

Provisional Translation (as of July 2015) *

Administrative Notice

April 27, 2015

To: Prefectural Health Department (Bureau)

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

Question and Answer Guide Regarding

“ Notification on Practical Operations of Electronic Study Data Submissions ”

The practical matters on electronic submission of study data for new drug applications have been notified in “Notification on Practical Operations of Electronic Study Data Submissions ” (PFBS/ELD Notification No. 0427-1 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 the “notification on practical operations ”). A question and answer guide for these matters has been compiled as shown in the appendix; therefore, we ask you to inform manufacturers and sellers under your administration regarding the technical notification on electronic submission.

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Appendix

Question and Answer Guide Regarding

“ Notification on Practical Operations of Electronic Study Data Submissions ”

Question 1:

In 1. (3) of the notification on practical operations, it is stated that even when the data has already been submitted electronically, “if additional analyses have been performed, the submission of relevant analysis datasets and programs may be requested.” What should I do if I used an existing analysis dataset without making any changes?

Answer:

Even when you have used an existing analysis dataset without any change, in principle, you must submit both the analysis dataset and the program.

Question 2

In 1. (4) of the notification on practical operations, it is stated that “if data on the product subject to re-examination were electronically submitted at the time of new drug application and a post-marketing study was requested as a result of that review, in principle, electronic submission of post-marketing study data will be required on application for re-examination.” Can electronic submission be requested for data from studies other than post-marketing clinical studies whose implementation was requested as conditions for approval?

Answer:

Regardless of whether it was set as conditions for approval, electronic submission will be requested for data from post-marketing clinical studies whose implementation was requested by PMDA in the review process.

Question 3:

Where do I obtain the electronic certificate for using the portal site? Also, should an electronic certificate be created per organization?

Answer:

For the portal site, use the Medicertified electronic certificate issued by the Medical Information System Development Center.

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One electronic certificate per user name will be required for the portal site. Because this electronic certificate is issued per natural person, the applicant must prepare the required number of electronic certificate for its staff.

For the method of obtaining the electronic certificate and the number of days it takes to obtain it, refer to the Medical Information System Development Center's website.

Question 4:

After making an advance notice of the application on the portal site, can I submit the electronic files to the PMDA window?

Answer:

Yes. But from the viewpoint of enabling early validation and preventing inconsistencies in file management, in principle, electronic files should be submitted via the portal site.

If the files are submitted to the PMDA window under unavoidable circumstances,, all electronic files that are to be submitted at a new drug application must be prepared and submitted at once. Note that if the submission is found to lack any necessary files, the application will not be received. If no advance notice of the application was made on the portal site and the electronic files were submitted to the PMDA window without using the gateway system at the time of the application, all subsequent submissions of the electronic files concerning this application must be made to the PMDA window.

The date on which each electronic file arrives is determined in the way described in 2. (3) of the notification on practical operations. However, note that if files are submitted to the PMDA window, PMDA will send each file to the server in the gateway system to confirm that it is free of viruses, which will take some time after the submission to the PMDA window.

Question 5:

When electronic files are submitted via the portal site, can I submit the new drug application on the same day as “the date on which each electronic file has reached PMDA” specified in 2. (3) of the notification on practical operations?

Answer:

Yes. However, because the application cannot be received if the virus check of the electronic files is not complete at the time the new drug application is received at the

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PMDA window, the applicant should take into account the processing time for the virus check, etc.

Question 6:

What should I do if an error occurs while transferring the files?

Answer:

If an error occurs, an error dialog will appear on the portal site. The error dialog will display information about the error with an email link to the portal manager.

When an error report is received, the portal manager will confirm whether there are any files that have not been transferred and will contact the applicant if any files need to be transferred again and how to transfer such files. Thus, the applicant should take necessary measures.

Question 7:

It is stated that with the requirement to electronically submit study data, the attachments to the new drug application of a product subject to electronic submission, in principle, should be submitted in accordance with the eCTD. How will the scope of the eCTD differ from that of the conventional CTD?

Answer:

As stated in 2. (1) of “Basic Principles on Electronic Submission of Study Data for New Drug Applications” (PFSB/ELD Notification No. 0620-6 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”), products subject to electronic submission are new drugs, which are categorized into (1) to (7), (9) and (9-2) listed in the appendix 2-(1) of the notification entitled “Approval Application of Pharmaceuticals” (PFSB Notification No. 1121-2 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014). However, application by the CTD has not previously been a necessity for new drugs categorized into (9-2) listed in the appendix 2-(1).

Therefore, for the time being, submission of the eCTD will not be required for new drugs categorized into (9-2) listed in the appendix 2-(1).

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Question 8:

If the application is withdrawn after having made a new drug application, how will the electronic data be handled?

Answer:

As stated in the notification of basic principles, the purpose of introducing the electronic submission of study data for new drug applications is to promote the establishment of a more practical and efficient evaluation and assessment process by accumulating study data of various products and enabling the cross-sectional analysis of these products.

Therefore, although the submitted study data and programs are regarded as a part of the appended documents for a new drug application, the study data and programs may be used by PMDA for the cross-product analyses unlike previously after discussion with the applicant, even when the application has been withdrawn.

Of the conventional appended documents that will now be submitted as an eCTD, protocols and other documents needed for analyses are expected to be used together for cross-product analysis, etc. However, other appended documents will be appropriately destroyed by PMDA upon withdrawal of the application.

Question 9:

If the SDTM and ADaM datasets have been created from a database that was summarized in formats other than the CDISC standards, can I submit the dataset that was summarized in formats other than the CDISC standards together to explain the relationship between the database that was used to create the datasets and the SDTM and ADaM datasets?

Answer:

If the dataset created in formats not conforming to the CDISC standards was converted into the CDISC standard format and the applicant has determined that submitting the original dataset will make it easier to explain the traceability of the CDISC-conformant dataset, such datasets may be submitted together with the Annotated CRF. However, in principle, the review will be performed using submitted data that has been converted into the CDISC standard format, and datasets that were created in formats other than the CDISC standard will only be used to understand the datasets in the CDISC standard format.

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Question 10:

In 1. (1) of the notification on practical operations, it states that in addition to the studies listed in 2. (1) b of the notification of basic principles, phase I and clinical pharmacology study results and clinical pharmacology analyses, including population analyses and simulation that form a major evidence for the dosage and administration, are subject to electronic submission if PMDA conclude it necessary. What kind of data are subject to electronic submission?

Answer:

Generally, the following data are subject to electronic submission:

- (1) Clinical studies where standard pharmacokinetic analysis was performed
 - (1) For example, phase I and phase II studies of antibacterial drugs, where the results of pharmacokinetics or pharmacokinetics/pharmacodynamics provide a major evidence for the dosage and administration
 - (2) Clinical pharmacology studies that provide a major evidence for dosage and administration or dose adjustment in pediatric, elderly, and hepatic or renal disorder patients
 - (3) Clinical pharmacology studies that provide a major evidence for dose adjustment because of drug interactions
 - (4) Studies investigating the effect of food, which provide a major evidence for dosage and administration, for example, when restrictions on diet are established for dosage and administration based on the study results
 - (5) Bioequivalence studies that provide a major evidence for efficacy, safety, and dosage and administration. For example, bioequivalence studies of both drug products, where the formulation used in pivotal study is different from the drug product to application or bioequivalence studies comparing the coadministration of a single drug product and administration of a combination drug product, where coadministration of a single drug product was used in pivotal study for a combination drug product
 - (6) Pharmacokinetic or pharmacokinetic/pharmacodynamic studies that investigated the comparability of reference products that provides a major evidence for the efficacy, safety, and dosage and administration of follow-on biologics(biosimilar)

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- (2) Population analysis (including simulations)
 - (1) Population analysis that investigated the similarity in pharmacokinetics or pharmacokinetics/pharmacodynamics between Japanese and non-Japanese subjects in a development using global clinical trials and bridging studies
 - (2) Population analysis that provides a major evidence for dosage and administration
 - (3) Population analysis that provides a major evidence for dosage and administration or dose adjustment in pediatric, elderly, and hepatic or renal disorder patients
- (3) Physiologically based pharmacokinetic model analysis (including simulations)

Physiologically based pharmacokinetic model analysis that provides major evidences for dose adjustment because of drug interaction and for dosage and administration or dose adjustment in pediatric, elderly, and hepatic or renal disorder patients

Question 11:

Please explain the following points concerning the electronic submission of study data from phase I and clinical pharmacology studies and clinical pharmacological analysis

- (1) With respect to the studies listed in 2. 2) b of the notification of basic principles, the technical notification states that ADaM datasets used for main analyses should be submitted. If the main purpose of a clinical study, such as phase I studies performed in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies), was the evaluation of pharmacokinetics, do I need to submit the analysis datasets on efficacy and safety? Also, with respect to analysis datasets on pharmacokinetics or pharmacokinetics/pharmacodynamics of phase I studies performed in both Japanese and non-Japanese subjects, is it acceptable to submit the analysis datasets in a format other than ADaM, as with clinical studies where standard pharmacokinetic analysis was performed (among the documents other than those listed in 2. 2) b of the notification of basic principles)?
- (2) Of the studies other than those listed in 2. 2) b of the notification of basic principles, the notification on practical operations states that with respect to clinical studies where standard pharmacokinetic analysis was performed, in principle, analysis datasets on efficacy and safety must be submitted in addition

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to the analysis datasets on pharmacokinetics or pharmacokinetics/pharmacodynamics. If the main purpose of the clinical studies where standard pharmacokinetic analysis was performed was to evaluate the pharmacokinetics or pharmacokinetics/pharmacodynamics, is it necessary to submit the analysis datasets on efficacy and safety?

- (3) If standard pharmacokinetic analysis was performed using a dataset that integrated the data from multiple clinical studies, what type of study data should I submit electronically?

Answer:

- (1) Analysis dataset of efficacy and safety from phase I studies performed in both Japanese and non-Japanese subjects may not necessarily need to be submitted. Therefore, if submission of the analysis dataset of efficacy and safety in the ADaM format is difficult, consult PMDA beforehand on whether or not the dataset needs to be submitted using “consultation on data format of electronic submission,” etc. With respect to the analysis dataset on pharmacokinetics or pharmacokinetics/pharmacodynamics from this study, formats other than ADaM may be acceptable in some cases. Thus, if it is difficult to submit the analysis dataset on pharmacokinetics or pharmacokinetics/pharmacodynamics in the ADaM format, consult PMDA beforehand in the same manner as explained above.
- (2) Of the studies other than those listed in 2. 2) b of the notification of basic principles, the analysis dataset on efficacy and safety may not necessarily need to be submitted for clinical studies where standard pharmacokinetic analysis was performed. Therefore, if it is difficult to submit such an analysis dataset in the ADaM format, consult PMDA beforehand on whether or not such a dataset needs to be submitted using “consultation on data format of electronic submission,” etc.
- (3) In principle, submission of datasets in the SDTM format will be required for individual studies, in addition to the analysis datasets that were used for integrated analyses. If it is difficult to submit the dataset in the SDTM format, consult PMDA beforehand using “consultation on data format of electronic submission,” etc.

Question 12

I would like to confirm the relationship between the data that are subject to electronic submission and the required format of the datasets.

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Answer:

The relationship between the data and the format of the datasets are shown below based on the section they are mentioned in the notification of basic principles.

Table Types and submission formats of documents subject to electronic submission

Section in notification of basic principles	Content		Individual clinical study data	Analysis dataset	
				Concerning efficacy and safety analysis	Concerning PK or PK/PD analysis
2. 2) a	Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration		SDTM	ADaM	
2. 2) b Note	Study data from phase I studies and clinical pharmacology studies listed right	Phase I studies of oncology drugs	SDTM	ADaM	ADaM
		Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies)			In principle, ADaM, but other formats may be acceptable in certain cases
		QT/QTc studies based on ICH E14 guideline			ADaM
2. 2) Note	Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA	Clinical studies where standard pharmacokinetic analysis was performed	SDTM	ADaM	ADaM is preferable, but other formats are acceptable
		Population analyses	formats other than CDISC standard would be sufficient		
		Physiologically based pharmacokinetic model analyses			
2. 2)	References other than a and b, which were deemed necessary by PMDA		SDTM*	ADaM*	
2. 2)	Integrated summary of safety and efficacy (ISS/ISE)		SDTM**	ADaM	

PK: pharmacokinetics, PD: pharmacodynamics

Note: Results of phase I and clinical pharmacology study results and clinical pharmacological analyses

*: If necessary, consult beforehand

** : In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset had been used for analysis, submission of SDTM study data is acceptable

Question 13:

In some cases, the study data of population analysis based on data from clinical studies performed in the later phases of development may be difficult to submit at the same time as other study data. Is it possible to submit such study data after making the new drug application?

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Answer:

Study data of population analyses based on data from clinical studies performed in the later phases of development may be submitted after the new drug application in some cases. If submission of some study data is difficult at the time of a new drug application, consult PMDA on the timing of submitting such data using “consultation on data format of electronic submission,” etc.

Question 14:

It is stated that during the transitional period, the electronic submission of certain data will be accepted. Will certain datasets from a single study be also accepted?

Answer:

The smallest acceptable unit of study data is by the study. During the transitional period, it is possible to submit the study data from some of the studies for which electronic submission is requested. However, submission of a part of such study data from one study (for example, only the SDTM) will not be accepted.

Question 15:

It is stated that the SDTM datasets should be prepared in English. Is there any change in the measure that “all adverse event terms should be preferably written in Japanese” as stated in “Format for Preparing the Common Technical Document for Submission of New Drug Applications to Reduce Total Review Time” (PFSB/ELD Administrative Notice dated January 17, 2011)?

Answer:

For the time being, for CTDs, the measure that “all adverse event terms should be preferably written in Japanese” will continue to apply.

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