FAQs on Electronic Study Data Submission (Excerpt)

1. Questions on new drug review and consultation

Q1-5: Regarding clinical trial consultations, consultations related to submission of electronic study data, and Pre-NDA meetings, please demonstrate the contents and points to consider of each consultation.

A: The contents and points to consider of each consultation are shown in the table below. If a sponsor wonders which consultation should be used for their questions, please confirm them at the pre-meeting as needed.

Category of consultations	Contents and points to consider
Clinical trial consultations	In this consultation, a sponsor and the PMDA identify which study data and/or analysis data are subject to be submitted electrically among the clinical data package necessary for the new drug applications. If the sponsor submits electronic data of all studies and analyses within clinical data package, it is sufficient to state it at a pre-meeting etc.
Consultation on exemption of submission of electronic study data	In this consultation, a sponsor and the PMDA discuss the following contents etc., regarding each study data identified to be subject to be submitted in the clinical trial consultation. ・ whether electronic submission of a part of or whole of the study data could be exempted, based on the circumstances of holding data, when it is difficult to prepare electronic study data, according to Question 2 in the "Question and Answer Guide Regarding the Basic Principles on Electronic Submission of Study Data for New Drug Applications", hereinafter referred to as "Q&A regarding notification of basic principles". ・ adequacy of the reason why study data would be submitted in another format than the CDISC standards and sufficiency of the contents of electronic submission (information of electronic study data and analyses), when electronic data in another format than the CDISC standards is submitted, according to Question 10 in the "Question and Answer Guide Regarding the Notification of Basic Principles".

Consultation on preparation of submission of electronic study data	In this consultation, a sponsor and the PMDA discuss the following contents etc., regarding study data and/or analysis data planned to be submitted. ・ method of storing data, handling of variables, submission method of electronic data, and strategy of storing data which cause the violations of CDISC conformity. ・ special circumstances, such as the situation in which submission timing of electronic study data is compelled to be different from submission timing of study results.
Consultation on data format of submission of electronic study data	In this consultation, the PMDA confirms the validation results, i.e., the explanation of "Error" of violations that would be detected when the PMDA performs validation at data submission, and the reasons why they cannot be corrected.
Pre-NDA meeting	In this consultation, the PMDA does a final confirmation of the contents of materials attached to approval application and scheduled submission date. The Sponsor should explain the contents of electronic study data submission using the Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data", and submit the Attachment 8 prior to the Pre-NDA meeting. The PMDA will check submitted data based on the Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" that received at the Pre-NDA meeting. So, sponsors should make sure there is no inconsistency between the Attachment 8 and the data planned to submit carefully before submitting the Attachment 8.

Q1-6:   In the "Technical Conformance Guide on Electronic Study Data Submissions" (hereinafter referred to as technical conformance guide) 3.6.1, it states, "Before transferring the electronic study data, the applicant should perform a validation, and necessary explanation should be given for any violations identified". Is it permissible to provide the necessary explanation for violations at the Pre-NDA meeting?

A: Applicants are required to provide the necessary explanation for violations at the consultation on data format for the submission of electronic study data. At the Pre-NDA meeting, the PMDA will confirm only the scope of data to be submitted; they will not discuss the contents of the data. Therefore, pre-NDA meeting should be conducted in general, after the necessary discussion about violations from

PMDA's validation rules in the "consultation on the data format for the submission of electronic study data". Applicants should submit the Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" reflecting the results of the "consultation on the data format for the submission of electronic study data", when they apply for the Pre-NDA meeting. At the Pre-NDA meeting, the PMDA will confirm whether the results of the "consultation on the data format for the submission of electronic study data" are correctly reflected only. When the new drug application is submitted, the PMDA will check submitted data based on the Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" that received at the Pre-NDA meeting.

Q1-6-1:　If a sponsor cannot complete datasets or perform validation prior to the Pre-NDA meeting, what should they do?

A:　Please consult with the PMDA at the Pre-NDA meeting. Even after Pre-NDA meeting, it will be necessary to provide explanations for violations of data format corresponding to the "technical conformance guide" 3.6.1(b) if they are detected and the sponsor decides not to correct them.

Q1-16:　When a sponsor performs validation with software that the vender claims is compatible with the software used by the PMDA, and then corrects data or explains the results, are there any particular points to consider?

A:　When the PMDA also confirms a situation as described above, the PMDA will accept electronic study data and begin the review if there are no inadequacies in the FD application data, eCTD, or other documents. However, if violations corresponding to the "technical conformance guide" 3.6.1(a) and (b) are detected by validation at the PMDA, and there is no necessary explanation for the violations prior to the submission of study data, the PMDA will require correction of data or explanation regarding the cause of the violation and the reasons why it cannot be corrected.

Q1-17:　If a detected violation is attributed to a bug of the validation software, is it necessary to correct the data?

A:　When there is no obvious violation based on a check of actual datasets, even though a violation is detected by the validation software, the sponsor may give the rationale that the violation is caused

by a bug in the validation software. Explain the rationale on Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" and the data guide, and consult with the PMDA at the consultation on data format of the submission of electronic study data. When the validation software vender publishes the bug, the sponsor may point to it as the explanation.

Q1-22:   Is it necessary to include Rule ID in the result of validation for the section of "Information about conformity of the electronic data to the CDISC standards" in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data"?

A: Yes. Please include the Rule ID of the published "PMDA Study Data Validation Rules" in validation results in the Attachment 8 (including in case of attaching validation report or data guide).

Q1-23:   Is there anything special to consider when the applicant provides the necessary explanation for the violations of "Error" (one of the severities of PMDA's validation rules) that cannot be corrected in data guide or the section of "Information about conformity of the electronic data to the CDISC standards" in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" based on section 2. (4) b of "Notification on Practical Operations of Electronic Study Data Submissions", hereinafter referred to as "notification on practical operations"?

A: Regarding violations of "Error" that cannot be corrected, PMDA evaluates the amount of influence on analyses conducted in the review process based on the explanation provided by the applicant. With the explanation such as "Data was stored as collected in CRF" or "Correction has not been made because it does not affect analyses conducted by the applicant", it is impossible to evaluate the influence on utilization of the data in the review process because it is not comprehensible how the data is stored. Therefore, please explain how the data is stored actually about the violation. When the applicant explains "it does not affect analyses conducted by the applicant", please explain the reason that led to the conclusion. Moreover, please explain the reason why it cannot be corrected.

Q1-24:   What kind of validation does PMDA conduct regarding the validation of electronic study data for the conformity of the electronic data to the CDISC standards?

A: The PMDA conducts validation for the consistency between SDTM datasets and ADaM datasets as well as validations of each SDTM or ADaM dataset. Moreover, the PMDA conducts validation for

the consistency between define.xml and each SDTM/ADaM dataset as well as validation for the structure of XML in define.xml. Please keep above points about validation in mind, when the applicant evaluates the conformity in advance.

Q1-26:   Regarding the section of "Information about conformity of the electronic data to the CDISC standards" in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data", is it acceptable to attach data guides instead of filling out the section?

A: As long as all of the necessary information to be described in the section of "Information about conformity of the electronic data to the CDISC standards" are included in the data guides, it is acceptable to attach the data guides instead. In this case, please mention that it refers to each data guide in the section of "Information about conformity of the electronic data to the CDISC standards" in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data".

2. Questions on the relationship between electronic submission data and eCTD

Q2-2:   Is it acceptable that the submission date of electronic study data is different from the submission date of eCTD? If acceptable, are there any rules for the order of submission?

A: It is acceptable that the submission date of electronic study data is different from the submission date of eCTD. There are no rules for the order of submission when the applicant uses eCTD v3.2.2. When the applicant uses eCTD v4.0 and submits (1) eCTD including only electronic study data and (2) eCTD with CTD documents and without electronic study data separately, (1) must be submitted before the submission of (2). Please refer to Appendix 1, "ICH Electronic Common Technical Document (eCTD) v4.0 Implementation Guide in Japan v1.2." of "Approval Application with Electronic Common Technical Document (eCTD)" (PSEHB/PED Notification No. 0705-1 dated July 5, 2017) in detail.

3. Questions on electronic submission gateway

Q3-6:   Will the PMDA perform validation of CDISC-conformant data when the applicant submits the electronic study data in response to inquiries?

A: Yes. The PMDA will apply the same concept of severity given in the validation rule shown in 3.6.1 of the "technical conformance guide". Please submit the electronic study data via the "study data submission" window of the portal site when submitting the CDISC-conformant data in response to inquiries.

Q3-33: In reference to Question 19 in the "Question and Answer Guide Regarding the Notification on Practical Operations of Electronic Study Data Submissions" (hereinafter referred to as "Q&A regarding notification on practical operations"), please advise about the format of the electronic study data and the submission method when electronic study data are submitted in advance of approval application or re-examination application for a new drug.

A: Please take note of the following points when submitting (optional) electronic study data at the consultation, etc.

- Please consult with the office in charge of review in advance about the studies and analyses subject to submission of electronic study data.
- Please submit electronic study data to the Office of Advanced Evaluation with Electronic Data during the period from 5 weeks before to the date on which the study results are scheduled to be submitted to the date of the study result submission. In this case, please use a recording medium and not the Gateway system.
- Before submitting electronic data, please submit the final version of Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" to the office in charge of review by email, etc. Since the contents of Attachment 8 should be agreed upon between the applicant and PMDA by the date of the electronic data submission, it is recommended that the final version or revised version of Attachment 8 be submitted by around 2 weeks before the scheduled date of electronic data submission.
- Before submitting electronic study data, please call the main telephone number of the Office of Advanced Evaluation with Electronic Data in advance to inform the review team category and brand name (or consultation reception number), and arrange the schedule of the recording medium submission date.
- On the date of electronic study data submission, please submit the reception slip and the recording medium with the electronic study data to the Office of Advanced Evaluation with Electronic Data by hand or mail. Please describe the consultation category, consultant applicant, reception number, brand name, non-proprietary name, and the date on which consultation materials are submitted on the face of the recording medium.

- If electronic study data are divided and submitted in the form of more than one recording medium, it is difficult for the PMDA to reproduce the original folder structure or to check if reproduction is successful. Therefore, please submit the data in a single medium by using BD (including multilayer disc), etc., in principle. If the data cannot be recorded in a single medium, even when using a two-layer DVD-R, multilayer BD-R/RE, etc., or if the data size exceeds 40 GB, please consult with the PMDA.

- The submission of a TSV file showing the contents of clinical study data submission is essential when submitting electronic study data, so please prepare the contents of clinical study data submission in tab-separated values (TSV file), place it in the same path as the "m5" folder, and submit it, as shown in section 3.7 of the "technical conformance guide".

- The name of the folder that contains the clinical study report should be the same as the name of the folder that contains the study data [*study id*/iss/ise]. Please make sure that information contained in the folder for the clinical study report corresponds one-to-one to that contained in the folder for the study data.

For the file size and folder structure of the electronic study data to be submitted, please follow the method specified in section 3 of the "technical conformance guide".

4. Questions on CDISC-conformant electronic study data

Q4-1:   What is the base date for the "Date Support Begins (YYYY-MM-DD)" and the "Date Support Ends (YYYY-MM-DD)" in the PMDA Data Standards Catalog?

A: The base date is the submission date recorded by the applicant on the FD application of the new drug application form.

Q4-2:   In the case where electronic study data is added or replaced during review, is it necessary to follow the standards with the same version number as those at the time of original submission?
If the "Date Support Ends" of the version used at the time of the original submission has already passed, what procedures should be followed?

A: Basically, it is necessary to use the same version as that used at the time of the original submission. To submit additional data to the previously submitted dataset, it is necessary to use the same version as that used for the original dataset.

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  However, on the following occasions where the application is submitted during the overlapping period, the applicant may submit new data using the newer version, as when there is:

•Submission of a completely new set of study data

•Submission of an entire set of previously submitted data along with additional data where both are created using the newer version of the standard

For details, see Figure 4-2.

Figure 4-2: Versions of Standards
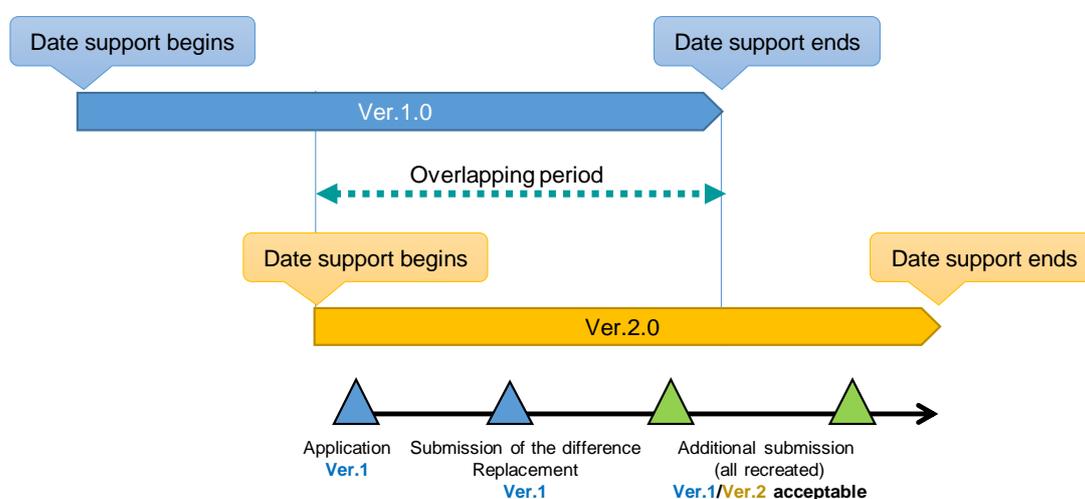
Q4-3:   Which files or contents will be included in the scope of CDISC-conformant validation performed by the PMDA?

A: The PMDA performs validation on SDTM datasets, ADaM datasets, dataset definition documents, controlled terminologies and dictionaries. When the data written in Japanese ("Japanese data" in 4.1.5 of the "technical conformance guide") is submitted, no validation is performed on Japanese data and the validation is performed on the corresponding alphanumeric dataset.

Q4-4:   When is it necessary to submit electronic datasets of integrated analyses (ISS/ISE)? What is the scope of electronic data on ISS/ISE that must be submitted?

A: As explained in Section 1.(2) of the "notification on practical operations", submission of electronic data for ISS/ISE will be requested when integrated analyses of multiple clinical studies were

performed for the assessment of specific efficacy or safety, such as assessments in special populations or of rare adverse events, and when the results are considered to be relevant to the assessment of efficacy, safety, and dosage and administration of the product. In order to confer with the PMDA on the scope of the submission of electronic data of integrated analyses, applicants should use clinical trial consultations, because a decision on the scope of the submission accompanies scientific evaluations. At the submission of data, definition documents and analysis programs (or program specifications) are required in addition to integrated analysis datasets. To confirm the details of such datasets, including file types to be submitted, etc., use "consultation on preparation of submission of electronic study data."

Q4-5: When is it necessary to submit electronic study data as attached documents in response to inquiries during a review? What is the scope of the electronic data that is subject to submission on such occasions?

A: In three cases, applicants must submit electronic study data as attached documents in response to inquiries during review:

• When the study is ongoing at the time of application and additional electronic data will be submitted during review (e.g., when the application has been filed based on electronic study data from interim analyses or interim reports of a long-term study)

• When an applicant makes important arguments (e.g., those affecting the main conclusions of efficacy and safety, considerations affecting prescriptions of dosage and administration or intended population) in the response to inquiries, and also when submission of analysis datasets used by the applicant are regarded as highly helpful for review

• When electronic data of clinical studies or analyses that are important for evaluating efficacy, safety, and dosage and administration is not submitted at the time of application

These electronic study data should be submitted as attached documents in response to inquiries and/or revision of the eCTD. In any case, it is also required that applicants send documents amended for additionally submitted data (e.g., documents or analysis programs that should be submitted together with the datasets). For details regarding the necessity of these documents, etc., please consult with the review team.

As stated in Section 4.1.1.3 of the "technical conformance guide", it is not necessary to uniformly submit additional datasets for analyses that the applicant performed in response to inquiries.

For more detailed information on format and method for electronic study data submission, refer to Section 2.(5) and (6) of the "notification on practical operations". If any adjustment is necessary, such

as the timing to submit additional electronic study data, etc., please consult with the review team.

Q4-6:   If the protocol, etc., is prepared in Japanese, is it necessary to translate the information on the design of the clinical study into English, and store it in the SDTM Trial Design Model domain? Please indicate parameters and codes that the PMDA requests at a minimum for the TS domain of SDTM.

A: It is not likely that much information will be lost when Japanese data are translated into English for storing in the Trial Design Model. Therefore, when the protocol, etc., is prepared in Japanese, each piece of information must be stored in English after translation.

If SDTM datasets are prepared in accordance with SDTM IG v3.1.3 or later versions, it is necessary to include parameters classified into "Required" or "Conditionally Required" in the TS domain. If SDTM datasets are prepared in accordance with SDTM IG v3.1.2, include parameters that can be stored based on Section 7.6.2-4 of the SDTM IG. For parameters using controlled terminologies and ISO codes, store appropriate code values. For Registry Identifier, store registration numbers issued by CLINICALTRIALS.GOV, EUDRAC, JAPIC, etc. For parameters using UNII, NDF-RT, DUNS, or SNOMED CT, it is acceptable to store only code values available to the applicant. Table 4-6 shows the relationship between codes and parameters that use the codes other than controlled terminologies or ISO codes.

Table 4-6   Codes Corresponding to TS Domain Parameters and WEB Sites

TSPARMCD	TSPARAM	Code	Website
CURTRT	Current Therapy or Treatment	UNII	FDA Substance Registration System http://fdasis.nlm.nih.gov/srs/srs.jsp
TRT	Investigational Therapy or Treatment	UNII	FDA Substance Registration System http://fdasis.nlm.nih.gov/srs/srs.jsp
PCLAS	Pharmacological Class of Investigational Therapy	NDF-RT	NCI Term Browser https://nciterms.nci.nih.gov/ncitbrowser/pages/multiple_search.jsf;
REGID	Registry Identifier	CLINICALTRIALS.GOV	ClinicalTrials.gov https://clinicaltrials.gov/
		EUDRAC	EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/search
		JAPIC	JAPIC Clinical Trials Information http://www.clinicaltrials.jp/user/cteSearch.jsp
SPONSOR	Clinical Study Sponsor	DUNS	TOKYO SHOKO RESEARCH https://duns-number-jp.dnb.com/search/jpn/login.asp

Q4-7:   In Section 3.(1)c of the "notification on practical operations," it states, "Use the WHO Drug Dictionaries Drug Code (WHO DDs) when coding drugs." Please explain the background of the need to use WHO DDs, and give an example of how to store WHO DDs data under the CM domain of SDTM.

A: In order to promote international standardization of clinical study data, and to allow cross-sectional evaluations in the future, use of WHO DDs is required for electronic study data submission. It is possible to use sponsor-defined codes if no WHO DDs equivalent codes are identified; in this case, it will be necessary to specify in the data guide which sponsor-defined codes have been assigned to which variables.

Table 4-7 presents examples of how to assign WHO DDs codes to the CM domain of SDTM. It is also

necessary to store WHO DDs ATC codes wherever possible.

In cases where it is impossible to identify the single ATC code in WHO DDs due to not collecting indication for use of the concomitant drug, please store not only single ATC code but also all ATC codes that correspond to the drug using the "Supplemental Qualifier special-purpose dataset."

Table 4-7 Relationship between CM Domain and WHO DDs

Variable Name	Variable Label	WHO DDs
CMDECOD	Standardized Medication Name	WHO DDs Generic name
CMCLAS	Medication Class	WHO DDs ATC text
CMCLASCD	Medication Class Code	WHO DDs ATC code

Q4-8:   In Section 3.(1)c of the "notification on practical operations", it states, "If data were collected in units that are commonly used where conversion of the data to those in SI units is possible, separately store the converted data in SI units in the SDTM dataset as data in the standard units and submit them". Please indicate the scope of variables that need to be converted to SI units. Also, if data are collected in units other than SI units, how can the original data and the converted data be stored within the SDTM dataset?

A: The use of SI units is required for all variables and parameters of test results to be stored in the Findings class domain of the SDTM dataset, as long as SI units are applicable. However, it is acceptable to store only the data in mmHg in the SDTM dataset without storing the converted data in SI unit for test results (e.g. blood pressure) collected in mmHg as conventional unit.

When the original data and the converted data in SI units are stored together in the SDTM dataset, store the converted data into "--STRESC" (or "--STRESN" if necessary) and the original data into "--ORRES" Also, in the data guide or dataset definition document, describe how each datum (original and converted) is stored, as well as the conversion equation.

In the case of multicenter or multiregional studies, etc., where different measurement units are used for capturing data by center or region, data in multiple units could be obtained for a single parameter (laboratory test). In such cases, it is possible to store data in uniform units other than SI units into "SUPP--" if necessary.

Examples of how to store data in conventional units and SI units into SDTM

  [Example 1] When values in domestically conventional units and internationally conventional units both exist:

  Store values in domestically conventional units under "--ORRES" and values in internationally

conventional units under "SUPP--." Store SI values under "--STRESC" (or "--STRESN" if necessary).

  [Example 2] When central clinical laboratory values and in-hospital clinical laboratory values both exist:

  Store central values under "--ORRES" and in-hospital values under "SUPP--." Store SI values under "--STRESC" (or "--STRESN" if necessary) after unifying them into a single unit per parameter and then converting.

Q4-9:   Some values need to be displayed in Japanese on analysis results, and such values need to be stored in datasets in Japanese. In such cases, should only datasets with alphanumeric values be separately prepared for electronic study data submission?

A: Basically, it is only necessary to submit datasets with alphanumeric values for electronic study data submission. For variables that can be properly translated (from those displayed in Japanese analysis results into English) without loss of information, it is acceptable to store the translated variables in datasets, and to submit only the datasets with alphanumeric values. In such cases, it is possible, in addition to the datasets with alphanumeric values, to submit together the original datasets with Japanese characters that were used for displaying analysis results instead of alphanumeric values, from the viewpoint of traceability between the original and translated datasets or to present reference materials. If certain information is likely to be lost when Japanese data is translated into English, follow Section 4.1.5 of the "technical conformance guide" for submission. In the case of datasets translated at the time of their creation, this should be described in the data guide.

Q4-10:   If datasets include languages other than English or Japanese, what procedures should be followed?

A: Basically, the requirement is that submitted datasets be entirely translated into English. However, the need to translate specific variables into English may depend on the level of importance of the relevant variables; thus, use the "consultation on preparation of submission of electronic study data" for each case if needed. In the event that datasets are translated, this should be described in the data guide.

Q4-11:   When translation is performed (e.g., from Japanese to English), is it necessary to certify the correctness of the translation?

A:　No written form is required, but the applicant is responsible for ensuring the accuracy of the translation.

Q4-12:　When Japanese datasets will be submitted in addition to alphanumeric datasets, is it necessary to create a dataset definition document for each dataset?

A:　The definition document is needed only for the alphanumeric datasets. Please store the definition document in the same folder as the alphanumeric datasets.

Q4-13:　If analysis software is used that requires no explicit program creation, is it permissible to submit an operational log instead of a program? Or will "the submission of specifications that show the analysis algorithm" be separately requested? Please indicate examples of the contents to be described in the "specifications that show the analysis algorithm."

A:　Submission of an operational log will be sufficient instead of the program, if the log clarifies the analysis algorithm. In the event that the operational log is unlikely to clarify the analysis algorithm, as in the case where "submission of the program itself is difficult," then "the submission of specifications that show the analysis algorithm" will also be needed. In the "specifications that show the analysis algorithm," please specify datasets and variables to be analyzed, and details of analytical methods.

Q4-14:　If datasets in a format other than the CDISC standards are converted into a CDISC-conformant format for submission, and if the source datasets and the Annotated CRF are to be submitted together as an explanation of traceability, under which folder should they be stored?

A:　Please store the source datasets (which means the datasets before conversion into a CDISC-conformant format), the explanation of traceability, and the accompanying files under the "legacy" folder.

Q4-15:　When submitting electronic data of an integrated analysis (ISS/ISE), in which folder should they be stored?

A: Basically, we expect that data from multiple studies subject to an integrated analysis will be combined into a single dataset, and that one analysis dataset will be submitted for each analysis. When datasets from multiple studies are consolidated by a program for analysis, it is possible to submit the datasets of each study and the program containing the process of consolidation. Regardless of whether or not datasets are integrated, store datasets for the integrated analysis within the "iss/ise" folder, which allows the folder name to be consistent with that including CSR in eCTD.

Q4-16:   When submission of the analysis program is difficult, submission of the "specifications that show the analysis algorithm" may be considered. In which folder should they be stored?

A: Store the analysis specifications in the "programs" folder. This should be explained in the data guide.

Q4-17:   In order to explain the process by which the variables of ADaM datasets were created, reference data used to create ADaM datasets (reference tables such as Lookup tables, Metadata, etc.) are to be submitted; in which folder should they be stored?

A: Store them in the "misc" folder. If an applicant submits programs used to create ADaM datasets and the reference data mentioned above is used in the program, it is also possible to store the reference data in the "programs" folder. This should be explained in the data guide.

Q4-18:   Data used to impute missing data (e.g., multiple imputation) are to be submitted as an ADaM data source; in which folder should they be stored?

A: Store them in the "misc" folder. The handling of missing data should be explained in the dataset definition document and in the data guide.

Q4-19:   In Section 4.1.1.4 of the "technical conformance guide", it states, "the character sets and the encoding system used to create the dataset should be described in the data guide;" please give specific examples of the character sets and encoding system that must be described.

A: Information on the character sets and the encoding system is needed to identify the characters

intended by the dataset creator.

Examples of character set information to be described in the data guide:

[Character set] JISX0208   [Encoding system] Shift-JIS

[Character set] JISX0208   [Encoding system] EUC-JP

[Character set] UNICODE (USC-2)   [Encoding system] UTF-8

Q4-19-1:   In connection with Q4-19 above, how can information be obtained on the encoding system used?

A: In principle, encoding system-related information can be obtained from the property of the dataset. In the case of an unconventional encoding system used for relevant character sets, provision of detailed data may be additionally requested.

Q4-19-2:   As shown in one of the examples in Q4-19 above, when the encoding system is UTF-8, is it necessary to include further information such as USC-2 for the character set, UNICODE?

A: No further information is necessary. However, if the given character set-related information does not work, additional detailed information may be requested.

Q4-20:   If the application is to be made based on the results of an interim analysis, is it permissible to include data obtained after the cutoff of the interim analysis up to the time of application with data submitted for the application?

A: If the application is to be made based on the results of an interim analysis, it is required that data up to the cutoff of the interim analysis be included in the electronic data submission; it is also acceptable, however, to include data after the cutoff. For instance, if the application is made after a certain period of time from the interim analysis, it may be useful to include data after the interim analysis. If the application is made including data after the interim analysis, clearly distinguish data before and after the cutoff, and the handling of the relevant data must be explained in the data guide.

Q4-21:   Is there anything special to consider when the SDTM IG v3.1.2 Amendment 1 is used for the creation of the SDTM datasets?

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A: PMDA does not perform the validation based on SDTM IG v3.1.2 Amendment 1. Applicants should perform validation of study data based on the version other than SDTM IG v3.1.2 Amendment 1 and take the necessary action. Moreover, applicants should specify the version of SDTM IG used for validation on the dataset definition document. Basically, it is recommended that applicants perform validation based on SDTM IG v3.1.3 in that situation.

Q4-22: Is it possible to store and submit the datasets/files not conforming to CDISC in the folder that is defined to store SDTM datasets or ADaM datasets?

A: Within the folder storing SDTM datasets or ADaM datasets, it is possible to store datasets in the SAS XPORT format conforming to the CDISC standards, together with the accompanying definition documents in the XML format, style sheets, and PDF documents. Do not store csv files, XML files other than definition documents, or SAS XPORT datasets not conforming to the CDISC standards.

Q4-23: In Section 3.(1)c of the "notification on practical operations", it states, "The use of SI units is recommended". Please indicate the SI units that the PMDA considers acceptable, and any other points that should be considered when storing data in SI units.

A: Currently, the PMDA considers the use of SI units, non-SI units that are accepted for use with SI units, and SI prefixes listed in published BIPM (Bureau International des Poids et Mesures) brochure as acceptable use of the SI units. Prefixes should be used to keep numbers in the range of 0.1–1000.

Q4-24: For a clinical study with interim analyses, when is it necessary to submit the interim analysis data in addition to the final analysis data? Please indicate the format and method for submission, and the points to consider when the interim analysis data and the final analysis data are to be submitted together at the time of application.

A: In a clinical study subject to electronic data submission, if a decision is made regarding discontinuation/continuation of the study, the need for an important study design amendment or the contents of the amendment, etc., based on the interim analysis results, applicants may be asked to submit the analysis datasets used for the interim analysis in addition to the final analysis data (or data at the final cutoff used for the application) at the time of application. If analysis datasets and analysis

programs used for the interim analysis are to be submitted, store them with the dataset definition document in the "misc" folder. It must be mentioned in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data" to the "Notification of Implementation Outline of Consultation and Confirmatory Investigation, etc.," and in the data guide that the analysis datasets used for the interim analysis are to be submitted. If no SDTM is created exclusively for the interim analysis, submission of SDTM for the interim analysis will not be necessary. Please use the clinical consultation to verify the necessity of electronic data submission of the interim analysis datasets and the scope of submission.

Q4-25: In Section 2.(6) of the "notification on practical operations", it states, "if the new drug application is to be made during a long-term study or based on the results of an interim analysis, the data from this clinical study submitted after the new drug application should include the data previously submitted at the time of the new drug application as well as the additional data". If data from long-term continuous studies with different study numbers are compiled (e.g., in a case where subjects who completed the phase III study, Study No. 001, were enrolled in the continuous treatment study, Study No. 002, and the data from Study No. 001 and Study No. 002 are compiled. [Note that submission of data from the phase III study was already made at the time of application]), how will the folder name be specified for additional electronic data submission?

A: Under the circumstances described above (to submit additional electronic data after the application), store the additional data (Study No. 001 and 002 combined) in the folder for Study No. 002 submission. For the methods and procedures of submission of CDISC-conformant datasets after the application, refer to the Answer to Q3-20.

  For combined data from multiple studies, it will be necessary to specify in the dataset which study each data comes from. The data guide must include points to consider, such as the fact that there is an additional submission of compiled data from multiple studies, the method for compiling data, and the presence/absence in the additional data of new subjects from the continuous treatment study. For details regarding methods for data compilation and submission, please utilize "consultation on preparation of submission of electronic study data" as needed.

Q4-26: Is it possible to submit "specifications that show the analysis algorithm" in English?

A: Yes.

* 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.

Q4-27:　Are there any issues to consider when multiple versions of CDISC standards, CDISC Controlled terminology, or external dictionaries are used in the same study?

A:　In the "notification on practical operations", it states that, "a single version of the standards must be used within a clinical study. If different versions are used for any parts of the same clinical study, it should be discussed with the PMDA in advance using consultations and then explained in the data guide with the reasons for the use of different versions indicated". At the PMDA, validation of study data will be conducted in the Gateway system based on the single CDISC standards version and single MedDRA version stated in the define.xml as well as single CDISC Controlled terminology version entered in the Gateway system. Applicants should also perform validation of study data based on the single CDISC standards version in the define.xml and single CDISC Controlled terminology version in the Gateway system, and correct study data or explain errors based on the results. Applicants should also specify all versions of CDISC standards, MedDRA, CDISC Controlled terminology, or external dictionaries used for the creation of datasets and for validation of study data in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data".

Q4-28:　Are there any points to consider when the CDISC Controlled Terminology version used to create the dataset and that used at validation are different?

A:　In the Gateway system, enter the CDISC Controlled Terminology version used at validation. In Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data", specify the versions of CDISC Controlled terminology used to create datasets and at validation. It is necessary to explain in the data guide if the CDISC Controlled Terminology version used to create datasets and the version used at validation are different, and to specify each.

Q4-29:　The sponsor plans to code drugs with IDF, convert to WHO DDs data using Cross Reference Tool Japan (CRT Japan), and then store in SDTM. Is it possible to submit data with blanks in the variables except for drug information converted by CRT Japan?

A:　If an applicant stores information such as drug names that cannot be converted by CRT Japan to the dataset, it is possible to submit only data that is converted by CRT Japan in the SDTM dataset.

Q4-30:   A sponsor collects the adverse event terms in Japanese during the clinical study, creates the AE domain in both Japanese and English, and creates figures or tables based on the English dataset. In this case, is it possible to submit only the English dataset? In the meantime, what should the sponsor do if the figures or tables are created based on the Japanese dataset?

A: In both cases, it is possible to submit only the English dataset if all information on the Japanese dataset is included in the English dataset. It is also possible to submit the Japanese dataset along with the English dataset.

Q4-31:   When submitting the additional data of the studies that were ongoing at the time of application during review, should CSR in eCTD M5 and electronic data be submitted as new or replace? In addition, is there anything special to consider for the storing methods?

A: Basically, when submitting the additional data of the studies, both storing CSR in eCTD M5 and study data in newly created folders as new data and replacing CSR and study data previously submitted with CSR and study data newly submitted in existing folders are acceptable. However, preferable method may depend on study design, and the method of preparing CSR and creating datasets. Therefore, please consult with the PMDA at the "consultation on preparation of submission of electronic study data" in each case if necessary. Either at the time of submission of application or submission of additional data, basically, it is necessary that the folder including CSR in eCTD M5 must correspond to the folder including study data in one-to-one basis regarding folder structure and information stored in each folder.

Q4-32: In reference to Question 10 in the "Question and Answer Guide Regarding the Notification of Basic Principles"(hereinafter referred to as "Q&A regarding notification of basic principles"), please advise us about the contents and methods of submission if electronic study data of clinical studies that are not formatted in accordance with the CDISC standards have to be submitted. It is also stated that if electronic data that are not formatted in accordance with the CDISC standards have to be submitted, a prior consultation with the PMDA should be carried out about the relevant studies and submission contents. In cases where a sponsor consults with the PMDA about the contents of electronic data to be submitted that are not formatted in accordance with the CDISC standards, which consultation should be used and what should be explained at the consultation?

A: When electronic study data of clinical studies that are not formatted in accordance with the

CDISC standards are submitted, at least the clinical study data containing data collected by CRF, etc. (information that would correspond to the SDTM dataset if it were CDISC-conformant), the analysis dataset and analysis program used for obtaining the results described in the CTD and the electronic data corresponding to the dataset definition document should be submitted. Therefore, please use the "consultation on exemption of submission of electronic study data" and make sure to explain the contents at the consultation, when the sponsor consults about the contents of electronic data to be submitted that are not formatted in accordance with the CDISC standards in advance. Please store electronic study data of clinical studies that are not CDISC-conformant in the legacy folder of the folder structure shown in section 3.5 of the "technical conformance guide".

Please also describe the standard pharmacokinetic analysis of clinical studies that are not CDISC-conformant in "4.(3) Study information which is planned to submitted as electronic data (clinical pharmacology, Standard pharmacokinetic analysis) scheduled for electronic data submission" in Attachment 8 "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data", as usual.

Q4-33: Prior to application for re-examination, an applicant submitted electronic study data on post-marketing clinical studies that are required to be submitted at re-examination, but the version used to create the data is not included in the list of versions acceptable at the PMDA(hereinafter, refer to as Data Standards Catalog) at the time of re-examination application. Does the applicant need to correct the data again and then re-submit the data?

A:　In this case, only the violations that occurred due to the difference in versions are acceptable for submission without re-correction of the data, at the time of re-examination application. However, regarding these violations, please make sure to explain this situation in the "consultation on data format of submission of electronic study data" that has to be carried out before the re-examination application.

Q4-34:　In reference to Question 3 in the "Q&A regarding notification of basic principles", when the same clinical study data as the data that have already been submitted to the PMDA in the past, are used for a new application in the situation where the prior application has not been approved yet, is it necessary to submit the same data for the new application? In the cases where it is necessary to submit the same data for the new application, if the version used to create the data for the prior application is not included in the Data Standards Catalog at the time of the new application, do we need to correct the data again and then re-submit the data even if the data for the new plication are the same one as

the data that have already been submitted?

A: If the applicant uses the same clinical study data as the data that have already been submitted to the PMDA for the prior application and the prior application has already been approved, according to Question 3 in the "Q&A regarding notification of basic principles", it is not necessary to submit the same data for the new application. However, like the case of this question, in the cases where it is assumed that the scheduled application date of the new application is earlier than the approval date of the prior application, it is necessary to submit the same data for the new application, even if the data are same as the data that have already been submitted. Therefore, please perform the validation in advance prior to the new application and take the necessary action. If the version used to create the data for the prior application is not included in the Data Standards Catalog at the time of the new application, the applicant needs to correct the data and then re-submit the data.

Q4-35:   When electronic study data that are not formatted in accordance with the CDISC standards are submitted, does the sponsor need to use the WHO-DDs when coding drugs?

A: The sponsor does not need to use the WHO-DDs.

5. Questions on electronic study data on clinical pharmacology

Q5-1:   Deleted

Q5-2:   Please provide a more precise definition and explanation of "clinical studies where standard pharmacokinetic analysis was performed".

A: These are clinical studies where the pharmacokinetics of a drug was evaluated using the method defined as a standard pharmacokinetic study in the "Clinical Pharmacokinetic Studies of Pharmaceuticals" announced on 1 June, 2001 by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare.

Q5-3:   In Question 12 of the "Q&A regarding notification on practical operations", what are "individual clinical study data" in "clinical studies where standard pharmacokinetic analysis was

performed"?

A: They involve not only SDTM datasets (e.g., PC domain or PP domain) related to pharmacokinetic or pharmacokinetic/pharmacodynamic analyses but also all SDTM datasets of the clinical studies subject to submission.

Q5-4: In the case of a population analysis being subject to submission, which data used to create the population analysis datasets - e.g., SDTM datasets, analysis datasets on standard pharmacokinetic analysis, and efficacy and safety analysis datasets of the clinical studies - are subject to submission?

A: For a population analysis, only electronic data related to the population analysis (such as analysis datasets for the population analysis) are subject to submission. In the case where each clinical study used for creation of population analysis datasets is inconsistent with studies that must be electronically submitted, as listed in Section 2(2) of the "notification of basic principles" and Section 1(1) of "notification on practical operations", it is unnecessary to submit the SDTM datasets, analysis datasets on standard pharmacokinetic analysis, and efficacy and safety analysis datasets of the clinical studies from which data was drawn.

Q5-5: In Section 3.(2)b(iii) of the "notification on practical operations", it states "Regarding data that were excluded from the analysis for reasons other than those specified in the analysis plan (for example, data excluded because they were determined to be outliers at the time of analysis), steps should be taken to clarify how the data were handled during the analyses, such as by flagging to identify them". Is it possible to explain the handling of excluded data during the analysis by submitting the following two types of datasets: the final datasets (from which outliers, etc., were excluded) and whole datasets (including outliers, etc., with flagging to identify them)?

A: Yes, it is possible. The above statement in the Notification means that it is necessary to submit datasets in a manner that clarifies why data was excluded from analyses; thus, submission can be made in other ways as long as it fulfills this aim.

Q5-6: Deleted

Q5-7:   Deleted

Q5-8:   Deleted

Q5-9:   When a sponsor submits results from all phase II and III studies (including long-term studies), which are generally regarded as the major evidence for evaluation of efficacy, safety, and dosage and administration in 2.2)a of the "notification of basic principles", is it necessary to submit data for clinical pharmacology analyses such as drug concentrations or the pharmacokinetic parameters included in these studies? If it is necessary, in what format should it be submitted?

A: It is necessary to submit the electronic data for clinical pharmacology analyses included in the clinical studies shown in 2. 2)a of the "notification of basic principles". It is necessary to submit the electronic data in the format that conforms to the CDISC standards, as shown in Q12 of the "Q&A regarding notification on practical operations", and submit programs or analysis specifications based on the "notification on practical operations" and the "technical conformance guide".

Q5-10:   Deleted

Q5-11:   Deleted

Q5-12:   Deleted

Q5-13:   Deleted

Q5-14:   Deleted

Q5-15:   Deleted

Q5-16:   Deleted

Q5-17:   Please demonstrate what kind of variables should be included in pharmacokinetics or pharmacokinetics/pharmacodynamics analysis datasets.

A: Please include the variables necessary for being 'analysis ready' datasets. For example, information on doses for an individual subject, information on actual elapsed time from the start of administration to sampling time, derived values needed for the analysis such as AUC used as a PK index, the change in a PD marker from baseline, and flags to extract records for analysis should be included in the dataset. When analysis datasets in ADaM format are submitted, the variables that are required in the ADaM IG need to be included.

Q5-18:   Regarding "Population analysis, including simulations" in 3.(2)c.(ii) "notification on practical operations", is it necessary to submit program or output files for covariate models or model evaluation so that it is possible to trace the series of processes used in establishing the final model?

A: As the basic model and final model represent the basic scope of submissions, it is not necessary to submit program or output files for covariate models or model evaluation. However, if the process of covariate models or model evaluation is complicated, and the sponsor considers that such files would aid understanding of the analysis method, it is possible to submit these files.

Q5-19:   Regarding 'Population analysis, including simulations' in 3.(2)c.(ii) "notification on practical operations", files with the output of major results should be submitted. Is it necessary to submit the files even if the major results are described in the analysis report?

A: If major results are described in the analysis report, it is not necessary to submit the output files, but this should be mentioned and explained in Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data".

Q5-20:   In 3.(2)c.(ii) "notification on practical operations", it states, "If simulation was performed, submission of the program used for the simulation and program procedures is desirable".   Various

simulations based on population analysis are conducted during drug development, which kinds of simulations are recommend to be submitted?

A:　Simulations used for decision-making are recommend to be submitted, for example, determination of the patient population to be administrated, or the dosage.

Q5-20-1:　Regarding Q5-20, is it necessary to submit programs used for Visual Predictive Check or datasets that are created for simulation?

A:　It is not necessary to submit data regarding simulation for model evaluation (such as Visual Predictive Check) or datasets created in a series of simulation processes.

Q5-20-2:　According to Q5-20, qualitative evaluation with figures could be the basis for dose setting. In this case, is it necessary to submit the program used to create figure, or is it enough to submit only the simulation data that is the base of the figure?

A:　When dose setting is conducted based on a figure that shows the simulation results visually, please submit the program used to create the figure. If it is difficult to submit the program used, submission of specifications that demonstrate the analysis algorithm would be sufficient, as shown in 3.(2)c.(ii) "notification on practical operations".

Q5-21:　Analysis results can be slightly different depending on the analysis software version.　When confirming the results of analysis during the review, will reviewers always use the same software version the sponsor used to prepare the results? Is it necessary for sponsor to complete the analysis with the latest version of the software?

A:　It is preferable for the PMDA to analyze in the same environment as the sponsor, but it is not realistic for to assume this will always be the case. Therefore, in some cases, the PMDA analysis will be conducted using a different software or version, with the understanding that analysis results would be slightly different depending on the environment. The sponsor does not necessarily need to use the latest version of the software.

Q5-22:   Have there been cases where the PMDA has sent inquiries after a new drug application because the reviewer had questions about the contents of submitted data or when the program doesn't run in the PMDA's environment?

A: Basically, the PMDA will not send inquiries regarding the contents of programs or data. Please record details such as definition files, analysis specifications, and program procedures in each briefing document.

Q5-23:   When a program requires modifications in order to run at the PMDA, does the sponsor need to modify and resubmit the program?

A: No, that will not be necessary.

Q5-24:   Have there been cases where the PMDA requires sponsors to submit variables not used in the population analysis (including simulations)?

A: In general, the PMDA won't require the creation and submission of a dataset with new variables after a new drug application. On the other hand, at the clinical consultation, the PMDA can propose the creation of a dataset with new variables (e.g., age, when considering dose setting in children).

Q5-25:   Please demonstrate how to store the dataset of integrated PK and PK/PD analysis and data for physiologically based pharmacokinetic model analysis.

A: Create a [study id/iss/ise] folder with the same name of the folder in the CTD Module 5, and create the folder for analysis under the [study id/iss/ise] folder, then store data in the folder for analysis.

Q5-26:   When PK analyses are conducted at multiple time points in a single study, in which folder should ADaM datasets for each time point be stored?

A: If timing of analysis for efficacy and safety is different from that of analyses for PK (e.g., [1] multiple PK analyses are conducted during the study period where a single analysis for efficacy and safety is conducted, or [2] the timing of PK data collection is different from that of efficacy and safety),

use different file names for the ADaM dataset based on analysis timing, and store them in [study id/iss/ise]¥analysis¥adam¥datasets folder. When the method above is difficult to apply, or when there are multiple time points to analyze as a whole study (i.e., when interim analysis is conducted and submitted with the final analysis), store the most important ADaM dataset for evaluation in [study id/iss/ise]¥analysis¥adam¥datasets folder, and store other datasets in the "misc" folder. If a sponsor needs to discuss which time point should be considered the most important for evaluation, or whether analyses at each time point should be submitted, please use clinical trial consultations. If the sponsor needs to discuss how to store data, please use "consultation on preparation of submission of electronic study data".

Q5-27:   Is there any particular format for the definition document for the analysis dataset for phase I and clinical pharmacology study results that are not based on CDISC standards and clinical pharmacology analyses? Is it possible to submit the definition document in English?

A: There is no particular format, and it is possible to submit the definition document created by the sponsor without any changes. It is also possible to submit the definition document in English.

Q5-28:   In the "technical conformance guide" 4.2.3.1, it is stated that if detailed information regarding analysis specifications on pharmacokinetics or pharmacokinetics/pharmacodynamics is included in documents such as the analysis plan, it is sufficient to submit only these documents. Is there a proper document in which such information can be stated?

A: Please include the information in the document submitted for new drug applications, such as Analysis specifications. Please include it on Attachment 8, "Supporting Document on Consultation on Data Format of Submission of Electronic Study Data".

Q5-29: Is it possible to submit attachment 5 of the "technical conformance guide" in English?

A: Yes, it is possible.

Q5-30: Please demonstrate the examples of clinical pharmacology of which Analysis Results Metadata is subjected to submission, when a sponsor submits the CDISC-conformant electronic study data on a

standard pharmacokinetics analysis.

A: In the case of a standard pharmacokinetics analysis, please submit Analysis Results Metadata for tables showing the results of statistical analysis using pharmacokinetics or pharmacodynamics parameters, etc.

Q5-31:   In Question 11 of the "Q&A regarding notification on practical operations", it states that regarding phase I studies performed in both Japanese and non-Japanese subjects and studies listed in 2. 2) c of the "notification of basic principles", analysis dataset of efficacy and safety from those studies may not necessarily need to be submitted. Regarding safety assessment of these studies, if adverse events and laboratory test values are counted simply using clinical study data (e.g., SDTM), and analysis datasets are not created regardless of the format (e.g., ADaM), is it necessary to create analysis datasets and submit them?

A: Regarding safety assessment of these studies, if adverse events and laboratory test values are counted simply using clinical study data (e.g., SDTM), and analysis datasets are not created, it is not necessary to create analysis datasets and submit them.

Q5-32:   Regarding Text Output of Phoenix Projects (*.phxproj) given as an example of the analysis specifications on pharmacokinetics or pharmacokinetics/pharmacodynamics and information to be submitted in accordance with these specifications in the "technical conformance guide" 4.2.3.1, please explain concretely which file should be submitted.

A: Please submit the file of Core Output.

Q5-33:   If physiologically based pharmacokinetic model analysis is performed for a drug (Drug A) which differs from a submitted drug in a PBPK model analysis report aimed to investigate drug interaction, is it necessary to submit the files for PBPK model analysis of Drug A as well as the files of a submitted drug?

A: Yes, it is necessary to submit the files of Drug A.