Provisional Translation (as of April 2020) *

Administrative Notice
March 18, 2020

To: Prefectural Health Department (Bureau)

Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health 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 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"). A question and answer guide for these principles has been notified in Question and Answer Guide Regarding "Basic Principles on Electronic Submissions of Study Data for New Drug Applications" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated January 24, 2019; hereinafter referred to as "Q&A regarding notification of basic principles")

Based on the experience of electronic submission of study data for new drug applications, we have decided to compile a new question and answer guide, with the revision of Q10 of the previous Administrative Notice, as shown in the appendix; therefore, we ask you to inform manufacturers and sellers placed under your administration regarding the basic principles on electronic submission.

In accordance with the release of this Administrative Notice, the previous Administrative Notice is abolished.

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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 November 21, 2014; Notification No. 1121-2, by the Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare). Are the newly defined cellular and tissue-based products included after 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: It is stated that the submission of electronic study data may not be necessary for studies with special circumstances under which it is difficult to prepare electronic study data, such as data that had not been stored electronically in investigator-initiated clinical trials or studies conducted in the past, etc. What kinds of studies are applicable?

Answer:
In principle, data specified in section 2 of the "notification of basic principles" are required to be electronically submitted if the application is submitted after the transitional period.
However, applicants need to consult with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") in advance, if it is difficult to prepare the electronic study data to be submitted due to the fact that data had not been stored electronically for a study that had been conducted a long time ago, etc., so that judgment can be made about the necessity of submission as well as submission details according to individual circumstances.
Regarding drugs that have been evaluated in advance for public knowledge-based application by the Pharmaceutical Affairs and Food Sanitation Council, the submission

of electronic data is not necessary; instead, it is acceptable to submit attached data mentioned in Question 1 in the "Questions and Answers on [Off-Label Use of Drugs Evaluated in Advance for Public Knowledge-Based Application by the Pharmaceutical Affairs and Food Sanitation Council]" (Administrative Notice by the General Affairs Division, Evaluation and Licensing Division, and Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 1, 2010).

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 so on 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.

Question 5: Regarding other phase I and clinical pharmacology studies, studies submitted as

reference material and studies other than stated above, it is stated in the principles "their electronic study data with reference to these studies and analyses (including datasets used in population analyses) are not necessarily required to be submitted, but they may become required if the 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 the 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 the 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 are taken so that the review will not be delayed.

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

Answer:
If judged necessary during the review process, such as when many patients turn out to be ineligible compared with the total number of patients enrolled or when there is some concern regarding the inclusion criteria, the submission of electronic data on screening failures may be requested. Therefore, if data on ineligible patients are collected in case report forms, etc., it is preferable to submit electronic data of such cases.

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.
For details, please refer to the "Notification on Practical Operations of Electronic Study Data Submissions" (PFSB/ELD Notification No. 0427-1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated April 27, 2015).

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 the 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.

Question 10: It is stated that it is not applied to studies of orphan drugs, etc. that had started before April 1, 2020. In which cases can submissions be made in a format other than the CDISC standards?

Answer:
Regarding products designated as orphan drugs and products requested for development by the Review Committee for Unapproved Drugs and Off-label Drugs, the submission of electronic data in anothe format than the CDISC standards is allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020, among the materials corresponding to item (2)-2 of the “notification of basic principles”.
For the submission of electronic data in a format other than the CDISC standards, applicants need to consult with the PMDA in advance about the applicable studies and submission contents.

Question 11: Regarding anti-HIV drugs, it is stated under “Handling of Approval Application for Manufacture or Import of Drugs for HIV infection” (PMSB/ELD Notification No. 1015, by the Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated November 12, 1998) that new drug applications may be made using materials attached to new drug applications submitted to foreign regulatory agencies so that approval review can be further expedited. Among the electronic data on drugs for which a new drug application is made in this way, should electronic study data that have not been submitted to foreign regulatory agencies and were collected in a format other than the CDISC standards, be submitted in conformance with the CDISC standards?

Answer:
It is not essential to submit with conversion to a CDISC standards-compliant format, regarding studies that have not been submitted to foreign regulatory agencies and were collected in a format other than the CDISC standards. However, applicants need to consult with the PMDA in advance about data subject to electric submission and the specific contents of the electronic data submission.