The Japanese eCTD and electronic submissions

Introduction

Electronic common technical document (eCTD) applications were implemented in Japan in 2004; however, at that early stage a paper CTD was submitted as the official dossier, with the eCTD only to be used as a reference. Since April 2009 the number of eCTD packages submitted as the official dossier has increased – paper Modules 3, 4 and 5 are no longer required if an eCTD is submitted as the official dossier; however, M1 and M2 are still required on paper. Most Japanese new drug applications (JNDAs) are now submitted with the eCTD as the official dossier (140 out of 142 JNDAs in FY2015).

The “Japan Revitalization Strategy” (adopted by the Cabinet on 14 June 2013) indicates that it is essential to strengthen the PMDA system with respect to both quality and quantity. Furthermore, the “Healthcare and Medical Strategy” (an agreement among relevant ministers, 14 June 2013) states that “the PMDA shall promote its analyses and research by utilising study data (eg, clinical data), and shall establish a rational and efficient process for evaluations and decisions in its reviews and consultations”. In order for the PMDA to take the initiative to conduct its analyses and research using data, it is important for the clinical data to be submitted in electronic format. Electronic data will enable the PMDA to conduct various analyses during the regulatory review process for individual products, which will allow the PMDA to make more objective and scientific decisions and further contribute to an increase in the quality of its reviews. Uniform methods of collecting study data from various products will also allow product cross-sectional evaluations and may enable utilisation of modelling and simulation. Electronic data submission could also provide advantages for applicants. Firstly, it may increase both the efficiency and the success rate of drug development for applicants if the PMDA utilises results obtained from various analyses of the electronic data for reviews and scientific consultations. Secondly, electronic submission could reduce the burden when submitting applications, for example, by reducing the number of inquiries from the PMDA, as the agency could conduct its own analysis using the electronic data (as mentioned in Notification No 0620-6, 20 June 2014).

Differences in eCTD between overseas and Japan

The International Conference on Harmonisation (ICH) eCTD aims for global harmonisation, and it is important to unify eCTD rules and specifications to share information and data among regulatory agencies. Leaf files (PDFs) for M1–M5 are structured according to the granularity specified by ICH, and with the backbone of extensible markup language (XML) then become eCTDs. The structure of M2–M5 in the eCTD is harmonised; however, not all specifications and rules are identical depending on the agency. The definition of XML is different depending on the viewer used by each agency; in version 3.2.2, the PMDA does not use document type definition (DTD), but “Schema” as the XML definition for M1. Furthermore, in Japan, the M5 is slightly different from other regions, with structure and contents of m5.3.7 unique to Japan.

One of the largest differences between Japan and other regions are the rules regarding lifecycles. The XML full backbone should be submitted in Japan when lifecycle management is required (eg, from 0000 to 0001), whereas only the differences are required to be submitted in other countries. Submission of the full backbone affects revision of hyperlinks in Japan. Therefore, applicants have to work on not only the revision of documents but also hyperlinking and other lifecycle settings, which pose a significant burden (so called “pseudo replacement”).

The eCTD version 4.0 changes

In December 2015, ICH-M8 (eCTD version 4.0) reached Step 4, which led to various workshops and seminars regarding eCTD Version 4.0 being held by the PMDA and other industry organisations in Japan. The PMDA has issued an ICH eCTD version 4.0 Implementation Guide, and a pilot study of eCTD version 4.0 will be conducted in 2018. In addition to the eCTD version 4.0, further electronic submission systems have been developed such as electronic data in the Clinical Data Interchange Standards Consortium (CDISC),
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and submission via an electronic gateway in order to facilitate regulatory review.

The eCTD version 4.0 has been improved based on the experiences from eCTD v3.2.2, as well as taking into consideration global harmonisation including the use of HL7. The definition is integrated and two XMLs in eCTD v3.2.2 (ICH backbone and regional backbone) have become a single XML backbone. Therefore, all documents in M1–M5 can be referenced. Furthermore, study tagging files (STFs), node extensions and “append” have been removed, whereas “Context of Use” and “Document Group” have been incorporated in version 4.0 to align with non-Japanese eCTD options.

Rules relating to document lifecycles have been changed in eCTD version 4.0. In version 3.2.2, replacement of documents must be on a one-to-one basis, whereas in version 4.0 the replacement of documents can be one-to-many or many-to-one. Therefore, multiple documents can be referenced when one document is replaced, and replacements can be done efficiently. Lifecycle capabilities are “new”, “replace” and “delete” in eCTD version 4.0, with deletion of the previous “append” lifecycle capability.

Rules relating to the reuse of documents have also been revised. In version 3.2.2, each submission is independent and when an applicant wants to use previously submitted documents, those documents should be resubmitted for the new application. However, in eCTD version 4.0, it is not necessary to resubmit those documents – it is sufficient to describe the document ID in XML.

The structure of folders in eCTD version 4.0 becomes flat and simplified (except for the CDISC structure), moving away from the stratified and complicated layout in version 3.2.2. The XML itself does not require folder structures, but five folders (i.e., M1–M5) still remain in eCTD version 4.0 conventionally.

Points to consider for eCTD version 4.0 in Japan

The eCTD version 4.0 is expected to be accepted from 1 April 2020 and will be mandatory from 1 April 2022, following a two-year transitional period. For eCTD version 4.0 in Japan, it is necessary to consider the following:

- The eCTD version 4.0 can reuse documents which were submitted for an approved application
- Only elements and attributes described in the specific Japanese Implementation Guide can be used
- Submission management information must comply with rules specified by the PMDA. In addition to the ICH “Controlled Vocabulary”, those specific to Japan should be used
- “jp clinical pharmacology study” should be added as key words from the “Code List of JP Study Type” to clinical pharmacology studies to be included in Module 5
- An application can only contain one submission (see Figure 1). Partial change approval applications must be submitted as separate applications
- No cover letter is required when an eCTD is submitted via the

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**Figure 1: eCTD v4.0 XML message overview.**
Technical methods relating to an update of the display name in keyword definition is the same as the ICH Implementation Guide. However, it is necessary to pay attention to the Japan-specific operational rules.

The same version of eCTD must be used throughout the lifecycle from initial submission through to final approval.

### Relationship between eCTD and electronic submission

In the case of the current eCTD version, the electronic data should be submitted separately from the eCTD. Moreover, electronic clinical data must be submitted with the information regarding to which eCTD (submission) the study data belong, and to which study report the data are related. In principle, electronic study data should be submitted after storing them in the folder structure according to the notification No. 0427001 dated 27 April 2015, and no additional subfolders should be created. To meet the Japan-specific requirements, the following should be submitted in m5.3.7:

- Listing of all subjects in pivotal studies
- Listing of subjects with adverse drug reaction
- Listing of subjects with serious adverse events
- Listing of subjects with laboratory abnormalities
- Figures showing changes in laboratory test values.

The PMDA is now considering abolishing these requirements if electronic clinical data are submitted in eCTD version 4.0. For the time being, these listings should be submitted even if electronic data are submitted in CDISC standards, with two exceptions: (1) the listing of all subjects in pivotal studies to support dosage and administration as well as confirmatory study; and (2) figures showing changes in laboratory test values. Procedures for the compliance inspection where the PMDA confirms the reliability of the data will remain the same for the time being, and electronic data will be handled as the reference to conduct the inspection.

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### Table 1: Types of study and formats subject to electronic submission.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Individual clinical study data</th>
<th>Analysis dataset</th>
<th>Efficacy and safety analysis</th>
<th>PK or PK/PD analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on results from all Phase II and Phase III studies (including long term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
<td>In principle, ADaM, but other formats may be acceptable in certain cases</td>
</tr>
<tr>
<td>Study data from Phase I studies and clinical pharmacology studies listed right</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
<tr>
<td>Study data from Phase I studies and clinical pharmacology studies listed right</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
<td>ADaM is preferable, but other formats are acceptable</td>
</tr>
<tr>
<td>Study data from Phase I studies and clinical pharmacology studies listed right</td>
<td>SDTM</td>
<td>ADaM</td>
<td>ADaM</td>
<td>Formats other than CDISC standard would be sufficient</td>
</tr>
<tr>
<td>Study data from Phase I studies and clinical pharmacology studies listed right</td>
<td>SDTM*</td>
<td>ADaM*</td>
<td>ADaM*</td>
<td>ADaM*</td>
</tr>
<tr>
<td>Study data from Phase I studies and clinical pharmacology studies listed right</td>
<td>SDTM**</td>
<td>ADaM</td>
<td>ADaM</td>
<td>ADaM</td>
</tr>
</tbody>
</table>

*If necessary, consult beforehand.

*In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset has been used for analysis, submission of SDTM study data is acceptable.
Electronic data and the method of submission

Electronic data should be submitted in CDISC standards. Individual study data should be prepared using the “Study Data Tabulation Model” (SDTM) and should be submitted along with the definition file for variables (e.g., Define.XML). For analysis datasets, the dataset based on the “Analysis Data Model” (ADaM) should be submitted along with its definition file (e.g., Define.XML) and the programme used for creating the ADaM dataset.

Types and submission formats of documents subject to electronic submission are summarised in Table 1. The PMDA’s system for electronic data submission has been developed on the condition that only English will be used in items that have controlled terminology and a code list recommended by CDISC standards. In cases where an item has no controlled terminology or code list recommended by CDISC standards, those items are also required to be recorded in English if possible. Japanese will be allowed for items that are considered both necessary and appropriate to be written in Japanese (e.g., written explanations and the physician’s comments on the course of each case), as certain information might be lost when translated from Japanese into English.

JNDA submission categories which require electronic data in CDISC standards are:
- Drugs with new active ingredients
- New combination drugs
- Drugs with new administration routes
- Drugs with new indications
- Drugs with new dosage forms (e.g., sustained release, new drug delivery system)
- Drugs with new dosages
- Biotechnology follow-on products
- Combination drugs similar to those of approved combination drugs.

However, drugs with an additional dosage form (e.g., capsules to tablets), generics and over-the-counter (OTC) are not subject to electronic data submission. Electronic data are mandatory for the following study data (deemed “evaluation data”):
- All Phase II and Phase III studies (including long-term studies) which support efficacy, safety, and dosage and administration
- Phase I studies and clinical pharmacology studies of:
  - Oncology drugs
  - Studies conducted in both Japanese and non-Japanese subjects (e.g., Phase I studies conducted for global development and bridging strategies)
  - QT/QTc studies based on ICH E14 guideline.

Electronic data from other studies may be required if the PMDA considers it necessary, for example:
- Clinical studies in which standard pharmacokinetics (PK) analysis was conducted (e.g., Phase I/II PK/PD is the pivotal study which supports dosage and administration. Clinical pharmacology is the pivotal study which supports dosage and administration for paediatrics, elderly or hepatic/renal disorder patients)
- Population PK (popPK) analysis including simulations, for example when similarity in PK/PD between Japanese and non-Japanese was evaluated in global development strategy or bridging strategy. popPK is the pivotal data which supports dosage and administration
- Physiologically-based PK model analysis including simulations. This includes physiologically-based PK model analysis that provides major evidence for dose adjustment because of drug interaction and for dosage and administration or dose adjustment in paediatric, elderly, and hepatic/renal disorder patients.

Furthermore, the integrated summary of safety (ISS) and the integrated summary of efficacy (ISE) may also be required to be submitted electronically in order for the PMDA to evaluate specific safety and efficacy (e.g., safety in special populations). Even if no Japanese data are integrated, ISS/ISE may be required for the electronic submission. Additional electronic data that differ from the data originally submitted should be submitted electronically where clinical data are submitted during the review process (e.g., long-term study data are available after the JNDA submission where the JNDA was submitted with interim data). Currently, only clinical study data are required to be submitted electronically. However, in addition to clinical data for approval, the PMDA plans to utilise electronic data for other study types such as nonclinical studies and post-approval clinical studies. Study types subject to submission of electronic data may be changed in the future.

In the case of a “Partial Change Approval Application” – an application for a new indication – electronic data should be submitted for studies categorised as evaluation data. If these were submitted in the previous applications, they need not be resubmitted. Even if electronic data were submitted in the past, the data set and programme should be submitted in cases where meta-analysis is conducted including new data, and new analysis is conducted for the partial change approval application.

Electronic submission via gateway system

The PMDA will start accepting electronic submissions (eCTD and electronic data) via its gateway system from 1 October 2016. During the transitional period and until 31 March 2020, applicants can choose to follow either current submission procedures (applicants physically deliver the dossier to the PMDA in electronic media and paper documents), or via the new gateway system. A combination of both approaches, either eCTD or electronic data submitted via the gateway, is also acceptable until 31 March 2020. When using this combined approach, the minimum unit of electronic data to submit via the gateway is one clinical study data set (only SDTM is not acceptable in this format). After 1 April 2020, submission via the gateway is mandatory for products falling under the submission categories which require electronic data submission.

The PMDA has posted the operation manuals of the gateway system in Japanese (see www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0030.html). A pilot study was conducted by five participating companies from January to April 2016 to check the operating system function and to identify any issues. Although some issues were identified, it was judged that the gateway system could be implemented with the issues to be resolved within a defined period of time.

The procedures of application via the gateway system will be as follows:
- Notification of the JNDA submission to the PMDA via portal site of the gateway system (one to five weeks before the planned submission date)
- Data transfer from the applicant to the PMDA via the gateway
- Virus check by the PMDA after all data are transferred to the server via the gateway system (date of electronic data arrival)
- Validation, confirmation of no significant error and acceptance by the PMDA (date of electronic data acceptance).
In order for applicants to submit JNDAs via the gateway system, user registration of the portal site is required after obtaining an electronic certificate to identify themselves officially. User registration began in August 2016. The applicant must still submit a paper application form with revenue stamp for the associated application fee after the date of electronic data arrival has been confirmed; this is regarded as the “Submission Date” of the JNDA. The “Date of Application Received” is the date on which the PMDA confirms that the application form has no administrative errors. If a significant error is identified during PMDA validation, regulatory review will not be started until a corrected data set has been submitted.

**Points to consider for electronic submission**

As mentioned above, if electronic data have significant errors then regulatory review will not commence. In order to avoid such situations, applicants are recommended to hold a consultation on data format of submission of electronic study data with the PMDA during the clinical development phase (three to four months before JNDA submission at the latest). This consultation system was initiated on 15 May 2015 to obtain advice on the contents of electronic data such as specifications, definition file and the programme to create a data set, however, it is not for data analysis or evaluation. It is free of charge if official minutes are not requested, and a fee of ¥94,500 is charged if minutes are requested (as of May 2016). Validation rules and the data standards catalogue are available on the PMDA website. If applicants wish to confirm which clinical studies require electronic data submission, they should check this at official consultation meetings.

**Conclusion**

The PMDA has been striving to promote an advanced regulatory system with electronic data submission and has issued various notifications related to this matter. The eCTD, CDISC and the gateway system are considered to be the trinity of electronic submission. Collaboration among stakeholders in regulatory affairs, clinical development, data management and information technology is essential for successful JNDA submission. As technology advances, the rules and regulations will evolve and we should continue to follow developments in electronic submission.

**Further reading**


Note: English translations of cited notifications are available on the PMDA website at: www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

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