

Notification number: 0620-6

June 20, 2014

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles on Electronic Submission of Study Data for New Drug Applications

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the system of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) with respect to both quality and quantity, and the Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that PMDA shall take the initiative in utilizing clinical data for its reviews.

With this, from fiscal year 2014, the Ministry of Health, Labour and Welfare has been providing support for PMDA for establishing its system to collect and analyze clinical study data for efficient development of orphan drugs, etc. as a part of the Initiative to Facilitate Development of Orphan Drugs. PMDA also established the Task Force for Advanced Review and Consultation with Electronic Data on September 1, 2013 and reorganized it into the Advanced Review with Electronic Data Promotion Group on April 1, 2014 to discuss specific operations of reviews and consultations that will further utilize the application data.

Based on the results of discussions we have had, we have compiled the principles entitled “the Basic Principles on Electronic Submission of Study Data for New Drug Applications” as shown in the Appendix in order to start accepting electronic study data from fiscal year 2016. We ask you to inform marketing authorization holder placed under your administration to utilize it for their business operations.

Please note that this notification describes only the general principles and that the details regarding electronic submission of study data for new drug application will be notified at

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

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a later date.

Please also be informed that the copy of this notification is also released to Federation of Pharmaceutical Manufacturers' Associations of JAPAN (FPMAJ) and other related associations.

Appendix

Basic Principles on Electronic Submission of Study Data for New Drug Applications

1. Background for requiring electronic study data submission of application

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the system of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) with respect to both quality and quantity, and the Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that PMDA shall promote its analyses and research by utilizing study data (e.g., clinical data) and shall establish a rational and efficient process for making evaluations and decisions in its reviews and consultations.

In order for PMDA to take initiative to conduct its analyses and research using data, it is important for the clinical data, first of all, to be submitted in an electronic format. Collecting clinical study results in the format of electronic data will enable various analyses to be conducted in application reviews for individual products, which will allow more objective and scientific decisions to be made and further contribute to an increase in the quality of its reviews. Uniform methods of collecting study data from various products will also allow product cross-sectional evaluations and may enable utilization of modeling and simulation. This modeling and simulation is an approach that has recently been gaining much attention and is expected to enable more accurate predictions, for example, of the relationship between pharmacokinetics and clinical effect, dose-response of clinical effect, and course of a disease and its prognosis. Promotion of research using the collected electronic study data is expected to contribute to increase efficiency of the developments of orphan drugs and pediatric drugs, which may have higher chances to face obstacles due to difficulty in collecting data for their small number of patients and due to their yet established evaluation methods.

Meanwhile, electronic clinical study data submission on an application is thought to provide many advantages for the applicants as well. Firstly, utilizing results obtained from various analyses conducted at PMDA, utilized in reviews and scientific consultations, may increase both the efficiency and success rate of drug development for the applicants. Secondly, electronic submission is thought to reduce the burden of the applicants when submitting applications. For example, many inquiries from PMDA in the present reviews

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required applicants to reanalyze clinical study data, but by having PMDA conduct those analyses, the inquiries are expected to reduce in number or to become more clarified. Furthermore, establishment of clinical data collection in Japan based on the widely and internationally used electronic format may not only allow both PMDA and the applicants to conduct appropriate and the latest analyses and evaluations with the consideration of international cooperation, but may also promote multi-regional research and development.

2. Products and data subject to electronic submission

1) Subject products

Applications for new drugs, which are categorized into from (1) to (7), (9) and (9-2) listed in the appendix 2-(1) of the notification entitled “Approval Application of Pharmaceuticals” (published on March 31, 2005; Notification No. 0331015, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), are subject to electronic submission.

2) Subject data

For data that will be submitted by the applicants as evaluation data, the below listed, in principle, are required to be electronically submitted according to each subject.

- 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 dosage and administration.
- b. For study results from phase I studies and clinical pharmacology studies, results from studies listed below are required to be electronically submitted.
 - Phase I studies of oncology drugs.
 - Phase I studies that have been conducted on both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies).

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- QT/QTc studies based on ICH E14 guideline.

Regarding other phase I and clinical pharmacology studies, studies submitted as reference material and studies other than stated above, their electronic study data (including datasets used in population analyses) are not necessarily required to be submitted, but they may become required if PMDA concludes it necessary.

In cases where integrated analyses have been conducted for multiple study results on efficacy or safety, the datasets for those analyses results (integrated summary of safety [ISS]/integrated summary of effectiveness [ISE]) may also be required to be electronically submitted.

Please note that utilization of electronic data for studies other than clinical studies (e.g. nonclinical studies) and for clinical studies conducted after approval are also concurrently being discussed, and that study types subject for submission of electronic data may possibly be modified in the future.

3. Electronic data and its method of submission

1) Data standards for submission

Clinical study data subject for submission should be in a format conforming to the standards according to the Clinical Data Interchange Standards Consortium standards (hereinafter referred to as CDISC standards).

Conformity of the electronic submission data to the CDISC standards must be ensured under the responsibility of the applicants.

Based on the applicants' current condition of preparing analysis data, the clinical pharmacological data for analysis are being considered for submission according to standards other than the CDISC standards, and the details regarding this submission will be notified at a later date.

2) Format of electronic data required for submission

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Individual study data should be prepared using the Study Data Tabulation Model (SDTM) and be submitted along with the definition file for variables (e.g. Define.XML). For analysis datasets, the dataset based on the Analysis Data Model (ADaM) should be submitted along with its definition file (e.g. Define.XML) and the program for creating the ADaM dataset.

For electronic data on ISS and ISE, if PMDA judges it to be necessary, in principle the dataset based on ADaM, its definition file (e.g. Define.XML), and the program for creating the ADaM dataset should be submitted, but it is recommended that before making a submission the applicants individually consult with PMDA regarding details of what to submit.

Although analysis dataset which is created in a format other than ADaM maybe acceptable in some cases as an exception, applicants are to individually consult with PMDA regarding details of what to submit (including definition files and programs for creating the analysis dataset).

PMDA is planning to develop a system for electronic data submission on condition that only English will be used in items that have controlled terminology and a codelist recommended by CDISC standards. In cases where an item has no controlled terminology or codelist recommended by CDISC standards, those items are also required to be recorded in English if possible, but Japanese will be allowed for items that are considered both necessary and appropriate to be written in Japanese (e.g. written explanations and the physician's comment on the course of each case).

The specific electronic data items that will be required for submission will be notified at a later date based on future discussions, along with the details regarding what items will be allowed to be written in Japanese and the methods of their submission.

3) Submission of analysis program

In order for PMDA to confirm the analysis results provided by the applicants, in principle the primary analysis program for the primary endpoint in a confirmatory study should be submitted. Other analysis programs (secondary analysis program, analysis program for items other than primary endpoints, or analysis program for

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studies other than confirmatory studies) will be individually judged for their necessity to be submitted, with the consideration of the importance of both the study and the endpoints in the review. Before submitting their data, applicants are to individually consult with PMDA for the details of what to submit. Additional programs may be required to be submitted even after an application if a further evaluation is judged necessary during the process of review.

In principle, an analysis program is to be submitted for those whose data source is from the ADaM dataset. However, if the analysis dataset has been created as an exception in a format other than ADaM, the applicant is to individually consult with PMDA prior to submission regarding the analysis dataset and analysis program.

Depending on the property of the analysis system that the applicant used, the details of the analysis may be required to be individually explained in cases where there is difficulty using that analysis program or if the analysis results cannot be reproduced at PMDA.

4) Preparing electronic data and the code to be used

The CDISC standards and the MedDRA version for preparing electronic data will be accepted in multiple versions including not only the latest but also the former version, considering the difference in the timing of the study conducted or of dataset created. The details of this will be notified at a later date based on future discussions.

Regarding coding while preparing electronic data, in principle, the controlled terminology and codelist are to be those recommended by CDISC and the values are to be in SI units. The specific coding and units that are acceptable will be notified at a later date based on future discussions.

4. Relationship of electronic data submission and eCTD

With the requirement to electronically submit clinical study data, all necessary documents and data in an application, in principle, should be submitted in accordance with eCTD. Subject data included in eCTD, method and timing of submission, the specific eCTD folder in which to store the individual electronic data, and other details will be notified at a later date based on future discussions. For applications in which the

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clinical data will be electronically submitted based on CDISC standards, submission of case report tabulations in eCTD is currently being discussed so that it will not become a requirement.

Furthermore, with the requirement to submit in eCTD format, electronic reviews and abbreviated submissions in paper are currently being discussed. The details of the subject data, range, and timing will be notified at a later date based on future discussions.

5. Consultation process regarding electronic data

Many matters regarding electronic submission of study data for new drug application require individual judgment, and in order for reviews to be conducted smoothly, applicants are recommended to consult prior to application the Consultation on Electronic Submission of Study Data for New Drug Application (tentative), which will be newly established at PMDA in the future. The consultation timing, content, process, and other details will be notified from PMDA at a later date based on future discussions.

The period from the issuance of this notification until the time when consultations are formally started at PMDA will be a pilot period, for products expected to be submitted by fiscal year 2017, in which matters regarding electronic submission can be consulted at pre-consultation meeting.

6. Information management regarding electronic data submission

Electronic data will be a submission requirement as a part of the application data, and its disclosure as an administrative document will be based on the principles and procedures specified in the Freedom of Information Act, as it is with the present application data. Therefore, the content of the submitted electronic data will not be accessed by a third party without confirmation by the applicant regarding a possibility to disclose the data. However, information may be shared with pharmaceuticals regulatory affairs authorities overseas based on a confidentiality agreement. Electronic data for each subject can only be accessed by relevant people from PMDA or Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare (including staff

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members of PMDA or Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare, and contractors who are in charge of the system in PMDA under a confidentiality agreement), and those data will be appropriately stored and managed so that their integrity is protected within PMDA.

7. Relationship between electronic data submission and conformity inspection

For conformity inspection of application data, the CDISC standards such as the Clinical Data Acquisition Standards Harmonization (CDASH) are encouraged to in the future be used from the time of data collection via electronic case report forms. In compliance assessments of study results whose data for clinical study reports were collected based on those electronic data, more efficient methods of assessment will be discussed with the consideration to reduce the burden of applicants based on the 5-Year Clinical Trials Vitalization Plan 2012 (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, March 30, 2012), which states the implementation of CDISC standards is being discussed as “further utilization of IT technology”.

For the time being, even in cases where study data for the application are electronically submitted, conformity inspection will be conducted in the present manner, including submission of case report tabulations, based on the Procedures of Document-based Compliance Assessment and GCP On-site Inspection Regarding Submitted Data for Drug Application (PMDA Notification No. 1012063 of the Pharmaceuticals and Medical Devices Agency, dated October 12, 2012).

8. Initiation timing of electronic data submission

Electronic data will be a requirement for those products that are submitted for application from fiscal year 2016, starting from a date that will be notified later.

An interim measure will be set for a certain period (about 2 years), and during this period, electronic data will not necessarily be required to be submitted, as in present applications. However, it is desirable for electronic data to be submitted as a requirement for all subject products as soon as possible.

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During the interim measure period, in cases where data cannot be submitted based on CDISC standards for all studies whose electronic submission is judged necessary, responses for inquiries from PMDA during the process of reviews, as in the present applications, are required to be submitted after conducting necessary analyses.

9. Glossary

- Clinical Data Interchange Standards Consortium (CDISC)

CDISC is an interdisciplinary nonprofit organization that establishes international standards for data collection, interchange, application, and storage for the purpose of promoting interoperability of clinical research data. The standards established by CDISC are adopted by the United States FDA as the standards for accepting application data. See CDISC's website (<http://www.cdisc.org/>) for more details.

- Study Data Tabulation Model (SDTM)

SDTM is one of the standards established by CDISC for the purpose of promoting submission of electronic applications to the administration regarding data on individual patients in clinical trials.

- Analysis Data Model (ADaM)

ADaM is one of the standards established by CDISC for the purpose of promoting submission of electronic applications to the administration regarding datasets for which it is necessary to conduct statistical analyses based on clinical trial data.

- Clinical Data Acquisition Standards Harmonization (CDASH)

CDASH is one of the standards established by CDISC for the purpose of electronically harmonizing the data items of case report forms at medical institutions.