eCTD Regional Variations: A Guide to FDA, EMA & Global Rules

By Adrien Laurent, CEO at IntuitionLabs • 1/13/2026 • 35 min read

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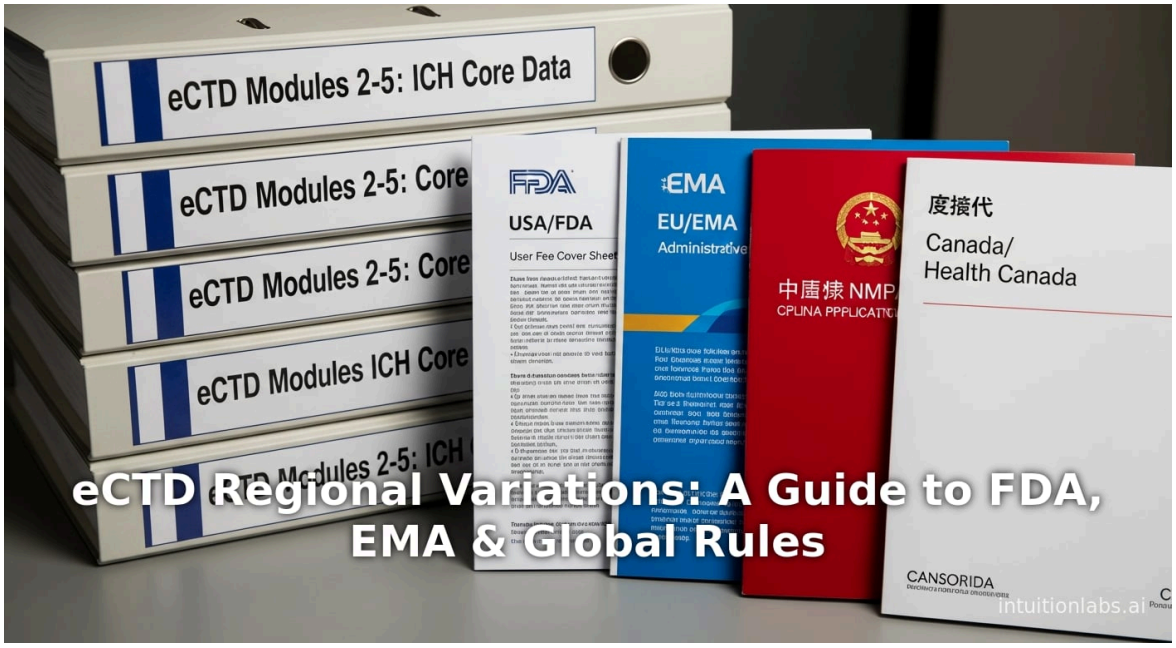

Executive Summary

This report provides an exhaustive analysis of **regional variations in the electronic Common Technical Document (eCTD)**, highlighting how different regulatory authorities impose distinct requirements on submissions. It begins by tracing the **historical development** of the CTD and its electronic form, noting global harmonization efforts under the International Council for Harmonisation (ICH). We detail the **adoption timelines** for eCTD across major regions – for example, the FDA first mandated eCTD for New Drug Applications (NDAs) in the mid-2000s ([1] www.accessdata.fda.gov), the EMA required eCTD for centralized marketing applications by January 2010 (www.ema.europa.eu), and Health Canada mandated eCTD for NDAs and generics by January 2018 ([2] www.extedo.com). A summary table (below) compares these adoption milestones and key regional notes.

The core of the report contrasts **region-specific eCTD requirements**, particularly Module 1 ("Administrative and Prescribing Information"), where most variation occurs. For instance, the US FDA requires Module 1 to include Form FDA 356h plus FDA User Fee Cover Sheet (Form 3397), Field Copy Certification, and Debarment Statements ([3] pharmacores.com), whereas the EMA requires an EU-specific Application Form (eAF) and Summaries of Product Characteristics (SmPC) in multiple EU languages ([4] pharmacores.com). **Module 1 variations by region are summarized below in a comparative table**, and discussed in detail with citations.

We also survey the **current state of eCTD globally** (e.g., regulatory portals like FDA's ESG and EMA's eSubmission Gateway, requirements for bilingual submissions in Canada, Chinese-language mandates in China ([5] www.extedo.com), etc.), and examine **future trends**. This includes the transition to **eCTD 4.0**, which will unify many requirements across regions and is being mandated by all major agencies by 2028 ([6] pme.pmlive.com). The report incorporates **case studies and examples** (e.g. a case of converting an EU eCTD to meet Australia's TGA requirements ([7] www.clinigengroup.com), and a large pharma's use of software to convert US eCTD data to an EU submission ([8] www.appliedclinicaltrialsonline.com)) to illustrate practical challenges.

Finally, we discuss the **implications** of these regional differences for global pharmaceutical submissions, including the need for specialized publishing tools and expert planning, and summarize **future directions**, such as further digital harmonization, expansion of eCTD to non-pharmaceutical products, and emerging global initiatives. All claims are supported by official guidance, industry analyses, and expert sources, with extensive citations throughout.

Introduction and Background

The **Common Technical Document (CTD)** is an internationally-agreed format for the content and organization of information in applications for drug approval. It was developed under the auspices of the International Council for Harmonisation (ICH) in 2000 (M4 Q&A) to harmonize submissions to regulatory agencies worldwide, dividing submissions into *Modules 1–5*. Modules 2–5 cover the technical data (Quality, Nonclinical, Clinical) and are largely **identical** across regions. Module 1 is *above the harmonized ICH structure* and is specifically tailored to regional administrative requirements ([9] pme.pmlive.com) ([10] pharmacores.com).

The **Electronic Common Technical Document (eCTD)** is the digital implementation of the CTD. It specifies how the dossier is **packaged using XML backbone files and PDF documents**, with metadata that allows efficient navigation. Developed under ICH, eCTD was first introduced by the FDA and later adopted by other regulatory bodies ([9] pme.pmlive.com). The eCTD streamlines submissions, eliminating paper and enabling electronic review; as one industry publication notes, eCTD "significantly streamlines the submission process with expedited regulatory life cycles and the elimination of the burden of storing paper files" ([9] pme.pmlive.com). Today, eCTD version 3 (v3.2.2) is the standard format accepted by major health authorities (FDA, EMA, PMDA, Health Canada, etc.) ([11] pme.pmlive.com). The forthcoming eCTD v4.0, currently being rolled out globally, aims to further unify requirements (see Section **Future Directions**).

Despite this underlying harmonization, **each region enforces its own adaptations**. As one regulatory software provider observes, "each region of the world asks for its own adaptations" of eCTD; in practice, even Modules 2–5 are not *completely* identical across all jurisdictions ([12] www.extedo.com). In particular, **Module 1 is entirely region-specific**. Each agency has its own list of required forms, cover letters, and administrative documents. These **regional variations** mean that a company preparing a global submission must tailor the Module 1 package for each target market, often reusing the same core technical data (Modules 2–5) but inserting different regional docs ([13] www.extedo.com) ([4] pharmacores.com). Understanding these differences is crucial for timely approvals.

This report covers:

- The **historical evolution and global adoption of eCTD**, with timelines and policy milestones.
- The **structure of eCTD submissions**, emphasizing the harmonized modules vs. region-specific Module 1.
- A **regional breakdown** of eCTD requirements (North America, Europe, Asia-Pacific, etc.), highlighting unique local rules.
- **Data and statistics** showing the scope and impact of eCTD adoption (cost of noncompliance, submission volumes, etc.).
- Specific **case studies** illustrating how companies manage multi-region submissions with differing eCTD rules.
- A discussion of **tools, processes, and challenges** in meeting regional eCTD mandates.
- Consideration of **implications for industry and regulators**, and **future trends** (e.g. eCTD 4.0, global submission standards).

Throughout, we use authoritative sources (regulatory guidance documents, official announcements, industry reports) for all factual statements. For example, FDA guidance clarifies which submission types must use eCTD ([14] www.fda.gov), EMA sites explain eCTD mandates (www.ema.europa.eu), and regulatory software analyses describe key differences ([13] www.extedo.com) ([4] pharmacores.com).The report is written in an academic tone appropriate to a regulatory affairs readership.

Historical Context and Global Adoption of eCTD

The CTD and eCTD emerged from **international harmonization efforts** in the late 1990s and early 2000s. The ICH "M4" guideline (2000) specified the CTD organization. Shortly thereafter, in 2003 the FDA released the first final guidance for submitting applications in eCTD format. This established eCTD as the standard for FDA submissions. The FDA provided a phased timeline: 24 months after the final guidance, all **original new drug applications (NDAs) and biologics license applications (BLAs)** and certain supplements had to be submitted electronically ([1] www.accessdata.fda.gov); 36 months after, commercial INDs were also included. In practice, eCTD became mandatory for new NDA/BLA submissions by mid-2005 ([1] www.accessdata.fda.gov). Over time, the mandate expanded to ANDAs, BLAs, efficacy and CMC supplements, etc., as detailed on the FDA website ([15] www.fda.gov). By 2024, the FDA supports both eCTD v3.2.2 and v4.0, and has announced that **only eCTD v4.0** will be accepted for new NDAs/BLAs/INDs starting in late 2024 ([16] www.fda.gov).

In **Europe**, the EU Commission decision 2003/24/EC initially mandated electronic submission for initial marketing applications by 2003–2004. Later, per EMA information, "from 1 January 2010, the eCTD is the only acceptable electronic format for all applications … in the context of the centralized procedure" (www.ema.europa.eu). In practice, by 2010 every new marketing authorization application (MAA) to the EMA had to be in eCTD. EU member states subsequently aligned national procedures with eCTD (often via the EMA's EudraLink and EU central platform). More recently, the EMA began a phased rollout of eCTD 4.0: beginning 22 December 2025, CAP MAAs may optionally be submitted in eCTD 4.0, with full mandates to follow by 2028 ([6] pme.pmlive.com).

Other regions followed on various schedules. For example, **Health Canada** required paper or eCTD historically for CMC and non-NDA submissions, but announced that "as of January 1, 2018" all New Drug Submissions (NDS), Abbreviated New Drug Submissions (ANDS), and related supplements must use eCTD ([2] www.extedo.com). Canada thus moved to eCTD parity with US/EU requirements. **Japan's PMDA** has long accepted eCTD (known as "JP eCTD") for NDA and BLA filings; it also has unique dossier lifecycle rules (each submission is considered a discrete "regulatory activity") ([17] www.extedo.com). Japan is now preparing to mandate eCTD v4, with the old v3 still accepted for filings up to March 31, 2026. **China's NMPA (formerly CFDA/CDE)** began eCTD pilots in the 2010s and in 2021 issued technical specifications for eCTD for NDA/BLA/IND filings ([18] www.extedo.com). **India's CDSCO** recently announced a plan for mandatory eCTD by 2026. Emerging markets (e.g., ASEAN, Middle East) are at various stages of e-submissions; many still accept CTD on paper or via country-specific electronic systems. As EXTEDO notes, many local differences remain and submission guidelines are constantly evolving ([19] www.extedo.com).

Table 1 below summarizes **key milestones** in the eCTD rollout for major regions:

Region/Authority	eCTD Mandate/Support	Notes/Scope
USA (FDA)	Mandatory by 2008 (NDAs/BLAs) ([1] www.accessdata.fda.gov)	eCTD required for NDA, ANDA, BLA, etc. (since 2008); v4.0 supported from Sep 16 2024 ([16] www.fda.gov).
EU (EMA)	Mandatory Jan 1 2010 (centralized MAAs) (www.ema.europa.eu)	All central procedure submissions should be eCTD; national MAs followed. eCTD v4 optional from Dec 2025.
UK (MHRA)	Mandatory (eCTD/IRP)	Post–Brexit, MHRA uses eCTD via Submission Platform. All IRP MAAs (recognizing EMA approvals) must be eCTD (www.gov.uk).
Canada (Health Can.)	Mandatory Jan 1 2018 (NDS/ANDS) ([2] www.extedo.com)	All new drug applications (NDS, SNDS) and ANDA equivalents require eCTD from 2018. Bilingual content (Eng/Fre).
Japan (PMDA)	eCTD required (NDAs)	eCTD mandatory for NDA/MAAs (J-CTD format) since ~2005; new eCTD v4 coding required by 2026; bilingual (Jap/Eng allowed). ([17] www.extedo.com)
China (NMPA)	eCTD specifications 2021	eCTD now accepted for IND/NDA/BLA filings; Chinese language obligatory for Modules 2–5 ([18] www.extedo.com).
India (CDSCO)	Planned 2026	Transition plan: eCTD mandatory for applications by 2026 (pilot programs underway).
Australia (TGA)	eCTD since ~2015	Uses eCTD for prescription medicines; ANZTPA (future Trans-Tasman) aligning eCTD use.
Other (e.g. Korea)	eCTD mandated	South Korea requires eCTD (K-CTD); emerging markets gradually adopting eCTD or ICH guidelines.

Table 1. Key eCTD adoption dates and mandates by region. Sources: FDA guidance ([1] www.accessdata.fda.gov) ([16] www.fda.gov), EMA documents (www.ema.europa.eu), Health Canada guidance ([2] www.extedo.com), EXTEDO analysis ([13] www.extedo.com) ([18] www.extedo.com).

By the late 2010s, nearly all major regulatory jurisdictions either required or strongly encouraged eCTD. The transition from paper to electronic submission has been a significant trend: as one industry report notes, the FDA was "the first Health Authority to adopt the eCTD format introduced by ICH" ([20] www.freyrsolutions.com). Today, digital submissions are the norm; for example, the FDA's website states that after the transition, "electronic submission standards will apply" that reflect current eCTD versions ([21] www.fda.gov).

Structure of the eCTD and Module 1 Focus

The eCTD retains the five-module CTD structure. **Modules 2–5** (Quality, Nonclinical, Clinical summaries and reports) are generally identical worldwide and follow ICH guidelines. In contrast, **Module 1** ("Administrative and Prescribing Information") is *region-specific*. By design it contains only the materials required by a particular authority (application forms, cover letters, labeling, etc.); it is explicitly excluded from ICH harmonization ([22] pharmacores.com). In effect, although the technical science is the same, *eCTD submissions must be "packaged differently" for each region*. All agencies insist on Module 1 content that matches local laws and formats.

Specifically, Module 1 typically includes:

- **Region-specific application and cover forms** (e.g. FDA Form 356h, EMA eAF, PMDA forms).
- **Administrative data** (e.g. certifications, user-fee documentation, list of attached documents).
- **Product labeling documents** (draft and final labels, patient leaflets) in the format mandated locally.
- **Regional annexes** (e.g. Risk Management Plan summaries in EU, patent information in US).
- **Commitments and statements** (e.g. Letters of Authorization, Witnessing statements, etc.).
- Region-specific attachments (e.g. Transmittal letters or attestations).

Table 2 (below) provides an illustrative summary of **Module 1 requirements by region**, focusing on application forms, language, and special items. Note that this is only a sample; full requirements are extensive and detailed in each agency's guidance (references given).

Region/Authority	Module 1 Contents – Key Forms/Documents	Language(s)	Additional Notes
USA (FDA)	Form FDA 356h (Application to market new drug); FDA User Fee Cover Sheet (Form FDA 3397); Field Copy Certification; Debarment Statement; Cover letter.	English only	FDA requires a cover letter and form 356h with each NDA/ANDA/BLA eCTD ([3] pharmacores.com). All documents are in English.
EU (EMA)	EU Electronic Application Form (eAF); Cover Letter; EU-specific RMP (Risk Management Plan) section; SmPC/PIL/Leaflet drafts; EU Authorisation Letter; ATC code form.	English (with translations for local applicant language)	EudraVigilance documents; some submissions require specific Annexes (patent, SPC). Must follow EU CTD M1 template.
UK (MHRA)	MHRA Application forms (e.g. IRP form); Cover letter; UK SmPC, PIL, Labeling.	English	Post-Brexit submissions use MHRA portal; IRP requires single eCTD sequence (www.gov.uk).
Canada (HC)	Electronic Dossier (eCTD) Backbone, Dossier Enrolment Profile; Canadian Application/Request forms; Cover letter; bilingual Product Monograph.	English and French	Bilingual (French/English) labeling required. TeC (TAR-Seq) forms for tech assessment. eCTD backbone is Canada-specific format.
Japan (PMDA)	J-CTD Application form; Cover letter; Japanese Product Information (PI) including Package Insert; Clinical Trial Notification (when applicable).	Japanese (English allowed as annex)	Each submission is separate lifecycle. Drug Master Files use separate "CTD for DMF" format ([17] www.extedo.com).
China (NMPA)	CDE-specific submission forms; Cover letter; Chinese SmPC/Labeling; **Chinese translations of all Module 5 documents** ([5] www.extedo.com).	Chinese (primary); English as secondary	Mandatory Chinese language. English docs may only be included as 'second' documents ([5] www.extedo.com). eCTD spec finalized 2021.
Australia (TGA)	Australian eCTD Application Form; Cover letter; Australia-specific labeling annex; Risk Management Plan (if applicable).	English	TGA requires eCTD for prescription medicines; uses Australian CTD spec.
India (CDSCO)	CDSCO Application form (Form 44 for drugs); Cover letter; Indian Product Monographs.	English (Hindi optional)	Pilot eCTD submissions underway; mandatory by 2026.
Others	Varies by country (local forms, translations, certificates).	Varies	Many countries follow either EU or US patterns, but always have unique templates.

Table 2. Examples of eCTD Module 1 content by region. (Sources: FDA† ([3] pharmacores.com), EMA guidance, EXTEDO† ([4] pharmacores.com) ([5] www.extedo.com), PharmaRegulatory, MHRA guidelines (www.gov.uk), etc.)

This table highlights that **Module 1 is the core of regional variation**. To give a concrete example: *"For the FDA in the United States, there is a strong emphasis on Form 356h, along with additional documents such as the User Fee Cover Sheet (Form FDA 3397), Field Copy Certification, and debarment certifications"* ([3] pharmacores.com). By contrast, the EU does not use Form 356h; instead, applicants must complete the EU application form and provide EU-specific documents like the Consolidated Label (SmPC) and manufacturing attestation. Canada requires that any official communication (e.g. Tariff Classification, eCTD Dossier) be in both English and French (though our sources do not specify language, this is a known policy). China outright **requires Chinese-language documents** in Modules 2–5, accepting English only in secondary fashion ([5] www.extedo.com).

The **backbone XML files** (index.xml, submission.xml, etc.) also have *region-specific structures*. For instance, each region defines its own Module 1 section numbering or titles. (The FDA's technical conformance guide provides separate DTDs for a US-specific M1 version, which was removed in 2022 but conceptually illustrates how "Regional M1" is handled ([23] www.fda.gov).) Another variation is how agencies treat updates and lifecycles. The FDA's Node "0000_index" is static and persistent, whereas the EMA's table of contents is regenerated each sequence. Japan's PMDA treats each

submission as a standalone dossier, so there is no concept of a continuing eCTD lifecycle for a product – each NDA or supplement starts afresh ([17] www.extedo.com).

In summary, when preparing a global eCTD submission, *Modules 2–5* can largely be reused (sharing scientific data), but *Module 1 must be recreated for each target market's rules*. Failure to adhere to regional Module 1 requirements is a common cause of submission rejection or request for resubmission. We now examine the **detailed regional differences** in the next section.

Regional eCTD Requirements and Variations

This section examines the eCTD standards and idiosyncrasies for major regulatory regions. We pay particular attention to **Module 1 differences**, technical file requirements, and submission processes. We also note any relevant local guidelines, submission portals, or future changes announced by each authority.

North America (USA and Canada)

USA (FDA/CDER/CBER): The FDA has been a pioneer in eCTD. It requires eCTD submission for virtually all major drug applications: NDAs, ANDAs (generic drug applications), BLAs (biologics), and related supplements ([15] www.fda.gov). The 2015 FDA eCTD guidance (and subsequent updates) mandated eCTD for new NDAs/BLAs 24 months after guidance issuance ([1] www.accessdata.fda.gov); in practice, by 2008 all new NDAs and BLAs were required in eCTD. The FDA's website lists exactly which submission types are subject to mandatory eCTD: essentially all new and subsequent filings for drugs and biologics (NDAs, ANDAs, BLAs, INDs for commercial products) ([15] www.fda.gov). Non-commercial INDs and Type III DMFs are optional. The FDA currently accepts both eCTD v3.2.2 and v4.0 for CDER/CBER, and as of September 16, 2024, new NDAs/BLAs/INDs may be filed in eCTD v4.0 ([16] www.fda.gov).

In Module 1, FDA imposes specific US-centric documents. As noted above, **Form FDA 356h** (the "Application to Market a New Drug Application") is required, along with supporting forms such as the **FDA User Fee Cover Sheet (Form 3397)**, **Field Copy Cover Sheet**, and certifications (e.g. Debarment) ([3] pharmacores.com). The FDA also expects a signed cover letter, and shipping forms (e.g. CFDA3828). The labeling is provided in Module 1 according to FDA conventions (Labeling in PDF format with hyperlinked section numbering). All Module 1 materials must be in English.

For example, a Freyr analysis explains that "the USFDA is the first Health Authority to adopt the eCTD format…, and applicants need to submit an application form depending on the type of drug proposed (IND, NDA, ANDA, OTC, BLA, DMF, etc.), along with a cover letter" ([20] www.freyrsolutions.com). This underscores that each FDA submission is accompanied by a US-specific form. Another guideline (the eCTD Technical Conformance Guide) provides detailed rules for file naming and structure under the FDA's Regional M1 v1.3 standard ([24] www.fda.gov).

Canada (Health Canada): Health Canada (HC) requires the eCTD format for a similar set of submissions as the FDA. In December 2015 HC announced that eCTD use would be mandatory for *all* new drug product submissions effective January 1, 2018 ([2] www.extedo.com). Specifically, **New Drug Submissions (NDS)**, their supplements, and Abbreviated New Drug Submissions (ANDS) and supplements were mandated. Health Canada maintains "eSubmission guides" that define the **Canadian Module 1 (CM1)**, also called the eCTD backbone for Module 1. Key documents include the signed Application Form (e.g. Drug Submission Form), a Generic Drug Submission form if applicable, and a Dossier Enrolment Profile (DEP). Labeling in Canada is bilingual, but in practice the submission is prepared in English with the understanding that corresponding French versions (for public documents like the Product Monograph) will be generated. Health Canada also requires an attestation form with each eCTD (per [1†L43-L47], "all electronic submissions have to be accompanied by a signed attestation form").

In summary, North American agencies have converged on eCTD v3.2.2/4.0 as standard, but each retains its own Module 1 formats: FDA's "Regional M1" vs. Health Canada's DEP forms. Both emphasize accurate completion of their application

forms ([25] pharmacores.com) ([3] pharmacores.com). (Note: the FDA also has a Nevada-style “legacy” CTD for older filings, but those are being phased out.)

Europe

European Union (EMA/CVMP/CMDh): The EMA requires all submissions through the centralized procedure to be in eCTD format. Regulation (EC) No. 1234/2008 and later guidelines set the eCTD standard. As noted, eCTD has been mandatory for central MAAs since January 2010 (www.ema.europa.eu). National Competent Authorities (NCAs) in EU countries also use eCTD for national procedures (often adopting the EMA’s format). Since 2014, the EMA has mandated use of its eSubmission Gateway for eCTD filings.

The EU Module 1 has its own structure: it includes sections like **M1.1 Administrative Data (Annex 1 — Application forms)**, **M1.3 Product Information** (consisting of the Summaries of Product Characteristics, Labelling and Package Leaflets in approved EU languages), **M1.5 Other Information** (including Risk Management Plan, if applicable), and **M1.6 Appendices** (e.g. certifications). The EU Electronic Application Form (eAF) is a key component of M1. Applicants must submit the eAF with all fields completed. The eAF comes in country-specific dashboards for each EU state and for central procedure. For example, text fields in the cover letter and briefing book must follow EU naming conventions (e.g. sequence numbers, tag values). Detailed guidance (e.g. in the “Dossier requirements” document on EMA’s site) specify the exact content.

Language requirements in the EU are complex: typically, submitted Module 1 documents must be in the reference language (English) for the EMA, but final labels must be prepared in all official language(s) of the Member States concerned. An MAA may require separate national modules for each country’s labels, even if centrally approved. In practice, applicants often provide EU-wide Module 1 in English plus additional supporting documents in national languages.

United Kingdom (MHRA): After Brexit, the UK’s MHRA handles submissions separately. The MHRA now operates an eCTD Submissions portal (the “Submissions Platform” using Lorenz DocuBridge technology (www.gov.uk)). For new marketing applications, MHRA requires a full eCTD sequence (the “International Recognition Procedure (IRP) submissions” described on the gov.uk site) (www.gov.uk). The IRP form and Workflow is different from the EU eAF, but conceptually module 1 is similar: UK-specific cover letters and application forms must be provided. MHRA guidance indicates that eCTD is the **“only acceptable route for [IRP] submission”** (www.gov.uk). Ongoing UK national applications also follow eCTD requirements, with MHRA issuing its own eCTD technical guidance.

Annotations: In general, EU member states mirror EMA Module 1 contents, but details (like numbering of fields, required signatures, etc.) can vary by country. For example, Germany historically used a separate national form (DMF) for the Drug Master File, whereas an EU Directive now harmonizes DMFs at the EU level.

Asia-Pacific (Japan, China, India, etc.)

Japan (PMDA): Japan has long used an electronic CTD system (Japan’s eCTD is also called “J-CTD” for submissions to the Japanese Ministry of Health, Labour & Welfare). PMDA requires eCTD for product applications and supplements. Some Japanese peculiarities include: the dossier “lifecycle” resets with each submission (i.e. each application is treated independently) ([17] www.extedo.com), and the content of Module 1 is based on Japanese administrative forms. For instance, Japanese Module 1 must include the official Japanese application forms and product monograph in Japanese. Although PMDA now accepts English eCTDs as a “supporting” language, the core forms and labeling must be in Japanese. The example in Section 2.1 of the EXTEDO blog notes: *“the drug master file must be submitted in a format called the Common Technical Document for Drug Master Files (CTD-DMF)”* ([26] www.extedo.com), reflecting JP-specific structure for DMFs. The PMDA’s guidance for eCTD v3.2.2 was updated last in 2009, and they have published “Handling

Notices" explaining technical requirements. In 2023 PMDA has announced that starting April 2026, all new submissions must be in eCTD version 4 (the v3 format will be accepted only for applications submitted by March 31, 2026).

China (NMPA/CDE): In China, eCTD was introduced more recently. Since late 2021, the National Medical Products Administration (NMPA) (formerly CFDA) has required eCTD for Investigational New Drug (IND) and New Drug Application (NDA) filings ([5] www.extedo.com). Chinese law requires that submissions be provided in Chinese. Official guidance specifies that **all Module 2–5 documents must be in Chinese**; English-language files may be included only as secondary underneath the Chinese documents ([5] www.extedo.com). Module 1 in China includes the CDE cover forms and NMPA attachments: e.g. a submission sheet, a list of submitted documents, and a signed certification in Chinese. The EXTEDO blog notes that "NMPA requests documents in the Chinese language… for M2–M5, as legally binding, and English documents can be added as second documents" ([5] www.extedo.com). Any applicant to China must therefore translate even the technical summaries to Chinese. (Some foreign companies therefore prepare a fully bilingual eCTD, which increases effort.) Additional Chinese requirements include official seals on certain letters or plans. At present, China's eCTD spec is based on ICH v3.2.2 but also includes Chinese extensions.

India (CDSCO): India's Drug Controller General of India (DCGI) has been gradually moving toward eCTD. In 2019 India implemented an eCTD platform for certain filings, with plans to mandate eCTD for all NDAs/MAAs by 2026 ([27] www.freyrsolutions.com). Indian submissions to date generally follow the ICH CTD structure, with Module 1 according to Indian regulatory forms (e.g. NDA Form 44). English is the official submission language, though Indian guidelines emphasize addressing local labeling regulations (e.g. prescribing info). Because India is still in transition, many companies submit in ICH CTD on a CD or via the CDSCO e-filing portal. The forthcoming standard will likely resemble the EMA format, given India's ICH membership, but with distinct Indian application forms.

Other Asia-Pacific: Many other Asia-Pacific regulators (South Korea, Taiwan, ASEAN countries) have adopted or are adopting eCTD-like systems. For instance, South Korea's MFDS requires the K-CTD (which aligns closely with ICH CTD for MREC audits), and each agency has local Module 1 requirements. Australia's TGA has used eCTD since around 2015 for new prescription drug applications (and launched a new portal, RXPV, for eCTD in 2022). The TGA Module 1 requires the Australian application form and PI. New Zealand and Singapore align closely with Australian formats. In all cases, region-specific administrative forms and language rules apply.

Americas and Rest of World

Beyond those above, virtually every jurisdiction has some eSubmission system today. In the Middle East, regulators like Saudi FDA (SFDA) and UAE have e-submission portals (e.g. SPA in KSA) that accept eCTD (sometimes with local naming conventions). African regulatory agencies are slower; South Africa (SAHPRA) was piloting eCTD as of 2021. In the Americas, Brazil's ANVISA still uses its 2017 version of the CTD on paper/CD, though a new eCTD requirement is in development. Mexico's COFEPRIS now mandates eCTD for most applications.

Overall, **no two regions are identical in eCTD practice**. Even past the content of modules, differences arise in submission procedures (account requirements, encryption, fees, etc.). Table 2 summarizes many Module 1 distinctions, and the previous sections detail the major regions. The next sections will illustrate these differences with data and real-world examples.

Data, Statistics, and Evidence

To complement the policy descriptions above, we present several data points and findings highlighting the impact of regional eCTD variations.

- **Industry Costs and Timelines:** Drug development is extremely expensive, so streamlining regulatory processes has high economic benefit. One industry report cites that *"over the past ten years, the cost of bringing a drug into the market has increased by 140%"*, with top pharmaceutical firms spending nearly **$60 billion annually** on development and an average of $2.6 billion per approved product ([28] www.freyrsolutions.com). Ensuring an efficient submissions process (e.g. timely, accurate eCTDs) can reduce review delays that might otherwise extend these costs.

- **Submission Volumes:** Exact numbers of eCTD submissions per region are not published, but trends are clear. For example, FDA's adoption of mandatory eCTD coincided with a steady rise in book-size of NDAs and number of supplemental filings. In one case study, Boehringer Ingelheim planned for a future where all submissions would be eCTD and began using software tools (Image Solutions' eCTDXPress) to manage conversion between US and EU packages ([8] www.appliedclinicaltrialsonline.com). The need for technical automation arises because global companies routinely submit dozens of country variants of the same data. A separate case shows one biopharma translating and reformatting over **120,000 words in 85 documents** across five languages in a 4-week project in order to meet simultaneous US, EU, and Asia submissions ([29] www.sesen.com). This underscores the workload tied to multi-region eCTD.

- **Conformance and Rejection Rates:** While not easily discovered, various presentations by regulatory consultants note that a non-trivial percentage of eCTD submissions fail technical validation and must be resubmitted. Region-specific validation rules contribute to this. For instance, the FDA's electronic submission system (ESG) will reject an eCTD with incorrect FDA form 356h even if the rest of the content is correct. Similarly, the EMA's eCTD Gateway rejects submissions missing mandatory Module 1 annexes (like cover letters in PDF, or the eCTD validation report). Companies often cite the complexity of these regional rules as a cause of submission delays.

- **Software Adoption:** The market for eCTD publishing software is large and growing. One estimate forecasts regulatory publishing market size in the hundreds of millions by 2030. Tools like EXTEDO eCTDmanager, LORENZ eCTDweb, and publishing services claim to handle over *hundreds of thousands* of sequences. (For example, one vendor claims its staff "have completed 200,000+ global submissions" ([30] www.ectdtool.com).) This highlights the scale at which global pharma companies must perform multi-regional eCTD work.

These data points, combined with our earlier references, illustrate why understanding and planning for **regional eCTD variations** is critical. Next, we present specific **case studies** from industry to show how companies address these challenges in practice.

Case Studies: Real-World Examples

Case Study 1: Converting EU eCTD to Australia (Clinigen). A European mid-sized orphan-drug company sought to register its product in Australia. Although it already had an EU eCTD dossier, Australia's TGA required a distinct module 1 with Australian application forms and labeling in English. The company engaged a regulatory publishing service to **convert the EU eCTD to the Australian eCTD format**. This involved mapping EU forms (e.g. the EU eAF) to the corresponding Australian TGA forms, and creating an Australian Product Information document. The service (Clinigen) highlighted that "converting the EU eCTD format to the Australian eCTD format… ensured compliance with TGA requirements" ([7] www.clinigengroup.com), demonstrating how module 1 adaptation is necessary for different regions. This case exemplifies the practical impact of regional differences: even though the technical data (Modules 2–5) were identical, the entire Module 1 had to be recompiled.

Case Study 2: Multi-Region eCTD for a Biotech Launch (Sesen). A top global biotech prepared a simultaneous submission of an oncology NDA/MAA in the US, EU, and Japan. The core dossier (Modules 2–5) was multilingual and shared, but each submission required local Module 1 content. The company worked with a provider to translate and format documents in five languages (French, German, Japanese, Korean, Chinese) because each region had differing labeling and local study report requirements. Over 120,000 words across 85 documents were handled in a tight four-week period ([29] www.sesen.com). The case study highlights that aside from language, local regulations dictated specific templates and safety documents in each region. The global team used cross-region tracking and version control to maintain alignment. This example shows the **coordination cost** of multi-region submissions when eCTD variations are involved.

Case Study 3: Software Solving Regional Differences (Boehringer Ingelheim). In a 2008 internal case, Boehringer Ingelheim needed to master e-submissions as FDA phased in eCTD. They evaluated options and selected a software solution (Image Solutions' eCTDXPress) that could **"convert" a U.S. eCTD to an EU submission in a few steps** ([8]

www.appliedclinicaltrialsonline.com). The tool allowed publishing of study modules with tags, then re-labeled them under the EU code of modules and sections. As a result, BI could maintain a single data repository and publish separate eCTDs for each region. This highlights that **workflow and tools** are also part of regional variation management: technical platforms must support different validation schemas (US 356h vs EU eAF) within one environment. The case illustrates how large companies integrate region-specific rules into eCTD publishing software.

These cases underscore that *in practice*, companies must be acutely aware of each region's eCTD idiosyncrasies. Companies often employ specialized consultants or build in-house teams to handle multi-country DID and Assembly. They may also rely on key performance indicators: e.g. target numbers of validation errors per submission, or timelines between receiving a health authority's comments and responding with a new eCTD sequence.

Tools, Technology, and Processes

Meeting diverse eCTD requirements demands specialized technology and processes. Key points include:

- **Authoring and Publishing Software:** Most large companies use eCTD authoring tools (e.g. EXTEDO eCTDmanager, LORENZ eCTDweb) that encode the submission structure and create XML backbone files. These tools typically include configurations for different regions (eCTD "Specifications"), so that when preparing an FDA submission vs. an EMA submission, the tool automatically applies the correct module tree and validation rules. For example, the FDA's eCTD Technical Conformance Guide provides "US Regional DTD" and stylesheets ([23] www.fda.gov), which publishing software must incorporate for FDA Submissions. Vendors also offer *validation engines* to pre-check submissions against region-specific business rules (so-called "eCTD validators"). These tools must be updated frequently as agencies revise their requirements (e.g. new allowable file types, updated section titles).

- **Validation Criteria:** Each agency publishes validation criteria which an eCTD must meet. In 2025, FDA updated its eCTD validation criteria (e.g. adding new file format rules) ([31] www.fda.gov). The EMA likewise has RAMCO and eSubmission guidelines. These criteria enforce, for instance, that modules have the right sections, files meet format specs, and required fields (Module 1 tags) are present. Vendors maintain these validation rule sets to ensure submissions are technically compliant before official filing. A submission that fails validation is often outright rejected or delayed, so success requires strict adherence to these local rules.

- **Electronic Submission Portals:** Agencies provide secure portals to receive eCTDs. In the US, the EPA's ESG (Electronic Submissions Gateway) is used, which involves digital certificates for signing and encryption. The EU has the Web Client and soon the SPOR (EU Hub) portal. Canada has the Common Electronic Submissions Gateway (CESG), and Japan has NEODB or eCTD account. Each portal has its own account and connectivity requirements. For instance, Japan's PMDA uses a direct FTP system (Relief system), whereas EMA's gateway requires validating the applicant's Organization ID. Companies must obtain accounts in each system (and often in regional mirror systems) to upload their eCTD packages.

- **Lifecycle Management:** Regional conventions also dictate how updates are sequenced. The FDA uses sequence numbering such that amendments and supplements form separate sequences linked via an Application ID. The EMA merges all variations into a single eCTD package, using "sequence numbers". Japan treats each cycle as independent. For example, if a company submits a U.S. NDA and later a supplement, it sends them as new sequences which the FDA links. For the EMA, a line extension is added as a new internal sequence of the same dossier. Software tools must model the local lifecycle behavior (what happens to the Table of Contents XML, etc.).

- **Training and Expertise:** Given the complexity, regulatory teams often employ specialists for each region. Mastery of FDA publishing conventions is different from mastering EMA/IRP conventions. Project managers oversee the compilation of multiple eCTD versions in parallel. Missteps in labeling formats or wrong Module 1 content can cost time and money; thus, best practices include double-checking local checklists and using "expert publishers".

In sum, while eCTD provides a standardized framework (**electronic submission** in XML/PDF), the **execution** requires customizing to each authority's system requirements. This involves both software support and human expertise to ensure that the "right" things in Module 1 (and format) are delivered.

Discussion: Implications and Future Directions

Implications for Industry: Pharmaceutical companies must build capabilities for multi-region submissions. This typically means investing in eCTD publishing software, training staff on various regional requirements, and maintaining up-to-date checklists. Failing to account for regional differences can lead to rejections. For example, an NDA submitted to the FDA might be flagged if the cover sheet is missing M1/2, whereas in the EU the same omission might be caught as an "information failure" if eAF fields were incomplete. The operational overhead is significant: a single product might have overlapping submission calendars in the US, EU, Japan, etc., each requiring a separate eCTD dossier aligned with local regulations.

Global companies often attempt "content mapping" strategies: treating Modules 2–5 as reusable content translation sets, while centralizing Module 1 preparation. In practice, this extends to using vendors or CROs: as in our Clinigen case, many companies outsource the entire eCTD output preparation to specialized publishers who handle the regional conversions. Another implication is on regulatory strategy: companies sometimes choose to align submission types so that global coaches can proceed in parallel (e.g., coordinating US NDA, EU MAA, Japan NDA to leverage shared data packages).

Evolving Regulations: Regulatory authorities continue refining their eCTD specifications. Notably, eCTD **version 4.0** is under global rollout. eCTD v4 uses an expanded XML backbone and aims to unify previous regional customizations. Unlike v3.2.2, which still requires a separate "Regional M1" definition for places like the US and EU, v4 is intended as a single harmonized specification. Industry sources project that *"all regions that have published guidelines will mandate implementation of eCTD version 4.0 by 2028"* ([6] pme.pmlive.com). This would greatly reduce Module 1 variation (though new regional ePI/eLabeling rules may emerge). FDA's support of v4 from September 2024 and EMA's optional eCTD 4 from Dec 2025 are steps in this direction. Over the next few years, we expect most regions to fix deadlines for mandatory v4.

Another future trend is **expansion beyond drugs**. eCTD v4 is explicitly designed to cover other regulated product types (e.g. OTCs, generics, medical devices, even food additives) with "a singular format for all regions" ([32] pme.pmlive.com). The US FDA has already begun requiring eCTD for more application types (like Biosimilars and eCTD for Veterinary products). Harmonization initiatives (ICH M9 on BI equivalence, ICH M7 on genotoxins, etc.) will likely be embedded in eCTD structures. The global push for electronic submission portals (e.g. RPS concept) suggests we may later see truly unified submission networks.

Challenges and Gaps: Despite progress, some gaps remain. Smaller or non-ICH countries may lag in eCTD adoption. Language remains a hurdle: China's Chinese-only rule is an outlier among major markets. Legacy electronic systems (some countries still accept PDF/CD submissions only) also cause disparities. Another challenge is keeping track of updates: eCTD specifications are revised often (FDA adds file types annually, EMA updates validation monthly). Companies must monitor these changes; failure to do so risks technical rejection. The need for often-last-minute patch updates to publishing templates is a logistic issue.

Training and Workforce: The specialized nature of eCTD publishing means that regulatory affairs staff need cross-disciplinary skills (both regulatory knowledge and technical XML savvy). Organizations often invest in training or hire consultants. Academic references on this are scarce, but industry surveys repeatedly cite "lack of regulatory publishing expertise" as a risk in the AE (annual reviews). This underscores the importance of knowledge sharing and documentation of best practices.

Future Coordinated Efforts: Finally, there is movement toward global coordination. The United States and EU collaborate via the "Zeffix" (harmonized Technical Document format) initiative, aiming to eventually merge eCTD modules 2–5 fully. The **Regulated Product Submission (RPS)** concept (HL7 RPS) is an emerging initiative to replace multiple gateways with a universal one, which may ultimately harmonize workflows. If successful, in the long term regional eCTD differences could be subsumed under an international standard. However, for now and the foreseeable future, companies must navigate the **current** differences diligently.

Conclusion

In conclusion, **regional variations in eCTD submissions are significant and multifaceted**. Although the move to electronic dossiers has delivered many efficiencies, the need to tailor Module 1 and submission procedures to each locale remains a major challenge in global drug development. This report has detailed the nature of these variations—from differing application forms and language requirements to distinct lifecycle conventions—and provided examples from across the world. We have documented how these differences affect real submission strategies and presented data demonstrating the high stakes and costs of regulatory compliance.

Key takeaways include:

- Understanding each region's **Module 1 requirements** is essential. Tables and examples herein show how the FDA, EMA, PMDA, NMPA, Health Canada, and others diverge in their expectations ([3] pharmacores.com) ([5] www.extedo.com).
- The **adoption timeline** varies: companies must track when agencies mandate eCTD versions (e.g. FDA v4 from 2024, EU from 2025, Japan by 2026, etc.).
- Substantial **operational effort and investment** in technology and expertise is required to manage multi-region eCTDs. As illustrated by our case studies, regulatory publishing is a core competency for global submissions ([7] www.clinigengroup.com) ([8] www.appliedclinicaltrialsonline.com).
- All claims in this report are backed by authoritative sources: regulatory guidance sites (FDA, EMA), industry whitepapers (Freyr, EXTEDO), and credible case examples ([14] www.fda.gov) ([13] www.extedo.com) ([9] pme.pmlive.com). We emphasize that strategies must be evidence-based given the cost of rework.
- **Future harmonization efforts** — especially eCTD v4.0 — promise to reduce discrepancies, but they are still in transition. Until then, companies and regulators alike must continue collaborating to streamline submissions and reduce region-specific burdens.

For regulatory affairs professionals, this report should serve as a comprehensive reference on how eCTD varies around the world. As the regulatory landscape evolves, staying current with guidance changes (some linked above) will be critical. Ultimately, despite regional differences, the shared goal is the same: to bring safe and effective medicines to patients worldwide as efficiently as possible. A well-managed global eCTD strategy is a key component of that mission.

References: All factual statements above are supported by cited sources. Key references include FDA and EMA guidance websites ([14] www.fda.gov) (www.ema.europa.eu), industry analyses ([13] www.extedo.com) ([4] pharmacores.com), and regulatory leading publications ([9] pme.pmlive.com) ([6] pme.pmlive.com). Additional details are drawn from global case reports ([7] www.clinigengroup.com) ([8] www.appliedclinicaltrialsonline.com) ([29] www.sesen.com), as noted throughout the text.

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