White Paper

# eCTD 4.0 Implementation Including Understanding of Regional Differences and Benefits

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# eCTD 4.0 implementation including understanding of regional differences and benefits

The Electronic Common Technical Document (eCTD) is the standard format for submitting applications, amendments, supplements, and other regulatory reports to health authorities around the world. The eCTD specification defines a harmonized structure for organizing, transmitting, and managing regulatory content using an Extensible Markup Language (XML) file, enabling consistent review through standardized viewing tools.

The adoption of eCTD submissions enabled the phasing out of paper-based processes, allowing for more automated and efficient submissions to regulatory bodies.

The initial eCTD specification (version 3.0) was finalized in 2003, and eCTD v3.2 has been the default version for more than 10 years since its release in 2008. For more than a decade, eCTD v3.2 has supported regulatory submissions worldwide; however, its underlying architecture imposes limitations in flexibility, data reuse, and long-term scalability.

To address these limitations and better support future regulatory and technological requirements, draft implementation guidelines for eCTD 4.0 were introduced between 2015–2016. eCTD 4.0 represents a significant evolution of the standard, introducing a more robust and flexible data-driven model, improved lifecycle management, and enhanced long-term sustainability. After many years of collaboration with regulatory bodies and industry sponsors, eCTD version 4.0 is finally accepted voluntarily in United States and European Union and is mandatory in Japan for new marketing authorization applications.

### Limitations of eCTD 3.x standard

In order to see the benefits of the new standard, it is key to look at the ways that v3.2 is lacking:

The structure caters only to human pharmaceutical submissions.

The structure varies by region and authority.

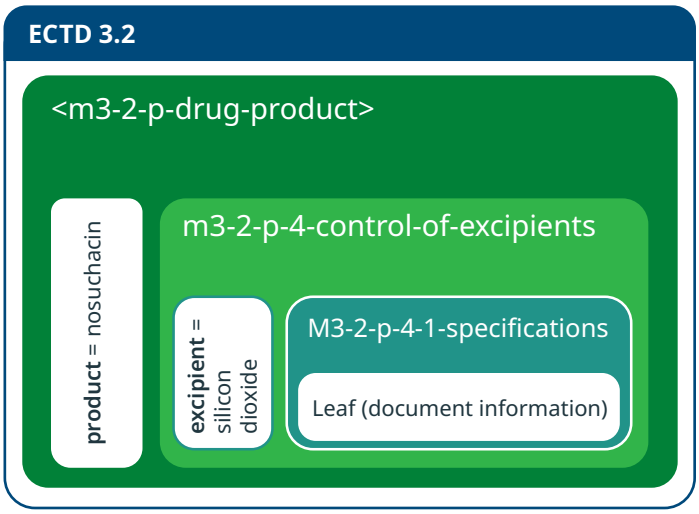
The metadata and table of contents are defined explicitly by structure changes to metadata, or the table of contents requires an updated structure.

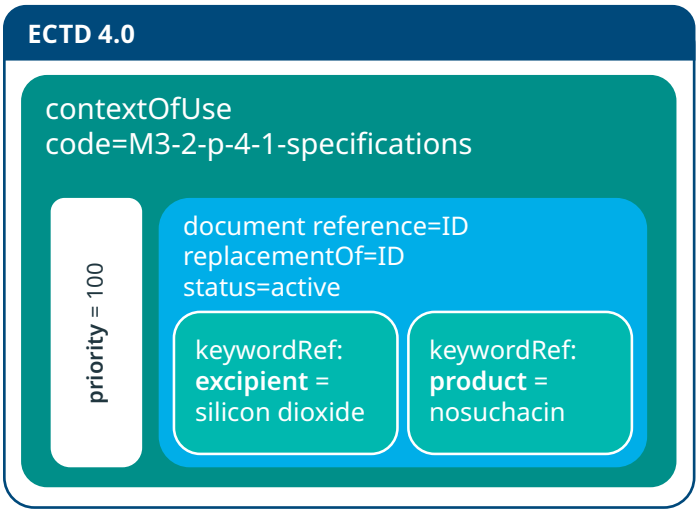
## Benefits to eCTD 4.0 standard

With the limitations of the eCTD 3.x standard in mind, eCTD 4.0 delivers a more flexible, harmonized, and future-ready approach to regulatory submissions. It enables improved lifecycle management, enhanced document reuse, and global consistency. Key benefits include:

- Supports all product types, including veterinary, tobacco, cosmetics, drugs, medical devices, food additives, and more. Applies a single format across agencies, regions, and centers.
- Reduces structural changes and software release cycles.
- Harmonizes submissions by packaging all content from Module 1 through Module 5 into a single XML exchange message.
- Allows metadata and keyword updates — such as display names, manufacturers, and group titles — without resubmitting physical files.
- Allows document order and priority within a section to evolve over time for more precise review.

- Enables advanced lifecycle management, including one-to-many or many-to-one document replacements.
- Allows document granularity to change while maintaining lifecycle relationships.
- Enables reuse of previously submitted documents through unique identifiers across submissions and regulatory activities.
- Simplifies updates through Controlled Vocabularies without requiring system or tool changes.
- Ensures consistent document grouping across ICH regions using group titles.
- Supports lifecycle management and reuse of v3.2.2 content.
- Allows additional region-specific metadata to be added as needed.




## How eCTD 4.0 helps regulators and sponsors

From an operational and regulatory perspective, eCTD 4.0 provides several advantages for regulators and sponsors:

- Enables easier automation of administrative processing through a data-driven structure and standard Controlled Vocabularies.
- Simplifies the implementation of new regulatory or legal requirements and dossier structure changes needed to support evolving business needs.
- Reduces workload through cross-application referencing.
- Lowers storage overhead through enhanced document reuse.
- Allows agencies to indicate whether submitted content has been assessed and to capture assessment outcomes, reducing the need for repeat review.
- Supports use of a common tool or single technical solution across all product types.
- Reduces maintenance effort for submission management and review tools, with fewer system updates required.

## Differences across regions

As with any globally adopted standard, regional differences in implementation and acceptance are expected. This is also the case for eCTD 4.0. Variations across regions may include differences in M1 submission structure, regional metadata and Controlled Vocabularies (CV), additional context of use in M2–M5, language and character support, study standards and group titles, group or worksharing submissions, and support for Forward Compatibility. Each of these areas is discussed in further detail below.

## M1 submission structure

The M1 structure is region-specific and reflects each authority's individual submission requirement whether under eCTD 3.2 or 4.0. While there may be similarities among regions, such as the cover letter and application form, it is important to understand the differences between eCTD 3.2 and 4.0 within the same region. These differences may include variation in folder structure or requirement for additional metadata.

**eCTD 4.0 M1 submission structure — regional comparison**

| | UNITED STATES (US) | EUROPEAN UNION (EU) | JAPAN (JP) |
|---|---|---|---|
| Reference Specification | Aligned with US eCTD M1 Specification v2.5 (DTD v3.3) | Aligned with EU eCTD M1 DTD v3.0.1 | Region-specific JP eCTD 4.0 M1 specification |
| Section Titles | Maintained from eCTD 3.2 | Maintained from eCTD 3.2 | Maintained, with additional JP-specific sections |
| eCTD 4.0 Codes | Differ from DTD element names | Differ from DTD element names | Differ from schema element names |
| Additional section/ attributes | No major additions beyond existing US structure | Supports EU-specific attributes (e.g., dosage form, strength) | Includes additional JP-specific sections and attributes |
| Regional Folder in M1 | Not required (us folder not used) | Not required (eu folder not used) | Required (jp folder must be present) |
| Additional Subfolders | Not Applicable | Not required | Allowed in JP M1 if required |

| SECTION | DESCRIPTION | CHANGES |
|---|---|---|
| For all sections, codes are changed but section titles are maintained. | | |
| jp_other | 対応可能な手段が他に無くやむを得ない理由がある場合に限り使用する。使用にあたっては事前に審査当局に相談すること。 | New section in JP eCTD 4.0 |
| jp_m1.13.4.1 | 機構への提出資料 | Section is changed from M1-13-04-01 機構への提出資料(写) |
| jp_m1.13.4.1.1 | 承認申請書上の製造方法欄における目標値/設定値等に関する一 覧表 | New section in JP eCTD 4.0 |
| jp_m1.13.4.1.2 | 新添加剤に関する提出資料 | New section in JP eCTD 4.0 |
| jp_m1.13.4.1.3 | その他 | New section in JP eCTD 4.0 |
| jp_m1.13.4.2 | 厚生労働省への提出資料（写） | Section is changed from m1-13-04-02 承認申請資料の訂正について（平成21年4月1日付） |
| m1-13-05 | eCTDの形式に関する留意事項等 | Removed in JP eCTD 4.0 |

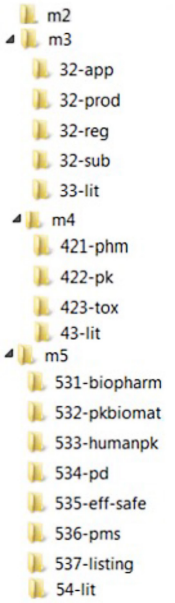
This table is an example for M1 difference in Japan from eCTD v3.2 to v4.0

## ICH submission structure

For M2 to M5, the ICH structure applies consistently for all regions. However, there are some notable differences in folder organization when comparing eCTD 3.2 and 4.0, which are outlined below:

- M2 — No additional folders are required.
- M3 — The subfolder should follow the standard naming convention shown in the screenshot but can be changed if needed.
- M4 — Additional folders can be added, and the subfolder follows the standard naming convention shown in the screenshot but can be changed if needed.
- M5 — Additional folders can be added, and the subfolder follows the standard naming convention shown in the screenshot but can be changed if needed.
  - » In accordance with the CTD organization, case report forms and individual patient data listings are located in folder 5.3.7.
  - » In eCTD 4.0, literature references and publication files should be placed in folder 5.4.

## eCTD 4.0 folder structure




## eCTD 3.2 folder structure


## Regional metadata control vocabulary

Regional variations exist in the use of metadata and Controlled Vocabularies (CVs) for eCTD 4.0 across different regions. For example:

- CVs for application type, submission type, and submission unit types are applicable for the US, EU, and JP.
- CVs for product category and substances are applicable for the EU and JP, but not for the US.
- CV for submission type for Category Event is applicable for JP, but not for the US and EU.
- CVs for submission mode, language, and territorial authority are applicable for the EU, but not for the US and JP.

In addition, regional metadata requirements may change between different versions of the eCTD specification within the same region. For example:

- DUNS number is applicable for US 3.3 but not for the US 4.0.
- Contact person organization is applicable for US 4.0 but not for the US 3.3.
- Submission date is applicable for JP 1.0 but not for the JP 4.0.
- Product category and application cross-reference are applicable for JP 4.0 but not for JP 1.0.

## Additional context of use in M2–M5

In JP 1.0, documents in folder 5.3.7 were organized into subfolders, but with the introduction of JP eCTD 4.0, additional context of use has been introduced within M5 (details are provided in the table below). These additional Context of Use (COU) are specific to Japan and are not applicable to other regions.

| CODE | DESCRIPTION (ENGLISH) | DESCRIPTION (JAPANESE) | KEYWORDS |
|---|---|---|---|
| jp_m5.3.7_other | Other documents under m5.3.7 | M5.3.7に格納されるその他の資料 | group title (O) |
| jp_m5.3.7.1 | Patient listings | 用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表 | study id_study title (O), study group order (O), site-id (O), document type (O), group title (O) |
| jp_m5.3.7.2 | List of adverse events | 実施された全ての臨床試験において副作用が観察された症例の一 覧表 | study id_study title (O), study group order (O), site-id (O), document type (O), group title (O) |
| jp_m5.3.7.3 | Serious adverse event list | 実施された全ての臨床試験において重篤な有害事象が観察された症例の 一 覧表 | study id_study title (O), study group order (O), site-id (O), document type (O), group title (O) |
| jp_m5.3.7.4 | List of abnormal laboratory test values | 実施された全ての臨床試験において臨床検査値異常変動が観察された症例の 一 覧表 | study id_study title (O), study group order (O), site-id (O), document type (O), group title (O) |
| jp_m5.3.7.5 | List of figures showing abnormal laboratory test values | 実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図 | study id_study title (O), study group order (O), site-id (O), document type (O), group title (O) |

## Language and character set support

It is understood that regional language support in the display names for the titles and keywords is a requirement for the JP region, but not for other regions. Furthermore, JP eCTD 4.0 specifications dictate that each attribute or field defines the type of values allowed. The following types can be used

| VALUE TYPE | VALUE ALLOWED |
|---|---|
| Text | UTF-8 characters (including Japanese characters) * can be used. |
| Fixed | Only the values given as examples can be used. |
| Alphabetic characters | Half-width/Single-byte alphabetic characters (a to z and A to Z) can only be used. |
| Single-byte numbers | Single-byte Arabic numerals (from 0 to 9) can only be used. |
| Single-byte alphanumeric characters | Only single-byte alphabets and single-byte numbers can be used. |

For EU region, the language and charset can be used if needed.

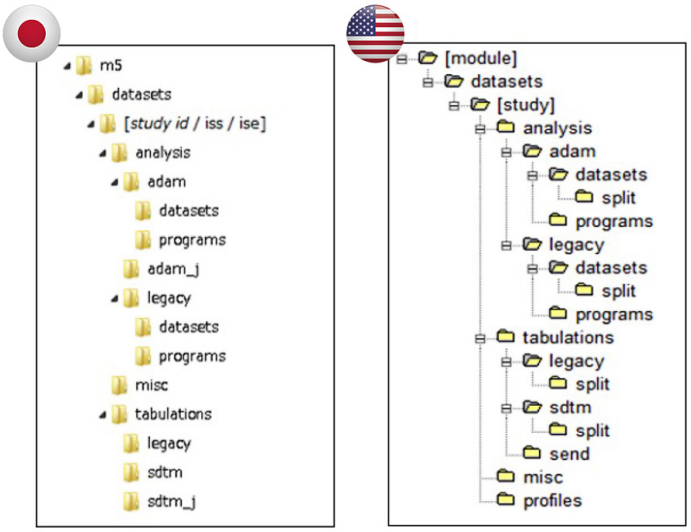
## Study standards and group title

For eCTD 4.0 in Japan, clinical studies are accepted in CDISC standard using ADaM and SDTM formats, similar to the US, though JP requires additional keywords for the studies. The Standard for Exchange of Nonclinical Data (SEND), one of the CDISC standards, is being considered for a potential requirement for electronic submissions in JP, but it is currently accepted for the US Additionally, for JP eCTD 4.0, clinical pharmacology documents require the addition of a File Description attribute, and dataset files (.xpt) require a character code for encoding, which is not required for US eCTD.

The table below illustrates the relationship between electronic study data and the selectable CVs to be used for Japan eCTD 4.0.

| | STUDY DATA CATEGORY | JP ANALYSIS TYPE | JP TERMINOLOGY (TABULATION) | JP TERMINOLOGY (ANALYSIS) |
|---|---|---|---|---|
| **SDTM dataset**<br><br>**(Files subordinate to "sdtm" or "sdtm_j" folder)** | jp_cdisc_single<br><br>jp_cdisc_ integrated | All | All | — |
| **ADaM dataset**<br><br>**(Files subordinate to "sdtm" or "sdtm_j" folder)** | | | — | All |
| **Electronic study data files other than those listed above** | All | | — | — |

The folder structure for study datasets is slightly different when comparing US and JP submissions; this is common for both eCTD 3.2 and 4.0.



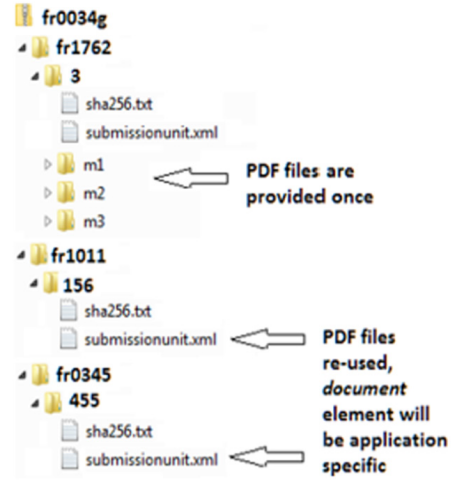

For the EU, group titles are allowed; however, details for study support are not included in the implementation guide.

## Group or worksharing submissions

Group submissions are supported across applications and regulatory activities in the US, but not in Japan. In the EU, grouped variations or workshare procedures are supported but are optional and the output structure is different from US. There are 2 different scenarios for group submission in EU:

1. Sending multiple submission units included in one transmission (providing one submissionunit.xml for each application involved and referencing the PDF files submitted together with one of the submissionunit.xml files). This scenario is feasible when most of the files are common (i.e. identical) for all the sequences included in the package.

**Referencing multiple applications using multiple XML files**




2. Sending multiple sequences in one transmission (providing only one submissionunit.xml for all sequences). This scenario is applicable when 100% of the files are common for all the sequences included in the package (for example, for PSUSA submissions).

One caveat to note, Forward Compatibility grouping will make all applications included in the group to switch to 4.0.

## Transition and Forward Compatibility

Though a unified format is employed by all agencies, the transition from eCTD v3.x to v4.0 is not universally accepted. For the US, submissions can be transitioned from eCTD 3.2.2 to eCTD 4.0 without requiring a transition sequence, a process similar to the EU, which allows regional submissions to be transitioned from eCTD 3.2.2 to eCTD 4.0. Unfortunately, Japan does not provide support for transitioning from JP 1.0 to JP 4.0, and the eCTD version number is maintained throughout the submission's lifecycle from initial submission to final approval.

## Other differences

When it comes to additional differences, US submissions require a cover letter in the m1.1 form (us_1.1) section, while Japan does not require one when submitting via gateway but does require it when submitting via other methods in the application/ sequence/m1/jp folder and should not be referenced in the submission unit XML file. Category Event is not allowed in the US and EU, but it can be submitted for Japan; Contact Party is required for US and EU submissions but excluded for Japan.

## Implementation

The timeline for implementation varies by region, with the mandatory date for implementation ranging from 2023 to 2029 and beyond for different health authorities. See the table below for more information regarding deadlines by region.

| REGION | TECHNICAL PILOT | IMPLEMENTATION DATES | IMPLEMENTATION DOCUMENTS | IMPLEMENTATION GUIDE VERSION |
|---|---|---|---|---|
| ANVISA, Brazil | 4Q 2026 (Planned) | 2027 (Voluntary)<br>TBD (Mandatory) | TBD | – |
| EC, Europe | 2024 CAPs (MAA completed)<br>2026 CAPs (Forward Compatibility - planned start Q1)<br>2026 non-CAPs (MAA - planned start Q2)<br>2026 non-CAPs (Forward Compatibility - planned) | 2025 (Voluntary for CAPs)<br>2026 (Voluntary for MRP/ DCP/NP)<br>2027 (Mandatory for CAPs)<br>TBC (Mandatory for MRP/DCP) | EC, Europe regional implementation page | 1.2 |
| FDA, United States | 2022 - 2Q 2023 (Completed)<br>2026 Forward Compatibility (Planned) | 2024 (Voluntary)<br>2029 (Mandatory) | FDA, United States regional implementation page | 1.8 |
| Health Canada, Canada | 2026 - 2027 (Planned) | 2027 (Voluntary)<br>2029 (Mandatory) | Health Canada, Canada regional implementation page | Draft |
| MFDS, Republic of Korea | TBD | 2027 (Voluntary)<br>TBD (Mandatory) | TBD | – |
| MHLW/PMDA, Japan | 2Q 2021 (Completed) | 2022 (Voluntary)<br>2026 (Mandatory) | MHLW/PMDA, Japan regional implementation page | 1.6 |
| Swissmedic, Switzerland | 2026 (Planned) | 2027 (Voluntary)<br>2030 (Mandatory) | Swissmedic, Switzerland regional implementation page | Draft |
| TGA, Australia | 2028 (Planned) | 2029 (Voluntary)<br>TBD (Mandatory) | TGA Implementation of ICH eCTD v4.0 Specification | – |

**Reference:** https://ich.org/page/ich-electronic-common-technical-document-ectd-v40

## How to prepare

The new standard aims to meet the evolving needs of the industry. As organizations adapt their systems and requirements, it is essential to understand and account for practical nuances. Careful implementation and thorough preparation are therefore necessary to ensure that all processes are transitioned correctly for applications at different stages with the health authorities.

When transitioning to eCTD 4.0, people, processes, strategies, and technologies must all be considered. Organizations should be aware of a few key factors in order to best prepare, such as the fact that:

- eCTD 4.0 XML is complex and cannot be easily adjusted manually.
- Lifecycle management (using Forward Compatibility) between eCTD v3.2.2 and v4.0 will be difficult without a proper and compliant toolset.
- There is no stylesheet available for eCTD 4.0 to easily view the submission TOC and content in the browser.
- To enable a seamless shift to eCTD 4.0, all PDFs need to be prepared for submission readiness with the latest compression standards.
- Metadata (user-defined vocabulary) should be streamlined for consistent use in both eCTD 3.2 and 4.0 submissions.
- Internal teams must be trained in relevant terminology and concepts and be aware of the most recent ICH and regional specifications and guidelines.
- It is also important to note that support for eCTD 3.x must continue concurrently until eCTD 4.0 is made universally mandatory, which is not until 2030 for some regions. Therefore, the two submissions will overlap in use, and organizations may fall behind in following relevant regulatory processes if the new standard is not properly established.

## Conclusion

The benefits of eCTD 4.0 are numerous and include an improved and more flexible structure, a single standardized format that can be used across multiple agencies, regions, and centers, and reduced structural changes over time. Additional advantages include enhanced metadata and keyword definitions, clearer display names, advanced lifecycle management, and improved document reuse.

As such, eCTD 4.0 represents an essential step toward streamlining the regulatory submission process, and understanding regional differences during implementation is critical to fully realizing its potential.

*Be prepared — eCTD 4.0 is here! Be ready to take advantage of its benefits and ensure you are properly equipped to make the transition.*

# About the author

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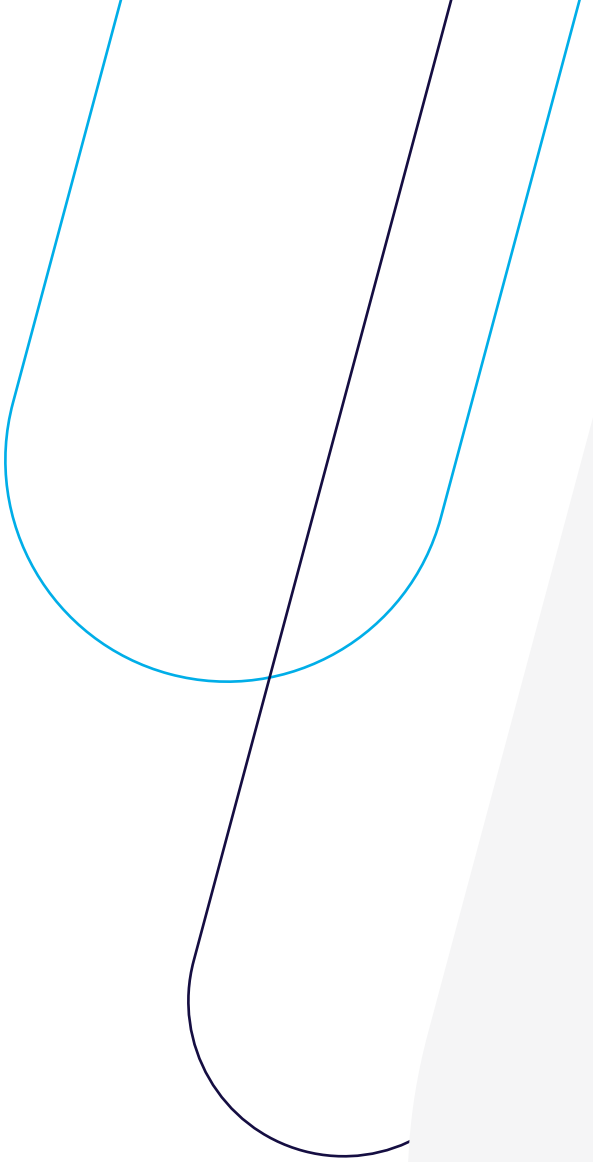
Sadia leads the team responsible for SmartSolve RIM Submission Management at IQVIA. She has over 20 years of experience in the IT and Life Sciences Industry. Sadia has extensive global knowledge of regulations and guidance for electronic submissions publishing.



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