Provisional Translation (as of April 2019) *

Notification No. 0124001
January 24, 2019

To: Prefectural Health Department (Bureau)

Director of the Office of Advanced Evaluation with Electronic Data,
Pharmaceuticals and Medical Devices Agency

Revision of Technical Conformance Guide on Electronic Study Data Submissions

The basic principles on electronic submission of study data for new drug applications 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 the 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 Submissions of Study Data for New Drug Applications]" (Administrative Notice of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated January 24, 2019).

The practical operations related to electronic submission of study data for new drug applications have been notified in the "Notification on Practical Operations of Electronic Study Data Submissions" (PFSB/ELD Notification No. 0427-1 by the Director of the 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) and the "Question and Answer Guide Regarding [Notification on Practical Operations of Electronic Study Data Submissions]" (Administrative Notice of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated January 24, 2019).

More detailed matters and precautions regarding electronic submission of study data for new drug applications have been notified in the "Technical Conformance Guide on Electronic Study Data Submissions" (Notification No. 0427001, by the Director of the Advanced Review with Electronic Data Promotion Group, Pharmaceuticals and Medical Devices Agency, dated April 27, 2015; hereinafter referred to as the Technical Conformance Guide).

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

Please refer to the attached revised Technical Conformance Guide.

Provisional Translation (as of April 2019) *

(Reference) The revised Technical Conformance Guide

Notification No. 0427001
Apri l 27, 2015

(Revised parts in Notification No. 0911001, by the Director of the Advanced Review with Electronic Data Promotion Group, Pharmaceuticals and Medical Devices Agency, dated September 11, 2017, Notification No. 0517001, by the Director of Office of Advanced Evaluation with Electronic Data, Pharmaceuticals and Medical Devices Agency, dated May 17, 2018, and Notification No. 0124001, by the Director of Office of Advanced Evaluation with Electronic Data, Pharmaceuticals and Medical Devices Agency, dated January 24, 2019, are underlined)

To: Prefectural Health Department (Bureau)

Director of the Advanced Review with Electronic Data Promotion Group,
Pharmaceuticals and Medical Devices Agency

Technical Conformance Guide on Electronic Study Data Submissions

Basic principles on the submission of electronic study data for new drug applications have been notified 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), and practical matters on the electronic study data submission have been notified in “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) and “Question and Answer Guide Regarding [Notification on Practical Operations of Electronic Study Data Submissions]” (Administrative Notice by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated April 27, 2015). More detailed matters and precautions regarding submission of electronic study data for new drug applications have been compiled as shown in the appendix; therefore, we ask you to inform manufacturers and sellers placed under your administration.

Appendix

Technical Conformance Guide on Electronic Study Data Submissions

1. Introduction

1.1 Purpose

Basic principles on the submission of electronic study data for new drug applications and re-examination applications have been described in the notification of basic principles and its question and answer guide, and practical matters on electronic study data submission have been described in the notification on practical operations and its question and answer guide. More detailed matters and precautions regarding the submission of electronic study data for new drug applications and re-examination applications are provided in this guide.

With the requirement to submit electronic study data for a new drug application, attachments to a new drug application of a product subject to submission of electronic study data, in principle, should also be submitted in accordance with the eCTD, and detailed matters and precautions concerning the submission of electronic files, including the eCTD, shall be described together in this guide.

1.2 Scope

The scope of this guide will include detailed matters and precautions on the submission of electronic study data for new drug applications and re-examination applications, and detailed matters and precautions regarding the submission of electronic files related to the subject product, including the eCTD. Various lists, tools, and links for the necessary files related to the content of this guide will be posted separately on the PMDA's website (http://www.pmda.go.jp/), which should also be referred to.

1.3 Definitions of terms

The system of terms used in this guide is shown in Attachment 1.

The terminology used in this guide, in principle, is the same as that used in the notification of basic principles and the notification on practical operations. However, because this guide includes detailed matters and precautions regarding the submission of relevant electronic files, including the eCTD, in addition to matters regarding the submission of electronic study data for new drug applications and re-examination applications, "electronic data" in the notification of basic principles and the notification on practical operations will be described as "electronic study data" in this guide to prevent the confusion of the terminology.

2. System requirements necessary for the submission of electronic study data

2.1 Basic system requirements

Upon the submission of electronic study data for a new drug application, the applicant shall prepare a computer connected to the Internet.

- Network device that supports HTTPS and UDP ports
- Anti-virus software
- Printer

2.2 Recommended environment

Refer to the operation manual on the PMDA's website (http://www.pmda.go.jp/) for the recommended environment (version).

- Microsoft Windows

- Microsoft Internet Explorer
- Adobe Reader
- Electronic application software (FD application software)
- PC which can perform the above operations

2.3 Method of obtaining a portal site account and electronic identification

There are three categories of portal site accounts (hereinafter referred to as user ID): company manager, company user manager, and company user. The applicant can register a company manager by a desired unit of management and register and manage the company user manager and company user for each management unit.

To register the user ID and use the portal site, the applicant will require electronic identification. Medicertified electronic identification issued by the Medical Information System Development Center may be used as an electronic identification.

The applicant will be responsible for managing their own user ID, password, and electronic identification.

2.4 Method of the submission of electronic study data

The applicant can submit the electronic study data by the method specified in 2. (2) of the notification on practical operations. However, when submitting data by the method shown in 2. (2) b. of notification on practical operations, the acceptable recording medium, in principle, are DVD-R/RW or BD-R/RE (including multi-layer disks, respectively). Consult the PMDA beforehand if you wish to submit in any other medium.

3. Submission of electronic study data for new drug applications

3.1 Basic flow of the submission of electronic study data

The applicant must confirm with the PMDA on the scope of the submission of electronic study data and the planned date of a new drug application, in principle, at the meeting prior to pre-NDA consultation and also by utilizing clinical trial consultations and "consultation on data format of the submission of electronic study data", etc., if necessary.

At the time of the pre-NDA consultation, applicants must outline the contents of the electronic study data that will be submitted to the NDA using the "Consultation form on data format for the submission of electronic study data" in Appendix 8 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)"

Then, the applicant shall make an advance notice of the application from the portal site from 5 weeks to 1 week before the scheduled application date set by the applicant and obtain the information (e.g., in the case of the eCTD, the eCTD receipt number) required to manage the electronic files to be submitted in the new drug application. The applicant shall then enter and register the information related to the application and transfer the electronic files necessary for the application [such as new drug application form data (hereinafter referred to as FD application data), eCTD, and electronic study data] over the portal site.

The "FD application data" should be submitted in the format specified in "Recording Items and Code Table for Application Using Flexible Disks" (PFSB/ELD Notification No. 1027-1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 27, 2014) and "Handling of Flexible Disk Applications" (PFSB/ELD Notification No. 1027-3, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 27, 2014).

3.2 Method of the submission of electronic study data

When referencing the electronic study data from the XML backbone of the eCTD, the method of submission will be specified separately. When submitting the eCTD and the electronic study data separately, these must be submitted, respectively, via the portal site.

3.3 Submission of electronic study data via the portal site

When submitting the electronic study data, the applicant must register, select, or enter the following additional information on the portal site. Examples of such additional information are as follows. Not all items need to be registered, selected, or entered at each submission.

- Original/draft response and attachments
- Gateway receipt number
- Information for identifying to which file the data is appended (such as eCTD receipt number, submission serial number, CTD section number, study number, study title, inquiry number)
- Identifier of each file (UUID defined by ISO/IEC 11578:1996 and ITU-T RecX.667 | ISO/IEC 9834-8:2005)
- Position of the electronic study data (such as addition, replacement, deletion)
- Identifiers of data subject to replacement or deletion
- File path
- Data analysis type
- Explanation of the file content

After registering, selecting, or entering the above details, register the "m5" folder containing the electronic study data to be submitted on the portal site and send it to the PMDA. The specific operations to be performed on the portal site will be specified separately.

3.4 File size of the electronic study data

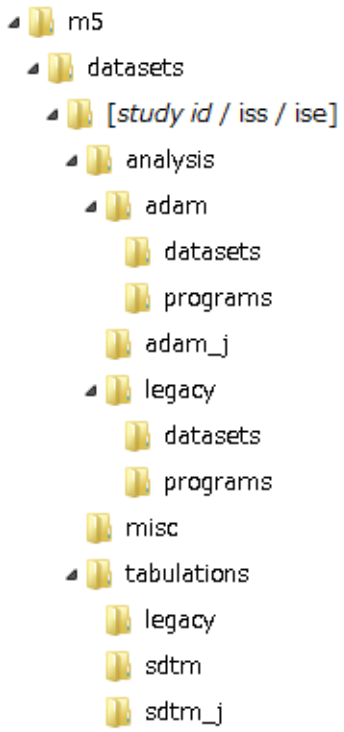
Of the electronic study data to be submitted to the PMDA, files other than datasets must not exceed the maximum file size of PDF specified in the "Electronic Common Technical Document Specification" (PSB/ELD Notification No. 0604001, by the Director of Evaluation and Licensing Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated June 4, 2003) (hereinafter referred to as eCTD notification) and "Handling of Electronic Common Technical Document Specification" (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) (hereinafter referred to as notification on handling of eCTD). Consult the PMDA beforehand if the size of a dataset file is 5 gigabytes or greater.

For files other than datasets, the upper limit for the size of each file of electronic study data to be submitted to the PMDA via the portal site is provided in other documents.

The upper limit for the total file size that can be submitted in a single operation is 40 gigabytes for electronic files submitted to the PMDA.

3.5 Folder structure

In principle, electronic study data should be submitted after storing it in the following folder structure, and no additional subfolders should be created. If storing the data in the following folder structure is difficult, the applicant must consult the PMDA beforehand and make a submission after agreeing on the folder structure and the storage of files. Hierarchies down to "m5¥datasets¥[*study id* / iss / ise]"cannot be changed.



Note the following points when storing the electronic study data into the abovementioned folder structure.

- The path length counting from the "m5" folder, including the file name, must be 160 characters or shorter.
- Folder names should be 32 characters or fewer, and must be comprised of the following characters.
  - Alphabetic characters from "a" to "z" [U+0061 to U+007A]
  - Numbers from "0" to "9" [U+0030 to U+0039]
  - Low line "_" [U+005F]
  - Hyphen-minus "-" [U+002D]
- File names should be 32 characters or fewer for datasets and 64 characters or fewer for files other than datasets (including the extension), and the name excluding the dot and the extension must be comprised of the following characters.
  - Alphabetic characters from "a" to "z" [U+0061 to U+007A]
  - Numbers from "0" to "9" [U+0030 to U+0039]
  - Low line "_" [U+005F]
  - Hyphen-minus "-" [U+002D]
- The data guide, define.xml, and style sheet must be stored in the same folder as their corresponding dataset. The style sheet should display the information in the define.xml, which is to be submitted to the PMDA.
- If there is no file to store the data, this folder should not be created.
- When storing the electronic study data in the field of clinical pharmacology in a format other than the CDISC standard, one example is to create and store it in a "cp" folder under the "analysis" folder as mentioned in the table below. In such a case, there will be no special restriction on the folder structure within the "cp" folder. The method of storing the data is not limited to that mentioned above. However, regardless of the method of storage, the above considerations on path length, folder name, and file name must be followed. It is preferable to consult the PMDA beforehand on the method of storing the data.

The usage method of each folder is as follows.

Folder name	Hierarchy	Description
m5	1	Shows that the electronic study data in this folder belongs to the CTD Module 5. This folder should not contain any files other than lower folders.
datasets	2	Folder for storing the electronic study data. This folder should not contain any files other than lower folders.
[*study id* / iss / ise]	3	Folder created for each study or for each integrated analysis results. Folder name should be the study number (such as study123) or the type of analysis (such as iss, ise) that allows the unique identification of each study. This folder should not contain any files other than lower folders
analysis	4	Folder for storing analysis datasets and programs. This folder should not contain any files other than lower folders
adam	5	Folder for storing ADaM datasets and programs. This folder should not contain any files other than lower folders
datasets	6	Folder for storing ADaM datasets.
programs	6	Folder for storing programs related to the creation of ADaM datasets, tables, or figures.
adam_j	5	Folder for storing the Japanese dataset that corresponds to the alphanumeric ADaM dataset. This folder should not contain any files other than the Japanese ADaM dataset.
cp	5	Folder for storing electronic study data on clinical pharmacology in formats other than the CDISC standard.
legacy	5	Folder for storing analysis datasets and programs in formats other than ADaM. This folder should not contain any files other than lower folders.
datasets	6	Folder for storing analysis datasets in formats other than ADaM.
programs	6	Folder for storing programs related to the creation of analysis datasets in formats other than ADaM, tables, or figures.
misc	4	Folder for storing data which is not appropriate for storage in the analysis or tabulations folder.
tabulations	4	Folder for storing datasets in which subject data and study-related information are displayed in a tabulation format. This folder should not contain any files other than lower folders.
legacy	5	Folder for storing non-SDTM datasets which are in a list format.
sdtm	5	Folder for storing SDTM datasets.

Folder name	Hierarchy	Description
sdtm_j	5	Folder for storing the Japanese dataset that corresponds to the alphanumeric SDTM dataset. This folder should not contain any files other than the Japanese SDTM dataset.

3.6 Validation of the electronic study data

Electronic study data, which is submitted via the portal site, will be validated according to the type of data. The results of the validation will be notified to the applicant via the portal site. The electronic study data, which violates the rules shown in 3.6.1 (a), should be corrected prior to the submission of a new drug application and, preferably, all data should be resubmitted.

If an error occurs during data transfer or while operating the portal site, contact the portal site help desk for directions.

3.6.1 Validation of CDISC-conformant data

The PMDA will perform validation of CDISC-conformant data using Pinnacle 21 Enterprise.

The rules used for validation have been classified by the level of importance taking into consideration the characteristics of each rule and based on conformity to the standards, ease of use of the data in review, quality of the clinical study data which the PMDA must know beforehand, and future uses of the clinical data by the PMDA. The levels of importance are shown below.

(a) Rules which, if violated, will cause the review to be suspended until corrections have been made

Very basic rules such as the presence/absence of necessary datasets for each clinical study

(b) Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made

In many cases, these rules are clearly stated in each standard and implementation guide, and if violated, the applicant should consult the PMDA before the application about the reason for the violation and the reason why it is not possible to correct it. These rules must also be explained in the data guide.

(c) Rules which, even when violated, will not necessarily require any explanation

The reason for the violation may be requested separately for the above (c) from the perspective of the quality of the clinical study data.

Details of the environment in which the PMDA performs validations, individual rules and their importance are published on the PMDA's website (http://www.pmda.go.jp/). Before transferring the electronic study data, the applicant should perform a validation, and necessary explanation should be given for any violations that are identified. Keep in mind that these rules may continue to be revised and that validation should always be performed after confirming the latest information. If any rules are revised, the content of the revision will be available for a certain period before the revised rules are applied.

3.7 Measures and the method of application in case <u>where the utilization of the gateway system is not feasible due to unavoidable circumstances</u>

In the cases where utilization of the gateway system is not feasible for some reason, such as the devices that comprise the portal site or the line connecting the Internet with the data center where these devices are installed and managed fail, sponsors might not be able to electronically submit the application data via the gateway system. In such a case, the application data will be received and processed by the PMDA window. Therefore, submit the documents and files recorded in an electronic medium necessary for application using PMDA window. Content of clinical study data should be submitted in a tab-separated values (TSV) file stored using the same path as for an m5 folder. Preparation methods for TSV files will be posted separately on the PMDA's website (http://www.pmda.go.jp/), which should be used as a reference, and TSV files should be named according to the naming rules for dataset files specified in 3.5.

4. Electronic study data to be submitted

4.1 CDISC-conformant electronic study data and relevant documents

4.1.1 Datasets to be submitted

4.1.1.1 Overview

CDISC standards should be used for the submission of clinical study data. For the latest standards and implementation guide (IG) of CDISC and the development status, refer to the CDISC's website (http://www.cdisc.org/).

CDISC provides SDTM as the standard for datasets comprising clinical study data collected from the CRF and other records in a tabulation format and ADaM as the standard for analysis datasets. Data should be summarized using the designated variables and submitted in accordance with the versions of SDTM and ADaM standards and IG that are accepted by the PMDA.

To avoid the complication of having to convert the collected data into a CDISC-conformant format upon application, it is preferable to decide on the method of data collection and analysis procedures that will conform to these standards from the planning stage of the clinical study. However, these standards do not indicate the items of the clinical study data required for the review. Therefore, the items of data to be collected from each clinical study must be established, which enables efficacy and safety evaluations of the drug and ensures the subjects' safety, by taking into consideration the characteristics of the target disease and the drug. If there are multiple methods of implementation based on the clinical study design or characteristics of the data to be collected or if some aspects of the dataset cannot or may not conform to the standards or IG upon creating a dataset conforming to these standards, the applicant should consult the PMDA beforehand.

CDISC standards, controlled terminologies to be used, and terms defined in dictionaries should be used without modifying spelling or notation, such as capital and small letters, when creating datasets.

4.1.1.2 SDTM datasets

The SDTM dataset is to be submitted, after the data collected from the CRF and other records are stored into the domain using variables designated by the version of SDTM and SDTM IG. The applicant may manage the clinical study data using their own unique format that includes SDTM, but even in such cases, the dataset to be submitted must be converted into formats that are in accordance with SDTM and SDTM IG.

In SDTM, the variables are classified into Required, Expected, and Permissible. If the variables contain collected data, the data for all variables must be submitted to the extent possible, regardless of the classification. Of the Permissible and Expected variables, the following must be submitted to the extent possible.

- Baseline flags (such as laboratory results, vital signs, ECG, pharmacokinetic concentration, and microbiology results)
- EPOCH designator (variables that designate the period)
- If the dataset contains --DTC, --STDTC, and --ENDTC variables, the corresponding Study Day variables (--DY, --STDY, and --ENDY)

SDTM dataset stores the data obtained in the study and does not include values used to impute missing data. Imputed data should be included in the ADaM dataset.

Basic rules of SDTM should be followed, for example, dates must be in accordance with ISO 8601 format, --DY must not contain 0, and even when the data was collected as Yes/No in the CRF, it must be stored as Y/N in SDTM dataset.

USUBJID has been prepared as a variable for storing the unique ID assigned to each individual subject across the entire application. It enables the data of one subject in multiple studies, for example, in a phase III study and the subsequent long-term study, to be summarized. Therefore, consideration should be given to ensure that each subject has the same USUBJID across all the studies in the application to the extent possible.

In SDTM, the domains of the Trial Design Model, such as TS domain, store information on the designs of clinical studies and thus contain useful information on the characteristics of the clinical studies. Its data should, therefore, be stored in accordance with the IG to the extent possible and be submitted.

In SDTM, it is possible to set a series of datasets called SUPPQUAL to include variables that are not specified in SDTM. These datasets may be used for data that cannot be allocated to each of the domains of SDTM. However, basically, variables related to main analyses should not be included in such datasets. If an applicant is considering to include a variable which is not mentioned specifically in the IG but may be important for the review in the SUPPQUAL, the applicant should consult the PMDA beforehand, and if the variable has been included in the SUPPQUAL, this should preferably be explained in the data guide.

Depending on the characteristics of the collected data, it may not fit into an existing domain of SDTM. In such a case, it is acceptable for the applicant to create a custom domain. To perform this, the applicant must confirm that the data does not fit into an existing domain, then create a custom domain according to the SDTM IG, and store the data under this domain. Explanation of the custom domain, together with the reason why it was necessary, should be described in the data guide. Also, when considering storing data under a custom domain, it is preferable to consult the PMDA beforehand.

4.1.1.3 ADaM datasets

The analysis datasets should be submitted after they are constructed in accordance with ADaM. It is not necessary to submit ADaM datasets for all analyses described in the statistical analysis plan. However, ADaM datasets

should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as primary efficacy analysis and secondary efficacy analyses (secondary analyses of primary variable and analyses of key secondary variables), primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety. The applicant should preferably consult the PMDA beforehand on the sufficiency of the datasets to be submitted. Even when the analysis results in the clinical study report had been created using datasets other than ADaM datasets, for analyses related to important results on efficacy and safety and the rationales for setting of the dosage and administration mentioned above, the analysis datasets based on ADaM that can reproduce these results should be submitted. It is not necessary to submit additional analysis datasets for analyses that the applicant performed after the new drug application in response to inquiries.

In ADaM, there is a dataset called Analysis Data Subject Level (ADSL), which contains subject level information, and this must be submitted for each study for which the ADaM datasets have been submitted. To make each analysis using the ADaM dataset easier, the core variables, including all covariates described in the protocol that are generally included in the ADSL dataset, in principle, should be included in each ADaM dataset. Examples of such variables include covariates, study (protocol number), study site (site number), region, country, assigned treatment, sex, age, race, analysis population flags, and other important baseline demographic variables.

Keep in mind that ADaM datasets other than ADSL can consist of various variables depending on the nature of the individual target analysis, and it is, therefore, important to explain the content of these datasets in the definition document and the data guide.

If the variables used in the SDTM dataset are also used in the ADaM dataset, these variables must have the same attributes and content.

4.1.1.4 File formats of datasets

The SDTM and ADaM datasets that conform to the CDISC standards should be submitted in the SAS XPORT file transport format Version 5 (hereinafter referred to as SAS XPORT format), which is the data transport format released by the SAS Institute, and as one file per dataset. The SAS CPORT Procedure must not be used when creating XPORT transport files by the SAS system. Similarly, for datasets that contain variables written in Japanese because it was considered necessary and appropriate (hereinafter referred to as Japanese items), the files should be in the SAS XPORT format, and the character sets or the encoding system used to create the dataset should be described in the data guide. The file name and the dataset name must be the same for the SDTM and ADaM datasets.

4.1.2 Definition documents and other appended documents of datasets

4.1.2.1 Definition documents of datasets

The definition documents of the SDTM and ADaM datasets in the Define-XML format by CDISC should respectively be created into the XML format files containing references to the style sheets that enable their contents to be displayed and stored in the same folder as their corresponding dataset, together with these

style sheets. The file name of the definition document should be “define.xml.” The definition document should include the definitions of datasets, variables, possible values of variables, and controlled terminologies and codes. The information on controlled terminologies and dictionaries should include their versions.

In order for the review of clinical study data to progress smoothly, it is important that the relationship between the analysis results shown in the application documents and the analysis datasets is easily understandable. Therefore, the definition documents of the ADaM datasets should preferably include Analysis Results Metadata, which shows the relationship between the analysis results and the corresponding analysis dataset and the variables used, for the analyses performed to obtain the main results of efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, shown in 4.1.1.3. The Analysis Results Metadata of each analysis should preferably include the following items.

- Figure or table numbers and titles showing the analysis results displayed in the clinical study report
- Purpose and reasons for performing the analysis
- Parameter name and code to be used
- Variables subject to analysis
- Dataset to be used
- Selection criteria for the records subject to analysis
- Corresponding description in the statistical analysis plan, analysis program name, and summary of the analytical methods
- Extract of the analysis program corresponding to the analysis method

For the format of the Analysis Results Metadata, the applicant should refer to the Analysis Results Metadata Specification for Define-XML by CDISC to the extent possible, but if it is difficult to include it into the definition document, it is possible to submit it as a separated file in PDF format, as specified in “Electronic Specifications of Common Technical Documents”, and “Handling of Electronic Specifications of Common Technical Documents”. The explanations in the definition document may be written in Japanese.

4.1.2.2 Annotated CRF

The Annotated CRF shows the relationship between each item of data collected from the CRF and the variables included in the dataset. For datasets that conform to the CDISC standards, SDTM variables will be used as variables that correspond to the items in the CRF. For the method of annotating, refer to the SDTM Metadata Submission Guideline (SDTM-MSG) by CDISC.

Data collected from the CRF should preferably be stored in the SDTM dataset whenever possible, prior to submission. However, if there are items of data that are not going to be submitted, it should be made clear in the Annotated CRF that the data is not included in the submitted dataset, and the reason why this data was not included should be provided in the data guide. However, it is not necessary to perform this if the reasons are clear.

The file format of the Annotated CRF, in principle, should be a PDF, as specified in “Electronic Specifications of Common Technical Documents”, and “Handling of Electronic Specifications of Common Technical Documents”, and

the file name should be “acrf.pdf.” In principle, it should be stored in the same folder as SDTM datasets.

4.1.2.3 Data guide

To promote the understanding of the content and characteristics of the dataset by reviewers during the review and enable the applicant to explain about the utilization status of and conformance to the data standards when creating the datasets, a dataset definition document as well as a data guide must be created for each of the SDTM and ADaM datasets, which, in principle, should be stored in the same folder as their corresponding dataset prior to submission.

At least the following items should be included in the data guide for the SDTM dataset.

- Clinical study name, protocol number
- Explanation of the clinical study design
- Standards, controlled terminologies, and dictionaries used and their versions
- Explanation of the subject data
- Explanation on conformance to the data standards (explanation of the validation results)

The data guide for the ADaM dataset should preferably include the following items.

- Clinical study name, protocol number
- Explanation of the clinical study design related to the analysis dataset
- Standards, controlled terminologies, and dictionaries used and their versions
- Considerations related to multiple analysis datasets
- Considerations on creating the analysis datasets
- Explanation of the datasets
- Explanation on conformance to the data standards (explanation of the validation results)

When creating data guides for the SDTM and ADaM datasets, although no specific format for the data guide is provided in the CDISC standards, the applicant may refer to the following documents for the content to include in each item.

- Data guide for SDTM datasets:
  http://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer's_Guide
- Data guide for ADaM datasets:
  http://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer's_Guide

Each document should in principle be created as a PDF, as specified in the eCTD notification and the notification on handling of eCTD, and the files for SDTM and ADaM should preferably be named “study-data-reviewers-guide.pdf”, “analysis-data-reviewers-guide.pdf”, or the like, so that their contents are identifiable. The data guide may be written in Japanese.

4.1.3 Version of standards to be used

When creating the dataset and the definition document conforming to the CDISC standards, refer to the PMDA's website (http://www.pmda.go.jp/) for versions of the CDISC standards, controlled terminologies, and dictionaries that are accepted by the PMDA. Acceptance of versions is judged based on the date of submission described in the new drug application by the applicant.

It is sufficient to use different versions within the same application, but the same version must be used within the same clinical study. If the applicant had referred to other versions for certain domains within the same clinical study, the version used and the reason for using that version must be explained in the data guide.

Datasets of integrated analyses of multiple clinical studies should be created using the same version, even if the version used to create the dataset of each clinical study was different. When standardizing the version, the reason that the specific version was chosen and considerations for converting to a different version should be described in the data guide.

4.1.4 Therapeutic area standards

To date, the Therapeutic Area Standards have been published for a number of diseases by the CDISC for storing data specific to each therapeutic area. These standards may be used for diseases for which standards have already been published. However, the standards used must be provided in the definition document of the dataset and the data guide.

4.1.5 Handling of data written in Japanese text

If variables had been collected in Japanese and there is a risk of losing certain information by translating it into English, as long as the descriptions in Japanese are necessary and appropriate, data written in Japanese (hereinafter referred to as Japanese data) may be submitted. Examples of variables that may contain Japanese texts are shown in Attachment 2 (but are not limited to these).

The method of storing Japanese data into datasets and the method of submission when a domain contains Japanese items, in principle, will be as follows. Examples are provided in Attachment 3.

- For the domain (dataset), create two datasets: the Japanese dataset and a dataset comprising letter sets specified by ASCII such as alphanumeric characters (hereinafter referred to as alphanumeric dataset).
- In the Japanese dataset, only the items written in Japanese should be Japanese and the rest should be alphanumeric data, similar to that in the alphanumeric dataset.
- The Japanese dataset and alphanumeric dataset must be identical in structure, except for the data lengths of the Japanese items and the corresponding alphanumeric character sequence, and the two datasets must also have an identical record number and record order. The applicant only needs to submit the definition document for the alphanumeric dataset.
- In the alphanumeric dataset, an English character sequence (such as "JAPANESE TEXT IN SOURCE DATA") which clearly states this is not the original data should be stored in the parts that correspond to the Japanese items. If the Japanese data must be stored by multiple variables or records due to restriction on the data length, this English character sequence must be stored in the corresponding record within the alphanumeric dataset.

- These English character sequences (such as “JAPANESE TEXT IN SOURCE DATABASE”) must be consistent within the same study, and it must be stated clearly in the data guide or the definition document (define.xml) of the dataset.
- For parts that correspond to the questionnaires and code lists that contain Japanese text, an appropriate English translation or English character sequence must be stored. When storing English character sequences and distinguishing each of the character sequences, take appropriate measures such as by attaching a number at the end of each sequence (example: “JAPANESE TEXT IN SOURCE DATABASE 01” and “JAPANESE TEXT IN SOURCE DATABASE 02”), and the link with the original Japanese text should be shown in the data guide.
- Alphanumeric datasets must be included in the designated folder. The Japanese dataset corresponding to the SDTM dataset must be included in the “sdtm_j” folder, and the Japanese dataset corresponding to the ADaM dataset must be included in the “adam_j” folder. The same dataset name and label name must be used for the two datasets.
- For domains that do not contain Japanese items, only the alphanumeric dataset must be included in the designated folder, and the submitted data must not contain any duplicates.

In principle, for Japanese data, both SDTM and ADaM datasets should be stored by the above method before they are submitted, but if the applicant plans to submit data from clinical studies containing Japanese data, it is preferable to consult the PMDA beforehand on the scope of such data.

4.1.6 Submission of programs

4.1.6.1 Programs to be submitted

With respect to the programs related to the electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted for the analyses performed to obtain the important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration shown in 4.1.1.3. The main purposes of requesting the submission of these programs are to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment. Also, although the programs to be submitted are not limited to specific software or versions, information on the environment in which the programs were created or run (operation system and software used and their versions) must be provided together in the data guide. If programs with macros had been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient.

4.1.6.2 File format of the programs

As stated in 4.1.6.1, although the programs to be submitted are not limited to specific software or versions, the file name should include the extension attached

by the analysis software. If the file name does not contain an extension, an explanation about the file format should be included in the data guide.

4.1.7 CDISC-conformant electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses

For the handling of CDISC-conformant electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses, refer to 4.1.1 to 4.1.6. Points to be considered especially for those data are described in this section.

4.1.7.1 SDTM datasets

PP domain storing pharmacokinetic parameters should be submitted as well as PC domain storing drug concentration data, since the pharmacokinetic parameters themselves are considered as data to capture the characteristics of the drug. Creating RELREC dataset based on SDTM IG is preferable when explaining the relationship of datasets between PC domain and PP domain. However, it would be also acceptable to explain those relationship in a document such as the data guide if it is difficult to create the RELREC dataset based on SDTM IG.

In the case where PC domain and PP domain are created by converting from datasets in a format other than CDISC standards, the traceability (the procedure of creating the PC domain and PP domain, the relationship between the information included in these domains, such as the relationship between the variables in PC domain and those in PP domain, etc.) should be explained in a document such as the data guide. In this case, PK parameters will not need to be recalculated from the PC domain for the purpose of the explanation of the traceability.

4.1.7.2 ADaM datasets

When ADaM datasets for PK or PK/PD analysis of blood and urine drug concentration are submitted, either a single dataset or multiple datasets would be acceptable as long as each analysis using the ADaM dataset can be performed easily without modification of the dataset.

When the datasets used for the analysis are in a format other than ADaM and are converted to ADaM datasets for a new drug application, it is not necessary to submit the original datasets used for the analysis. However, if the original datasets are useful for explanation of traceability between datasets or contents of analysis, it may be submitted and used for the explanation.

4.2 Electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses

Matters that need to be followed with respect to the specific contents of the submission, including the "Explanation of electronic data package on clinical pharmacology", as well as the electronic study data on clinical pharmacology and programs are shown below.

4.2.1 "Explanation of electronic study data package on clinical pharmacology"

Submission of the "Explanation of electronic study data package on clinical pharmacology" is not necessary because this form should be created by the PMDA based on the information about content of the clinical pharmacology study data provided via the portal site when electronic study data is submitted through the

gateway system. In the case of submissions using the PMDA window during system failure, TSV files should be submitted according to Section 3.7.

Necessary information for creating "Explanation of electronic study data package on clinical pharmacology" by the PMDA are as follows:

- Study ID (letter sets identifying each study)
- File path (including file name)

  Entering file path is not necessary because the gateway system imports file path automatically.
- Type of analysis performed (Enter STS (standard pharmacokinetic analysis), POP (population analysis), PBPK (physiologically based pharmacokinetic model analysis), or Other (other than the above) using abbreviation). STS includes pharmacokinetic/pharmacodynamic analysis performed by the same method.
- Explanation of the file content

  Details must be described specifying the use of each file and its relationship to other files. Description should be 100 characters or less.

4.2.2 Specific content of the electronic study data to be submitted

Matters that must be followed with respect to standard pharmacokinetic analysis, population analysis, and physiologically based pharmacokinetic model analysis are shown below. Regardless of the type of analysis performed, file name and dataset name must be the same when the datasets are submitted in the SAS XPORT format.

For handling of CDISC-conformant electronic study data on phase I and clinical pharmacology study results and clinical pharmacology analyses, refer to section 4.1.7.

4.2.2.1 Standard pharmacokinetic analysis

Details of the analysis dataset and dataset definition document in the case where analysis datasets are submitted in a format other than ADaM for the submission of the electronic study data on standard pharmacokinetic analysis are as follows:

(1) Analysis datasets

Both analysis datasets for calculating PK or PD parameters and analysis datasets for statistical analysis using calculated PK or PD parameters (excluding the case where only summary statistics of parameters are derived) should be submitted.

File format example:

- SAS XPORT format (*.xpt)
- ASCII Format Data Files
- Phoenix Projects (*.phxproj)
- WinNonlin Files (*.pmo, *.pwo)

(2) Dataset definition documents

- The dataset definition document should include at least the variable names and the explanation of the variables and must be created by referring to Attachment 4. If the definitions are provided in the analysis result report, it would be sufficient to mention this fact and clearly state the relevant page number in the analysis result report.
- The file format, in principle, should preferably be a PDF, as specified in the eCTD notification and the notification on handling of eCTD.

4.2.2.2 Population analysis (including simulations)

Details of the analysis dataset and dataset definition document for the submission of the electronic study data on population analysis are as follows:

(1) Analysis dataset

Analysis dataset, which is finally used for model building of base model and final model, etc., and corresponds to program files for the model as shown in 4.2.3.2 (1), should be submitted.

File format example:

- SAS XPORT format (*.xpt)
- ASCII Format Data Files

(2) Dataset definition documents

Refer to 4.2.2.1(2)

4.2.2.3 Physiologically based pharmacokinetic model analysis (including simulations)

Details of the files, datasets, and dataset definition documents for the submission of the electronic study data on physiologically-based pharmacokinetic model analysis are as follows:

(1) Files that contain information on the model structure used for the analysis, the set values of drug and physiological parameters, analysis procedures, and sensitivity analysis of the results

The file format is optional.

(2) Clinical study datasets, including blood concentration data

If the datasets were created or modified to be analyzed using a specific software for PBPK model analysis, the electronic files of the created or modified datasets should be submitted in the format for the specific software (Simcyp PE Data Files (xml format), etc.). If the datasets were not created or modified for a specific software for PBPK model analysis, the datasets can be submitted in an optional file format.

(3) Dataset definition documents

Refer to 4.2.2.1(2)

4.2.3 Specific content of programs to be submitted

4.2.3.1 Standard pharmacokinetic analysis

Details of the analysis specifications on pharmacokinetics or pharmacokinetics/pharmacodynamics and information to be submitted in accordance with these specifications are as follows:

- This will include detailed information on the analyses that were performed, such as the analysis algorithms (for example, the method used to calculate the pharmacokinetic parameters) and the handling of data below the lower limit of quantitation. If this information is included in the analysis dataset itself [such as Text Output of Phoenix Projects (*.phxproj)], it would be sufficient as long as this is stated clearly. If this information is included in documents such as the analysis plan, it would be sufficient to just submit these documents.
- The file format is optional.

4.2.3.2 Population analysis (including simulations)

Details of the programs files, files into which major results are outputted, and files on simulation (such as program procedures) for the submission of electronic study data on population analysis are as follows.

(1) Program files

Program files for analysis using base model and final model, etc., should be submitted.

File format example:

・ASCII Format Data Files

(2) Files into which major results are outputted (such as NONMEM output)

Output files including the analysis output using base model and final model, etc., should be submitted. The file format is optional.

(3) Files on simulation

As files for simulation, program files for generating simulation data, performing simulation and making figures and tables showing simulation results should be submitted. If a dataset, etc. related to existing information is used in the simulation, the dataset, etc. including such information, should be submitted. If it is difficult to submit those programs, the submission of specifications that show the analysis algorithm would be sufficient.

The program procedures should be submitted and the details are as follows:

- Describes the detailed procedures of running the program.
- It must include at least the program file names and the explanation of the programs and must be created by referring to Attachment 5. If it is not necessary to perform special processes, such as designating the path name, to use the submitted program, basically, the submission of program procedures is not necessary.

5. Relationship between the electronic study data and eCTD for new drug applications

5.1 Relationship between the electronic study data and eCTD

In principle, all the electronic study data should be referenced from the eCTD backbone. However, if the eCTD is submitted according to the methods described in the eCTD notification and the notification on handling of eCTD, information or files related to the electronic study data should not be included in the eCTD backbone or the eCTD folder structure. However, whether or not the electronic study data is being submitted must still be described, per study report, in the list of attachments in Module1.

5.2 Obtaining the eCTD receipt number from the portal site

When submitting the eCTD, the applicant must enter the scheduled date of submission and necessary information beforehand and obtain the eCTD receipt number from the portal site. Some examples of necessary information are as follows:

- Brand name of the product subject to application
- Application category
- New application/application for minor change
- Original/reference
- Scheduled submission date

5.3 Submission of the eCTD via the portal site

When submitting the eCTD, the applicant must register, select, or enter administrative information on the portal site. Some examples of administrative information are as follows. Not all items need to be registered, selected, or entered at each submission.

- Original/reference/formal/draft/replacement
- Gateway receipt number
- eCTD receipt number
- Submission sequence number
- Form (code)
- Application category
- Generic name of the product

- Brand name of the product
- Statement concerning virus check
- Checksum value of XML instance (eCTD backbone)
- Execution check environment
- Contacts for the regulatory affairs manager and eCTD technical manager
- Remarks

After registering, selecting, or entering the abovementioned details, register the top level folder of the eCTD to be submitted on the portal site and send it to the PMDA. The details on operating the portal site will be specified separately.

5.4 Receipt of the eCTD submitted via the portal site

The PMDA will perform a virus check and validation of the eCTD and notify the applicant of the results together with the assessment on the acceptance of the eCTD. For the content of validation performed on the eCTD, in principle, refer to the operation manuals of the eCTD verification tool published on the PMDA's website (http://www.pmda.go.jp/).

5.5 Relationship of the eCTD life cycle and electronic study data

Because the electronic study data is part of the document to be appended to the application form, when changing (adding, replacing or deleting) the electronic study data, it is appropriate to revise the eCTD. If the eCTD is submitted separately from the electronic study data, submission of administrative information related to the electronic study data (as shown in 3.3) enables the identification of the eCTD related to this electronic study data. The applicant should consider the following points when submitting the electronic study data.

(1) Electronic study data submitted upon the initial submission of the eCTD

After submitting the electronic study data for the initial submission, once the PMDA notifies the acceptance of the electronic study data, it is not possible to submit additional electronic study data related to the initial submission.

(2) Electronic study data appended to the responses to inquiries

Electronic study data appended to the responses to inquiries should be submitted as an attachment to responses via the portal site, without linking it to the specific eCTD submission sequence number.

(3) Electronic study data submitted during the revision of the eCTD

- Of the electronic study data submitted in above (2), those which have been approved to be included upon the revision of the eCTD by the PMDA should be formally submitted upon the revision of the eCTD.
- Only submit the difference with the previously submitted datasets. It is not necessary to resubmit the electronic study data submitted with the previous submission sequence number.
- If there is no eCTD to be submitted with the electronic study data, consult the PMDA beforehand on the method of submission.
- Once the PMDA notifies the acceptance of the electronic study data, it is not possible to submit additional electronic study data related to this submission sequence number.
- When submitting the electronic study data after the committee on drugs, follow the procedures in this section.

5.6 Change request during the submission of electronic study data

When submitting the electronic study data during the revision of the CTD or eCTD, describe the electronic study data in the change request shown in Appendix 6 of "Confirmation of the Progress Status of New Drug Review" (PMDA Notification No. 1227001, by the Chief Executive of Pharmaceuticals and Medical Devices Agency, dated December 27, 2010). It is not necessary to list all the files to be submitted in the

change request; it is only necessary to verify the presence or absence of the set of electronic study data related to each study. However, this procedure is not necessary if the revised CTD is submitted using the gateway system shown in 2. (2) a of the notification on practical operations.

6. Submission of electronic study data on applications for re-examination

When submitting the electronic study data at the time of application for re-examination, it should be submitted electronically by the method specified in sections 3.4 to 3.7 of "3. Submission of electronic study data for new drug applications". However, "3.1 Basic flow of the submission of electronic study data" and "3.3 Submission of electronic study data via the portal site" at the time of application for re-examination should be as follows:

6.1 Basic flow of the submission of electronic study data

The applicant should use a "consultation on data format of submission of electronic study data", etc., and confirm with the PMDA about the contents of the electronic study data to be submitted for re-examination application and the timing of re-examination application, etc. at a pre-meeting held 1 to 3 months before application for re-examination, in principle. When conducting a pre-meeting, the contents of the electronic study data to be submitted at the time of re-examination application should be summarized by using Attachment 8, "Consultation form on data format for the 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)" and the form should then be submitted.

The applicant should then make an advance notice of the application via the portal site during the period from 5 weeks to 1 week before the scheduled date for re-examination application set by the applicant. The applicant should then enter and register the information related to the application and transfer the electronic files necessary for the application (FD application data, electronic study data, etc.) via the portal site.

6.2 Submission of electronic study data via the portal site

When submitting the electronic study data, the applicant must register, select, or enter the following additional information on the portal site. Examples of such additional information are as follows. Not all items need to be registered, selected, or entered at each submission.

- Original/draft response and attachments
- Gateway receipt number
- Information for identifying to which file the data is appended (such as study number, study title, inquiry number)
- Identifier of each file (UUID defined by ISO/IEC 11578:1996 and ITU-T RecX.667 | ISO/IEC 9834-8:2005)
- Position of the electronic study data (such as addition, replacement, deletion)
- Identifiers of data subject to replacement or deletion
- File path
- Data analysis type
- Explanation of the file content

After registering, selecting, or entering the above details, register the "m5" folder containing the electronic study data to be submitted on the portal site and send it to the PMDA. The specific operations to be performed on the portal site will be specified separately.

7. Submission of electronic study data when study results are practically evaluated before new drug applications or re-examination 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.) or products for which the evaluation of results from post-marketing clinical studies is carried out before re-examination applications (at the consultation on the package insert revisions, a request for removal of the approval conditions, etc.), if electronic study data are submitted when the study results are practically evaluated, the electronic study data should be submitted electronically by the method specified in sections 3.5 and 3.6 of "3. Submission of electronic study data for new drug applications". However, "3.1 Basic flow of the submission of electronic study data" and "3.4 File size of the electronic study data" should be as follows:

7.1 Basic flow of the submission of electronic study data

Those who intend to apply should use a consultation on data format of submission of electronic study data, etc., and confirm with the PMDA about the content of electronic study data at a pre-meeting before the submission of study results, in principle. When conducting a pre-meeting, the contents of the electronic study data to be submitted at the time of study result submission should be summarized by using Attachment 8 "Consultation form on data format for the 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)" and the form should then be submitted.

After that, the necessary electronic files (electronic study data, etc.) should be submitted during the period from 5 weeks before the date on which the study results are scheduled to be submitted to the date of the study result submission by using a recording medium.

7.2 File size of the electronic study data

Files other than datasets must not exceed the maximum file size of PDF specified in the eCTD notification and the notification on handling of eCTD. Consult the PMDA beforehand if the size of a dataset file is 5 gigabytes or greater.

8. Other

For products that require the submission of the electronic study data but do not necessarily require the attachment to a new drug application to be a CTD, such attachments to the new drug application may be submitted electronically by the method specified in 3. In such a case, the standard electronic specification of the attachments to the new drug application will be provided separately.

Provisional Translation (as of November 2016)

Attachment 1

System of terminology used in this guide

- Electronic files (all files to be submitted via the portal site)
  - Electronic data for application (= electronic study data) (note: “electronic data” in the notification of basic principles)
    - Clinical study data
      - [Clinical study data that excludes the electronic study data on clinical pharmacology]
        - CDISC-conformant data (= data conformant to CDISC)
          - Dataset (= dataset for submission)
            - SDTM dataset (= dataset according to SDTM)
            - Analysis dataset (= ADaM dataset = dataset according to ADaM)
          - Definition file (= define.xml)
        - Legacy data
          - Dataset
          - Definition file
        - Program file
          - Program for analysis
          - Program for creating datasets
      - [Electronic study data on clinical pharmacology] (electronic study data on clinical studies where standard pharmacokinetic analysis was performed, population analysis, and physiologically-based pharmacokinetic model analysis)
        - CDISC-conformant dataset (= data conformant to CDISC)
          - Dataset (= dataset for submission)
            - SDTM dataset (= dataset according to SDTM)
            - Analysis dataset (= ADaM dataset = dataset according to ADaM)
          - Definition file (= define.xml)
        - Data in a format other than CDISC standards (= data when submitting analysis dataset in a format other than ADaM)
          - Dataset (= dataset for submission)
            - Analysis dataset (= dataset in a format other than ADaM)
            - Datasets other than analysis dataset (information on pharmacokinetic and physiological parameter values set in the physiologically-based pharmacokinetic model analysis)
          - Dataset definition document
          - Files into which major results were outputted
          - Files on simulations
          - Program procedure
        - Analysis specification (or documents containing comparable information)
        - Program file
          - Program for analysis
          - Program for creating datasets
        - Explanation of electronic study data package on clinical pharmacology
    - Documents to be appended
      - aCRF (Annotated CRF)
      - Data guide (ie. Reviewer's Guide)
        - SDRG
        - ADRG
  - eCTD (excluding electronic study data)
  - FD application data
  - [Other data to be submitted via the portal site]

Provisional Translation (as of November 2016)
Attachment 2

Examples of variables which may contain Japanese text

Domain Prefix	Variable Name	Variable Label	Type	CDISC Notes (for domains) Description (for General Classes)	Core
Common	--REASND	Reason Not Done	Char	Reason not done. Used in conjunction with --STAT when value is NOT DONE.	
Common	--RELNST	Relationship to Non-Study Treatment	Char	An opinion as to whether the event may have been due to a treatment other than study drug. Example: "MORE LIKELY RELATED TO ASPIRIN USE."	
DM	INVNAM	Investigator Name	Char	Name of the investigator for a site.	Perm
CO	COVAL	Comment	Char	The text of the comment. Text over 200 characters can be added to additional columns COVAL1-COVALn.	Req
SE	SEUPDES	Description of Unplanned Element	Char	Description of what happened to the subject during this unplanned Element. Used only if ETCD has the value of "UNPLAN".	Perm
SV	SVUPDES	Description of Unplanned Visit	Char	Description of what happened to the subject during an unplanned visit.	Perm
CM	CMTRT	Reported Name of Drug, Med, or Therapy	Char	Verbatim medication name that is either pre-printed or collected on a CRF.	Req
CM	CMMODIFY	Modified Reported Name	Char	If CMTRT is modified to facilitate coding, then CMMODIFY will contain the modified text.	Perm
CM	CMINDC	Indication	Char	Denotes why a medication was taken or administered. Examples: NAUSEA, HYPERTENSION.	Perm
EX	EXADJ	Reason for Dose Adjustment	Char	Describes reason or explanation of why a dose is adjusted.	Perm
SU	SUTRT	Reported Name of Substance	Char	Substance name. Examples: Cigarettes, Coffee.	Req
SU	SUMODIFY	Modified Substance Name	Char	If SUTRT is modified, then the modified text is placed here.	Perm
SU	SUDOSTXT	Substance Use Consumption Text	Char	Substance use consumption amounts or a range of consumption information collected in text form.	Perm
AE	AETERM	Reported Term for the Adverse Event	Char	Verbatim name of the event.	Req
AE	AEMODIFY	Modified Reported Term	Char	If AETERM is modified to facilitate coding, then AEMODIFY will contain the modified text.	Perm
AE	AEACNOTH	Other Action Taken	Char	Describes other actions taken as a result of the event that are unrelated to dose adjustments of study treatment. Usually reported as free text. Example: "TREATMENT UNBLINDED. PRIMARY CARE PHYSICIAN NOTIFIED."	Perm
DS	DSTERM	Reported Term for the Disposition Event	Char	Verbatim name of the event or protocol milestone. Some terms in DSTERM will match DSDECOD, but others, such as "Subject moved" will map to controlled terminology in DSDECOD, such as "LOST TO FOLLOW-UP."	Req
MH	MHTERM	Reported Term for the Medical History	Char	Verbatim or preprinted CRF term for the medical condition or event.	Req
DV	DVTERM	Protocol Deviation Term	Char	Verbatim name of the protocol deviation criterion. Example: IVRS PROCESS DEVIATION - NO DOSE CALL PERFORMED. The DVTERM values will map to the controlled terminology in DVDECOD, such as TREATMENT DEVIATION.	Req

* 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.

Domain Prefix	Variable Name	Variable Label	Type	CDISC Notes (for domains) Description (for General Classes)	Core
PE	PEORRES	Verbatim Examination Finding	Char	Text description of any abnormal findings. If the examination was completed and there were no abnormal findings, the value should be NORMAL. If the examination was not performed on a particular body system, or at the subject level, then the value should be null, and NOT DONE should appear in PESTAT.	Exp
QS	QSTEST	Question Name	Char	Verbatim name of the question or group of questions used to obtain the measurement or finding. The value in QSTEST cannot be longer than 40 characters.	Req

(Reference: SDTM Ver.1.2, SDTM IG Ver.3.1.2, and later versions; descriptions have been partially omitted.)

Provisional Translation (as of November 2016)
Attachment 3

Sample methods for storing Japanese data

Example 1) Storing the verbatim term in Japanese without translating it into English
AE domain (alphanumeric dataset)

- For text items for which data was collected in Japanese, store the English character sequence (such as "JAPANESE TEXT IN SOURCE DATABASE") (collect AETERM in Japanese).

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-12	2005-10-12		Headache
2	ABC123	AE	123101	2	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-13T13:05	2005-10-13T19:00		Back pain
3	ABC123	AE	123101	3	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

AE domain (Japanese dataset)

- For text items for which data was collected in Japanese, store them in Japanese without translating.

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	*頭痛*	2005-10-12	2005-10-12		Headache
2	ABC123	AE	123101	2	*背部痛*	2005-10-13T13:05	2005-10-13T19:00		Back pain
3	ABC123	AE	123101	3	*肺塞栓*	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

Example 2) If translation of the original text into English is difficult and the English character sequence needs to be distinguished from one another
QS domain (alphanumeric dataset)

Row	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	QSTEST
1	ABC123	QS	123101	1	QSTEST1	JAPANESE TEXT IN SOURCE DATABASE01
2	ABC123	QS	123101	2	QSTEST2	JAPANESE TEXT IN SOURCE DATABASE02
3	ABC123	QS	123101	3	QSTEST3	JAPANESE TEXT IN SOURCE DATABASE03

QS domain (Japanese dataset)

Row	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	QSTEST
1	ABC123	QS	123101	1	QSTEST1	*自分で布団を敷けますか？*
2	ABC123	QS	123101	2	QSTEST2	*ぞうきんがけはできますか？*
3	ABC123	QS	123101	3	QSTEST3	*ラジオ体操をしても平気ですか？*

Provisional Translation (as of November 2016)

Attachment 4

(Reference) Dataset definition file

Dataset: XXXXX ("XXXXX" is the dataset name)

No.	Variable [*1]	Description [*2]
1	ID	Unique subject identifier
2	STUDYID	Study number
3	TIME	Time of the event relative to the first dosing of the study drug
4	AMT	Amount of drug administered
5	DV	Plasma concentration
6	CMT	Number of the compartment where the parameter was measured 1 = Dosing 2 = Parent drug 3 = Metabolite
7	MDV	Missing dependent variable data item for DV 0 = Valid PK measurement 1 = Other (missing or invalid value, dosing event, start of urine sampling)
X	XXXX	••••••

*1: Provide the variable name.

*2: Provide the description of the variable.

Provisional Translation (as of November 2016)
Attachment 5

(Reference) Program procedure

No.	Program file name *1	Description *2
1	xxxxxx	Software used: ○○ Ver.● Purpose: Used for ••••. Considerations for use: • Designate the folder to output the file with the following line. xxxxx <- “path name” • • Designate the folder to store the data file of •••• with the following line. xxxxx<- “path name” • Run the program up to the following line. ExportData(XXXXX) • Perform the •••• file (xxxxxx) for simulation on the CSV file (“xxxx”) outputted into a designated folder (xxxxx). • Store the output file (xxxxx) to the folder (xxxxx) designated above. • Resume the program from the line below, then import and analyze the stored output file (xxxxx). xxxxx <- importData(XXXXX)
X	xxxxxx	Software used: ○○ Ver.● Purpose: Used for ••••. Considerations for use: ••••

*1: Provide the file name of the program.

*2: Provide the description (such as the software used, purpose, considerations for use) of the program.