Provisional Translation (as of June 2014) *

Administrative Notice
June 20, 2014

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 "Basic Principles on Electronic Submission of Study Data for New Drug Applications"

The basic principles on electronic submission of study data for new drug application have been notified in 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. A question and answer guide for these principles has been compiled as shown in the appendix, so we ask you to inform manufacturers and sellers placed under your administration regarding the basic principles on electronic submission.

Appendix

Question and Answer Guide Regarding
"Basic Principles on Electronic Submission of Study Data for New Drug Application"

Question 1: It is stated in the principles that the subject applications for electronic submission are applications of new drug, which is categorized into from (1) to (7), (9) and (9-2) listed in the appendix 2-(1) of the notification entitled "Approval Application of Pharmaceuticals" (published on March 31, 2005; Notification No. 0331015, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). Will the newly defined cellular and tissue-based products be included when the Law for Partial Revision of the Pharmaceutical Affairs Act is enacted (Act No. 84 of 2013)?

Answer:
Cellular and tissue-based products will not be included.

Question 2: Will electronic data submission be required for investigator-initiated clinical trials or past clinical trials whose data have been not electronically collected?

Answer:
In principle, data specified in section 2 of the Basic Principles on Electronic Submission of Study Data for New Drug Application (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) are required to be electronically submitted if the application is submitted after the interim measure period.

Question 3: Will re-submission of electronic data be required for clinical trial data that have already been submitted to PMDA in the past based on CDISC standards but will be used as an evaluation data for a new application?

Answer:
If electronic data based on CDISC standards have already been submitted for application in the past, it is basically not required to re-submit the same data. However, applicants

are recommended to individually consult with PMDA prior to application because there may be cases where datasets or programs are required to be newly submitted even if they are from the same study, for example, in cases where additional analyses have been conducted for a new application.

Question 4:
It is stated in the principles "Please note that utilization of electronic data for studies other than clinical studies (e.g. nonclinical studies) and for clinical studies conducted after approval are also concurrently being discussed, and that study types subject for submission of electronic data may possibly be modified in the future." What specifically may be the expected modifications?

Answer:
Regarding data of those other than clinical studies, nonclinical study data of toxicity studies based on SEND (The Standard for Exchange of Nonclinical Data), which is one of the CDISC standards, are currently being considered for a future requirement of electronic submission. Electronic submission of quality data may also become a requirement, but this is not currently being discussed in detail.

Data on post-marketing clinical studies may possibly become a requirement for submission of electronic data, as in clinical trials, and the details are expected to be discussed in the future.

Question 5:
It is stated in the principles " Regarding other phase I and clinical pharmacology studies, studies submitted as reference material and studies other than stated above, their electronic study data (including datasets used in population analyses) are not necessarily required to be submitted, but they may become required if PMDA concludes it necessary." Will the reviews be delayed if it takes time to submit study data in CDISC standards for those that became further necessary during the review process after an application?

Answer:
In order for reviews to be conducted smoothly, it is important to conduct sufficient consultations with PMDA prior to an application regarding electronic data that will become necessary, at the Consultation on Electronic Submission of Study Data for New

Drug Application (tentative), which will be newly established at PMDA in the future. There may be cases where even going through this process, submission of further electronic data may become necessary as an exception during the review process after application, but most are generally thought to be matters that can be managed while continuing the review, and utmost measures will be taken so that the review will not be delayed.

Question 6: Will electronic data be necessary regarding screening failures who became ineligible?

Answer:
In principle, submission is not necessary at the time of application regarding electronic data on screening failures that became ineligible, but they may be required to be submitted during the process of the review if judged necessary. For example, submission may be required in studies where there are many screening failures when compared to the number of eligible cases or where there is some concern regarding the inclusion criteria.

Question 7: It is stated in the principles, "In cases where integrated analyses have been conducted for multiple study results on efficacy or safety, the datasets for those analyses results (integrated summary of safety [ISS]/integrated summary of effectiveness [ISE]) may also be required to be electronically submitted." In which cases will submission be required?

Answer:
Electronic submission will be required for datasets in cases where the applicant have conducted analyses on combined data from multiple studies, such as risk assessments of serious adverse events with low frequency, and if those data have been recorded on CTD and have been considered important in conducting reviews. Applicants are recommended to consult the Consultation on ElectronicSubmission of Study Data for New Drug Application (tentative) that is to be newly established at PMDA in the future.

Question 8: Cooperation with the academia may be expected in the future regarding use of electronic data. What kind of cooperation may possibly be expected?

Answer:
Cooperation with the academia will be discussed in the future with consideration of confidentiality and intellectual property right of the submitted data. For example, cooperation with the academia may need to be considered in the process of establishing new models at PMDA in which the latest scientific knowledge must be taken into account. In such cases, virtual data may possibly be used instead of the submitted electronic data. To be specific, scientific and appropriate investigations with the opinions of relevant people including the pharmaceutical companies will be discussed so that those investigations will be conducted smoothly.

Question 9: It is stated in the principles that the submitted electronic data of clinical studies for application must conform to the CDISC standards. Do those data have to conform to the CDISC standards from the time of clinical trials?

Answer:
Electronic data submission will be required from fiscal year 2016 regarding data of clinical studies (evaluation data) that will be included in the application of new drugs, and those data are expected to be submitted based on CDISC standards such as SDTM and ADaM. Therefore, although data of case report forms are not currently required to be collected using CDISC standards such as CDASH (Clinical Data Acquisition Standards Harmonization) at the time of a clinical trial, it is encouraged to actively consider use of CDISC standards from the time of clinical trials.