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CTD vs eCTD: Key Differences in Pharma Submissions Explained

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[Revised May 8, 2026] This article has been updated to reflect the latest eCTD 4.0 timelines from FDA and EMA, India's CDSCO eCTD transition status, and current global adoption figures as of 2026.

Executive Summary

The **Common Technical Document (CTD)** is the internationally harmonized format for **drug regulatory submissions**, originally defined by the International Council for Harmonisation (ICH) in the early 2000s (globalforum.diaglobal.org). It consists of five modules (administrative/region-specific information plus high-level summaries and detailed Quality, Nonclinical, and Clinical data) that serve as the backbone for all major new drug applications (globalforum.diaglobal.org) (www.lifescienceintellipedia.com). For decades, sponsors submitted CTD dossiers on paper (or as PDFs) to regulatory agencies in the US, EU, Japan and elsewhere, enabling consistent review processes across regions (globalforum.diaglobal.org) (www.lifescienceintellipedia.com).

Over the past two decades, a digital evolution of the CTD – the **electronic CTD (eCTD)** – has become the de facto global standard. First adopted by ICH as a Step 4 specification in October 2003 (v3.0), with the current v3.2.2 revision finalized in 2008 ([admin.ich.org](https://www.ich.org)) (globalforum.diaglobal.org), eCTD preserves the CTD content structure but adds an XML “backbone” (index) that unambiguously references each document and tracks lifecycle changes (globalforum.diaglobal.org) (globalforum.diaglobal.org). By 2022, about 94% of all FDA submissions were in eCTD format (globalforum.diaglobal.org). Virtually all major markets now require or accept eCTD (US, EU, Japan, Canada, South Korea, etc.), with emerging markets (e.g. Middle East, China, Latin America) rapidly adopting or piloting eCTD as well (globalforum.diaglobal.org) (www.extedo.com).

Compared to legacy CTD submissions, eCTD offers critical advantages: it greatly eases electronic navigation and review, supports incremental updates, enables electronic validation and archival, and can significantly shorten review cycles (ectd247.com) (www.freyrdigital.com). However, it also imposes strict technical requirements on file formats, naming, and sequencing, raising implementation costs for sponsors and requiring robust publishing platforms (pharmacystandards.org) (www.appliedclinicaltrials.com). This report provides an in-depth examination of the **CTD vs. eCTD differences**: it covers historical background, technical and regulatory distinctions, adoption data, benefits and challenges, real-world case studies, and future trends (including the upcoming eCTD 4.0 standard). All claims are supported by extensive citations from regulatory guidelines, industry reports, and expert analyses.

Introduction and Background

Origins of the CTD and Need for Harmonization

Drug regulatory dossiers have grown enormously in size and complexity since the mid-20th century. In the United States, **new drug applications (NDAs)** were required as early as 1938, and by the 1960s firms were submitting mountains of documents (often in triplicate) for each application (globalforum.diaglobal.org). Parallel trends occurred in Europe (especially after the thalidomide crisis), where separate national dossiers created duplication and delays (globalforum.diaglobal.org). In this “paper era,” reviewers manually accessed physical binders of trial reports, protocols, manufacturing records, and lab notebooks, impeding efficient cross-referencing and scientific review (globalforum.diaglobal.org) (globalforum.diaglobal.org).

To streamline these submissions, the **ICH (International Council for Harmonisation)** began developing the **Common Technical Document (CTD)** in 1989 (globalforum.diaglobal.org). The CTD standardized the organization of submission modules across the three founding ICH regions (US, EU, Japan). It divides the dossier into three common modules and two region-specific components:

- **Module 1 (Regional Administrative Information)** – region-specific application forms, labeling, and other administrative documents (not harmonized internationally).
- **Module 2 (Summaries and Overviews)** – high-level summaries of quality (CMC), nonclinical, and clinical data (Quality Overall Summary, Nonclinical Overview/Summary, Clinical Overview/Summary) (www.lifescienceintellipedia.com).
- **Module 3 (Quality)** – detailed Chemistry, Manufacturing and Controls (CMC), including drug substance and product characterization, manufacturing procedures, and **stability data**.

- **Module 4 (Nonclinical)** – pharmacology and toxicology study reports.
- **Module 5 (Clinical)** – **clinical trial study reports** (safety, efficacy), literature references, etc.

By capturing the key components of a drug application in a uniform outline, the CTD eliminated redundant writing and simplified cross-border filings. As Loebel notes, the CTD “became the mandatory or strongly recommended format” for most NDAs and MAAs in the US, EU, and Japan over subsequent years (globalforum.diaglobal.org). In practice, living harmonized documents (e.g. FDA Form 1571 or EMA forms) plugged into Module 1, while the rest of the modules were globally consistent. Industry and regulators alike recognized that a single dossier structure would reduce the filing burden and facilitate global review (pmc.ncbi.nlm.nih.gov) (globalforum.diaglobal.org).

Evolution Toward Electronic Submissions: NeeS and eCTD

In the 1990s and early 2000s, agencies began experimenting with electronic submissions. Early initiatives (e.g. FDA’s CANDa project, EU’s DAMOS/SEDAMM) aimed to exchange documents electronically, but lacked a unified format (globalforum.diaglobal.org) (globalforum.diaglobal.org). The arrival of PDF (Adobe Acrobat *Portable Document Format* in 1993) provided a practical digital medium, enabling entire study reports and files to be exchanged. As one analyst notes, by the late 1990s PDFs became the “de facto standard for electronic regulatory documents” (globalforum.diaglobal.org). Sponsors could submit “electronic CTDs” by providing the same CTD modules as PDF files, often with an electronic table of contents; these submissions were sometimes called **NeeS** (Non-eCTD electronic Submissions) (globalforum.diaglobal.org).

However, NeeS (essentially PDF dossiers with a cover) had drawbacks: it offered no built-in tracking of document versions or lifecycle, and reviewers could not easily distinguish new from old content between submission batches (globalforum.diaglobal.org). By the mid-2000s, all parties realized a more robust electronic standard was needed to manage iterative regulatory activities.

The Birth of the eCTD Standard

Recognizing this, ICH initiated the **eCTD** specification in 1997 (ICH M2 guideline). This led to a key publication: “*Electronic Common Technical Document (eCTD) Specification*”, which reached ICH Step 4 as version 3.0 in October 2003 and was revised through version 3.2.2 in July 2008 (admin.ich.org). The current **eCTD v3.2.2** specification thus dates from 2008 (globalforum.diaglobal.org). Unlike legacy CTDs, eCTD includes a machine-readable “backbone” that mirrors the CTD’s structure. Loebel (2024) describes the original design goals:

“The eCTD was built **on an XML standard**, with a *complete hierarchical organization* for Modules 2–5. It enforced standardized folder and file naming, assigned unique IDs to each document, and added lifecycle attributes to indicate what is new or changed in each submission (globalforum.diaglobal.org).”

In other words, eCTD retains the five-module content of the CTD but requires each file to be accompanied by XML metadata. Each eCTD submission is organized into numbered sequences: an initial sequence (commonly “0000”) and subsequent updates. The backbone XML (`index.xml` plus region-specific files) explicitly lists

every file and section, effectively replacing static PDF tables-of-contents with a dynamic schema (pharmacystandards.org) (globalforum.diaglobal.org).

Table 1 (below) summarizes some key technical distinctions between legacy CTD (paper/PDF) submissions and eCTD submissions:

Feature	Paper/Traditional CTD	Electronic CTD (eCTD)
Submission Medium	Paper binders or flat PDFs (Nees) delivered physically or by email.	Fully electronic package with XML backbone. Delivered via digital gateway (e.g. FDA ESG, EMA eSubmission system).
Table of Contents (TOC)	Manual TOC in first pages; cross-references on paper or PDF bookmarks.	XML <i>index.xml</i> for Modules 2–5 (and region-specific XML for Module 1) defines TOC and links every document (pharmacystandards.org).
Modules Structure	Same 5-module structure, but no machine-readable enforcement.	Same 5-module outline but enforced via XML. Module 1 remains country-specific (a separate XML file).
Document Granularity	Firms could bundle multiple reports into one volume; pagination diverse.	“Leaf” concept: each stand-alone document is a separate file (“leaf”) in the XML tree (pharmacystandards.org). Finer control needed.
Version Control / Lifecycle	None inherent – sponsors note changes in cover letters.	Each submission sequence explicitly flags operations: new, append, replace, or delete on each document (pharmacystandards.org).
Navigation	Reviewers flip pages or search PDFs; compare volumes manually.	Hyperlinked bookmarks and XML allow quick navigation and full-text search across documents (ectd247.com) (pharmacystandards.org).
Validation	No technical checks; minor format issues tolerated.	Automated validation: file naming (lowercase, no spaces), PDF restrictions (embedded fonts, PDF/A, bookmarks) (pharmacystandards.org).
Checksum and Integrity	Not applicable (paper) or basic digital hashes.	eCTD records an MD5 checksum for every file in the XML backbone, and <i>index-md5.txt</i> holds the checksum of <i>index.xml</i> itself; agencies use these to verify file integrity (pharmacystandards.org).
Global Harmonization	Structure harmonized (ICH CTD) but no standard file format.	Structural content harmonized (ICH CTD), with a global standard XML schema (ICH eCTD spec v3.2.2) for digital exchange (globalforum.diaglobal.org).

Each of the above differences has tangible regulatory and operational impact, as discussed in the sections below.

Regulatory Mandates and Adoption

Following ICH Step 4 approval of eCTD in 2008 (globalforum.diaglobal.org), major regulatory agencies rapidly mandated electronic submissions:

- **United States (FDA/CDER & CBER):** The FDA first encouraged electronic INDs/NDAs in the 2000s and progressively mandated eCTD. Under PDUFA goals enacted in 2012, the FDA required that most NDAs/BLAs be submitted eCTD by 2017 (www.accessdata.fda.gov) (globalforum.diaglobal.org). As of

the late 2010s, exceptions for large NDAs, IND/BLA (which may accept non-eCTD formats briefly) have closed, making eCTD mandatory for virtually all major drugs. By 2022 the FDA reported processing ≈ 8 million eCTD submissions, constituting $\sim 94\%$ of its total volume (globalforum.diaglobal.org). The FDA's public guidance emphasizes that reviewers "can easily find and access the information they need" in eCTD (www.fda.gov).

- **European Union (EMA):** The EMA required eCTD for all *centralized* MAA submissions starting January 1, 2010 (www.ema.europa.eu). Under the EU eSubmission roadmap, eCTD later became mandatory for new applications in the decentralised (2015) and mutual-recognition (2017) procedures, and for national procedures (new national MAAs from 1 July 2018 and all other submission types from 1 January 2019) (esubmission.ema.europa.eu), so the legacy NeeS format has been phased out for these procedures. Regionally, Module 1 requirements vary (e.g. EU Module 1 includes an XML *EU application form*, legally binding product information) (www.extedo.com).
- **Japan (PMDA):** The Japanese PMDA also requires eCTD for NDAs/BLAs. Region-specific specifics exist (e.g. Japan's approach to lifecycle management resets each regulatory action) (www.extedo.com). Japan has moved first to eCTD 4.0 (HL7 RPS): it is mandatory from April 2026, and v3.2.2 is accepted only for approval applications filed by 31 March 2026 (www.pmda.go.jp) (admin.ich.org).
- **Canada (Health Canada):** Health Canada requires electronic filing in either eCTD or a defined non-eCTD electronic format depending on the regulatory activity type; eCTD submissions follow local Module 1 requirements, such as attestation forms (www.extedo.com).
- **Other Regions:** South Korea, China, Taiwan, Switzerland, Gulf Cooperation Council (GCC) countries, and others have implemented eCTD standards (often with local Module 1 variations) (globalforum.diaglobal.org). China's NMPA, for instance, allows NDAs in eCTD format but requires Chinese-language translations for all key documents (www.extedo.com). In Latin America, Brazil and Mexico are rolling out requirements for CTD/eCTD (notably Brazil is developing a CTD for registration). Many Middle East/North Africa regulators have recently moved from paper/CTD to eCTD: for example, Saudi Arabia mandated eCTD from July 2016, UAE from Oct 2017, Oman from Jan 2015, etc. (www.biomapas.com). Asia-Pacific regulators (India, ASEAN states) are likewise transitioning, though timelines vary. *Fig. 1* (below) summarizes high-level global eCTD adoption:

Region	Current eCTD Status	Note
United States	eCTD mandatory (CDER/CBER)	NDAs, ANDAs and BLAs since May 2017; commercial INDs and master files since May 2018 (www.fda.gov) (www.accessdata.fda.gov) (globalforum.diaglobal.org).
European Union/EEA	eCTD mandatory (centralized)	Centralized MAA since 2010 (www.ema.europa.eu); others via eCTD preferred.
Japan	eCTD v4.0 mandatory (from April 2026)	PMDA-specific Module 1 and lifecycle rules; v3.2.2 accepted for approval applications filed by 31 March 2026.
Canada	eCTD mandatory or recommended (by activity)	Some activities, including certain master files, use a non-eCTD electronic format.

Region	Current eCTD Status	Note
South Korea	eCTD accepted/required	By ministerial regulations.
China (NMPA)	eCTD accepted (IND/NDA)	Chinese-language docs required (www.extedo.com).
GCC States	eCTD mandatory by 2020	Common GCC-eCTD M1 formats. Saudi/UAE/Oman/Qatar/Jordan as of 2015–2020 (www.biomapas.com).
Emerging markets	Phasing in/optional	India (eCTD mandate expected by industry, not yet confirmed in a CDSCO notice (www.freyrsolutions.com)), ASEAN (ACTD/eCTD), Latin America (e.g. Mexico's CTD).

Table 1: Key differences between legacy CTD submissions and electronic CTD (eCTD). [CTD = Common Technical Document; eCTD = Electronic CTD; M1–M5 = Modules 1–5].

Technical and Procedural Differences

Content Structure and File Organization

By design, **CTD and eCTD share the same logical content structure (Modules 1–5)**

(globalforum.diaglobal.org). All safety, efficacy, and quality data belong in the corresponding CTD module whether in paper or electronic form. The critical differences arise in *how* that content is packaged and managed:

- Module 1 (Regional Information)** – In the CTD, Module 1 (forms, labeling, regional information) is not harmonized. Each jurisdiction has its own template/requirements (e.g. FDA Form 1571 for INDs or Form 356h for NDAs, BLAs and ANDAs, EMA *Application Form*, Japanese application forms). With paper CTDs, these were cover pages or binders unique to each region. In eCTD, each country's M1 is implemented via a region-specific XML file (e.g. `us-regional.xml`, `eu-regional.xml`) (pharmacystandards.org). For example, FDA Module 1 content is indexed in the `us-regional.xml` backbone, with application forms such as Form 356h supplied as fillable PDFs, while EMA includes the *EU-signed PDF form* or eAF for EU centralized procedures. As Extedo notes, M1 remains **the principal source of regional variation** in an otherwise harmonized dossier (www.extedo.com).
- Modules 2–5 (Common Modules)** – These modules are identical in concept between CTD and eCTD. Modules 2 (summaries), 3 (quality), 4 (nonclinical), and 5 (clinical) contain the same review content in both CTD and eCTD dossiers (globalforum.diaglobal.org). In a paper CTD, these would be printed volumes (with an overall table of contents inserted) (globalforum.diaglobal.org). In eCTD, these modules are represented by file folders (`/m2`, `/m3`, etc.) within each sequence. The key innovation of eCTD is the “backbone” index which hierarchically organizes these folders. Specifically, each eCTD sequence folder contains:
 - `/m1/`, `/m2/`, `/m3/`, `/m4/`, `/m5/` directories with all the submission PDFs.

- An **index.xml** file (the Module 2–5 TOC) that maps each PDF to its proper CTD section (pharmacystandards.org).
- A region-specific XML file (`us-regional.xml`, etc.) for M1 content (pharmacystandards.org).
- An `index-md5.txt` file holding the MD5 checksum of `index.xml` (the checksum of each document is recorded in its leaf entry in the XML backbone), used to verify integrity (pharmacystandards.org).
- A validation stylesheet (CTOC) that defines the presentation and rules (www.fda.gov).

For example, `index.xml` might have entries linking a Quality Overall Summary file in the `m2` folder to Section 2.3, a drug-product specification file in `m3` to Section 3.2.P.5, and a clinical study report in `m5` to its Section 5.3 location. This machine-readable index enforces consistent organization: every document is tagged with a known CTD location. In contrast, traditional CTDs have no such enforced indexing – sponsors had to rely on their internal filing and reviewers flipped through printed contents.

- **Document Granularity** – In paper CTDs, companies sometimes combined many tables or reports into a single large volume. eCTD, by contrast, requires high granularity: each standalone document (e.g. each Clinical Study Report, each batch record) must be a separate PDF file (“leaf”) (pharmacystandards.org). This “leaf granularity” rule simplifies embedded hyperlinks/bookmarks and lifecycle tracking. For instance, unlike a scanned paper CTD where a single PDF might hold two study reports back-to-back, eCTD demands each study report be its own file (with bookmarks) (pharmacystandards.org). This level of disaggregation is essential for FDA’s *Study Tagging Files*, where each clinical study is submitted as a set of mini-files (protocol, datasets, etc.) with metadata (www.extedo.com).

Lifecycle and Version Management

A defining difference is **how revisions are handled**. In paper CTDs, updates (e.g. response to queries, supplemental data) often meant replacing entire sections. There was no formal “version control” other than collection of replaced volumes. In eCTD, each submission is designated a “sequence” (e.g. 0000, 0001, ...) and uses explicit XML attributes to indicate changes. In the index XML, every `<leaf>` element includes an operation attribute with values: **new**, **append**, **replace**, or **delete**. This tells reviewers exactly which documents are new or superseded by each sequence (pharmacystandards.org).

- **Addition of new documents:** e.g. a new clinical trial report in the next sequence would be marked `operation="new"`.
- **Replacing old documents:** if a protocol is amended, the updated protocol file is submitted with `operation="replace"`, linking it to the previous version in the archive.
- **Deleting documents:** if an old drug substance specification is withdrawn, a `delete` operation removes it from the active dossier view (while preserving record of its prior existence).

These lifecycle tags make it *programmatically* possible to assemble the “current view” of the dossier at any time (globalforum.diaglobal.org) (pharmacystandards.org). By contrast, a neeS (PDF list) approach could not automatically convey which files had changed – often requiring the sponsor to explain changes in a cover letter

or transmittal form (globalforum.diaglobal.org). The eCTD mechanism, invented for this reason, ensures regulators always have a complete revision history at their fingertips.

File Formats and Validation Rules

Legacy paper CTDs had minimal technical constraints (aside from page size or binder baud). In eCTD, *technical conformance* is strictly controlled. Most documents are submitted as PDF files meeting each agency's PDF specification (PDF/A is accepted but not universally required, and some non-PDF formats such as study datasets are permitted in specified locations), with requirements such as (pharmacystandards.org) (pharmacystandards.org):

- **File Naming:** Only lowercase letters, digits, hyphens/underscores. No spaces or special characters (pharmacystandards.org). For example, an invalid name like `My Study Report.pdf` must be `study-report-123.pdf`.
- **PDF Settings:** Fonts must be embedded; no manuscript annotations, macros, or encryption (so the agency can index it) (pharmacystandards.org). When interactive form fields are used (e.g. Module 1 forms), bookmarked links must be relative.
- **Bookmarks/Hyperlinks:** Large PDFs (e.g. long clinical reports) must include bookmarks reflecting their internal structure (pharmacystandards.org). Self-links are disallowed, and external URLs are discouraged.
- **Size Limits:** Agencies generally cap file sizes (often ~300 MB) to allow reasonable processing.
- **Checksum Verification:** Each file's MD5/SHA is checked on receipt to ensure no corruption occurred in transit (pharmacystandards.org).
- **Validation Schemas:** The backbone XML must adhere to the ICH DTD (v3.2.2) or HL7 schema (v4.0 pilot) for Modules 2–5. Each region's Module 1 XML must conform to its local schema or XSD (for example, `US-regional.xsd`) (pharmacystandards.org).

Serious violations of these rules can cause a submission to fail technical validation and require resubmission, although agencies grade validation errors by severity (FDA, for example, distinguishes high-severity errors from medium and low ones). Agencies have demonstrated little tolerance for technical errors: a 2011 report stated that FDA was rejecting around 7% of eCTD applications due to errors (www.appliedclinicaltrials.com) (ectd247.com). The Applied Clinical Trials report notes that “agencies are beginning to demand greater compliance with the published specifications ... for example, the FDA began checking for dozens of errors related to PDFs in 2010” (www.appliedclinicaltrials.com). In short, sponsors cannot merely scan paper into PDF – diligent quality control and use of publishing software (to validate against ICH schemas) is essential in eCTD.

Overall, the technical strictness of eCTD is a double-edged sword: it **ensures consistency and machine-readability**, but increases sponsor burden (special expertise, tools, and time to validate each submission). The payoff is that modern submissions become more readily searchable and interoperable (enabling software-aided review and further data reuse).

Benefits and Challenges of eCTD vs. CTD

Benefits of eCTD

Enhanced Navigation and Review Speed: The primary advantage of eCTD is reviewer efficiency. Regulators can instantly search across thousands of pages and hyperlink between sections (ectd247.com) (pharmacystandards.org). Multiple reviewers at different sites (even different continents) can simultaneously access the same dossier in the electronic gateway (ectd247.com). ECTD247 summarizes: “[E]lectronic submission allows them [authorities] to handle large volumes more quickly...with several reviewers working simultaneously on documents, and quickly identifying new elements in a submission” (ectd247.com) (ectd247.com). ECTD247 argues that the resulting accelerated submission cycle can gain sponsors months of marketing in major markets (ectd247.com).

Reduced Cost and Time: Electronic archives eliminate physical storage, printing, and courier costs. ECTD247 notes that e-submissions are much cheaper and faster than managing bound paper: “searching and viewing information in a large amount of paper documents is long and painful,” whereas in eCTD “a significant cost reduction” and “accelerated submission cycle” are achieved (ectd247.com). One industry white paper assesses that eCTD has provided “significant productivity benefits to both health authorities and industry” (www.freyrdigital.com), and even calls it “the global gold standard for drug regulatory submissions” (www.freyrdigital.com). By facilitating global filings, eCTD also accelerates time-to-market: firms can reuse the same eCTD dossier framework when submitting to multiple countries, needing only to swap Module 1 content and local particulars (globalforum.diaglobal.org) (ectd247.com).

Better Lifecycle Management: Pharmaceuticals evolve through a long lifecycle of amendments, supplements, and renewals. CTD on paper has no official version control, making it hard to track changes over time. ECTD’s built-in lifecycle (new/replace/delete) ensures every amendment or annual report is stamped into the record. Regulators can instantly construct the “current view” of a dossier given a sequence number (globalforum.diaglobal.org) (pharmacystandards.org). This transparency reduces errors: eCTD247 notes that adoption of lifecycle-managed eCTD “allows authorities to...quickly identify (life cycle management) the new elements in a submission” (ectd247.com). In practical terms, sponsors save time assembling updates because only new/changed documents must be compiled (the publisher does not re-send the entire dossier each time).

Data Integration and Future Potential: While eCTD v3.x is still essentially a collection of PDFs, the use of XML standards lays the groundwork for future data-driven submissions. Breaking the CTD into structured pieces (and tagged metadata) facilitates downstream analysis, machine learning, and cross-product comparisons. A recent review observes that if PDF content were broken into database fields, regulators could “more efficiently abstract and analyze” submission contents (pmc.ncbi.nlm.nih.gov). Early initiatives like FDA’s Quality Metrics/KASA programs and EMA’s eAF integration are already exploiting structured components of eCTD. Ultimately, eCTD is envisioned to evolve into true “structured submissions” (see **Future Implications**).

Challenges and Disadvantages

Technical Complexity and Cost: Implementing eCTD is not trivial, especially for smaller companies or agencies. Sponsors must invest in specialized publishing software (or hire vendors) to generate compliant eCTDs. These tools must handle XML backbones, validations, checksum generation, PDF standards, and regional customizations. Training staff on eCTD rules is a learning curve. In the early years of eCTD adoption, many companies built significant backlogs of eCTD training and had to scramble to meet new submission deadlines. For example, in 2016 the FDA began issuing a third acknowledgement of submissions specifically to eCTD formats up to a certain size (www.fda.gov), indicating an institutional effort to standardize workflows. The costs of software licenses, validation infrastructure, and labor can be substantial, potentially offsetting some of the savings on paper.

Rigidity and Validation Failures: While strict rules ensure quality, they can also cause delays. Validation errors graded as serious can force a resubmission. Applied Clinical Trials reported that by 2011, around 7% of eCTD submissions to FDA were being rejected for technical errors (www.appliedclinicaltrials.com). Similarly, the Belgian and French agencies have been known to refuse entire NeeS or eCTD dossiers that do not fully meet their insertion standards (www.appliedclinicaltrials.com). In contrast, pre-eCTD submissions often passed with reservations. This means sponsors must build robust internal QA checks, which adds process overhead.

Transition Issues in Emerging Markets: Not all regions have kept pace consistently. In many emerging markets, regulatory IT systems and sponsor readiness lag. The “**FROM PAPER TO DIGITAL**” report highlights that agencies with limited resources will struggle to implement eCTD (www.biomapas.com). For companies, this creates a compliance burden: one must track multiple dossier formats (for example, preparing eCTD for EU/US while still generating CTD or NeeS for other countries). Module 1 diversity remains a headache: firms must maintain separate Module 1 documents for every country and ensure mapping in XML. In some cases (e.g. China), language barriers add extra files (Chinese translations) (www.extedo.com). Such fragmentation somewhat undercuts one of eCTD’s promises: true global harmonization.

Remaining Static Content: Experts note that even with eCTD, the actual data often remain locked in PDFs. MacDonald *et al.* (2021) argue that current eCTD processes produce a regulatory “snapshot in time” of documents, which still **traps data** inside static files and prevents seamless data reuse (pmc.ncbi.nlm.nih.gov). For example, if a reviewer wants to analyze all case report forms across studies, they still must open each PDF report. Therefore, in the eyes of some (especially digital-future advocates), eCTD is an intermediate step. It is more navigable than paper CTDs, but less fluid than fully structured data submissions. Future eCTD versions (and new paradigms) aim to address this.

In summary, the shift from CTD to eCTD has yielded clear benefits in standardization, efficiency, and multi-country coordination (ectd247.com) (www.extedo.com), but it also imposed substantial technical demands on all parties. The balance of these trade-offs continues to evolve as both technology and regulatory policy advance.

Global Adoption: Data and Case Studies

Adoption Statistics

Quantitative data illustrate the rapid uptake of eCTD. Table 2 (below) and the data points here summarize global trends:

Metric / Fact	Value / Detail	Source
FDA NDA eCTD submissions (2015)	85% of NDAs were submitted electronically in eCTD format (ectd247.com).	ECTD247 industry report
FDA eCTD submission share (2022)	94% of all submissions to FDA electronic gateway were eCTD (globalforum.diaglobal.org).	U.S. regulatory statistics (per FDA reports)
EMA centralized procedure (since 2010)	eCTD mandatory for all centralized MAAs (www.ema.europa.eu).	EMA regulation
Growth in FDA e-submissions (2006–2015)	From ~2.3% to ~85% of NDAs submitted as eCTD (ectd247.com).	ECTD247
Typical eCTD application size	50–1000s of files, sometimes >1 GB per application. (Depends on product).	Regulator publications
eCTD-capable jurisdictions (2024)	eCTD accepted or required in the US, EU/EEA, UK, Japan, Switzerland, Canada, South Korea, China, Taiwan and GCC states, and being implemented in Brazil, Mexico, Egypt, Singapore and Turkey (globalforum.diaglobal.org).	DIA Global Forum (2024)

Table 2: Adoption and usage figures for eCTD. (Various sources; see text for citations.)

By most measures, eCTD is now ubiquitous in regulated markets. FDA data indicate that by 2015, roughly **85% of all new drug applications were being submitted in eCTD format** ([ectd247.com](#)). That number rose to over 90% by the early 2020s (with nearly all large NDA/BLA submissions being eCTD). Similarly, EMA's centralized filings switched to 100% eCTD after 2010 ([www.ema.europa.eu](#)). ECTD247 illustrates the scale involved: it states that FDA handles more than 20,000 requests per month, representing more than 50 kilometers of paper ([ectd247.com](#)).

Case Study: MENA Region and Developing Markets

Examining specific regions highlights the challenges and benefits of the CTD-to-eCTD transition. In the **Middle East and North Africa (MENA)**, many regulators historically accepted only paper or simple CTD. A 2023 report outlines the recent eCTD rollout: Saudi Arabia (Gulf region) mandated eCTD in mid-2016, UAE in Oct 2017, Oman Jan 2015, Bahrain Nov 2016, Qatar by 2020, and Jordan in early 2019 ([www.biomapas.com](#)). These countries generally follow a common GCC-eCTD specification for their local Module 1. The move has been credited with improving dossier tracking, but has required substantial capacity-building. According to the

report, these agencies faced “**challenges for those agencies who lack needed human and/or material resources**” to implement eCTD (www.biomapas.com). Sponsors filing in MENA must now allocate publishing resources to these markets similarly to EU/US.

Another illustrative case is **India**. Historically, India accepted paper and CTD-format dossiers for new drug and clinical trial approvals, and CDSCO has since moved many applications onto its SUGAM online portal. Industry consultancies such as Freyr expect eCTD to become mandatory, starting with priority categories such as new drug applications; as of this update we have not located a CDSCO notice making eCTD mandatory, so sponsors should check CDSCO's official notices (freyrsolutions.com).

In the **Pharmaceutical Industry** itself, many companies conducted phased roll-outs of eCTD capabilities. Large multinational firms often built in-house regulatory publishing groups, while smaller biotech firms lacking in-house expertise frequently outsourced eCTD publishing to specialist vendors.

A **data point** from Applied Clinical Trials (2011) is notable: it reported that by then “the FDA now receives over 50% of new drug applications (originals and supplements) in eCTD format” (www.appliedclinicaltrials.com). That figure has continued to climb in the past decade. The same article warned that regulators were beginning to refuse submissions not meeting eCTD standards: the Belgian agency demanded full eCTD conformance since 2007, and one French regulator reportedly rejected half of NeeS dossiers for validation failures (www.appliedclinicaltrials.com). These examples foreshadowed the current rigor: nowadays authorities run technical validation on every eCTD sequence and can require resubmission when serious errors are found.

Multiple Perspectives

Industry Perspective

Pharmaceutical companies largely view eCTD as an indispensable tool for global filings, despite its upfront costs. Regulatory professionals note that eCTD tilts the focus from formatting to content quality and strategy. Lifescience Intellipedia notes that with eCTD, sponsors “can clone, update, and re-use content across versions effortlessly” (www.lifescienceintellipedia.com). Global executives appreciate the harmonization: once an eCTD is built for one region, much of it can be re-filed elsewhere, cutting duplication.

However, industry also voices concerns. Smaller biotech and generic firms often lack the IT budget of Big Pharma, although ECTD247 notes that submitting in eCTD can ease partnerships with larger companies, whose submission processes are generally already eCTD-based (ectd247.com). Some companies have reported delays due to occasional tech glitches with submission portals or validation. There is also “resistance” noted colloquially: internal teams accustomed to simple PDFs may be slow to adopt new workflows. The GlobalForum article even quips that industry “resistance is futile” as agencies force the move to eCTD. In practice, any life-cycle regulatory update now requires preparing a sequenced eCTD package plus cover letters. The onus of getting every checkbox correct has turned regulatory publishing into a full-time discipline in many firms.

Regulator Perspective

Regulatory agencies benefit from eCTD through efficiency in data handling and comparison. In agencies' own words, eCTD submissions "make it easier for FDA to review data" and "simplify the process for submitters" (www.fda.gov). Review divisions can quickly navigate to requested sections, run searches, and track previous interactions with a dossier. Multiple reviewers can annotate and share references without physically mailing pages.

On the flip side, regulators have had to upgrade IT infrastructure and train staff. The FDA's Electronic Submissions Gateway (ESG) infrastructure and eReview tools underwent continual upgrades (e.g. handling PDF/A compliance, supporting large volumes) to support the eCTD deluge (www.fda.gov). Agencies periodically release **Important Notices** highlighting changes (e.g. older DTD sunset notice, eCTD v4 readiness) (www.fda.gov). Regulators also contend with data ownership issues: while company data are submitted via eCTD, much of it cannot be easily extracted for aggregated analysis. Agencies have begun initiatives (like FDA's IDMP/PQ/CMC projects) to remedy this, but the transition is ongoing.

Technical Service Providers

Organizations providing eCTD publishing and validation services have seen business growth. Companies like EXTEDO, Freyr, Informa, and numerous consultancies emphasize eCTD expertise as part of their offering. They highlight the **4 pillars** of successful eCTD publishing: simplification, cost reduction, usability, and strong support (knowledgenet.sarjen.com). Technical vendors stress that eCTD can only deliver its promise if sponsors use the *right tools* – proper software automating index generation, validation engines, and translation of regulatory requirements into system checks. Anecdotally, when agencies switched to mandatory eCTD, many small vendors offered "template services" to convert legacy CTDs into eCTD with minimal rewrite, though quality varied.

Data Analysis and Trends

From the data gathered, several trends emerge:

- **Rapid Uptake, Plateauing at Compliance:** The pace of e-submission growth was extremely steep in the late 2000s and 2010s. Once eCTD mandates arrived, virtually all submissions in the US/EU switched to eCTD. Figures like "94% of submissions eCTD" (globalforum.diaglobal.org) suggest we are near saturation in the major markets. Future growth may come from emerging markets catching up.
- **Shift in Rejection Reasons:** Prior to eCTD, submissions might be delayed by missing data or study results. Now, a non-trivial fraction are delayed by format violations (www.appliedclinicaltrialsonline.com). This has created a new category of quality assurance: technical submission quality. We can infer that agencies have systematically reduced leniency: e.g. SwissMedic insists sponsors self-validate before submission (www.appliedclinicaltrialsonline.com).

- **Preparatory Trends:** Leading firms have been preparing for eCTD 4.0 (HL7 RPS) even before mandates. Job postings, regulatory conferences and in-house seminars have featured eCTD v4 tracks heavily. The ICH approval of eCTD 4.0 in 2015 initiated global planning (see next section). Notably, the EMA has been running *Technical Pilot* programs and published draft guidance, indicating a strategic shift towards data-model submissions (acceleration by IDMP and SPOR).
- **Software Market Growth:** The demand for eCTD publishing tools is reflected in market reports. Recent market research lists the eCTD submission software market at dozens of vendors with services and software, projecting double-digit growth as newer versions roll out (dataintel.com). Integration with Document Management Systems (EDMS) and Clinical Trial data (CDISC) is increasingly in demand.

Future Directions and Implications

Moves Toward eCTD 4.0 and Beyond

A major upcoming evolution is **eCTD v4.0**, based on the HL7 RPS standard (Regulated Product Submission). Approved by ICH in 2015, eCTD 4.0 is already in production use in several regions and has been mandatory in Japan since April 2026 (admin.ich.org). It retains the concept of modules but abolishes the rigid ICH module hierarchy in favor of a more flexible activity-based model. Key advantages include two-way communication (regulators can respond via RPS messages), parameterized content paths (allowing splitting/merging of documents dynamically), and true global harmonization of backbone (single XML for Modules 1–5) (pharmacystandards.org). Karl Loebel (2024) notes that eCTD4 addresses many shortcomings of v3.x and is “driven by an HL7 RPS standard... [which] can define any kind of submission to agencies” (globalforum.diaglobal.org) (globalforum.diaglobal.org).

Mandates for eCTD 4.0 are now taking effect. Japan was first: PMDA made eCTD v4.0 mandatory from April 2026 and accepts v3.2.2 only for approval applications filed by 31 March 2026 (www.pmda.go.jp). The FDA has accepted voluntary eCTD v4.0 submissions since 2024, and the ICH status table lists mandatory FDA use from 2029 (fda.gov) (admin.ich.org). In the EU, optional use for new centralised MAAs began on 22 December 2025, use becomes strongly recommended from Q1 2027 and mandatory for new centralised MAAs from Q1 2028; the EU eCTD v4.0 Implementation Guide is still a draft (v1.2, October 2024) (esubmission.ema.europa.eu) (ema.europa.eu). Health Canada plans voluntary use in 2028 and mandatory use in 2030 (admin.ich.org) (globalforum.diaglobal.org). Thus, over the next few years eCTD 3.2.2 will gradually give way to 4.0 globally. While the transition poses another training/validation challenge, the industry expects a relatively smooth backbone since the underlying content (modules) changes little. Notably, daily operations are anticipated to be similar: submitting XML data about the documents, but with richer metadata on top (globalforum.diaglobal.org).

The implications of eCTD 4.0 tie into broader regulatory digitization: structured submission data, integration with therapeutic area ontologies, and real-time product histories. The Accumulus Synergy initiative (a consortium led by industry) is already building cloud-based exchange platforms, suggesting that in the future the entire regulatory dossier could live in a shared cloud data environment (pmc.ncbi.nlm.nih.gov)

([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Digital health data standards (FHIR, etc.) may eventually link with eCTD records, enabling precompetitive analyses. The COVID-19 pandemic, by demanding rapid global reviews, has underscored the need for interoperable regulatory networks ([pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)).

Evolving Regulatory Ecosystem

Moving beyond eCTD, regulators and industry are exploring **dynamic electronic submissions**. Examples include:

- **Real-World Evidence and Continuous Updates:** Regulators encourage use of real-world data (RWD) in submissions. eCTD allows adding large appendices, but not as easily as a continuous database feed. Future submission systems may allow sponsors to update evidence on an ongoing basis (e.g. adding new post-marketing safety data via feeds). Such capabilities would blur the distinction between marketing applications and safety reporting.
- **Regulatory Knowledge Management:** Agencies want to mine past submissions for knowledge (comparing similar products, identifying risk factors). Structured content (metadata, standardized vocabularies like IDMP) will enable cross-analysis. ECTD 4.0's more granular data could accelerate this.
- **Global Harmonization Efforts:** The ICH's focus is shifting to reducing region-specific differences. For instance, eCTD 4.0 pushes for unified product definitions (RPS parameterization) and encourages eventual elimination of divergent national formats. As Extedo points out, sponsors habitually adapt to regional rules; the industry is eager for true global convergence (www.extedo.com) (www.extedo.com).
- **Digital Submissions for All Products:** While CTD/eCTD primarily covers drugs and biologics, parallel efforts are expanding to other products. The ICH RPS model is being extended to medical devices and combination products. In future, medical device 510(k) or drug-device combination submissions could flow through an RPS-based channel.

In summary, while the CTD/eCTD framework is still the dominant standard for drug submissions today, it is gradually evolving into a broader “regulatory knowledge exchange” ecosystem. The **implications** are profound: pharmaceutical companies must build sophisticated information management capabilities (often aligning with IT strategies and quality systems) (www.appliedclinicaltrials.com). Regulatory agencies must also continually invest in digital infrastructure and staff skills. Ultimately, however, the movement toward electronic submissions and data-driven review is justified by the promise of faster drug development and better-informed regulatory decisions, supporting public health.

Discussion and Conclusions

The transition from CTD to eCTD represents a fundamental modernization of pharmaceutical regulatory submissions. The CTD provided much-needed global harmonization of content (five-module structure) (globalforum.diaglobal.org); the eCTD adds a second dimension of format and process (XML backbone, lifecycle control) (globalforum.diaglobal.org) (globalforum.diaglobal.org). Together they have shaped how new therapies are approved worldwide.

Historically, paper CTDs were cumbersome to compile, transport, and review. The adoption of eCTD has vastly improved the regulatory workflow: reviewers now navigate diverse applications electronically, sponsors leverage document reuse, and agencies achieve cost savings in review capacity (ectd247.com) (globalforum.diaglobal.org). The evidence is clear: regulatory bodies report processing millions of eCTD submissions efficiently, and industry cites reduced time-to-approval in parallel with eCTD usage (ectd247.com) (globalforum.diaglobal.org).

At the same time, eCTD compliance has become a fully-fledged discipline. The technical stringency of eCTD (PDF standards, XML schemas, validation requirements) has raised the bar for submission quality. As the Applied Clinical Trials article noted, a flawed eCTD can be outright rejected (www.appliedclinicaltrials.com), incentivizing sponsors to form dedicated eCTD teams and leveraging software tools. The precise tracking of documents improves accountability, but also demands rigorous process control from dossier preparation through to final submission.

Looking ahead, eCTD 4.0 and emerging digital paradigms promise even greater change. The shift to a data-centric model (HL7 RPS, IDMP standards, cloud systems) will blur the line between “submission” and “database.” Regulatory authorities envision a future where updates are continuous and analytics-driven, with multinational regulatory collaboration enabled by living, connected dossiers (pmc.ncbi.nlm.nih.gov) (globalforum.diaglobal.org). For instance, initiatives like FDA’s Technology Modernization Action Plan (TMAP) and Data Modernization Action Plan (DMAP) and the EMA’s telematics strategy explicitly name eCTD modernization as a goal (pmc.ncbi.nlm.nih.gov) (globalforum.diaglobal.org).

In conclusion, while the CTD vs. eCTD transition has already delivered substantial benefits (standardization, efficiency, traceability), it is only an intermediate step in the broader digital transformation of pharma regulation. All stakeholders – industry, regulatory, and technology providers – must continue adapting. Sponsors should treat the CTD/eCTD not as a static checklist but as part of a dynamic regulatory dialogue, leveraging each update to better demonstrate product safety and efficacy. Regulators, in turn, should aim to refine submission specifications to gradually unlock data utility (e.g., structured CMC data or safety surveillance). If successful, the ongoing evolution from paperwork to eCTD to a future cloud-based reference model will ultimately bring therapy innovations to patients faster and safer, fulfilling the goals that first drove CTD harmonization decades ago (pmc.ncbi.nlm.nih.gov) (pmc.ncbi.nlm.nih.gov).

References

All claims and data above draw from authoritative sources, including regulatory guidelines (FDA/EMA publications), ICH documents, peer-reviewed analyses, and industry reports. Key citations include ICH and agency guidelines on CTD/eCTD structure, published eCTD implementation statistics (www.appliedclinicaltrials.com) (globalforum.diaglobal.org), and expert commentaries on the historical development and future of regulatory submissions (globalforum.diaglobal.org) (pmc.ncbi.nlm.nih.gov).

Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

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