Provisional Translation (as of June 2022)*

PSEHB/PED Notification No. 0401-10
April 1, 2022

To: Prefectural Health Department (Bureau)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Notification on Handling of Submission of Electronic Study Data for New Drug Applications

Regarding review for approval of the marketing of drugs (hereinafter referred to as "approval review"), the "Japan Revitalization Strategy - Japan is BACK -" (adopted by the Cabinet on June 14, 2013) indicates that it is essential to strengthen the system of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"), and the "Healthcare and Medical Strategy" (an agreement among relevant ministers, June 14, 2013) further states that the PMDA itself shall carry out analyses and research by utilizing clinical data, etc.

With this, regarding the submission of electronic study data at the time of new drug applications for the marketing of drugs, the basic principles and the practical operations have been notified in the "Basic Principles on Electronic Submission of Study Data for New Drug Applications" (PFSB/ELD Notification No. 0620-6, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 20, 2014; hereinafter referred to as "notification of basic principles") and in the "Notification on Practical Operations of Electronic Study Data Submissions" (PFSB/ELD Notification No. 0427-1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated April 27, 2015; hereinafter referred to as "notification on practical operations"), respectively.

Based on the experience of submission of electronic study data, we have decided to consolidate the notification of basic principles and the notification on practical operations and summarize them as shown in the Appendix; therefore, we ask you to inform manufacturers and sellers placed under your administration to utilize them for their business operations.

Further details and precautions on submission of electronic study data for new drug applications are separately specified by the PMDA in the "Technical Conformance Guide on Electronic Study Data Submissions" (PMDA/CPE Notification No. 0401003 and PMDA/CRS

* 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.

Notification No. 0401001, by the Director of Center for Product Evaluation and the Director of Center for Regulatory Science, Pharmaceuticals and Medical Devices Agency, dated April 1, 2022; hereinafter referred to as “technical conformance guide”), which should also be referenced.

In accordance with the release of this notification, the notification of basic principles and the notification on practical operations are abolished.

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Appendix

Notification on Handling of Submission of Electronic Study Data for New Drug Applications

1 Background for requiring electronic study data submission

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the system of the PMDA, and the Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that the 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 the PMDA to take initiative to conduct its analyses and research using data, it is important for the clinical study data, first of all, to be submitted in an electronic format. Collecting clinical study data 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 electronic study data from various products will also allow cross-product evaluations and may enable utilization of modeling and simulation. The 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 increasing 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 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 the 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 the PMDA in the present reviews required applicants to reanalyze clinical data, but by having the 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 the PMDA and the applicants to conduct the appropriate and latest analyses and evaluations with the consideration of international cooperation, but may also promote multi-regional research and development.

Electronic data of clinical study may be submitted at time points other than when new

drug applications are made, such as when an application for re-examination or post-approval surveillance of quality, efficacy and safety of conditionally approved drugs (hereinafter referred to as "interim evaluation") is made and when the evaluation of study results is practically carried out before new drug applications. This notification will use "electronic study data" as a collective term for electronic data of clinical study that are submitted at all time points.

2 Products and data subject to electronic study data submission

Products and data subject to electronic study data submission are as follows. Please note that utilization of electronic data for studies other than clinical studies (e.g. nonclinical studies) and so on are also concurrently being discussed, and that study types that require submission of electronic study data may possibly be modified in the future.

(1) Submission of electronic study data for new drug applications

a. 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" (PFSB Notification No. 1121-2, by the Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014), are subject to electronic submission. The submission of electronic study 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.

b. Subject data

The data that are subject to electronic submission for new drug applications include evaluation data that are considered to provide the major evidence for the efficacy, safety, and dosage and administration as well as data on studies or analyses that are considered to contribute to the establishment of the dosage and administration and are focused on the evaluation of efficacy, safety, or pharmacokinetics.

For studies and analyses data that will be submitted by the applicants, the below listed, in principle, are required to be electronically submitted according to each subject. However, the submission of electronic study data may not be necessary for studies with special circumstances for which it is difficult to prepare electronic study data, such as data that had not been stored electronically in studies conducted in the past, etc.

For an application for partial changes, it is not necessary to resubmit electronic

study data that have already been electronically submitted at the time the approval was obtained. However, if results of this clinical study are part of an integrated analysis in relation to the application for partial changes or if additional analyses have been performed, the submission of relevant electronic study data may be requested.

(a) Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be a major evidence for evaluation of efficacy, safety, and dosage and administration, which are submitted as the evaluation data.

(b) Data on results from the following phase I studies and clinical pharmacology studies.
- 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).
- QT/QTc studies based on the ICH E14 guideline.

For phase I studies of oncology drugs, in general, a phase I study that provides a rationale for the dosage and administration for phase III studies is applicable. Regarding phase I studies conducted in Japanese and non-Japanese subjects, electronic study data must be submitted regardless of whether the phase I study was performed as part of a global clinical trial or in a single region. In relation to QT/QTc studies based on the ICH E14 guideline, submission of electronic study data is required as "Other data" shown in (c) below for clinical pharmacological analyses (drug concentration-response analysis, etc.) conducted as an alternative to QT/QTc studies.

(c) Other data
- Other phase I studies and clinical pharmacology studies, studies submitted as reference data and studies other than stated above

Regarding other phase I studies and clinical pharmacology studies, population analyses, and physiologically based pharmacokinetic model analyses, data on studies or analyses that are considered to contribute to the establishment of the dosage and administration and are focused on the evaluation of efficacy, safety, or pharmacokinetics need to be electronically submitted. Electronic study data on other studies and analyses are not necessarily required to be submitted, but submission may be required for reference data that are considered to provide major evidence for the dosage

and administration, etc. if the PMDA concludes it necessary.

- Integrated Summary of Safety (ISS)/Integrated Summary of Effectiveness (ISE)

  Regarding analyses that integrate efficacy or safety results of multiple studies, if integrated analyses of multiple clinical studies were performed for the assessment of specific efficacy or safety, such as assessments in special populations or to understand the characteristics of rare adverse events, and their results provide the important evidence for the assessment of efficacy, safety, and dosage and administration of the product submitted for the application, then submission of electronic study data is required.

(2) Submission of electronic study data for applications for re-examination or middle assessment

Electronic submission of post-marketing study data may be requested upon the application for re-examination or middle assessment. Regarding products for which new drug applications are made while appended with electronic study data after April 1, 2020, and for which conduct of a post-marketing clinical study is required during the review process, in principle, electronic submission of the post-marketing study data is required on the application for re-examination or middle assessment, regardless of the relationship with approval conditions. If a consultation about package insert revisions, a request for the removal of approval conditions, etc. are made prior to the application for re-examination or middle assessment based on the results of a post-marketing clinical study, it is preferable to submit electronic study data at that point as far as possible.

For the time being, electronic submission of post-marketing surveillance data is not required.

(3) Submission of electronic study data of products for which the evaluation of study results is practically carried out before new drug applications

Regarding products for which the evaluation of study results is practically carried out before new drug applications (products subject to the SAKIGAKE designation system, anti-HIV drugs, etc.), it is preferable to submit electronic study data when the study results are practically evaluated as far as possible.

3 Method of electronic study data submission, etc.

(1) Method of electronic study data submission

When submitting electronic study data, the gateway system must be used in accordance with the “New Drug Applications Using the Gateway System”

(PSEHB/PED Notification No. 0401-7, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022).

Electronic study data to be submitted for an application must be submitted as part of appended documents.

(2) Validation for the acceptance of electronic study data

a. Basic principles of the validation rule

Of all submitted electronic study data, the PMDA will perform the validation of data that conform to the Clinical Data Interchange Standards Consortium standards (hereinafter referred to as "CDISC standards").

During the validation, if the PMDA identifies a major violation of the standard rules that affects the receipt of the submitted data, the PMDA will immediately inform the applicant of this violation. In such situation, the applicant must correct the data and resubmit. The application review will not be initiated until such violations are corrected. It is to note that, in case of submission of electronic study data for new drug applications described in 2 (1), the time taken to correct such violations will not be included in the total review time as established in the "Principles on Handling of New Drug Applications to Improve Predictability of Approval of New Drugs and the Total Reviewing Period" (PFSB/ELD Notification No. 1006-1 and PFSB/CND Notification No. 1006-1, by the Director of Evaluation and Licensing Division and the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, dated October 6, 2014). Please refer to the technical conformance guide for the validation tool used by the PMDA, the PMDA's principles on the severity of violations, details of the validation environment, and the individual rules that apply.

b. Prior confirmation of conformity by the applicant

The applicant should confirm in advance the conformity of the data to the CDISC standards prior to the application by referring to the published validation rules that the PMDA uses and information on the PMDA validation environment. As a result of the confirmation, if a violation of the rules is identified, which is deemed important by the PMDA as described in the technical conformance guide, the data should be corrected. If a violation of the rules that requires an explanation is identified, but is unable to be corrected, the details and reasons for the violation should be explained in the reviewer's guide (Study Data Reviewer's Guide and Analysis Data Reviewer's Guide) (see 4. (2) b (d)).

(3) Submission of additional electronic study data after submitting an application

Prior to the application, reach an agreement with the PMDA on electronic study data to be submitted for the application using consultations and submit all of the necessary documents at the time of the application. However, if the application is to be made during a long-term study or based on the results of an interim analysis, the data from this clinical study submitted after the application should include the data previously submitted at the time of the application as well as the additional data.

In exceptional cases, submission of electronic study data that have not been previously submitted or submission of additional datasets or programs for studies in which electronic study data had already been submitted may become necessary in the review process. Even in such cases, the submitted datasets must conform to the CDISC standards in principle. Electronic study data to be submitted, timing of submission, etc. should be decided after consultations with the PMDA.

With respect to the submission of electronic study data that was requested in the review process, analyses that are necessary for the assessment of efficacy and safety, such as analyses that were planned for the study, must be performed by the applicant and the results must be submitted.

(4) Relationship between eCTD and electronic study data

a. Relationship between eCTD and electronic study data

Electronic study data are part of the data to be appended to the new drug application form, and therefore in principle, must be included in the eCTD.

b. Points to consider on submission of the eCTD and electronic study data

Electronic study data must be submitted with the information regarding to which study report the data is related. Please refer to the technical conformance guide for the type of information to be included and the detailed method for including such information.

c. Addition, replacement, or deletion of electronic study data during eCTD revision

When adding, replacing, or deleting electronic study data during eCTD revision as instructed in an inquiry during review, submit the data subject to change along with the type of operation known for other documents in the eCTD, and revise the eCTD. Please refer to the technical conformance guide for the type of information to be included and the detailed method for including such information. It is not necessary to provide the name of each electronic study data file to the list of appended documents. However, whether or not relevant electronic study data has been submitted must be indicated for each report in the list of appended documents.

4 Standards of electronic study data to be submitted and details on the data

(1) Data standards for submission

Clinical study data subject for submission should be in a format conforming to the CDISC standards.

However, it is not applied to studies of orphan drugs, etc. that had started before April 1, 2020.

In data in 2 (1) b (c), the datasets on clinical pharmacological analyses may be acceptable for submission according to standards other than the CDISC standards based on the applicants' current condition of preparing analysis data.

(2) Details on electronic study data that conform to the CDISC standards

a. Format of electronic study data required for submission

Individual study data should be prepared using the Study Data Tabulation Model (SDTM) and be submitted along with the definition file for variables (define.xml), an annotated case report form (hereinafter referred to as "annotated CRF"), and the reviewer's guide. For analysis datasets, the dataset based on the Analysis Data Model (ADaM) should be submitted along with its definition file (define.xml), the program for creating the ADaM dataset, analysis program, and the reviewer's guide.

For electronic study data on an integrated analysis (ISS/ISE), in principle, the dataset based on ADaM, its definition file (e.g. define.xml), the program for creating the ADaM dataset, analysis program and the reviewer's guide should be submitted.

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

b. Datasets and definition file to be submitted

(a) Necessity of the submission of SDTM and ADaM datasets

In principle, the SDTM datasets should be submitted after storing the data collected from the CRFs in each domain as much as possible based on the corresponding variables designated by the SDTM and SDTM implementation guide (IG). Further, the datasets of the Trial Design Model storing information on the plans of clinical studies that were performed should be included. The analysis dataset may take on the different structures of variables depending on the characteristics of the individual analyses. However, the datasets to be submitted must have been composed in accordance with ADaM and ADaM IG.

In principle, when submitting electronic study data of an integrated analysis (ISS/ISE), the analysis dataset based on ADaM should be submitted. However,

if the SDTM dataset was used for the analysis, then submission of that SDTM dataset is sufficient. It is not absolutely necessary to submit the SDTM datasets of individual studies. However, submission may be requested if there is an existing SDTM dataset of the integrated analysis.

(b) Submission of the definition file of datasets

The definitions of variables in SDTM and ADaM datasets (hereinafter referred to as "metadata") must be respectively summarized according to the Define-XML format provided by CDISC and submitted together with the style sheet. Please refer to the technical conformance guide on the required contents of metadata.

(c) File format of datasets and definition file

Please refer to the technical conformance guide on the file format of datasets and definition files that conform to the CDISC standards. If English is used in a dataset, use the character set specified in ASCII. When using languages other than English, including Japanese, explain in the reviewer's guide the character set and encoding scheme used.

(d) Documents to be submitted with the dataset

In addition to the dataset definition file, submit reviewer's guide and an annotated CRF demonstrating the relationship between each item of data collected from the CRF and variables included in the dataset.

The reviewer's guide should include an explanation of the points that should be made clear during the review, such as the conformity degree to the CDISC standards (validation results), and particularly the points that do not affect the acceptance of the data but may become a problem when using the data. The reviewer's guide may be written in Japanese.

Please refer to the technical conformance guide for details and the file format of such documents to be submitted with the dataset.

(e) Traceability between data

To secure the traceability of data collected in clinical studies, such as from CRFs to the study results for evaluation, it is recommended that the data collected such as from CRFs and other records are summarized into datasets in the SDTM format, and these datasets are used to create analysis datasets in the ADaM format.

When the ADaM datasets are not prepared from the SDTM datasets, such as

when SDTM and ADaM datasets have been individually prepared from a database summarized in a format other than SDTM, explain the traceability between the submitted data (such as the procedures in which both datasets were prepared, the relationship between the variables in the database used for the preparation and those in the SDTM and ADaM datasets, and whether there was any information used during the preparation of the ADaM datasets that was not included in the SDTM datasets) in the reviewer's guide.

For the time being, clinical study data that are already summarized in a format other than SDTM would be expected to be converted into the SDTM format on submission of the application. In this circumstance, it must be mentioned in the reviewer's guide that the data have been converted. Moreover, the data must be converted to a form that complies with the standards specified by SDTM whenever possible; however, if this is difficult to perform for some of the data, such as when there are data that cannot be converted in accordance with the controlled terminology recommended because of the setting at the time of data acquisition, discuss with the PMDA prior to the application using consultations and explain the exception in the reviewer's guide.

(f) Handling of data in Japanese

The systems that are used by the PMDA to process electronic study data are principally designed to process data in English. Therefore, electronic study data should be entered according to the controlled terminology and the dictionaries recommended in the CDISC standards. Even if there is no recommended terminology or dictionaries, it is preferable for the submitted data to be in English.

If data are summarized in Japanese, submit a dataset that has been appropriately translated to English. However, if there are variables for which information may be compromised by translation to English, the data may be submitted in Japanese. In this circumstance, two versions of the dataset must be submitted: A dataset comprised only of alphanumeric and a dataset containing variables described in Japanese. Please refer to the technical conformance guide for the variables for which data may be submitted in Japanese and the content of each dataset.

c. Programs

In addition to the datasets concerning clinical studies, programs used to create the ADaM datasets and analysis programs must be submitted in order for the PMDA to understand the process in which the dataset was created and analyzed.

In principle, an analysis program is to be submitted for those whose data source is from the ADaM dataset. However, given the major purpose of each program, it is not necessary to submit the programs in a format or content that allows the PMDA to use them without any modification. Although there are no specific software or versions that should be used, information about the environment in which the program was created and executed (the operating system and software used, and the versions) should be provided in the reviewer's guide, etc. If programs with macros were used, it is preferable to submit the macro programs as well. However, if submission of the macro programs is difficult or submission of the programs itself is difficult because the creation of datasets and programs was outsourced, submission of specifications that show the analysis algorithm would be sufficient.

If the analysis dataset has been created as an exception in a format other than ADaM, the applicant is to individually consult with the 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 the PMDA.

d. Controlled terminology, dictionaries and units that are recommended

When preparing electronic study data, encoded information must also be included for data that can be encoded using the controlled terminology recommended by the CDISC, MedDRA for events, and WHODrug Global for drugs. The values are to be in SI units, in principle.

Please refer to the PMDA's website (https://www.pmda.go.jp/) for the list of acceptable codes.

Basically, if there is a recommended standard code, it is not advisable to use a code defined by the applicant. However, if a code other than the recommended one was used at the time of data collection due to unavoidable circumstances or if recommended controlled terminology does not exist, it is sufficient to construct a dataset using a custom code defined by the applicant. In principle, in this case, the same code must be consistently used for the same variable throughout the same application. Moreover, if a custom code defined by the applicant was used or any extension was made to the standard code, that should be explained in the definition file and the reviewer's guide of the dataset.

Regarding units, if data were collected in units that are conventionally used in guidelines for diagnosis, treatment, and therapeutic evaluation for various diseases where conversion of the data to those in SI units is possible, separately store the

converted data in SI units in the SDTM dataset as data in the standard units and submit them. The conventional units may be used in application documents. The ADaM dataset must include the units used in application documents.

e. Versions of CDISC standards

Regarding versions of CDISC standards used for creating electronic study data, please refer to the "PMDA Data Standards Catalog" on the PMDA's website for the versions that are acceptable. The acceptable versions may be updated on revision of various standards. Therefore, it is advisable to use the latest version when preparing the data.

Please note that datasets created using a version other than the acceptable one on applications must be converted using the acceptable version.

Different versions of the CDISC standards may be used in different studies within the same application; however, a single version of the standards must be used within a clinical study or an analysis. If different versions are used for any parts of the same clinical study or the same analysis, it should be explained in the reviewer's guide, with the reasons for the use of the different versions indicated.

(3) Details of electronic study data of clinical pharmacology analyses

When submitting electronic study data of a study or an analysis that includes clinical pharmacology analyses, the data with information on all of the files related to electronic study data on clinical pharmacology must be submitted, regardless of the format of data to be submitted. Please refer to the technical conformance guide for details on information to be submitted.

When submitting electronic study data that conform to the CDISC standards, necessary electronic study data should be submitted according to 4 (2). When submitting electronic study data that conform to the CDISC standards, handling as described in 4 (3) a (b) is sufficient for an analysis program related to a standard pharmacokinetic analysis.

As described in 4 (1), in data in 2 (1) b (c), the datasets on clinical pharmacological analyses may be acceptable for submission according to standards other than the CDISC standards. However, in case of submission in a format other than the CDISC standards, electronic study data listed in a. to c. below must be submitted for each analysis.

The following points must be considered with respect to the clinical pharmacological analysis dataset.

- Regarding the data that were excluded from the analysis for reasons other than those specified in the analysis plan (e.g., excluded data because they were determined to be outliers at the time of analysis), steps should be taken to clarify how the data were

handled during the analyses, such as by flagging to identify them.

- Considering the purpose of the analyses, such as to compare Japanese and non-Japanese subjects or different ethnic groups within Asia, attributes of the subjects and other necessary information such as ethnicity and regions should be able to be identified when appropriate.

a. Details on standard pharmacokinetic analysis

(a) Datasets and definition file to be submitted

Datasets from pharmacokinetic or pharmacokinetic/pharmacodynamic analysis should preferably be submitted in the ADaM format; however, submission of formats other than ADaM is sufficient. When submitting a dataset in a format other than ADaM, the definition file together with the analysis dataset must be submitted.

(b) Programs

Regarding an analysis program related to a standard pharmacokinetic analysis, while analyses that calculate pharmacokinetic or pharmacodynamic parameters using a non-compartment analysis do not require submission of the analysis program, pharmacokinetic or pharmacokinetic/pharmacodynamic analysis specifications must be submitted. For analyses used for statistical evaluation of pharmacokinetic or pharmacodynamic parameters, the analysis program must be submitted.

b. Details on population analysis, including simulations

(a) Datasets and definition file to be submitted

The analysis dataset and its definition file must be submitted. The dataset and its definition file may be submitted in formats other than the CDISC standards.

(b) Programs

In principle, the programs of models that were important in the model building process, such as base model and final model, and files with the output of major results should be submitted. If simulation was performed, submission of the program used for the simulation and program procedures is desirable. If it is difficult to submit the program itself, submission of specifications that show the analysis algorithm would be sufficient.

c. Details on physiologically based pharmacokinetic model analysis, including simulations

(a) Datasets and definition file to be submitted

The files containing information, such as the structure of the model used for analysis, the set values of drug and physiological parameters, the analysis procedures, and the results of sensitivity analyses must be submitted. In addition, if necessary, the dataset of clinical studies containing the pharmacokinetic data used in the analysis and the definition file for that dataset should be submitted. The dataset and its definition file may be submitted in formats other than the CDISC standards.

(b) Programs

Essentially, submission of programs is not required; however, the software used for the analysis must be clearly stated.

5 Relationship between electronic study data submission and compliance assessment

For compliance assessment of application documents, 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 study 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, dated 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 electronic study data for the application are submitted, compliance assessment 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 and Procedures of Document-based Compliance Assessment and GPSP On-site Inspection of Application Data for Interim Evaluation, Re-examination, and Re-evaluation of Drugs (PMDA Notification No. 0831001 of the Pharmaceuticals and Medical Devices Agency, dated August 31, 2020).

6 Consultation process regarding electronic study data

Many matters regarding submission of electronic study data for applications should be considered individual basis, and in order for reviews to be conducted smoothly, applicants are recommended to consult with the PMDA by utilizing consultations prior to the application. Please confirm the scope of data subject to electronic study data submission by

utilizing the existing framework of clinical consultations offered by the PMDA. To confirm the details of electronic study data submission, please use the “consultation on preparation of submission of electronic study data” etc.

7 Information management regarding electronic study data

Electronic study data will be a submission requirement as a part of the application documents, 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 documents. Therefore, the content of the submitted electronic study 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 foreign pharmaceuticals regulatory agencies based on a confidentiality agreement.

Furthermore, electronic study data for each subject can only be accessed by relevant people from the PMDA or Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare (including staff members of the PMDA or Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labour and Welfare, and contractors who are in charge of the system in the PMDA under a confidentiality agreement), and those data will be appropriately stored and managed so that their integrity is protected within the PMDA.

8 Glossary

Please refer to the glossary of terms used in this notification and further details and precautions on submission of electronic study data for an application that are provided in the separate documents such as the technical conformance guide.

- 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 interoperation 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 (https://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 regulatory agencies regarding data on individual patients in clinical studies.

- Analysis Data Model (ADaM)

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

9 Others

Relevant notification is revised as shown in the attachment.

Provisional Translation (as of June 2022)*

Attachment

Revision of Relevant Notification

1 Principles on Handling of New Drug Applications to Improve Predictability of Approval of New Drugs and the Total Reviewing Period (PFSB/ELD Notification No. 1006-1 and PFSB/CND Notification No. 1006-1, by the Director of Evaluation and Licensing Division and the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 6, 2014)

After revision	Before revision
1 Pre-consultation meeting on review schedule (The first part is omitted.) Please note that applications for products with a particularly short target reviewing period, such as products that have been granted priority review <u>or with submission of electronic study data for a new drug application</u>, require detailed adjustments of the specific review schedule <u>or the scope of the data subject to electronic submission</u>. (The rest is omitted.)	1 Pre-consultation meeting on review schedule (The first part is omitted.) Please note that applications for products with a particularly short target reviewing period, such as products that have been granted priority review, require detailed adjustments of the specific review schedule. (The rest is omitted.)

(The underlined parts are revised.)

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