Provisional Translation (as of April 2024)*

Administrative Notice
April 8, 2024

To: Prefectural Health Department (Bureau)

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

Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications"

Regarding submission of electronic study data at the time of new drug applications for the marketing of drug, it has been notified in the "Notification on Handling of Submission of Electronic Study Data for New Drug Applications" (PSEHB/PED Notification No. 0401-10, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022; hereinafter referred to as "notification on electronic study data"). The question and answer guide for the matter has been notified in the "Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic 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 April 1, 2022; hereinafter referred to as "Q&A regarding notification on electronic study data").

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, including the revision of Q7, Q10, and Q18, as shown in the appendix; therefore, we ask you to inform manufacturers and sellers placed under your administration regarding the notification on electronic submission.

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

* 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.

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Appendix

Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications"

Question 1: It is stated that the subject products for electronic study data submission are applications for new drug, which are categorized into from (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, by the Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014). 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 for which it is difficult to prepare electronic study data, such as data that had not been stored electronically in investigator-initiated clinical studies or studies conducted in the past, etc. What kinds of studies are applicable?

Answer:
In principle, data specified in section 2 of the notification on electronic study data are required to be electronically submitted if the application is submitted.
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 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 study data is not necessary; instead, it is acceptable to submit appended

documents 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 of 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: It is stated, “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 that require submission of electronic study 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 4: In 2 (1) b of the notification on electronic study data, it is stated that even when the data has already been submitted electronically, “if additional analyses have been performed, the submission of relevant electronic study data may be requested”. What should be submitted if an existing analysis dataset without making any changes is used?

Answer:
Even when an existing analysis dataset is used without any change, in principle, both the analysis dataset and the program for analysis should be submitted.

Question 5: Cooperation with the academia may be expected in the future regarding use of electronic study 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 electronic study 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 study 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 6:
Regarding anti-HIV drugs, it is stated in "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 documents attached to new drug applications submitted to foreign regulatory agencies so that approval review can be further expedited. Among the study data on drugs for which a new drug application is made in this way, should 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 study data 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 electronic submission and the specific contents of electronic study data submission.

Question 7:
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 application for re-examination (at a consultation about package insert revisions, a request for removal of approval conditions, etc.), we would like to make sure points to consider, such as the contents of electronic study data submission and submission methods, when submitting electronic study data at the time of the evaluation of study results.

Answer:

(1) Basically, electronic study data of studies and analyses subject to evaluation should be submitted.

(2) Electronic study data submission should be carried out during the period from the date of submission of the consultation application to the date which the consultation materials are scheduled to be submitted.

(3) Even if electronic study data are submitted when study results were practically evaluated, they remains part of the document to be attached to the new drug application form or re-examination application form. Accordingly, electronic study data should be resubmitted via the gateway system at the time of new drug application or re- examination application.

(4) Prior to the submission of electronic study data, conformance of the data with the CDISC standards should be confirmed. If a violation of the rules is identified, which is deemed important by the PMDA as described in the "Technical Conformance Guide on Electronic Study Data Submissions" (PMDA/CPE Notification No. 0401003 and PMDA/CRS Notification No. 0401001, by the Director of Center for Product Evaluation and the Director of Center for Regulatory Science, Pharmaceuticals and Medical Devices Agency, dated April 1, 2022), the data should be corrected. If a violation of the rules that requires an explanation is identified, but is unable to be corrected, the details and reason for the violation should be explained in the reviewer's guide, etc.

(5) In addition, the following points should be considered for each product.

(a) Products subject to the SAKIGAKE designation system

When submitting individual study/analysis results, electronic study data corresponding to the results should be submitted for prior assessment. It is acceptable to submit only electronic study data of studies or analyses that can be submitted at this point of time.

(b) Anti-HIV drugs, products subject to prior assessment consultation, products subject to package insert revision consultation, or products for which removal of approval condition is requested

For prior assessment, electronic study data should be submitted at once for studies and analyses that are subject to submit as mentioned in section 2 of the notification on electronic study data.

Question 8:

If the application is withdrawn after having made an application, how will electronic study data be handled?

Answer:
The purpose of introducing the submission of electronic study data for 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-product analysis of these products.

Therefore, although the submitted electronic study data are regarded as a part of the appended documents for an application, electronic study data 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 the 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: In the “Revision of “Approval Application with Electronic Common Technical Document (eCTD)”” (PSEHB/PED Notification No. 0218-4, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 18, 2022), it is stated that new drug applications to be made on or before March 31, 2026 may be submitted using the previous eCTD form. If the appended documents are submitted using the previous eCTD form, is it necessary to include electronic study data in the eCTD as specified in 3 (4) a of the notification on electronic study data?

Answer:
If the appended documents are submitted using the previous eCTD form, electronic study data should also be separately submitted from the eCTD like previously. Even if separately submitted from the eCTD, electronic study data will be handled in accordance with the notification on electronic study data.

Question 10: I would like to confirm the relationship between the data that are subject to electronic

submission and the required format of the datasets.

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 on electronic study data.

Table: Types and submission formats of documents subject to electronic submission

<table>
<tr><th rowspan="2">Section in notification on electronic study data</th><th colspan="2" rowspan="2">Content</th><th rowspan="2">Individual clinical study data</th><th colspan="2">Analysis dataset</th></tr>
<tr><th>Concerning efficacy and safety analysis</th><th>Concerning PK or PK/PD analysis</th></tr>
<tr><td>2 (1) b (a)</td><td colspan="2">Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be a major evidence for evaluation of efficacy, safety, and dose and administration</td><td>SDTM</td><td colspan="2">ADaM</td></tr>
<tr><td rowspan="3">2 (1) b (b)</td><td rowspan="3">Data on result from phase I studies and clinical pharmacology studies listed right</td><td>Phase I studies of oncology drugs</td><td>SDTM</td><td colspan="2">ADaM</td></tr>
<tr><td>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)</td><td>SDTM*1</td><td>ADaM*2</td><td>In principle, ADaM*2, but other formats may be acceptable in certain cases</td></tr>
<tr><td>QT/QTc studies based on the ICH E14 guideline</td><td></td><td></td><td>ADaM*2</td></tr>
<tr><td rowspan="3">2 (1) b (c)</td><td rowspan="3">Other Phase I studies and clinical pharmacology studies, which were deemed necessary by PMDA</td><td>Clinical studies where standard pharmacokinetic analysis was performed</td><td>SDTM*1</td><td>ADaM*2</td><td>ADaM is preferable, but other formats are acceptable</td></tr>
<tr><td>Population analyses</td><td colspan="3" rowspan="2">formats other than CDISC standard would be sufficient</td></tr>
<tr><td>Physiologically based pharmacokinetic model analyses</td></tr>
<tr><td>2 (1) b (c)</td><td colspan="2">References which were deemed necessary by PMDA</td><td>SDTM*3</td><td colspan="2">ADaM*3</td></tr>
<tr><td>2 (1) b (c)</td><td colspan="2">Integrated summary of safety and efficacy (ISS/ISE)</td><td>SDTM*4</td><td colspan="2">ADaM</td></tr>
</table>

PK: pharmacokinetics, PD: pharmacodynamics

*1: Format other than SDTM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020

*[2]: Formats other than ADaM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020

*[3]: If necessary, consult in advance

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

Question 11:
Will electronic study 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 study 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 study data of such cases.

Question 12:
It is stated that the submitted electronic study 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 conducting clinical studies?

Answer:
Electronic study data submission is required for clinical study data that are included in the application, and those data are 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 conducting clinical studies, it is encouraged to actively consider use of CDISC standards from the time of conducting clinical studies.

Question 13:
If the SDTM and ADaM datasets have been created from a database that was summarized in a format other than the CDISC standards, can I submit the dataset that was summarized in a format 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.

Question 14: 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" (Administrative Notice of the Evaluation and Licensing Division, Pharmaceutical Food Safety Bureau, Ministry of Health, Labour and Welfare, 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.

Question 15: 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 study data in a format other 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 studies corresponding to 2 (1) b of the notification on electronic study data.
For the submission of electronic study 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 16:
What are points to consider when data created in a format other than the CDISC standard is converted to the CDISC standards-compliant data and submitted?

Answer:
Even if data created in a format other than the CDISC standard is converted to the CDISC standards-compliant data, it is basically necessary to submit electronic study data at the time of application. However, if there are unavoidable circumstances, submission after the application may be acceptable only for clinical studies that fall under 2 (1) b (c) of the notification on electronic study data and that the start date (the day when the first subject was enrolled) is before June 20, 2014. In such cases, the applicant should consult with the PMDA in advance.
Even if electronic study data is submitted after the application, the submission should be made as early as possible. The acceptability of electronic study data submission that will be made after the application and the specific timing of the submission should be agreed with the PMDA in advance.

Question 17:
As stated in 2 (1) b (c) of the notification on electronic study data, regarding other phase I studies, clinical pharmacology studies, population analyses and physiologically based pharmacokinetic model analyses, etc., data on studies or analyses that are considered to contribute to the establishment of the dosage and administration and are focused on the evaluation of efficacy, safety, or pharmacokinetics need to be electronically submitted. What kind of data are subject to electronic study data submission?

Answer:
If the evaluation of pharmacokinetics or pharmacodynamics is used as the evidence for setting the proposed dosage and administration or the dosage and administration in a confirmatory study, the evidence for a caution in the package insert of the ethical drug by the applicant, or the applicant's judgment on the need for dose adjustment in specific patients, electronic study data on the study and analysis are subject to submission. Examples of such studies and analyses are shown below.

(1) Clinical studies where standard pharmacokinetic analysis was performed
   (a) 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

(b) Clinical pharmacology studies that provide a major evidence for the dosage and administration or dose adjustment in pediatric, elderly, and hepatic or renal disorder patients

(c) Clinical pharmacology studies that provide a major evidence for the caution because of drug interactions

(d) Studies investigating the effect of food, which provide a major evidence for the dosage and administration, for example, when restrictions on diet are established for the dosage and administration based on the study results

(e) Clinical pharmacology studies that provide a major evidence for the dosage and administration or dose adjustment in relation to sex, body weight (obesity, etc.), severity of disease, genetic factors such as genetic polymorphism, alcohol, and smoking.

(f) Relative bioavailability studies that investigated the influence on the pharmacokinetics by administration site using subcutaneous injection preparation, patch, etc.

(g) Bioequivalence studies that provide a major evidence for the efficacy, safety, and dosage and administration. For example, bioequivalence studies of both drug products, where the formulation used in confirmatory studies 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 confirmatory studies for a combination drug product

(h) 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 (biosimilars)

(2) Population analysis (including simulations)

(a) Population analysis that investigated the similarity in pharmacokinetics or pharmacokinetics/pharmacodynamics between Japanese and non-Japanese subjects in the development using global clinical trials and bridging studies

(b) Population analysis that the applicant considers as evidence for setting dosage and administration for confirmatory studies

(c) Population analysis including data from phase III studies

(d) Population analysis that provides a major evidence for the dosage and administration or dose adjustment for drug interactions, pediatric and elderly

patients as well as patients with hepatic or renal impairment, etc.

(3) Physiologically based pharmacokinetic model analysis (including simulations)
   (a) Physiologically based pharmacokinetic model analysis that provides a major evidence for the dose adjustment because of drug interactions and for the dosage and administration or dose adjustment in pediatric and elderly patients as well as patients with hepatic or renal impairment, etc.
   (b) Physiologically based pharmacokinetic model analysis used as the evidence for not conducting clinical drug interaction studies

For studies investigating the effect of intrinsic or extrinsic factors on pharmacokinetics and pharmacodynamics, if the applicant considers that it is necessary to issue a caution on pharmacokinetics or pharmacodynamics in the package insert, electronic study data are subject to submission. Even if the applicant determines that a caution is not necessary, if the 90% confidence interval of the geometric mean ratio of pharmacokinetic parameters does not fall entirely within the range of 0.8 to 1.25 (assuming a lognormal distribution of the pharmacokinetic parameter) in studies investigating the influence on pharmacokinetics, electronic study data are subject to submission.

For studies aimed at investigation of absolute bioavailability and mass balance studies, electronic study data are not subject to submission, in principle.

Question 18:
Please explain the following points concerning the submission of electronic study data from phase I studies and clinical pharmacology studies and clinical pharmacological analyses.

(1) Of the studies listed in 2 (1) b (b) of the notification on electronic study data, 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 studies listed in 2 (1) b (c)?
(2) Of the studies listed in 2 (1) b (c), 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 electronic study data should be submitted?

Answer:

(1) Analysis datasets 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 datasets of efficacy and safety is difficult, consult with the PMDA in advance on whether or not the datasets need to be submitted using consultations. With respect to the analysis datasets 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 datasets on pharmacokinetics or pharmacokinetics/pharmacodynamics in the ADaM format, consult with the PMDA in advance in the same manner as explained above.

(2) Of the studies listed in 2 (1) b (c), in principle, with respect to clinical studies where standard pharmacokinetic analysis was performed, analysis datasets on efficacy and safety must be submitted in addition to the analysis datasets on pharmacokinetics or pharmacokinetics/pharmacodynamics. However the analysis datasets 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 analysis datasets, consult with the PMDA in advance on whether or not such datasets need to be submitted using consultations.

(3) In principle, submission of electronic study data will be required for individual studies subject to electronic submission, in addition to the analysis datasets that were used for integrated analyses. If it is difficult to submit electronic study data, consult with the PMDA in advance using consultations.

Question 19:

In some cases, electronic 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 electronic study data after making the application?

Answer:
Electronic study data of population analyses based on data from clinical studies performed in the later phases of development may be submitted after the application in some cases. If submission of some electronic study data is difficult at the time of an application, the acceptability of electronic study data submission that will be made after the application and the specific timing of the submission should be agreed with the PMDA in advance using consultations.