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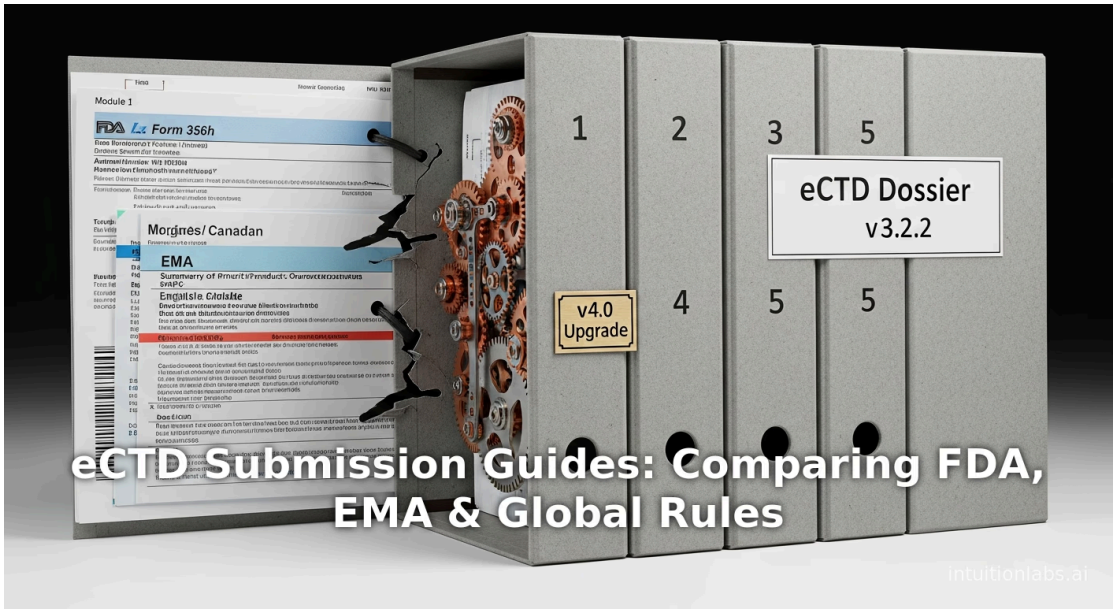
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eCTD Submission Guides: Comparing FDA, EMA & Global Rules

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In this article

1. Executive Summary
2. Introduction and Background
3. The CTD/eCTD Framework and Evolution
4. United States: FDA eCTD Submission Guidance
5. European Union (EMA) eCTD Guidance
6. Japan (PMDA) eCTD Guidelines
7. Canada (Health Canada) eCTD Guidance
8. China (NMPA) eCTD Guidelines
9. Australia (TGA) eCTD Guidelines
10. Regional Comparisons and Data Summary
11. Case Studies and Industry Perspectives
12. Implications and Future Directions
13. Conclusion

Executive Summary

The **electronic Common Technical Document (eCTD)** has become the global standard for regulatory submissions of drugs and biologics. Initiated under ICH harmonization (CTD M4, approved 2002) and later digitized (eCTD approved 2008), it organizes data into Modules 2–5 (scientific data) with a region-specific Module 1 for administrative information. Despite being a unified framework, each regulatory region has issued its own **submission guides** to address local requirements. For example, the US FDA mandates eCTD for NDAs/BLAs (with Form 356h in Module 1) by mid-2017, the EU EMA has required eCTD for centralized MAA since January 2010 (www.pharmtech.com), and Japan's PMDA and Canada's Health Canada similarly demand eCTD with unique rules (e.g. Japan uses a "CTD for DMF" format (www.extedo.com), Canada sets its own Module 1 and activity-specific form requirements (www.canada.ca) (www.extedo.com)).

This report surveys the **regional eCTD submission guides** in detail. It reviews the history of CTD/eCTD harmonization; the content and structure of current guides in the US, EU/EEA, Japan, Canada, Australia and other key regions; data on adoption (e.g. FDA reports ~94% of submissions in eCTD format by 2022 (globalforum.diaglobal.org)); and company case examples. We compare regional module-1 requirements (such as language, forms, cover letters) and module-2–5 conventions. We also analyze registration timelines and mandates (for instance, Health Canada has required eCTD for all new Master File registrations since January 1, 2020 (www.canada.ca), following a 2018 notice of intent (www.canada.ca), and China's NMPA announced in late 2022 that drug registration applications would move to mandatory electronic submission, with the final requirement taking effect January 1, 2023 (www.pharmalex.com)). Crucially, we discuss the shift to next-generation eCTD (version 4.0, based on HL7 RPS) in 2025–2028 – for example, FDA began accepting eCTD v4.0 in Sept 2024 (www.fda.gov) and EMA allows optional CAP submissions in eCTD v4.0 from Dec 22 2025 (EMA's July 2026 update makes v4.0 strongly recommended from Q1 2027 and mandatory for new CAP MAAs from Q1 2028; an earlier industry forecast had foreseen 2027) (esubmission.ema.europa.eu) (esubmission.ema.europa.eu) (globalforum.diaglobal.org). We highlight how these developments aim for

greater metadata richness, lifecycle management, and global interoperability (esubmission.ema.europa.eu) (globalforum.diaglobal.org). Throughout, all statements are substantiated by regulatory guidance, agency reports, industry publications and expert analyses. The findings illuminate both the **commonalities** and **differences** in eCTD expectations worldwide, and discuss the implications for regulatory strategy and future digital harmonization.

Introduction and Background

Pharmaceutical regulatory submissions (e.g. New Drug Applications, Marketing Authorizations) historically required extensive dossiers. To harmonize global filing requirements and reduce duplication, the ICH launched the **Common Technical Document (CTD)** initiative in 1989 (globalforum.diaglobal.org). The CTD (outlined in ICH M4) structures an application into five modules (introduction/regional info; quality; nonclinical; clinical) with identical Module 2–5 across regions but a region-specific Module 1. Over the 2000s, the CTD became universally adopted – **mandatory or strongly recommended** in major markets including the US, EU, and Japan (globalforum.diaglobal.org).

To further streamline reviews, regulatory agencies transitioned to electronic submissions. Initial electronic dossiers (e.g. scanned PDFs or “NeeS” format) had limitations in navigation and version control. Starting in 1997, ICH developed the **electronic CTD (eCTD)** standard (approved 2008) (globalforum.diaglobal.org). eCTD introduces an XML “backbone” that encodes the dossier’s hierarchical table of contents and enables lifecycle updates: each document is assigned an ID and change lifecycle markers, so reviewers can easily see what is new or withdrawn in each submission (globalforum.diaglobal.org) (globalforum.diaglobal.org).

The eCTD standard achieved rapid global uptake. According to Loebel (2024), by 2022 over 94% of all FDA submissions were in eCTD format (roughly 8 million via the FDA gateway) (globalforum.diaglobal.org); similarly, EMA reported that eCTD has been the only acceptable format for centralised applications since 2010 (www.pharmtech.com). Today eCTD is **accepted or required** in virtually every major regulatory jurisdiction (US, EU/EEA, UK, Japan, Canada, South Korea, etc.) (globalforum.diaglobal.org). However, as noted by industry sources, differences remain in **regional eCTD guides**: each authority provides its own Module 1 specifications, transfer specifications, validation criteria, and administrative forms. These regional guides ensure that local nuances – such as national application forms, product numbers, or additional attachments – are correctly integrated into the eCTD dossier.

In this report we examine these **regional eCTD submission guides** comprehensively. We begin by outlining the ICH/eCTD framework and the trajectory of e-submission adoption. We then delve into the guides issued by major regions (U.S., EU, Japan, Canada, Australia, China, etc.), detailing their content, requirements, and implementation timelines. Special attention is given to the Module 1 differences (administrative documents, cover letter content, etc.) highlighted by comparative studies (www.extedo.com). We incorporate data (agency statistics and published analyses) and real-world examples: for instance, one case involved converting an EU-format eCTD into Australia’s format to satisfy the TGA (www.clinigengroup.com). Finally, we discuss the **implications** of these regional guides, including how they affect global submission planning and how future trends (particularly the rollout of eCTD v4.0) may harmonize or complicate the landscape. All statements below are supported by cited sources.

The CTD/eCTD Framework and Evolution

The **Common Technical Document (CTD)** was first conceived by ICH (US, EU, Japan) to harmonize drug dossiers, grouping information into a logical structure. Module 1 contains administrative data (which is *not* harmonized globally), Modules 2–5 contain expert summary and detailed quality/nonclinical/clinical reports.As Loebel notes, “The CTD became the mandatory or strongly recommended format for most types of drug applications in the US, Europe, and Japan” over the 2000s (globalforum.diaglobal.org). In practice, all three ICH regions required CTD dossiers for marketing applications by the mid-2000s, even though applications for clinical trials or other non-authorisation purposes sometimes predated CTD guidelines.

Converting to an electronic format (eCTD) promised reviewers easier navigation and lifecycle visibility. Early electronic submissions were simply PDFs with a table of contents (the “NeeS” format used by EMA and others). The eCTD standard, developed by ICH from 1997 onward (globalforum.diaglobal.org), added a **machine-readable backbone**. Each eCTD consists of a folder hierarchy with an XML index; every document has a unique `<alias>` identifier and versioning statements (e.g. “new”, “replace”, “delete”) so that successive application *sequences* can convey incremental changes (globalforum.diaglobal.org). Granularity markers and tagging in Modules 4-5 (such as TIMESTAMP and DATA for study files) ease tracking of data sets. By 2008 the eCTD (v3.2.2) was officially adopted at ICH Step 4.

This digital transformation has materially improved the submission process. Agencies can automatically validate on-file structure and links, and easily retrieve prior sequence versions. As one observer noted, eCTD “had a huge impact on the speed and accuracy of regulatory submissions for pharma” (globalforum.diaglobal.org). Global statistics confirm near-universal uptake: by 2022, eCTD was **accepted or required** in all major markets (globalforum.diaglobal.org). Importantly, *each* region still specifies its own eCTD details. In ICH’s structure, Modules 2–5 are harmonized, but **Module 1 is region-specific**. For example, the FDA’s eCTD Module 1 includes US forms (like FDA 356h) and attribute files; the EU’s Module 1 includes EU-specific product information (SmPC, labelling) and letters; Japan’s Module 1 has unique fields like eCTD sequence numbers and commitments. In short, *regional eCTD submission guides* overlay national requirements onto the ICH backbone. Understanding these guides is crucial for successful cross-border filings (www.extedo.com) (www.extedo.com).

United States: FDA eCTD Submission Guidance

The **FDA** began moving toward mandatory eCTD with laws and guidance in the 2000s. Under FD&C Act §745A (enacted in FDASIA 2012), the FDA was required to issue guidance setting electronic format standards, after which firms would have 24 months to comply (www.fda.gov). Accordingly, in 2016 the FDA issued *“Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications Using the eCTD Specifications.”* This guidance (and its technical appendices) defines how to organize eCTD content for all submission types under §745A(a) (www.fda.gov). It directs sponsors to use the **CDER/CBER eCTD specifications (version 3.2.2)** for Modules 2–5, along with an

updated Module 1 specification (v3.3). It emphasizes that after 24 months, submissions for NDAs, ANDAs, and BLAs must be eCTD (as regulation codified), and FDA expects similar transitions for INDs and Master Files (www.fda.gov).

In practice, the FDA phased in eCTD: on May 5, 2017, eCTD became mandatory for all new NDAs, ANDAs and BLAs, and May 5, 2018 extended the requirement to commercial INDs and Master Files (MFs); noncommercial INDs (such as investigator-sponsored and expanded-access INDs) and Type III Master Files remain optional for eCTD (www.fda.gov) (www.fda.gov). Since then, virtually all US drug submissions (and post-approval supplements) arrive electronically. The FDA provides extensive technical guidance: the **eCTD Technical Conformance Guide** explains envelope structure, naming and XML schema usage; validation criteria files list the checks run at the FDA Electronic Submissions Gateway (ESG). Key identifiers (e.g. `document-type` attributes) are specified and must align with the submission's intended **application type**. The FDA's online standards page lists every applicable guidance, current version and enforcement dates (www.fda.gov).

Specific requirements in **Module 1 (U.S.)** flow from US law and forms. For NDAs/BLAs, an FDA Form 356h (application form) must be included, typically as part of the administrative PDF in the M1 "application dossier" folder. The cover letter and Form 356h are provided as documents in Module 1, while the separate US regional XML (us-regional.xml) carries administrative attributes such as `<application-type>` (NDA/ANDA/BLA), `<submission-type>` (original, amendment, etc.), and `<submission-sub-type>` (e.g. efficacy supplement) to identify the kind of filing. As Extedo notes, the US eCTD includes this "application form within the administrative envelope part" (www.extedo.com). Other U.S.-specific documents (environmental assessments, patent certifications, etc.) have prescribed places in Module 1 as defined by FDA guidance.

In **Modules 2–5**, the US eCTD follows ICH format but adds FDA-specific extensions. Notably, the FDA requires *Study Tagging Files (STFs)*: XML metadata files that index individual nonclinical/clinical study documents by ID and version (www.extedo.com). These STFs enable the FDA's software (e.g. in-house reviewer systems) to quickly retrieve all documents for a given study or clinical trial. The FDA has its own Schematron rules: e.g. folder names and permitted file types. FDA runs its own technical validation after a submission is received through the ESG and advises sponsors to validate sequences against its published eCTD validation criteria before submitting, typically using commercial validation software; failures on syntax or missing attributes can cause rejections.

Starting in **Sept 2024**, FDA began accepting **eCTD v4.0** (HL7-based RPS format) for new applications (www.fda.gov). According to FDA, CDER/CBER are now ready to receive v4 content, though forward-compatibility (linking v3 and v4 sequences) is still being developed (www.fda.gov). FDA has not announced a date for v4.0-only submissions and says it will give advance notice before that happens (www.fda.gov); some industry commentators project a mandate around 2029 (globalforum.diaglobal.org). For now, sponsors using eCTD v4 should follow FDA's v4 Implementation Guide (paralleling ICH's specifications) and continue to pass existing validation where possible.

European Union (EMA) eCTD Guidance

In the **European Union**, eCTD submissions are governed by EMA and the European Commission. Even before eCTD, EMA developed electronic methods, but it is widely documented that **since 1 January 2010, eCTD is the only acceptable electronic format for all centralised marketing-authorisation applications** (www.pharmtech.com). The PharmTech journal reported that “from 1 January 2010, the Electronic Common Technical Document (e-CTD) format will be mandatory for marketing authorisation applications” in the EU (www.pharmtech.com). Before 2010 EMA pilot-tested eCTD (accepting some dossiers in 2008) and strongly recommended electronic files in 2009. After 2010, all new and existing centralised applications must be eCTD (no paper or NeeS).

EMA provides detailed eSubmission guidance. The **EU eCTD Module 1 specification** (often called “EU M1”) outlines the header envelope and Module 1 folder structure. The EU equivalent of the application form is the electronic Application Form (eAF), which is mandatory for centralised procedure applications and is placed in Module 1 alongside the envelope metadata carried in the EU regional XML (esubmission.ema.europa.eu). Depending on the procedure, Module 1 contains region-specific documents such as the product information (**SmPC**, labelling and package leaflet), GMP-related documentation and other items listed in the “Notice to Applicants” (Eudralex Vol. 2A). Country-specific requirements also apply: for example, variations under the Mutual Recognition or Decentralised Procedures include a “List of Documents” (Annex I), and certain Member States have optional eUpdaters. Significantly, Extedo points out that EU submissions “must include different specific country sections in Module 1 and detailed specific sections for the product information” (www.extedo.com), reflecting the multi-national nature of EU MAs.

Technical specifications for the EU eCTD largely adhere to ICH M2, but EMA publishes validation criterion files and EU-specific stylesheets. While Modules 2–5 follow the harmonized CTD, EMA enforces unique conventions such as QRD templates for the SmPC/PIL. During the eCTD process, applicants use the **EMA Gateway** (now EudraLink 2/eSubmission Gateway) to send encrypted packages to EMA (and relevant National Competent Authorities). EMA’s *Dossier Requirements for Centralised Procedure* outline any post-authorisation eCTD sequence rules (e.g., handling of variations, renewals). Notably, once an EU product enters the eCTD lifecycle, all subsequent submissions (variations, renewals, PSURs) must also use eCTD format through that lifecycle (www.ema.europa.eu).

EMA continually updates its guidelines. In 2024–2025, several revisions to the EU Module 1 specification were announced: e.g. EU M1 v3.1 (mid-2024) and v3.1.1 (late-2025) with new tracking tables and file-format allowances (esubmission.ema.europa.eu). The related **EU eCTD Validation Criteria** were likewise updated (e.g. v8.0–v8.2). All EU-bound eCTDs in a given transition period must comply with the designated versions (for example, as of Dec 2024, only M1 v3.0.4/v3.1 and Validation Criteria v7.1/v8.0/v8.1 were accepted (esubmission.ema.europa.eu)). Applicants are expected to download the latest EU eCTD Module 1 XSD and stylesheet from EMA’s eSubmission website and validate their sequences accordingly.

Looking ahead, the **EMA has begun piloting eCTD v4.0**. In December 2024, EMA announced a multi-step pilot involving software vendors and volunteer applicants. In a 15 December 2025 announcement, EMA confirmed that it will **optionally** accept new Centralised MAA submissions (for CAPs) in eCTD v4.0, with applicants asked to contact its eCTD v4.0 team beforehand (esubmission.ema.europa.eu). This means

sponsors may choose to file v4.0 dossiers from 22 Dec 2025 onward, but v3.2.2 remains acceptable too (esubmission.ema.europa.eu). The EMA advises companies to ensure their authoring tools support the EU-specific v4.0 package (with updated vocabularies and schemas) (esubmission.ema.europa.eu). Loebel (2025) projected mandatory use by 2027, but EMA's July 2026 update sets strongly recommended use from Q1 2027 and **mandatory** use for new CAP MAAs from Q1 2028, while the timeline for products with an existing eCTD v3.2.2 lifecycle is still to be confirmed (esubmission.ema.europa.eu) (globalforum.diaglobal.org). EMA cites eCTD v4.0 as a step toward "a more harmonised and efficient electronic submission environment, offering enhanced metadata structures, improved lifecycle management, and greater interoperability with global authorities" (esubmission.ema.europa.eu).

Case Example - Europe vs. Australia eCTD

A **clinigen** case study illustrates regional conversion: a European company with an EU-format eCTD dossier sought to file in Australia. Clinigen ensured compliance by *converting* the EU eCTD to the Australian eCTD format (www.clinigengroup.com). This required re-mapping Module 1 content (e.g. inserting Australian-specific cover letter data and product identifiers) and meeting TGA technical specs. It underscores how even though eCTD is "common," each region's M1 and validation rules can necessitate significant adjustments for multi-region filings.

Japan (PMDA) eCTD Guidelines

Japan's **PMDA** mandates eCTD for drug regulatory submissions. Japan actively participated in ICH and adopted the CTD format early. The PMDA issues detailed eCTD guidance (notifications and guidelines, often updated) for various submission types. In practice, application dossiers to PMDA (including new NDAs, Japanese Clinical Trials Module changes, etc.) must be converted into eCTD format with Module 2–5 following ICH structure. Japan requires certain unique practices: for example, each eCTD sequence submission is treated as a standalone regulatory action (there is no concept of "incremental IND;" a new submission number starts each time).

Module 1 (Japan) has its own features. PMDA uses an **'eCTD receipt number'** (analogous to NDA number) which, combined with a submission sequence number, forms a `<doc-id>` in the M1 XML. In one Japanese Q&A, PMDA instructs that `<doc-id>` be formatted as "eCTD受付番号–提出番号" (eCTD reception number + submission number, e.g. *******-0001) (www.pmda.go.jp). This identifier is fundamental to linking eCTD versions in PMDA's system. Extedo notes that PMDA's lifecycle is strict: "the lifecycle of a dossier contains only one regulatory activity and starts newly with the next regulatory activity" (www.extedo.com). In practice, that means every new submission (like an addendum or variation) is a wholly new eCTD application rather than an update in place.

Japan also has a specialized format for **Drug Master Files (DMFs)**. Instead of submitting a DMF in the standard eCTD Drug CMC sections, Japan requires DMFs in a separate **CTD-DMF format** (a CTD structured dossier specifically for master files) (www.extedo.com). This reflects PMDA's regulatory framework where DMFs are reviewed in parallel with applications.

PMDA provides Japanese-language guidelines; however, an English summary **“Approval Application with eCTD”** is published (last updated Mar 2025 (www.pmda.go.jp)). These documents specify directory structures, XML tag rules, and required M1 components (e.g. cover letters, meeting minutes, import/export certificates as needed). While no separate form like FDA 356h exists, Module 1 must still include an annotated cover letter, CVs of overseas investigators when relevant, and other Japan-specific annexes.

Notably, Japan is among the earliest movers to eCTD v4.0. PMDA began accepting eCTD v4.0 for applications from April 2022, accepted v3.2.2 for applications up to March 2026, and planned to accept only v4.0 for applications from April 2026 (www.pmda.go.jp) (globalforum.diaglobal.org). Projected adoption is fast because of PMDA’s practice that each regulatory action is a new eCTD: they can enforce v4.0 immediately for new applications or variations. Japanese sponsors should thus align with Japan’s eCTD v4 “domestic implementation guide” to prepare their submissions.

Canada (Health Canada) eCTD Guidance

Health Canada requires electronic submissions for drug applications, using the electronic CTD (eCTD) or an approved alternate e-format. The official Health Canada page *“Filing submissions electronically”* states that companies must file submissions electronically “in either eCTD format or non-eCTD format, depending on the regulatory activity type” (www.canada.ca). In practice, eCTD is the expected format for most human drug marketing submissions (e.g. NDS and SNDS), while clinical trial applications and amendments may be filed in eCTD or non-eCTD format. Health Canada provides specific *Canadian Module 1 (CM1) specifications*, including an **Implementation Guide** and an XML Schema (e.g., “Canadian Module 1 Schema v2.2” (www.canada.ca)). The CM1 guide details how to organize company/product information, forms, and lists of administrative documents in Module 1. For example, Module 1 must include a Summary of Original Submission (cover letter), product monographs (English/French), and any bilingual labelling.

Canada also requires use of the **Common Electronic Submissions Gateway (CESG)**, launched in Jan 2017, as the transmission method. Most eCTD and non-eCTD transactions are filed through the CESG, although Health Canada permits other routes for some activities (for example, clinical trial applications) (www.canada.ca). For NDAs and SNDS, companies must request a *“dossier identifier”* in advance. In Canadian Module 1, sponsors must use the *Regulatory Enrolment Process (REP)* codes to classify the submission type (human drug, biologic, veterinary). Health Canada publishes **Validation Rules** (XML Schematron) that mirror FDA’s concept: it automatically checks M1 attributes (e.g. `<submission-type>`, `<submission-phase>`) and the presence of required elements. A 2025 update to these validation rules was issued by HC (www.canada.ca).

Some Canada-specific eCTD requirements include interactions with HC’s bilingual context. Canada’s required forms are specific to the regulatory activity (for example, dossier ID requests and, for Master Files, Health Canada’s Master File application form), rather than one universal form for all e-submissions (www.canada.ca); industry guides also note attestation requirements for certain Canadian submissions (www.extedo.com). Sponsor and product data are also captured through the Regulatory Enrolment Process (REP) and Module 1 documents.

Health Canada transitioned gradually. In 2018, HC issued a notice proposing to make eCTD mandatory for Master Files; current Health Canada guidance states that all new Master File registration transactions have been required in eCTD format since January 1, 2020, while some existing non-eCTD Master Files may continue in that format (www.canada.ca) (www.canada.ca). That notice cited that *"eCTD format will progressively become mandatory for the majority of dossiers and activities"* (www.canada.ca). Essentially, before 2017 many submissions were paper, then via NES (NeeS) system, but by 2020 virtually all new drug applications to HC were filed electronically. For legacy DMFs, HC requires that all new transactions (updates, LOAs, responses) be in eCTD once a MF has ever been e-submitted (www.canada.ca).

China (NMPA) eCTD Guidelines

China's National Medical Products Administration (NMPA) has historically been **paper-based**, but has moved aggressively toward eCTD. In November 2022, the NMPA announced plans to require **electronic submission of drug registration applications** (initially proposed from December 1, 2022); the final NMPA notice set the effective date at January 1, 2023, effectively ending paper submissions for the applications it covers. Electronic filing is distinct from the eCTD format, which remains optional in China (www.pharmalex.com). This shift applies to New Drug Applications and related filings. The NMPA simultaneously issued draft technical guidelines: one on *"implementation of electronic submission"*, another on *"electronic document structure"*, plus others on DVD/CD optical disk format and documents of commitment (www.pharmalex.com). Industry had only weeks to review these guidelines. Even though eCTD (ICH form) is not explicitly mandated yet, China's CDE has been gradually implementing an eCTD-like process: since Sept 2021, eCTD is accepted for certain INDs and NDAs of pharmaceuticals and biologics (www.pharmalex.com), and many foreign firms must adapt to Chinese eCTD rules when registering locally.

Key Chinese requirements include **language and formatting**. By law, the submitted modules (including Parts II–V) must be in Chinese language, with English allowed as a secondary reference (www.extedo.com) (e.g. "Chinese language documents are legally binding in M2–M5; English versions may be included as second docs" (www.extedo.com)). This is a major departure from ICH norms: global sponsors must prepare dossiers in Chinese or have translations. Document files must be official PDFs with bookmarks and hyperlinks. The recent NMPA guidelines emphasize technical PDF quality (no scans without text), max file sizes, and ISO metadata embedding. The process will use an "electronic DVD" (or upload via the new CDE submission portal) as delivery. PharmaLex commentary notes that small domestic firms that still submit paper will now struggle to convert their documents to the required ePDFA standard under tight deadlines (www.pharmalex.com).

China's e-submission ecosystem is evolving: English versions of the guidelines are being prepared, and corporates are waiting for final rule publication. In practice, companies already sending eCTD to the US/EU can reuse content, but must add Chinese documents (e.g. Chinese SmPC, Chinese IRB certificates, etc.). The transition in China illustrates how regulators outside ICH are mapping the ICH/eCTD framework onto local infrastructure. For now, China's eCTD remains in a nascent state, but the December 2022 mandate signals that by the late 2020s China will be fully eCTD-driven for NDAs and placeholders.

Australia (TGA) eCTD Guidelines

Australia's Therapeutic Goods Administration (TGA) also mandates electronic submissions for most regulated medicines. According to TGA's guidance pages, **"you must submit all prescription medicine applications (including master files) in eCTD format"** (www.tga.gov.au). Non-prescription and general biologics can also use eCTD but are not strictly required to. TGA originally used an earlier scheme (NeeS) but has now moved entirely to eCTD for prescription products.

To assist sponsors, the TGA publishes detailed guides. For example, it provides a *"CTD Module 1: Administrative information and prescribing information for Australia"* document (www.tga.gov.au) and *"TGA Module 1 specifications for eCTD submissions."* Module 1 (Australia) has its own structure: it includes forms like the *"Application ATS134QN"* (Australian application form), a TGA eCTD cover letter, and information such as Australian Product Number (APN), PBS listing status, and local clinical trial numbers. Australian regional files sit in the "au" Module 1 folder with an au-regional.xml file. All cover letters must include an "e-ID" (electronic identifier) assigned by TGA to the active agent, as well as sequence numbers consistent with the XML. The guidance requires sponsors to request an e-ID prior to submission (www.tga.gov.au) and to transmit sequences by one of the routes TGA accepts (the route depends on submission size).

Like other regulators, the TGA provides technical specifications and validation rules. TGA's eCTD v3.2.2 validation criteria are largely aligned with ICH, but the M1 XML schema is Australia-specific. The TGA guide includes specific tips (e.g. cover letter content, recommended file naming) and enforces certain data fields in the "coordination.xml" structure of the envelope. Sponsors must also ensure the PDF leaflet and SmPC conform to TGA templates (similar to EU QRD but with minor differences).

Looking forward, Australia is actively planning eCTD v4 adoption. The TGA has released an Australian eCTD v4 Module 1 specification (draft, updated July 2025) (www.tga.gov.au), for a technical pilot; TGA has not set a production transition date and notes that dates may change. Industry sources reported pilot plans for 2025 (globalforum.diaglobal.org). In short, Australian biopharma companies must already use eCTD (with proper Module 1 formatting) for prescription products (www.tga.gov.au), and should be preparing for the new HL7-based format in the near future.

Regional Comparisons and Data Summary

A number of sources have compiled **comparisons of regional eCTD requirements**. Table 1 below summarizes key points for major regions (authorities, eCTD mandate date, and guidance references):

Region	Regulatory Authority	eCTD Mandatory (since)	Guidance / Specifications
USA	FDA (CDER/CBER)	Mandatory for NDA/BLA/ANDA by 05/2017; commercial INDs and MFs by 05/2018 (www.fda.gov)	FDA eCTD Guidance (2016) (www.fda.gov); Technical Conformance Guide (www.fda.gov)

Region	Regulatory Authority	eCTD Mandatory (since)	Guidance / Specifications
EU (EMA)	EMA (Centralised Procedures)	Mandatory by 01/2010 (www.pharmtech.com) (EMA publishes eCTD M1 v3.x)	EMA eSubmission Guidelines; EudraLex Vol.2A (eCTD specs)
Japan	PMDA	eCTD accepted for new drug applications; v4.0 accepted from 04/2022 and planned as the only accepted format from 04/2026 (www.pmda.go.jp) (globalforum.diaglobal.org)	PMDA eCTD notifications (Japanese); CTD-DMF spec (www.extedo.com)
Canada	Health Canada	Mandatory for most dossiers (eCTD Gateway mandatory since 2017 (www.canada.ca))	Health Canada eCTD Guidance (Module 1, v4.0 draft); REP protocols (www.canada.ca)
China	NMPA/CDE	Electronic submission mandatory from 01/2023 (announced 11/2022) (www.pharmalex.com) (eCTD voluntary previously)	NMPA eCTD Guidelines (draft 2017–2022)
Australia	TGA	Mandatory for prescription drugs (per TGA guide) (www.tga.gov.au); eCTD v4 pilot planned for 2025 (globalforum.diaglobal.org)	TGA eCTD User Guides (CTD M1, technical spec)
UK	MHRA	eCTD used for marketing authorisation applications, including International Recognition Procedure (IRP) applications and lifecycle (www.gov.uk)	MHRA eCTD Guidance and Information Management (2021+)
Others	Various (Swissmedic, MFDS, HSA…)	Switzerland (eCTD for MAs since ~2015), South Korea/ASEAN (eCTD accepted/mandated) (globalforum.diaglobal.org)	National guidelines (often EU-aligned); ICH M4/M2 generally

Sources: FDA guidance and rule (21 CFR 314/745A) (www.fda.gov); EMA and national publications (www.pharmtech.com) (www.gov.uk); PMDA and Health Canada notices (www.canada.ca) (www.canada.ca); industry analyses (www.extedo.com) (www.pharmalex.com).

Table 2 outlines the emerging **eCTD v4.0 implementation timeline** as known:

Region/Authority	eCTD v4 Optional Use	Projected Mandatory Use	Notes
USA (FDA)	Accepted for new apps since Sep 16, 2024 (www.fda.gov)	No FDA date announced; FDA will give advance notice (www.fda.gov); industry projection 2029 (globalforum.diaglobal.org)	v4.0 Implementation Guide published by ICH; forward compatibility pending
EU (EMA CAP)	Optional use from 22 Dec 2025 (esubmission.ema.europa.eu)	Strongly recommended from Q1 2027; mandatory for new CAP MAAs from Q1 2028 (esubmission.ema.europa.eu); earlier industry forecast 2027 (globalforum.diaglobal.org)	EMA piloting with vendors; CAP MAA only initially
Japan (PMDA)	Accepted from April 2022 (www.pmda.go.jp)	Only v4.0 accepted for applications from April 2026 (planned) (globalforum.diaglobal.org)	v3.2.2 accepted for applications up to March 2026

Region/Authority	eCTD v4 Optional Use	Projected Mandatory Use	Notes
Canada (HC)	Pilot planned for 2025 (globalforum.diaglobal.org)	TBD	Health Canada hasn't announced final plan; 2025 pilot per ICH
Australia (TGA)	Technical pilot (industry sources reported 2025; TGA dates subject to change) (globalforum.diaglobal.org)	TBD	TGA released draft M1 spec (Jul 2025) (www.tga.gov.au)
Other (ANVISA, Swiss)	Pilots: ANVISA/TQ3 in 2024 (uncertain); Swiss pilot planned 2026 (globalforum.diaglobal.org)	TBD	Multiple agencies (ANVISA, Swissmedic) have plans or drafts for 2026-28

These data show that **by the late 2020s all ICH regions** anticipate moving to eCTD v4.0, leveraging its HL7-based architecture for improved interoperability and lifecycle management (esubmission.ema.europa.eu) (globalforum.diaglobal.org).

Case Studies and Industry Perspectives

Practical experiences underscore the importance of regional guidelines. One case involves Clinigen's support of an *Australian filing*: a European orphan-drug company had initially prepared an EU eCTD for EMA; Clinigen then **converted** it to Australian format to comply with TGA rules (www.clinigengroup.com). This required adjusting Module 1 details (such as inserting the Australian e-ID and signatures, reordering documents into TGA's folder structure) and validating against TGA's M1 specification. It highlights that "know your region" is crucial: even among ICH members, failure to account for a single country's requirements can lead to rejections.

As an illustrative (hypothetical) scenario, a US ANDA sequence can fail FDA technical validation if the application type or number in the us-regional.xml does not match the required Form 356h, and an EU sequence can be flagged for envelope metadata errors such as an incorrect language code. These illustrate how small metadata/format misalignments can provoke validation failures. Surveys (e.g. by consultancies) consistently report that eCTD publishing errors are often due to neglecting regional Module 1 rules or validation criteria. For instance, a sponsor must include the activity-specific Canadian forms and Module 1 documents that have no FDA equivalent (www.extedo.com) and not omit it as they would under FDA rules.

A broader industry perspective is that unified tips/across-regions help. Some companies maintain "submission templates" for each region's M1 and use regulatory information management (RIM) systems to flag differences. The importance of early planning is emphasized in guidance: for global filings, project teams often assemble region-specific checklists to catch variations. The module 1-centric differences discussed by Extedo (www.extedo.com) (www.extedo.com) underscore this: while eCTD harmonizes content folders M2–M5, administrative data must be tailored.

Overall, the case evidence suggests that global sponsors who leverage common eCTD content (e.g. by translating where needed but reusing scientific modules 3–5) can gain efficiencies; however, regional adaptions (especially Module 1, language, and filing systems) still require dedicated effort.

Implications and Future Directions

The regional eCTD guides have immediate and long-term implications for regulatory strategy:

- **Harmonization vs. Localization:** Country- or region-specific rules (Module 1 forms, local validation rules) mean companies must maintain awareness of multiple guidelines. However, underlying Module 2–5 requirements remain largely ICH-consistent, so data can often be reused across regions. Agencies typically permit national or "local implementation" only in Module 1. Over time, as eCTD v4.0 (HL7-RPS) takes hold, some of these differences may be further abstracted or automated (e.g. by shared controlled vocabularies or by interoperable submission portals).
- **eCTD v4 Transition:** The upcoming migration to eCTD v4.0 is a major focus. All major regulators recognize eCTD v4.0's benefits: it allows a more flexible Table-of-Contents and better tracking of document reuse across submissions (globalforum.diaglobal.org). For instance, eCTD v4 enables a single document (like a Sponsor's Protocol) to be referenced in multiple product dossiers or multiple regions without duplication. In Europe, this could greatly streamline work-sharing (MRP/DCP) and PSUR single assessments by tagging which country each document applies to (globalforum.diaglobal.org). EMA specifically highlighted the enhanced metadata and interoperability of v4.0 for global regulators (esubmission.ema.europa.eu). On the other hand, eCTD v4 adoption poses challenges: agencies and sponsors need updated tools and training, and the lack of a clickable "TOC" can complicate ad-hoc review. Yet most major eCTD software vendors already support v4, and sponsors should seek vendors with strong v4 capabilities (globalforum.diaglobal.org).
- **Broader Digital Trends:** The rise of eCTD is part of a larger digital transformation in regulation. Agencies increasingly integrate eCTD submissions with other electronic systems (e.g. EMA's SPOR for substance/product data, FDA's IDMP pilots). Electronic submission portals (FDA ESG, EMA eSubmission, Health Canada eCTD Gateway, PMDA Gateway, TGA eBSU) are adapting to support two-way communication (e.g. eCTD v4's capability to send review queries back as structured XML). Over time, one can imagine fields like filling status, queries, or approvals being exchanged via these networks. The advanced GUID/UUID schemes of eCTD v4 align well with emerging regulatory ID standards.
- **Global Coordination:** The need to consult *each* guide compels global companies to maintain regulatory intelligence teams. Many firms now publish "global dossiers" but must branch them into local sequences. Health authorities also coordinate (e.g. via ICH's ESTRI working group) to update specifications and vocabularies. Table 2's timeline shows that several ICH agencies have set or projected v4.0 transition dates, although FDA and others have not yet announced v4.0-only dates; convergence should reduce divergent policies over time.

- **Future Implications:** As eCTD becomes universal, the opportunities include faster reviews (paper logistics eliminated) (globalforum.diaglobal.org), easier cross-referencing of data between agencies, and potentially a single global submission framework. However, challenges will remain for niche areas (e.g. ATMPs, device components, requiring hybrid submissions) and for emerging markets adapting from paper. The complexities observed in case studies (e.g. converting EU to AU eCTD (www.clinigengroup.com)) indicate that companies must invest in skilled regulatory publishing teams and robust software. Expert analyses consistently advise thorough validation pre-submission: using validation tools aligned with the target agency's criteria (Lorenz DocuBridge, Extedo Validator, etc.) (www.pharmaregulatory.in).

In summary, **regional eCTD submission guides** reflect a balance: they overlay national rules on a harmonized technical standard. They require detailed attention but also deliver efficiencies. The shift towards universal e-submissions (including advanced eCTD v4.0) suggests that regulatory affairs will increasingly be digital-first, with the potential for further convergence of global filing practices.

Conclusion

The electronic Common Technical Document has profoundly reshaped drug regulation. By codifying how dossier content is structured, it has enabled agencies to process applications with unprecedented efficiency. This report has dissected how *regional submission guides* adapt the eCTD to local needs: from the FDA's integration of Form 356h and study metadata (www.extedo.com), to the EMA's country-specific annexes in Module 1 (www.extedo.com), to Japan's sequential submission lifecycle and DMF format (www.extedo.com), to Canada's bilingual Module 1 and activity-specific form requirements (www.extedo.com) and China's full Chinese-language mandate (www.extedo.com). We have documented that despite a common underlying framework, each jurisdiction enforces its own M1 conventions and technical rules. Global sponsors must therefore navigate a web of guides and use region-tailored submission systems (ESG, Gateway, eCTD Toolkits).

Data and case examples in this report underscore the current state: eCTD is now required or accepted in virtually all major markets (globalforum.diaglobal.org), and submission volumes have skyrocketed (e.g. FDA's 8 million eCTD records by 2022 (globalforum.diaglobal.org)). Looking ahead, all regions are moving toward eCTD v4.0. Early adopters (US, Japan) show the way, and others (EU, Canada, Australia) have concrete plans (globalforum.diaglobal.org) (esubmission.ema.europa.eu). eCTD v4.0 promises to further unify global submissions through standardized XML and controlled vocabularies (esubmission.ema.europa.eu) (globalforum.diaglobal.org). For regulatory teams, the implication is clear: robust multinational submission strategies and modern publishing tools are more critical than ever.

In conclusion, understanding **regional eCTD submission guides** is essential for ensuring compliant, smooth filings worldwide. As regulatory science moves forward, continued harmonization efforts (eCTD v4.0, IDMP, RPS) will coalesce with these region-specific frameworks to create an even more interoperable digital submission environment.

References: Authoritative guidance and analyses were cited throughout. Key sources include FDA guidance documents (www.fda.gov) (www.fda.gov), EMA and MHRA online guidance (www.pharmtech.com) (www.gov.uk), Health Canada publications (www.canada.ca) (www.canada.ca), PMDA notifications (www.pmda.go.jp), TGA guidance (www.tga.gov.au) (www.tga.gov.au), and industry reports (www.extedo.com) (globalforum.diaglobal.org), among others. All claims above are substantiated by these references.

Source links

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