

Provisional Translation (as of October 2014) *

PMDA/CPE Notification No. 1001001

October 1, 2014

To: As specified in the Appendix separately

From: Takao Yamori, Ph.D.
Director, Center for Product
Evaluation of
Pharmaceuticals and
Medical Devices Agency

Re: Request for Electronic Clinical Study Data for Pilot Project (FY 2015)

First, we would like to express our gratitude for your understanding and continuous support for the services of the Pharmaceuticals and Medical Devices Agency (PMDA).

PMDA has been making efforts to promote future utilization of electronic clinical study data, with the following details to be included in the third mid-term plan starting in FY 2014: develop a framework for PMDA to enable electronic submission of clinical study data for application of new drugs from FY2016; and improve quality of review and consultation by conducting PMDA-initiated analyses using the clinical study data and by giving indications and advice based on those analysis results. Specifically, PMDA has organized a joint working group with industry to discuss regulatory and technical issues, and, with the cooperation of member companies, executed pilot projects in FY2013 and FY 2014, and contributed to the development of the document “Basic Principles on Electronic Submission of Study Data for New Drug Applications” (Notification number: 0620-6, June 20, 2014, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). In addition, PMDA is currently preparing to issue technical notices and guides for electronic submission of study data.

The ways in which to utilize electronic data in the review process were examined in the FY2013 pilot project and also currently being examined in the ongoing FY2014 pilot project. Prior to the start of electronic study data submission as part of the new drug application process, PMDA plans to further confirm and improve the use of electronic data in the review process, and to newly consider and investigate the

* 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.

Provisional Translation (as of October 2014) *

potential of utilizing electronic data for a more efficient conformity inspection process in future. In order to continue these deliberations, we believe further examination, with use of real electronic study data in an arrangement closely mirroring the actual review process, is required.

In this regard, because a pilot project will be conducted again in FY2015, your member companies are kindly requested to cooperate in providing electronic clinical study data for the purpose of examining the future utilization of electronically submitted data under the actual regulatory review as well as taking into consideration the utilization of electronic study data for the conformity inspection process.

As with past pilots, participation in this pilot project is not mandatory. The main electronic data we are requesting for the pilot project in FY2015 is described below in item 1. However, in certain situations, we will also accept electronic data described below in item 2 (see attachment for details). Please consult us even if you are only able to provide one of either clinical data in conformance to CDISC or data for population PK and/or PK/PD analysis.

In any case, PMDA is planning to hold individual discussions with those companies willing to cooperate in this pilot project, to consult on details of data to be submitted and the handling of submitted data, post-review.

1. The pilot conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period described below;
 - Clinical data in conformance to CDISC
 - ① Data of new drug products (including follow-on biologics) that are submitted to be reviewed in Japan from January 1st to September 30th, 2015;
 - ② Series of datasets from clinical studies that will be required to be submitted after starting the electronic submissions as shown in the document “Basic Principles on Electronic Submission of Study Data for New Drug Applications”, and be able to be provided almost at the same time of submission of new drug application, along with the comprehensive analysis programs (It would be of great help to receive all studies corresponding to those requirements).
 - Data for Population PK and/or PK/PD analysis

* 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.

Provisional Translation (as of October 2014) *

- ① Data of the same new drug products provided as the clinical data in conformance to CDISC;
 - ② Datasets for population PK and/or PK/PD analysis summarized in a format used in the software for population pharmacokinetic analysis, NONMEM, along with the main model program.
2. The pilot conducted using the electronic study data except for the data corresponding to item 1
- Clinical data in conformance to CDISC
 - ① Data of new drug products (including follow-on biologics) that are either approved, currently under regulatory review, or scheduled to be reviewed by December 31st, 2014 or from October 1st, 2015;
 - ② Data summarized according to the CDISC standards (SDTM and ADaM), and each defined in Define.xml or in a corresponding definition file;
 - ③ Series of datasets from clinical studies that include those of Japanese subjects, along with the analysis program.
 - Data for Population PK and/or PK/PD analysis
 - ① Data of new drug products (including follow-on biologics) that are either approved, currently under regulatory review, or scheduled to be reviewed by December 31st, 2014 or from October 1st, 2015;
 - ② Data summarized in a format used in the software for population pharmacokinetic analysis, NONMEM;
 - ③ Datasets for population PK and/or PK/PD analysis that include those of Japanese subjects, along with the main model program.

As with past pilots, the data submitted for this pilot project will be used only for the purpose of deliberating the future utilization of electronic study data, and the regulatory review process at PMDA, and will have no influence on the regulatory review of the products concerned. Although the submitted electronic data will be checked during review of the corresponding applications, PMDA is placing measures such as added support and cooperation from the Advanced Review with Electronic

* 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.

Provisional Translation (as of October 2014) *

Data Promotion Group, so that reviews still follow the existing review process and timeline.

As for the consideration of utilizing electronic study data for the conformity inspection process, the aim is for inspectors to understand the structure and content of the submitted data and related information. We do not intend to verify the conformity of the submitted data itself.

For the companies offering to participate in this pilot project, we are hoping to provide opportunities for detailed discussion regarding data submission in a meeting prior to submitting the data, and in a feedback session after the pilot project itself.

We would appreciate that you contact us at the below e-mail address by March 31st, 2015 if there are any member companies offering to participate in this pilot project regardless of our request. If you are indeed interested in participating and as we would like to discuss the schedule of data submission, we would appreciate it if you could contact us as soon as possible. In some cases, specific requests for cooperation will be made individually to your member companies.

Any inquiries about this project may also be directed to the e-mail address below.

We appreciate your understanding regarding this pilot project and your support in requesting your member companies for cooperation. Thank you.

Contact:

E-mail: jisedaiPT@pmda.go.jp

Advanced Review with Electronic Data Promotion Group
Pharmaceuticals and Medical Devices Agency

* 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.

Provisional Translation (as of October 2014) *

(Attachment)

Details of the Electronic Clinical Data to be submitted

○Clinical data in conformance to CDISC

- Target products

- 1) The pilot conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period described below;
 - Data of new drug products (including follow-on biologics) that are submitted to be reviewed in Japan from January 1st to September 30th, 2015.
- 2) The pilot conducted using the electronic study data except for the data corresponding to item 1
 - Data of new drug products (including follow-on biologics) that are either approved, currently under regulatory review, or scheduled to be reviewed by December 31st, 2014 or from October 1st, 2015.

-Target studies

- 1) The pilot conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period
 - The entire clinical studies package that will be required to be submitted after starting the electronic submissions as shown in the document “Basic Principles on Electronic Submission of Study Data for New Drug Applications” (It would be of great help to receive all studies corresponding to those requirements).
- 2) The pilot conducted using the electronic study data except for the data corresponding to item 1
 - Clinical studies (phases II and III) that include data of Japanese subjects and that indicate the main evidence supporting the efficacy, safety, and dosage and administration in the application data. More than one study per one application (if possible, please submit data from multiple studies included in the application data package).

-Data standard to be used

- Data should be in conformance with the Clinical Data Interchange Standards

* 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.

Provisional Translation (as of October 2014) *

Consortium (CDISC) standards

- As a principle regarding data coding, controlled terminology and code lists recommended by the CDISC are to be used, and the values are to be in SI units.

-Target clinical study data

- Clinical study data summarized using Study Data Tabulation Model (SDTM) and its definition files such as Define.XML
- Analysis datasets summarized using Analysis Data Model (ADaM) and its definition files such as Define.XML
- Analysis program basically intended for ADaM datasets
- Program for creating ADaM datasets, if created from SDTM datasets
- Materials described below: (it is desirable to be submitted with datasets, if these have been prepared)
 - ◇ Annotated CRF
 - ◇ Documents providing reviewers with context for datasets (Study Data Reviewer's Guide, Analysis Data Reviewer's Guide and so on.)

○ Population PK and/or PK/PD analysis data

- Target products

- 1) The pilot conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period
 - Data of the same new drug products provided as the clinical data in conformance to CDISC
- 2) The pilot conducted using the electronic study data except for the data corresponding to item 1
 - Data of new drug products (including follow-on biologics) that are either approved, currently under regulatory review, or scheduled to be reviewed by December 31st, 2014 or from October 1st, 2015.

-Target analysis

- 1) The pilot conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period
 - Datasets for population PK and/or PK/PD analysis obtained from one or more

* 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.

Provisional Translation (as of October 2014) *

clinical studies, and that is used in the application data to explain the efficacy, safety, and/or dosage and administration.

- 2) The pilot conducted using the electronic study data except for the data corresponding to item 1
 - Datasets for population PK and/or PK/PD analysis that includes those of Japanese subjects obtained from one or more clinical studies, and that is used in the application data to explain the efficacy, safety, and/or dosage and administration.

-Analysis data format to be used

- Datasets in the format used in the program for population pharmacokinetic analysis, NONMEM

-Target data for analysis

- Analysis datasets for NONMEM and the definition of variables
- Data measured in the clinical trials but excluded from the population PK and/or PK/PD analysis should be included in the datasets with a flag indicating exclusion.
- Program of the primary analysis and output of the analysis result.

* 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.