Provisional Translation (as of April 2019) *

Notification number: 0124-4
January 24, 2019

To: Prefectural Health Department (Bureau)

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

Revision of Notification on Practical Operations of Electronic Study Data Submissions

Regarding the electronic submission of study data at the time of new drug applications for the marketing of drugs, the basic principles 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 the "Question and Answer Guide Regarding [Basic Principles on Electronic Submission of Study Data for New Drug Applications]" (Administrative Notice by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 20, 2014) in order to start accepting electronic submission of study data from fiscal year 2016 onwards. Practical operations related to the submission of electronic data at the time of new drug applications have also been notified 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").

Based on the experience of electronic submission of study data for new drug applications, we have decided to revise the "notification on practical operations"; therefore, we ask you to inform manufacturers and sellers placed under your administration to utilize for their business operations.

Please refer to the attached revised notification on practical operations.

Provisional Translation (as of April 2019) *

(Reference) The revised Notification on Practical Operations
* The underlined parts are changes from the last version of the body of the notification except for attachment.

Notification number: 0427-1
April 27, 2015

(Revised parts in Notification No. 0124-4, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated January 24, 2019, are underlined)

To: Prefectural Health Department (Bureau)

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

Notification on Practical Operations of Electronic Study Data Submissions

To begin accepting electronic submission of study data in 2016, the basic principles of electronic submission of study data for new drug applications have been detailed in "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 "Question and Answer Guide Regarding [Basic Principles on Electronic Submission of Study Data for New Drug Applications]" (Administrative Notice by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 20, 2014). The notification on practical operations pertaining to submission of electronic study data for new drug applications are summarized herein. We ask you to inform manufacturers and sellers under your administration to utilize it for their business operations.

Further details and precautions on submission of electronic study data for new drug applications are separately specified by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") in "Technical Conformance Guide on Electronic

Study Data Submissions" (PMDA/AREDPG Notification No. 0427001, by the Director of Advanced Review with Electronic Data Promotion Group, PMDA, dated April 27, 2015; hereinafter referred to as "technical conformance guide"), which should also be referenced.

1. Handling of clinical study data subject to electronic submission

(1) Scope of Data subject to electronic submission

In principle, the data that are subject to electronic submission for new drug applications are evaluation data that are considered to provide the major evidence for the efficacy, safety, and dosage and administration as indicated in the "notification of basic principles".

In other words, these data are the results from phase II and III studies in most cases, including long-term studies. If multiple phase II studies are conducted, those that provide the evidence for setting the dosage and administration are qualified for electronic submission.

In addition, as with phase II and III studies, assessment of electronic data may be performed for studies that are considered to contribute to the establishment of the dosage and administration and are each focused on the evaluation of efficacy, safety, or pharmacokinetics. For example, submission of data that conform to the CDISC standards (SDTM and ADaM datasets) will be required for phase I studies of oncology drugs and QT/QTc studies as listed in 2. 2) b. of the "notification of basic principles". Further, phase I studies involving Japanese and non-Japanese subjects that were used to compare the pharmacokinetics within and outside of Japan in a development using global clinical trials or bridging studies form an important evidence for setting the dosage and administration. In such cases, study data must be electronically submitted regardless of whether this phase I study was performed as part of a global clinical trial or in a single region. In addition, regarding the phase I and clinical pharmacology study results and clinical pharmacology analyses (including population analyses and simulations), it is necessary to submit electronic data of materials are considered to provide major evidence for dosage and administration based on the pharmacokinetic or pharmacodynamic evaluation. Reference materials that are considered to provide major evidence for dosage and administration should also be submitted electronically.

(2) Electronic submission of integrated analysis (ISS/ISE) data

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, submission of datasets from such analyses may be requested. Moreover, depending on the content of the integrated analyses, submission may be requested even if no data on Japanese subjects are

included. PMDA should be consulted for details regarding whether or not electronic submission is required based on the objective of the individual integrated analyses.

(3) Electronic submission of data for an application for partial changes

In principle, study data to be submitted as evaluation data for an application for partial changes must be electronically submitted. However, it is not necessary to resubmit the study data that have already been electronically submitted at the time the approval was obtained.

Even when the data have already been electronically submitted, 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 analysis datasets and programs may be requested.

(4) Handling of post-marketing study data

Electronic submission of post-marketing study data may be requested upon application for re-examination. Regarding products for which new drug applications are made while appended with electronic 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. If a consultation about package insert revisions, a request for the removal of approval conditions, etc. are made prior to application for re-examination based on the results of a post-marketing clinical study, it is preferable to submit the electronic study data at that point as far as possible. The data must comply with the CDISC standards.

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

(5) Handling 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 the electronic data when the study results are practically evaluated as far as possible.

2. Format and method of electronic data submission

(1) Format of electronic data submission

The data to be electronically submitted for a new drug application must be submitted as part of an attachment to the new drug application as stated in the "notification of basic principles". Refer to the technical conformance guide for the file format and folder structure for the electronic data submission.

(2) Method of electronic data submission

In principle, the data should be electronically submitted via the gateway system indicated in a. below for efficient processing and sharing of information between the applicant and PMDA and for managing the progress of the review process. However, if the gateway system is not accessible due to unavoidable circumstances, data may be submitted using the PMDA window in the form of the recording medium shown in b. below. Electronic files to be submitted via the gateway system are the formatted data, including the new drug application form, that are specified by regulations concerning the enforcement of laws for ensuring the quality, efficacy, and safety of pharmaceuticals and medical devices (FD application data concerning Form No. 22 and Form No. 23; hereinafter referred to as "FD application data") as well as eCTD, excluding electronic data, and electronic data, including programs and documents specified in the 3 below. Electronic files of other relevant document files, such as a list of the committee members involved in the preparation of the application document or a copy of the registration certificate of the drug master file, etc., and the response to inquiries made during the product review, including the documents attached to the response, can be submitted via the gateway system. For details of the gateway system, please refer to "Electronic data for application - Information about the portal site" on the PMDA's website (http://www.pmda.go.jp/).

a. Submission via the gateway system

To submit data via the gateway system, use the "New Drug Application Electronic Data Portal Site" (hereinafter referred to as "portal site") provided on the internet by PMDA.

Electronic certificate will be required for user registration and submission of electronic files through the portal site. Refer to the technical conformance guide for recommended environment for using the portal site such as acceptable forms of electronic certificate.

b. Submission of recording medium to the PMDA window

To submit the recording medium to the PMDA window, bring or post the recording medium containing all the electronic files to be submitted with the application. Refer to the technical conformance guide for acceptable recording media.

(3) Handling of the date of a new drug application

If electronic files are submitted via the gateway system as attachments to the new drug application, after each electronic file reaches the gateway system server, the date on which PMDA confirms that these files are free from problems such as virus infection will be considered the date on which each electronic file has reached PMDA.

On and after the day when all necessary electronic files have reached PMDA as attachments to the new drug application, the new drug application with a revenue stamp of the processing fee will be received by PMDA as in the past. The date on which the content of this application form, descriptions in documents such as the amount of revenue stamp, and the formatted data such as the new drug application form are confirmed to be free of error will be considered the "receipt date of the new drug application".

The results of the validation of electronic files other than formatted data, such as the new drug application form, including validation concerning the receipt of electronic data stated in 2. (4), will not be used to determine whether or not to receive the new drug application.

The application date written in advance on the new drug application form, including FD application data, and eCTD will be handled as in the past.

(4) Validation for the acceptance of electronic data

a. Basic principles of the validation rule

PMDA will perform the validation of all submitted electronic data. Validation of conformance to the CDISC standard will be performed using a tool known as the Pinnacle21 Enterprise.

During the validation, if PMDA identifies a major error that affects the receipt of the submitted data and no prior consultation or explanation was provided regarding this error, PMDA will immediately inform the applicant of this error. In such situation, the applicant must correct the data and resubmit. The application review will not be

initiated until such errors are corrected. It is to note that the time taken to correct such errors will not be included in the total evaluation period 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 by the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, dated October 6, 2014). Refer to the technical conformance guide for the PMDA's principles on the severity of errors, 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 degree of the data to the CDISC standards prior to the application by referring to the published rules and information on the PMDA validation environment. Therefore, if an error is identified, which is deemed important by PMDA as described in the technical conformance guide, but is unable to be corrected, a prior consultation should be held with PMDA using "consultation on data format of submission of electronic study data " to discuss the details and reasons for this error prior to the application. In addition, the error must be explained in the data guide (Study Data Reviewer's Guide and Analysis Data Reviewer's Guide) (see 3. (1) a. (iv)). Furthermore, details pertaining to other errors must be explained in the data guide.

(5) Relationship between the electronic data and eCTD

a. Submission of CTD documents associated with the start of electronic data submission

As stated in 4. in the "notification of basic principles", with the start of electronic data submission, CTD documents, in principle, should be submitted via eCTD.

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

The data subject to electronic submission described in the notification of basic principles and in this notification are part of the documents to be attached to the new drug application form, and therefore in principle, must be included in eCTD.

However, if eCTD is to be submitted by a method shown in "Electronic Specifications of Common Technical Documents" (PMSB/ELD Notification No. 0604001, by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare, dated June 4, 2003)

and "Handling of Electronic Specifications of Common Technical Documents" (PFSB/ELD Notification No. 0527004, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated May 27, 2004), the study data should be separately submitted from eCTD. Moreover, it must be submitted with the information regarding which eCTD the study data belongs to and to which study report the data is related. 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 study data during eCTD revision

When adding, replacing, or deleting 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 the other documents in eCTD, and revise eCTD. Refer to the technical conformance guide for the type of information to be included and the detailed method of including such information. It is not necessary to provide the name of each electronic data file to the list of attachments and the request for change. However, whether or not relevant electronic data has been submitted must be indicated in each report.

d. Handling of the electronic data to be submitted as an attachment to the response to inquiry

The electronic data to be submitted as an attachment to the response to inquiry during review is not part of eCTD. Therefore, it is not necessary to revise eCTD on submission of such data. Moreover, the electronic data must be, in principle, submitted to the reviewer via the gateway system or in a recording medium if the system is not accessible. The electronic data must include information on the relevant response. Refer to the technical conformance guide for the type of information to be included and the detailed method for including such information.

(6) Submission of additional electronic data after submitting a new drug application

Prior to the new drug application, reach an agreement with the PMDA on the data to be electronically submitted for the new drug application using consultations and submit all of the necessary documents at the time of the new drug application. However, if the new drug 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 new drug application should include the data previously submitted at the time of the new drug application as well as the additional data.

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

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

3. Details on the electronic data to be submitted

(1) Electronic data that conforms to the CDISC standards

a. Datasets and definition file to be submitted

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

For data subject to electronic submission listed in 1. (1), submit the SDTM datasets and the ADaM datasets used for main analyses, except in the case of data on the results of a phase I study and clinical pharmacology study and a clinical pharmacology analysis as shown in 3. (2).

In principle, the SDTM datasets should be submitted after storing the data collected from the case report forms (hereinafter referred to as "CRFs") in each domain (where possible) based on the corresponding variables designated by the SDTM and SDTM implementation guide (IG). Further, include the datasets of the Trial Design Model storing information on the plans of clinical studies that were performed. 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 the electronic data of an integrated analysis (ISS/ISE), submit the analysis dataset based on ADaM. However, if an 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.

(ii) 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 CDISC-specified Define-XML format and submitted together with the style sheet. Refer to the technical conformance guide on the required content of metadata.

(iii) File format of datasets and definition file

Refer to the technical conformance guide on the file format of datasets and definition files that conforms 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 data guide the character set and coding system used.

(iv) Documents to be submitted with the dataset

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

The data 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 trying to use the data. The data guides may be written in Japanese.

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

(v) Traceability between data

To secure the traceability of data collected in clinical trials, 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 data guides.

For the time being, clinical study data that is already summarized in a format other than SDTM would be expected to be converted into the SDTM format on submission of the new drug application. In this circumstance, it must be mentioned in the data 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 by the setting at the time of data acquisition, discuss with the PMDA prior to the application using consultations and explain the exception in the data guide.

(vi) Handling of data in Japanese

The systems that are used by PMDA to process electronic data are principally designed to process electronic data in English. Therefore, electronic data should be entered according to the controlled terminology and code list recommended in the CDISC standard. Even if there is no recommended terminology or codes, 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. Refer to the technical conformance guide for the variables for which data may be submitted in Japanese and the content of each dataset.

b. Submission of 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.

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 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 with a

data guide and Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" of the "Implementation guidelines for clinical trial consultation and confirmation of certification, etc., conducted by the Pharmaceuticals and Medical Devices Agency" (PMDA Notification No. 0302070 of the Chief Executive, dated March 2, 2012). 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 demonstrate the analysis algorithm would be sufficient.

c. Controlled Terminology, code lists, and units that are recommended

Data may be coded using codes, such as CDISC controlled terminology and MedDRA. Refer to the PMDA's website (http://www.pmda.go.jp/) for the list of acceptable codes. Use the WHO Drug Dictionaries Drug Code (WHO DDs) when coding drugs.

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 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 new drug application. Moreover, if custom code defined by the applicant was used or any expansion was made to standard code, that should be explained in the definition file and data guide of the dataset.

The use of SI units is recommended. If data were collected in units that are commonly 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.

d. Versions of CDISC standards

Regarding standards used for creating datasets, multiple versions are acceptable. Please refer to the "PMDA Data Standards Catalog" on the PMDA's website (http://www.pmda.go.jp/) 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 that is no longer acceptable on new drug applications must be converted using an 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. If different versions are used for any parts of the same clinical study, it should be discussed with the PMDA in advance using consultations and then explained in the data guide, with the reasons for the use of the different versions indicated.

(2) Electronic data of phase I and clinical pharmacology study results and clinical pharmacology analyses

a. Data standards at submission

Among the data on phase I and clinical pharmacology study results and clinical pharmacological analyses that are subject to electronic submission, in principle, the electronic data of the studies listed in 2. 2) b. of the notification of basic principles should be submitted in the format that conforms to the CDISC standards. Meanwhile, the electronic data of studies listed in 2. 2) c. of the notification of basic principles should be submitted in the format conformable to the following specifications.

(i) Clinical studies where standard pharmacokinetic analysis was performed

Individual clinical study data should be submitted in the SDTM format. Datasets from pharmacokinetic or pharmacokinetic/pharmacodynamic analysis should preferably be submitted in the ADaM format; however, submission of formats other than ADaM is sufficient. Datasets on efficacy and safety analysis should be submitted in the ADaM format.

(ii) Population analysis, including simulations

Submission in formats other than the CDISC standards would be sufficient.

(iii) Physiologically based pharmacokinetic model analysis, including simulations

Submission in formats other than the CDISC standards would be sufficient.

b. Types of electronic data to be submitted

When submitting electronic data on phase I and clinical pharmacology study results and clinical pharmacological analyses, submit the “Explanation of electronic data package on clinical pharmacology” that includes information on all of the files related to the electronic data on clinical pharmacology. Refer to the technical conformance

guide for details on the information to be described in the "Explanation of electronic data package on clinical pharmacology."

Of the data on phase I and clinical pharmacology study results and clinical pharmacological analyses that are subject to electronic submission, the necessary electronic data from the studies listed in 2. 2) b. of the notification of basic principles must be submitted in accordance with section 3. (1) a. Meanwhile, the following electronic data should be submitted for studies listed in 2. 2) c. of the notification of basic principles.

Refer to the technical conformance guide for details on the electronic data to be submitted.

(i) Clinical studies where standard pharmacokinetic analysis was performed

In principle, the submission of an SDTM dataset and analysis dataset is required. Analysis datasets should be submitted for efficacy and safety in addition to the datasets from pharmacokinetic or pharmacokinetic/pharmacodynamic analysis.

The necessary electronic data in the SDTM dataset should be submitted in accordance with section 3. (1) a.

When submitting the analysis dataset in the ADaM format, the necessary electronic data should be submitted in accordance with section 3. (1) a. Meanwhile, when submitting the dataset of pharmacokinetic or pharmacokinetic/pharmacodynamic analysis in a format other than ADaM, submit the definition file together with the analysis dataset.

(ii) Population analysis, including simulations

Submit the analysis dataset and its definition file.

(iii) Physiologically based pharmacokinetic model analysis, including simulations

Submit 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. In addition, if necessary, submit the dataset of clinical studies containing the pharmacokinetic data used in the analysis and the definition file for that dataset.

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

- Regarding the data that were excluded from the analysis for reasons other than those specified in the analysis plan (for example, 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.

c. Submission of programs

Of the data on phase I and clinical pharmacology study results and clinical pharmacology analyses that are subject to electronic submission, the necessary programs of the studies listed in 2. 2) b. of the notification of basic principles must be submitted in accordance with section 3. (1) b., preferably together with the pharmacokinetic or pharmacokinetic/pharmacodynamic analysis specifications. Meanwhile, the following programs should be submitted for studies listed in 2. 2) c. of the notification of basic principles.

Refer to the technical conformance guide for details on the pharmacokinetic or pharmacokinetic/pharmacodynamic analysis specifications and the programs of population analyses.

(i) Clinical studies where standard pharmacokinetic analysis was performed

When submitting an analysis dataset in the ADaM format, submit the necessary programs in accordance with section 3. (1) b., preferably together with the pharmacokinetic or pharmacokinetic/pharmacodynamic analysis specifications.

In principle, when submitting a dataset from a pharmacokinetic or pharmacokinetic/pharmacodynamic analysis in formats other than ADaM, submission of programs is not necessary. However, submission of pharmacokinetic or pharmacokinetic/pharmacodynamic analysis specifications is desirable.

(ii) Population analysis, including simulations

In principle, submit 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. 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 demonstrate the analysis algorithm would be sufficient.

(iii) Physiologically based pharmacokinetic model analysis, including simulations

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

4. Process of consultations concerning electronic data

Confirm the scope of evaluation data that are subject to electronic submission by utilizing the existing framework of clinical consultations offered by the PMDA. To explain and confirm the details of the data to be electronically submitted, use the "consultation on data format of submission of electronic study data", etc.

5. Initiation timing of submission of study data and interim measure

This notification will apply to products for which new drug application is made on or after October 1, 2016.

Further, in line with this requirement, the attachments to the new drug application of a product subject to this notification must, in principle, be via the eCTD. Moreover, the eCTD and study data must, in principle, be submitted via the gateway system.

Eventually, study data of all the studies requiring electronic submission will need to be electronically submitted. However, until March 31, 2020, there will be a transitional period during which the data from some of the studies for which electronic submission is possible may be electronically submitted. However, note that in that situation, the application will be reviewed using the conventional review process, and it should be discussed with the PMDA in advance using consultations.

During the transitional period, the gateway system will accept the submission of the eCTD or study data alone. Moreover, the PMDA window will accept submission of the eCTD or study data in a recorded medium as well as an application with original documents in paper that are attached to the new drug application form.

In cases in which electronic study data are not included in the materials appended to the new drug application although the application is classified into a category in which are subject to electronic submission, the submission of eCTD through the gateway system is acceptable, even after the transitional period.

6. Other

(1) Revision of relevant notifications

Relevant notifications are revised as shown in the attachment.

(2) Glossary and other information

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

Attachment

Revision of Relevant Notifications

1. On Organization of Application Dossier Appended to New Drug Application (NDA) for Approval (PMSB/ELD Notification No. 899, by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare, dated June 21, 2001)

After revision	Before revision
Part 4 Considerations for Editing Application Dossier Appended to New Drug Application VII. 6. The clinical study report, which is submitted as a document on clinical study results, should contain the protocol, case report form, and sample patient information and consent form as appendices. When submitting study data on new drug application based on "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), the randomization method and codes (identity of patients and allocated clinical studies), documents on the statistical methods, documents on the method and procedure of standardization between study sites and quality assurance (if performed), publications based on the study, and major publications referenced in the clinical study report should preferably be submitted together. Other documents do not normally need to be included in the application dossier but must be prepared and promptly submitted when requested by the reviewing authority.	Part 4 Considerations for Editing Application Dossier Appended to New Drug Application VII. 6. The clinical study report, which is submitted as a document on clinical study results, should contain the protocol, case report form and sample patient information and consent form as appendices. Other documents do not normally need to be included in the application dossier but must be prepared and promptly submitted when requested by the reviewing authority.
Part 4 Considerations for Editing Application Dossier Appended to New Drug Application VII. 7. The following tables and figures of cases should be submitted by including in Part 5 "7. Patient data tables and case reports." Upon electronic submission of all the necessary data for a new drug application based on the notification on practical operations, tables of cases that fall under (1) and (5) below, of those related to the clinical study for which data has already been	Part 4 Considerations for Editing Application Dossier Appended to New Drug Application VII. 7. The following tables and figures of cases should be submitted by including in Part 5 "7. Patient data tables and case reports." (1) Tables of cases from major studies that became the basis for dose setting and major verification studies on efficacy

electronically submitted, do not need to be submitted. (1) Tables of cases from major studies that became the basis for dose setting and major verification studies on efficacy (2) Tables of cases from all clinical studies conducted in which adverse reactions were observed (3) Tables of cases from all clinical studies conducted in which serious adverse events were observed (4) Tables of cases from all clinical studies conducted in which laboratory abnormalities were observed (5) Figures that appropriately display the changes in laboratory values from all clinical studies conducted (Rest is omitted)	(2) Tables of cases from all clinical studies conducted in which adverse reactions were observed (3) Tables of cases from all clinical studies conducted in which serious adverse events were observed (4) Tables of cases from all clinical studies conducted in which laboratory abnormalities were observed (5) Figures that appropriately display the changes in laboratory values from all clinical studies conducted (Rest is omitted)

2. Handling of Electronic Specifications of Common Technical Documents (PFSB/ELD Notification No. 0527004, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated May 27, 2004) Attachment 1

After revision	Before revision
2.1 Requirements for application with an eCTD When applying with an eCTD, all documents must be electronically submitted. However, until the receipt of the electronic signature becomes possible, pages with signatures or print/seal must be scanned and electronically stored before attaching to eCTD. When doing this, the applicant must also submit a statement showing that these pages have been correctly scanned both electronically and on paper. When submitting eCTD via the gateway system, it is not necessary to submit the paper statement at the time of submission of the first sequence; however, it should be prepared and submitted on request from PMDA. The electronic file of the statement must be included in Part 1, Section 3.	2.1 Requirements for application with an eCTD When applying with an eCTD, all documents must be electronically submitted. However, until the receipt of the electronic signature becomes possible, pages with signatures or print/seal must be scanned and electronically stored before attaching to eCTD. When doing this, the applicant must also submit a statement showing that these pages have been correctly scanned both electronically and on paper. The electronic file of the statement must be included in Part 1, Section 3.
2.2 Components to be included in eCTD When submitting the application as an eCTD, it must include the following components. Folder structure eCTD instance and eCTD DTD Leaf file CTD Part 1 instance XML schema and leaf file Style sheet, including Part 1 style sheet.	2.2 Components to be included in eCTD When submitting the application as an eCTD, it must include the following components. Folder structure eCTD instance and eCTD DTD Leaf file CTD Part 1 instance XML schema and leaf file Style sheet, including Part 1 style sheet.

Electronic data is a part of the documents to be appended to the new drug application form; however, for the time being, it must be separately submitted from eCTD and information or files related to the electronic data should not be referenced from the eCTD backbone or included in the folder structure. For methods on separately submitting the study data from eCTD, refer to "Technical Conformance Guide on Electronic Study Data Submissions" (PMDA/AREDPG Notification No. 0427001, by the Director of Advanced Review with Electronic Data Promotion Group, PMDA, dated April 27, 2015) (hereinafter referred to as technical guide). Enter whether or not study data was submitted in Module 1 "List of Attachments." It is not necessary to list all submitted datasets; instead, it is only necessary to show whether there is any data for each of the studies.	
3.2 eCTD cover letter The eCTD cover letter (Form 1) is a form for eCTD application which is required for each submission of application documents. Therefore, the eCTD cover letter should be included as a PDF file as part of the eCTD document and also submitted as a paper document. When submitting eCTD via the gateway system, submission of a paper cover letter is not required at the time of submission of the first sequence; however, it should be prepared and submitted on request from PMDA. The eCTD cover letter file is to be saved in the m1/jp folder. If there are multiple applicants, a cover letter may be prepared for each of the respective applicants.	3.2 eCTD cover letter The eCTD cover letter (Form 1) is a form for eCTD application which is required for each submission of application documents. Therefore, the eCTD cover letter should be included as a PDF file as part of the eCTD document and also submitted as a paper document. The eCTD cover letter file is to be saved in the m1/jp folder. If there are multiple applicants, a cover letter may be prepared for each of the respective applicants.
4.7.2 List of attachments List of attachments must be submitted in both PDF and Excel format. When preparing the list in Excel format, include the following items in one row to allow sorting and extraction of data. CTD No. Title Author Study duration Study site Report type (domestic, overseas) Publication Evaluation document/reference document Whether or not study data were submitted	4.7.2 List of attachments List of attachments must be submitted in both PDF and Excel format. When preparing the list in Excel format, include the following items in one row to allow sorting and extraction of data. Attachment No. Title Author Study period Study site Report type (domestic, overseas) Publication Evaluation document/reference document
5.1.1 Top level folder name The applicant should use the eCTD receipt number issued beforehand by the reviewing authority as the top level folder name.	5.1.1 Top level folder name The applicant should use the eCTD receipt number issued beforehand by the reviewing authority as the top level folder name.

Application for the eCTD receipt number must be made 3 weeks before the planned date of the new drug application by the company, and the applicant must go through the process for issuing the eCTD receipt number. Details on this process will be included in a separate notification.	Application for the eCTD receipt number must be made 2 weeks before the planned date of the new drug application by the company, and the applicant must go through the process for issuing the eCTD receipt number. Details on this process will be included in a separate notification.
5.1.2 Additional folder Submission of the table of cases, preclinical report, and clinical study report should be handled by creating folders as shown below.	5.1.2 Additional folder The table of cases, preclinical report and clinical study report should be handled by creating folders as shown below.
5.1.2.2 Preclinical study and clinical study report folder In principle, when creating folders for individual reports comprising Part 4 and Part 5, create a folder for each report. Folder name, in principle, must allow the unique identification of the study through the use of the study number. When submitting study data via the gateway system, provide the relevant study data the same name as the [study id/iss/ise] folder in which it will be stored.	5.1.2.2 Preclinical study and clinical study report folder In principle, when creating folders for individual reports comprising Part 4 and Part 5, create a folder for each report. Folder name must allow verification of its content, such as the study number.
7.1.1 Submission Refer to the technical guide for methods on submitting the eCTD documents via the gateway system. When applying without using the gateway system, submit the eCTD documents to the PMDA window.	7.1.1 Submission After undergoing the procedures for new drug application, submit the eCTD documents to PMDA.
7.1.2 Receipt confirmation If the eCTD documents were submitted via the gateway system, PMDA will check for viruses and validate the documents and then notify the applicant of the judgment result of whether they are acceptable for receipt or not via the gateway system. If submission was made without using the gateway system, PMDA will confirm the submitted documents, and when the documents are determined to be acceptable for receipt, PMDA will stamp a seal of receipt on the output paper of the eCTD cover letter. The applicant should deem that notification of the acceptance of receipt via the gateway system or the seal of receipt confirms the receipt of the application.	7.1.2 Receipt confirmation PMDA will confirm the submitted documents, and when the documents are determined to be acceptable for receipt, PMDA will stamp a seal of receipt on the output paper of the eCTD cover letter. The applicant should deem that this seal of receipt confirms the receipt of the application.
7.2 Submission medium When submitting eCTD without using the gateway system, the electronic media for submission, in principle, must be CD-R/RW, DVD-RAM/R/RW, or PCMCIA Type 2 card (recording media such as hard disk and memory). If the data are < 1.4 MB, submission of an FD is acceptable. Consult PMDA beforehand if you wish to submit in any other media.	7.2 Submission medium The electronic media for submission, in principle, must be CD-R/RW, DVD-RAM/R/RW, or PCMCIA Type 2 card (recording media such as hard disk and memory). If the data are < 1.4 MB, submission of an FD is acceptable. Consult PMDA beforehand if you wish to submit in any other media.

(Rest is omitted)	(Rest is omitted)

3. 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 by the Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, dated October 6, 2014)

After revision	Before revision
1 Pre-consultation meeting on review schedule (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 or with submission of electronic data for a new drug application, require detailed adjustments of the specific review schedule or the scope of the data subject to electronic submission. (Rest is omitted)	1 Pre-consultation meeting on review schedule (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. (Rest is omitted)