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# Electronic Submission and Utilization of CDISC Standardized Clinical Study Data in Japan

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In Japan, the submission of subject-level electronic clinical study data for new drug applications began on October 1, 2016 and included a transitional period that expired on March 31, 2020. Currently, most new drug applications (NDAs) require the submission of electronic clinical study data, which are considered important to provide information about a drug at the review and are required by the Pharmaceuticals and Medical Devices Agency (PMDA).

Standardization of submitted electronic clinical study data is essential to efficient review, using data analyses for applications of various drugs submitted by multiple companies given limited review time and human resources. For most clinical trials, the PMDA requires study data to be submitted in accordance with CDISC standards.

This paper provides an overview of the advanced review with electronic data project and the current state of electronic data submission in Japan, as well as future expectations for data standards, based upon the experiences of receiving and utilizing CDISC-compliant clinical study data at the PMDA.

**Keywords:** new drug application; CDISC validation; regulatory submission

## Background of Electronic Data Submission in Japan

In recent years, the utilization of advanced analytical methods using data obtained at any stage in new drug development for efficient drug development has been widely discussed. The "Health and Medical Care Strategy"[1] mentions that the Pharmaceuticals and Medical Devices Agency (PMDA), the regulatory review agency in Japan, should promote research and analysis based on clinical study data as one factor strengthening the agency. Considering this background, and with the aim of a more rational and efficient evaluation in review and consultation, as well as greater predictability of efficacy and safety of the drugs, the PMDA initiated the project for the submission of subject-level clinical study data with new drug applications (NDAs) and their use in the regulatory review process. The primary purpose is to use the submitted study data for the review of each drug. Additionally, it has been considered that the accumulated study data of multiple drugs, such as drugs that have the same mechanism of action, can be used for cross-product analysis, which will be useful for building a knowledge base for reviewing similar drugs.

## Activities of the Project

The PMDA conducted pilot studies using clinical study data voluntarily submitted by pharmaceutical companies from the second half of 2013 to 2015 to inform the regulations regarding study data submission and the process of new drug review.[2] The Ministry of Health, Labour and Welfare (MHLW) issued the "Basic Principles on Electronic Submission of Study Data for New Drug Applications" in 2014 and the "Notification on Practical Operations of Electronic Study Data Submissions" in 2015.[3,4] The PMDA also issued the "Technical Conformance Guide on Electronic Study Data Submissions"[5] based upon the experiences of the pilot studies. These documents clarify the scope of data submission, the standards to be followed for study data, and other technical details. The PMDA also published the Data Standards Catalog on standards and their versions to be used when submitting data, and the Frequently Asked Questions website to promptly answer detailed technical questions. The PMDA began offering consultation meetings related to the submission of electronic study data in 2015. Consultation meetings were later divided into three categories: consultation on exemption, preparation, and format of submission of electronic study data – each with different aims.

The PMDA officially started accepting electronic data submissions in October 2016, with a 3.5-year transitional period. Since April 1, 2020, subject-level clinical study data in an electronic format have been submitted with most new drug submissions. The notifications and other related documents have been revised appropriately, based on the knowledge gained as the project progresses and the experiences of the actual review of submitted data. The latest revision of the notifications was issued in April 2022. The two separate notifications were combined into a single notification after addressing overlapping content.[6] In addition, matters relating to the use of the Electronic

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Submission Gateway were removed and combined into a new notification. As for consultation meetings on electronic data submission, the required consultation categories have been reviewed and clarified according to compliance with the notifications and the quality of the actual submitted data. Please refer to the PMDA website for the most recent information.[7]

## Implementation of CDISC Standards

The PMDA recognized that standardization of data would be critical to introducing the use of electronic study data in the new drug review process without increasing the review period. Data standardization will also play a key role in the future utilization of the accumulated study data. Although the clinical studies and analyses included in NDAs are diverse, many types of clinical studies and analyses require their data to be submitted in compliance with the CDISC standards in Japan.

From the beginning of the project, the PMDA planned to introduce CDISC standards, which are international standards for clinical study data for regulatory review and requested the submission of CDISC-compliant data in the pilot study to understand the features of the standards through exposure to actual clinical study data. Based on the experience gained from the initial pilot studies conducted to confirm the feasibility of data submission and utilization, the PMDA considered which data and related materials should be submitted, using which standards. As a result, the notifications and the guide noted that Study Data Tabulation Model (SDTM) datasets, Analysis Data Model (ADaM) datasets, their definition files in Define-XML format, and annotated Case Report Form (CRF) should be submitted. It was also specified in the notifications that the Reviewer's Guide for each of the SDTM and ADaM datasets, the programs for analysis, and the programs for the creation of ADaM datasets should be submitted. The information about datasets that was found to be particularly useful in the pilot study was Analysis Results Metadata, which is essentially contained in define.xml. In the first stage of the new drug review process, the reviewers generally review the clinical study results presented in the submitted materials, such as Clinical Study Reports. If there is something they would like to investigate further, they analyze the relevant data. In such a review procedure, the information that details the relationship between the study results and analysis datasets is very useful. Submission of the Analysis Results Metadata is strongly recommended in the Technical Conformance Guide.

The PMDA introduced CDISC data validation using validation software at the time of data submission/receipt through the Electronic Submission Gateway to check the compliance of the study data with CDISC standards and to maintain the quality of data from the aspect of data standardization and utilization.[6] The rules used for the validation are published on the PMDA website and are updated as necessary — such as, for example, when a new version of a standard is accepted. Each validation rule has one of three severity levels based on its importance: a violation of a rule with severity of "Reject" requires the sponsor to correct the data, a violation of a rule with severity of "Error" requires correction of data or an explanation of the reason for the violation in the Reviewer's Guide, and a violation of a rule with severity of "Warning" does not require any actions by the sponsor but will provide additional information about the data to the reviewers. The explanations for non-compliance are important for reviewers to understand the characteristics of the study data depending on the specific study design during analysis of the data in a limited review period.

## Current Situation of Study Data Submission in Japan

**Table 1** lists the number of consultation meetings for electronic data submission. Since the consultation system was established in 2015, the number of consultation meetings has continued to increase. In particular, the number of "consultations on data format" was highest in 2020. The major reason for this high number was that the transitional period ended in the last fiscal year.

**Table 1:** Number of Consultation Meetings for Electronic Data Submission.

| Japanese fiscal year | | | Number of consultations |
|---|---|---|---|
| 2015 (May 15, 2015–Mar 31, 2016) | | | 11 |
| 2016 (Apr 1, 2016–Mar 31, 2017) | | | 55 |
| 2017 (Apr 1, 2017–Mar 31, 2018) | | | 70 |
| 2018 (Apr 1, 2018–Mar 31, 2019) | | | 90 |
| 2019 (Apr 1, 2019–Mar 31, 2020) | Consultation on data format | 114 | 161 |
| | Consultation on preparation | 44 | |
| | Consultation on exemption | 3 | |
| 2020 (Apr 1, 2020–Mar 31, 2021) | Consultation on data format | 207 | 282 |
| | Consultation on preparation | 57 | |
| | Consultation on exemption | 18 | |
| Total | | | 669 |

The results of the CDISC validation of the study data had to be explained in consultation meetings prior to all data submissions. In addition, results were allowed to be explained in several separate consultations for one submission. As noted above, based on the readiness of data submission in the industry and the quality of the submitted data, the contents of the consultations were reviewed. As of April 2021, it is no longer necessary to request consultation on data format solely to explain the results of the CDISC validation.

**Table 2** shows the number of NDAs for which electronic study data were submitted. Note that the period until March 31, 2020, was the transitional period, and data submission was not necessarily required during that period. Even during the transitional period, the study data were submitted for a certain number of new drug applications. The number of applications after 2020 is expected to be close to the number of NDAs annually. **Table 2** also shows the number of NDAs that required additional actions, such as data correction or additional explanations for validation errors, during the data submission process. Although the percentage of such NDAs is around 30% **(Table 2)**, there were few cases where data correction was required. In most cases, the reason additional actions were needed was because of a lack of explanations for validation errors caused by, for example, a lack of validations done by applicants in advance of data submission, or discrepancies of versions of standards between descriptions in the define.xml and input to the Electronic Submission Gateway.

## Utilization of Submitted Study Data

The submitted data are used to review the new drug from the early stage of the review process in the New Drug Review Offices of the PMDA. There are three major purposes /timings in the review process during which the reviewers analyze the data: for the initial discussion on approval or disapproval at the first review team meeting, to organize the inquiries to the sponsor with further review after the first review team meeting, and for supporting the discussion at the meeting with external experts. The reviewers not only confirm the reproducibility of the primary analyses but also perform various analyses based on the review issues in the limited time available for review. For most NDAs, high-quality data compliant with CDISC standards have been submitted with appropriate metadata and there have been few instances of reviewers inquiring with sponsors about the contents of the data. At present, the sponsors provide the results of the analyses in the review report. However, in the background of developing the review report, various internal analyses are conducted to support PMDA review, and it is expected that the review process will become more sophisticated in the future based on more active data analyses. Furthermore, the PMDA is considering utilizing the accumulated study data in review-related activities, such as the preparation of guidelines related to drug evaluation, to contribute to drug development.

## Summary

Submission of subject-level electronic clinical study data for new drug applications has progressed smoothly within a relatively short period in Japan. The study data were utilized in the review process without major issues and the regulations were appropriately updated according to the quality of the data. This is largely because most of the submitted study data are compliant with the CDISC data standards and sufficient metadata are submitted. CDISC standards are critical to the review of new drugs, and efficient review using standardized data will be further promoted. Continual updates of the CDISC standards and further dissemination with a view to utilizing various data sources in drug development are expected.

## Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the official views of the Pharmaceuticals and Medical Devices Agency.

## Competing Interests

The author has no competing interests to declare.

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**Table 2:** Number of New Drug Applications (NDAs) for Which Electronic Study Data are Submitted and NDAs that Need Additional Actions during the Data Submission Process.

| Japanese fiscal year | Number of NDAs | Number of NDAs that needed additional actions |
|---|---|---|
| 2016 (Oct 1, 2016–Mar 31, 2017) | 10 | 7 (70%) |
| 2017 (April 1, 2017–Mar 31, 2018) | 31 | 13 (42%) |
| 2018 (April 1, 2018–Mar 31, 2019) | 33 | 10 (30%) |
| 2019 (April 1, 2019–Mar 31, 2020) | 42 | 10 (24%) |
| 2020 (April 1, 2020–Mar 31, 2021) | 122 | 36 (30%) |
| Total | 238 | 76 (32%) |

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