry of Health, Labour and Welfare (MHLW) and PMDA notifications,[3,4] frequently asked questions (FAQs),[5] and PMDA-sponsored workshop materials.[6]

Notifications

The notifications are issued in Japanese and, to date, all notifications have been translated into English. The notifications detail the rules for providing electronic data for submission, such as whether trial data should be based on Clinical Data Interchange Standards Consortium (CDISC) standards. If the requirements cannot be addressed by the notifications, the applicants refer to the FAQs on the PMDA website.

FAQs

The FAQs are updated on an irregular schedule and focus on more detailed topics than the notifications. The PMDA released the Japanese version of the FAQs in April 2019 and posted its excerpt in English on the PMDA's English website. However, the PMDA revised the Japanese version of the FAQs in April 2021, but the English version of the FAQs has remained since April 2019. When referring to the FAQs posted on the PMDA's English website, please keep in mind that the versions posted are different.

The PHUSE Best Practices for the Submission of Data in Japan project has translated some further important Questions and Answers (Q&As), issued in April 2019 and April 2021.

Workshops

If the FAQs do not address the requirements, the applicants can refer to presentation materials at PMDA workshops that have been held every one or two years since 2015. The workshops are open to the public to approach the PMDA with questions. The presentation materials and some Q&A responses are conducted and published on the PMDA website; however, all references are written in Japanese. If you want to read the documents of the PMDA workshops, it is recommended that you ask your Japanese counterparts to help you or translate each file on the translation website.

Hardware/Software requirements

The PMDA requires that electronic data be submitted using the PMDA's application for electronic data system (Gateway system) at the time of application and declares that the PMDA will use Pinnacle 21 for validation. The instructions for the PMDA's Gateway system are accessible on the PMDA website, but written in Japanese only. In fact, the Graphical User Interface (GUI) for the Gateway system is built in Japanese. The available validation rules and versions of Pinnacle 21 are described on the PMDA website.
If the above steps do not resolve the applicant's problem, the applicant should contact the PMDA. One of the methods for enquiry is to have a consultation meeting. There are three frameworks for consultation with the PMDA regarding electronic data submission:

- Consultation on exemption of submission of electronic study data
- Consultation on preparation of submission of electronic study data
- Consultation on data format of submission of electronic study data

Consultation materials are usually written in Japanese but can also be written in English. However, it is necessary to prepare a document that describes the details of the consultation content in Japanese, and the consultation itself is conducted in Japanese.

Another method is to enquire through industry groups. The working group for electronic data submission of the PMDA serves as the contact for four industry groups: the Japan Pharmaceutical Manufacturers Association (JPMA), the Pharmaceutical Research and Manufacturers of America (PhRMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the Japan Contract Research Organization Association (JCROA). Companies that belong to any of these organisations can make enquiries to the PMDA through the industry group.

3. Basis for Making Decisions when Submitting Electronic Data in Japan

3.1. Notifications from the Japanese regulatory agency

The PMDA has mandated the requirements for the submission of electronic data at the time of application for drug approval and the notifications for the electronic data have been issued. Below is a requirement regarding folder structure.

3.1.1 Case study: m5 folder structure

When submitting electronic data to the PMDA, it is necessary to store and submit the data according to the m5 folder structure, as described in the technical conformance guide. (See section 3.5 Folder structure of the technical conformance guide.) The PMDA has its specific regulations on the folder structure: the character limit of the folder name and file name, and the characters that can be used. When submitting the same electronic data package to the FDA, it is necessary to confirm that the deliverables must address PMDA regulations.

3.2. PMDA FAQs

Notifications from the Japanese regulatory agency are updated irregularly, and there are some questions that cannot be answered by notifications. In such situations, the applicant should refer to the PMDA FAQs. The FAQs regarding the electronic data submission are available on the PMDA website. The FAQs are divided into five categories, as described below. Some FAQs have an English translation. The PHUSE Best Practices for the Submission of Data in Japan project translated the remaining untranslated FAQs into English. The FAQs translated into English will be included in the PHUSE Advance Hub. The FAQs in the PHUSE Advance Hub are not endorsed by the PMDA and are provided by the team as a convenience. Sponsors should confirm alignment with the PMDA FAQs for the latest information.

1. Questions on new drug review and consultation
2. Questions on the relationship between electronic submission data and the Electronic Common Technical Document (eCTD)
3. Questions on the electronic submission gateway
4. Questions on CDISC-conformant electronic study data
5. Questions on clinical pharmacology electronic study data

The case studies below are examples of FAQs regarding application electronic data.

3.2.1 Case study: Handling of languages other than English

FAQs Q4-10 and Q4-11 have descriptions about languages other than English in the datasets.

As described in Q4-10, the dataset needs to be created in

English. However, the necessity to translate from a language other than English to English depends on the importance of the relevant variable. If necessary, the applicants will confirm the translation with the PMDA through the preparation consultation. In addition, if a translation is performed, it is necessary to note that in the Reviewer's Guide. As described in Q4-11, the appropriateness of the translation must be validated by the applicants, but it is not necessary to submit a certificate.

3.2.2 Case study: Analysis results metadata in the field of clinical pharmacology

The PMDA's technical conformance guide states that "It is desirable to include Analysis Results Metadata in the definition document for Analysis Data Model (ADaM) datasets."

Q5-30 in the FAQs has a description about Analysis Results Metadata (ARM) in the clinical pharmacology area.

According to Q5-30, in studies with standard pharmacokinetic analysis, applicants are asked to submit ARM for the statistical analyses using Pharmacokinetics/Pharmacodynamics (PK/PD) parameters. However, if the applicants submit the analysis datasets in formats other than ADaM, the applicants don't have to submit ARM.

3.3. PMDA workshops

In the workshops held by the PMDA, common questions and the points to note are related to the mandated submission of electronic data for the application, but some topics in the workshops have no descriptions in the notifications or FAQs. An example is shown below.

3.3.1 Case study: Explanation of additional data errors after the submission for cut-off analysis

For long-term studies, applicants often do the cut-off analyses for the submission and the final analyses after the submission.

At the "Briefing Meeting on the Experience and Points to Consider in Submission of Electronic Data at the Time of Application" held on 28 February 2017, the 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".

3.4. Hardware/Software requirements

When submitting electronic data using the PMDA Gateway system, applicants may encounter issues specific to the system that are not described in the notification. Pinnacle 21 is another system the PMDA mandates for electronic data submission. Applicants must refer to these system requirements.

3.4.1 Case study: Gateway system

- If the file size of one electronic file exceeds 10 Gigabytes (GB) and the file size of all electronic files exceeds 100 GB, it is necessary to contact the PMDA.
- When submitting electronic data through the Gateway system, ensure that the file name and folder name do not use prohibited characters. In particular, ensure that the file name does not use uppercase letters.

3.4.2 Case study: Pinnacle 21

- For FDA submission, the variable of the Study Data Tabulation Model (SDTM) Demographics domain, DM.ARM (Description of Planned Arm; required) for Screen Failures is set to blank, but for PMDA submission, a blank will cause an error. When applying to the PMDA, describe the reason in the issues summary of the Reviewer's Guide.
- When performing Define validation with Pinnacle 21, please note that the categories of ADaM Class differ depending on the ADaM Implementation Guide (ADaMIG) version. Currently, the supported ADaMIG version is different between the FDA and the PMDA. In ADaMIG v1.0, "Occurrence Data Structure" does not exist in the category.

3.5. Contact with the PMDA

The PMDA provides consultation on the submission of electronic study data at three frameworks regarding electronic data submission and two regarding general topics including electronic data. For the category of consultations and points to consider, please refer to PMDA FAQ Q1-5. The data and file size to be submitted at the time of application will be explained in the preliminary interview scheduled for a new drug approval examination.

There is a working group for electronic data submission to the PMDA that meets with JPMA, PhRMA, EFPIA and JCROA organisations to answer general questions regarding electronic data submission and Gateway systems. However, the questions are limited to general topics, and topics specific to a company or project are not allowed. Enquiries are open to the public, but Q&As are conducted in Japanese. In addition, the PMDA has an email address for enquiries regarding the next-generation examination/consultation system. Enquiries about the homepage for general electronic data applications can be made in English, but enquiries about the Gateway system are in Japanese.

4. Recommendations

Although notifications are available in English and global personnel can obtain basic information on applications in Japan from them, if you refer to more detailed information or communicate with the PMDA, content and communication in Japanese are inevitable. Therefore, it is recommended to collaborate with colleagues who understand Japanese (for example, Japanese counterparts) to prepare PMDA applications.

5. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members, respective companies/organisations or regulators' views or policies. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities.

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8. References

1 Industry Experiences Submitting Standardized Study Data to Regulatory Authorities

2 FDA and PMDA Study Data Submission Distinctions

3 Japanese notifications
- Notification of Basic Principles (March 18, 2020)
- Q&A Regarding Notification of Basic Principles (March 18, 2020)
- Notification on Practical Operations (January 24, 2019)
- Q&A Regarding Notification on Practical Operations (March 18, 2020)
- Technical Conformance Guide (January 24, 2019)

4 ICH M8/PMDA: Notifications regarding eCTD
- Approval Application with Electronic Common Technical Document (eCTD) (July 5, 2017)
- Appendix 4: Specification for Submission Formats for eCTD v1.2 (June 5, 2018)
- Partial amendment of "Handling of digitized specifications of common technical documents" (August 24, 2016) (Japanese language only)

5 PMDA: FAQs on Electronic Study Data Submission (Excerpt)
- FAQs on Electronic Study Data Submission (April 2019)

6 PMDA: Workshop materials (Japanese language only)

9. Appendix

9.1. FAQs about application electronic data (partially translated)

Of the FAQs related to electronic data submitted in April 2021, the PHUSE Best Practices for the Submission of Data in Japan project selectively translated FAQs. FAQs translated by the PMDA into English, however, are based on the excerpt of April 2019. If the FAQs have been updated and translations by the PMDA added, please refer to the PMDA FAQs.