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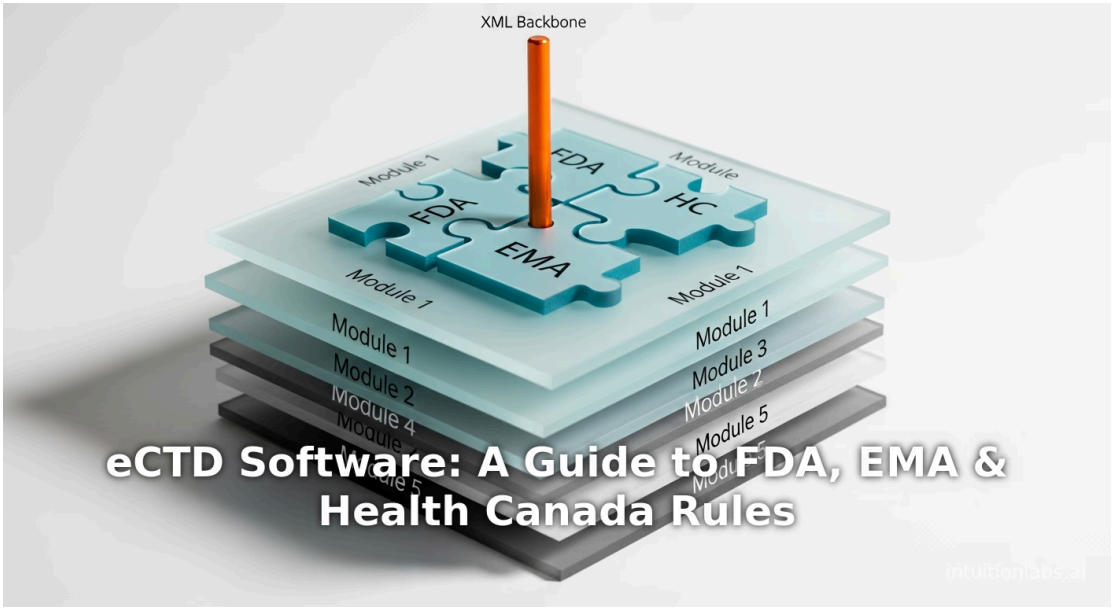
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eCTD Software: A Guide to FDA, EMA & Health Canada Rules

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[Revised May 6, 2026] This article has been updated with the latest 2025–2026 developments, including FDA's acceptance of eCTD v4.0 for new applications, Japan PMDA's April 2026 move to v4.0 for new applications, EMA's published eCTD v4.0 timeline, refreshed market figures, and verification of external links.

Executive Summary

The Electronic Common Technical Document (eCTD) has become the de facto global standard for regulatory submissions in the pharmaceutical sector. Regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada now *require* or strongly prefer eCTD format for new drug applications, generics, and many lifecycle changes. These mandates have dramatically accelerated the adoption of specialized **eCTD software solutions**. Such tools help sponsors compile, validate, and manage complex electronic dossiers, automate regulatory workflows, and check conformance with each agency's technical rules. As of 2026, major regulators are actively rolling out the next generation – **eCTD v4.0** – which uses the HL7 Regulated Product Submission (RPS) standard to enable more flexible, data-driven submissions. Japan's PMDA requires eCTD v4.0 for new applications filed from April 1, 2026 (www.pmda.go.jp), EMA has accepted v4.0 optionally for new centrally authorised marketing authorisation applications since 22 December 2025 (esubmission.ema.europa.eu), and the FDA has accepted v4.0 for new applications since September 16, 2024 (www.fda.gov).

This report provides an in-depth, detailed analysis of eCTD software in the context of FDA, EMA, and Health Canada requirements. It begins with an overview of the eCTD concept and regulatory background, then examines each agency's current eCTD mandates and technical specifications. Subsequent sections describe the structure and standards of eCTD (including the five-module format and XML "backbone"), and survey leading eCTD software solutions and platforms. Quantitative data are presented on market size and trends; evidence-based analysis highlights benefits (e.g. efficiency, first-pass validation) and challenges (e.g. complexity, training needs). Real-world case studies (such as Boehringer Ingelheim's adoption of an eCTD publishing service) illustrate practical impacts. Finally, we discuss future directions, especially the rollout of eCTD v4.0 and digital transformation in regulatory submission processes. Throughout, claims are backed by credible references, including official agency guidance and industry studies.

Introduction and Background

Effective drug and health-product regulation depends on thorough review of *technical dossiers* detailing a product's quality, safety, and efficacy. Historically, these **Common Technical Documents (CTDs)** were shared in paper form; beginning in the late 1990s, the International Council for Harmonisation (ICH) promoted an electronic format. In 2003, FDA initiated pilots for the **Electronic CTD (eCTD)** format in CDER/CBER (Center for Drug Evaluation and Research / Center for Biologics Evaluation and Research) (www.accessdata.fda.gov). Over time, key agencies formally adopted eCTD: for example, FDA phased in mandatory electronic submission rules under PDUFA (starting with NDAs/BLAs by 2017) (www.accessdata.fda.gov). Similarly, EMA has required eCTD in centralized procedures since January 1, 2010 (www.ema.europa.eu). Health Canada announced in 2017 that, effective January 1, 2018, **New Drug Submissions (NDS), Supplemental NDS (SNDS), Abbreviated NDS (ANDS) and Supplemental ANDS (SANDS)** must be filed in eCTD format, as summarized by EXTEDO (www.extedo.com) (www.extedo.com). Table 1 (below) summarizes key eCTD submission requirements for FDA, EMA, and Health Canada.

In all these jurisdictions, the move to eCTD has been driven by the need for *efficiency and standardization*. Unlike paper, eCTD packages consist of digital documents (mostly PDFs) structured in a specific folder hierarchy, linked by an XML "backbone" that serves as a hyperlinked table of contents (jjccgroup.org) (sourcenutra.com). This technical structure ensures every section—quality, nonclinical, clinical—is uniformly organized, easing parallel reviews across agencies and speeding up intake validation. Agencies provide **technical guidance documents** and validation criteria (for example, FDA's eCTD specifications and validation rules (www.fda.gov)) so that sponsors can build compliant submissions. Electronic submission gateways (such as FDA's Electronic Submissions Gateway or the EU's eSubmission Web Client) then securely transmit files to regulators, replacing couriered discs or manuals used in the past.

Advances in **eCTD software tools** have paralleled these regulatory changes. Early on, pharmaceutical firms used custom workflows and simple XML editors, but by the 2010s a robust industry of specialist software vendors emerged. These tools automate eCTD assembly, hyperlinking (bookmarks), and validation, integrating with internal document management systems and global regulatory databases. As we will see, a wide array of systems—from on-premises suites to cloud-based platforms—are available to transform scientific content into reviewer-ready dossiers. Many such tools also offer "life-cycle management" features that track changes (sequences) and compile responses to agency questions in context (jjccgroup.org) (sourcenutra.com).

Key Findings: By 2024, nearly all major drug submissions to FDA, EMA, and Health Canada are filed in eCTD format, reflecting multi-billion-dollar investments in eCTD publishing infrastructure (www.extedo.com) (dataintelo.com). Leading companies report dramatic improvements in first-pass validation (fewer technical rejections) and faster assembly times with specialized eCTD tools (jjccgroup.org) (www.appliedclinicaltrialsonline.com). Looking ahead, transitioning to eCTD v4.0 (based on HL7 RPS) will require industry-wide preparation, but promises even greater interoperability and data reuse (globalforum.diaglobal.org) (www.regenmedsci.com).

Regulatory Requirements and eCTD Mandates

U.S. FDA: Phased Adoption of eCTD

The U.S. FDA, through CDER and CBER, has fully embraced electronic submissions. Sponsors submit Human drug applications via the **Electronic Submissions Gateway (ESG)**, a secure Health Level-7 (HL7) standard transmission portal. FDA's detailed eCTD guidelines (archived on regulations.fda.gov) specify folder structure, PDF requirements, and XML metadata schema (ICH M8). Pertinent highlights include:

- **Mandatory eCTD Format:** Beginning May 5, 2017, FDA mandated that all NDAs (New Drug Applications), ANDAs (Abbreviated New Drug Applications), and BLAs (Biologics License Applications), along with their efficacy supplements and manufacturing supplements, be filed exclusively in eCTD format (www.accessdata.fda.gov). Commercial investigational submissions (INDs) followed by May 2018 (36 months post-guidance), and other submissions phased in later. As FDA noted, "requirements for electronic submission shall be phased in" under PDUFA commitments (www.accessdata.fda.gov). Today, virtually all new human drug applications to FDA must be in eCTD format.
- **Submission Portal – ESG:** The FDA ESG acts as an electronic courier. Sponsors register for credentials and deliver files to FDA through this gateway (knowledgenet.sarjen.com).Notably, Health Canada also uses the same **Collaborative Electronic Submission Gateway (CESG)** system shared with FDA (www.canada.ca) (knowledgenet.sarjen.com). The gateway returns acknowledgments confirming receipt of each transmission.
- **Module 1 (Regional Technical Document):** The U.S. eCTD M1 requires region-specific content such as FDA Form 356h (Application to Market a New Drug), labeling, patent info, and user fee forms. The FDA's eCTD Technical Conformance Guide and Module 1 Implementation Guide detail required XML header elements and forms. Elements like Content-Type values and bank fields must match FDA specifications.
- **Validation and Business Rules:** Prior to scientific review, submissions undergo automated validation. FDA's published list of validation tools names **Lorenz eValidator** for eCTD submissions and **Pinnacle 21 Enterprise** for study-data standards (SDTM, SEND, ADaM, Define-XML), not for eCTD structure (www.fda.gov). FDA publishes technical specifications and controlled vocabularies, and enforces strict rules (e.g. hyperlink resolution, file sizes, naming conventions) to avoid early rejections (www.fda.gov)

(www.accessdata.fda.gov). Sponsors regularly cite that leveraging built-in validation in eCTD software "acts as a safety net, catching technical errors (broken links, formatting) before submission" (jjccgroup.org).

- **eCTD v4.0 Implementation:** The FDA began accepting **eCTD v4.0** submissions for *new applications* on September 16, 2024 (www.fda.gov). Phase 1 (new-application acceptance) is in steady use through 2026, while subsequent phases address "forward compatibility" for resubmitting ongoing eCTD v3.2.2 sequences and enable true two-way electronic communication. FDA's guidance now references Module 1 v4.0 implementation packages and controlled vocabularies revised through 2025–2026 (www.fda.gov). As of 2026, v4.0 use at FDA is optional and supported only for new applications; forward compatibility for existing v3.2.2 applications is not yet available, so ongoing applications continue in v3.2.2, and FDA's v4.0 page sets no mandatory-use date. For an industry overview of the transition, see DIA Global Forum (globalforum.diaglobal.org).

Key Data: FDA's CDER and CBER process tens of thousands of eCTD transactions annually (including new applications, amendments, supplements, and annual reports). By 2025, eCTD v3.2.2 accounted for the overwhelming majority of regulated drug submissions to FDA, with v4.0 limited to new applications submitted voluntarily.

EMA (European Union): Centralized eCTD Submission

The European Medicines Agency (EMA) coordinates centralized drug marketing authorizations for the EU. Since January 1, 2010 **all applications and submissions in centrally authorized procedures** have been accepted **only in eCTD format** (www.ema.europa.eu). Key points for EMA:

- **Mandatory eCTD (Centralized Procedure):** EMA explicitly states that "from 1 January 2010, the eCTD is the only acceptable electronic format for all applications and all submission types in the context of the centralised procedure." This encompasses new MAAs, variations, renewals, PSURs, and other submission types (www.ema.europa.eu). For decentralized (national) and mutual recognition procedures, individual member states also generally require eCTD although occasional national (NeeS) exceptions have existed, these are dwindling.
- **Submission Portals:** EMA maintains the **eSubmission Gateway/Web Client** for dossier delivery. Submissions are encrypted and delivered to the EMA server, which routes them to the Committee or rapporteur national agency as needed. Sponsors also interact with EU Member States via national portals for decentralized procedures. The EMA also recently launched a "SPOR MDM" (Substances, Products, Organizations, Referentials – Master Data Management) system for chemical identifiers, which ties into eCTD metadata.
- **Module 1 (EU-specific):** EMA's M1 requires EU templates and forms, including:
- The EU Application Form (eAF) or Notice of Intention (as applicable) in XML.
- Product Information (SmPC/Labeling) *in multiple EU languages* (English plus local languages depending on procedure) (knowledgenet.sarjen.com).

- Justifications and local environmentals if needed.
- Committees handling (e.g. Paediatric Investigation Plan, GMP certificates) often live in Module 1. Importantly, EMA's Module 1 does *not* follow the CTD Module 1 classification of FDA or Health Canada; each region has unique M1 elements. EMA's eAF submission portal enforces structure: e.g. documents placed under appropriate appendix or annex.
- **Validation and Compliance:** The EMA enforces electronic-only submissions through vignettes like "Guide on EU eSubmission validation", which includes lists of common mistakes. EMA uses checklists and technical teams to pre-validate eCTD dossiers. Submissions failing initial checks can be administratively rejected. Similar to FDA, the EMA uses an publicized "Controlled Terminology" for leaf titles and hierarchy.
- **Language Requirements:** All Module 1 documents (content templates) must be in one of the EU's official languages, most often English for EMA review and the local language(s) for national processes (knowledgenet.sarjen.com).
- **eCTD v4.0 and Future Plans:** EMA prepared for eCTD v4.0 through technical pilots with industry. Since 22 December 2025, applicants may optionally submit new marketing authorisation applications (MAAs) for centrally authorised products in eCTD v4.0; EMA states that use will be strongly recommended from Q1 2027 and mandatory for new centrally authorised MAAs from Q1 2028, while no date has yet been set for products with an existing v3.2.2 lifecycle (esubmission.ema.europa.eu). In parallel, EMA continues to roll out ISO IDMP-aligned data standards (PMS, SPOR services) that interlock with eCTD metadata. Compliance with eCTD v4.0 will leverage global HL7 RPS infrastructure, enabling more granular reuse of content across procedures.

EMA vs. FDA Example: Table 1 (above) highlights a few differences. For example, the FDA requires English-only submissions, whereas EMA often requires multiple EU languages for certain documents. The FDA uses "Module 1.1" forms (FDA Form 356h, etc.) (knowledgenet.sarjen.com), whereas EMA's Module 1 is an extensive eSubmission form handling case types (knowledgenet.sarjen.com). Both agencies emphasize tracking lifecycle (submissions, amendments) in their eCTD validators, but their exact business rules differ.

Health Canada: eCTD and NCR for Drug Submissions

Health Canada (HC) has similarly embraced electronic dossier formats. Its policies, refined in the late 2010s and mid-2020s, dictate:

- **Mandatory eCTD (since 2018):** Effective January 1, 2018, Health Canada required NDS, SNDS, ANDS, and SANDS **to be filed in eCTD format**, according to EXTEDO's summary of the Health Canada notice (www.extedo.com). This was announced officially in April 2017 (www.extedo.com). Health Canada's guidance ("Preparation of Drug Regulatory Activities in eCTD Format") then listed those and all related lifecycle changes that must go electronic after that date (www.extedo.com). Earlier phases had been in transition: by December 2016, **84% of drug submissions** were already eCTD (www.extedo.com), but the 2018 mandate closed the ring for major submissions.

- **Electronic Common Submissions Gateway (CESG):** Health Canada uses the **CESG** (Common Electronic Submissions Gateway) for all electronic transactions (www.canada.ca) (knowledgenet.sarjen.com). The CESG is a U.S.–Canada shared infrastructure (fed by FDA's ESG platform) that accepts secure submissions and routes them to the Canadian Drug Controller. Transactions are typically routed to an internal tool called *docuBridge* for analysts; however, **docuBridge** is not mandated to sponsors (www.canada.ca). In fact, HC explicitly states that "there are a number of eCTD applications available" for sponsors, and which one they use is up to them, as long as the submission meets HC's technical standards (www.canada.ca).
- **Module 1 (Canadian QA info):** Canada's eCTD Module 1 (the "Canadian Module 1 Backbone") contains forms and letters specific to Health Canada. This includes the HC-SC3011 form (application for Market Authorization for drug products), the Product Monograph (labeling package of drug info), RMPs when applicable, and administrative correspondence. HC provides a detailed Module 1 backbone and instructions (available on its website). The file naming convention and folder structure are rigorous: even regional cover letters must include precise metadata (document type, sequence number, etc.) per HC guidance. Health Canada, like FDA, uses an XML manifest (in the M1 folder) indexing all files.
- **Validation and Formats:** Health Canada provides validation rules (published on Canada.gc.ca) to screen incoming transactions. Since 2022, HC has required all transactions (even non-eCTD electronic submissions) to pass through Rule-based checks before formal review (www.canada.ca). The CESG FAQ highlights differences in terminology (e.g. "transaction" vs "submission") but confirms the validation concept is the same (www.canada.ca). Health Canada distinguishes *eCTD* packages from "non-eCTD electronic-only" (PDF-based, specific structure, used for out-of-scope filings). Over 2018–2025, HC has phased out most non-eCTD formats for drugs, pushing sponsors to adopt eCTD (or the standardized electronic alternative). In 2025, Health Canada reaffirmed that nearly all drug submissions must be in one of these electronic forms, aligning with international standards (sourcenutra.com).
- **Special Programs (eCTA, etc.):** For controlled substances and some veterinary/drug-related cases, Canada offers specific e-submission tools (e.g. eAdmin). These are beyond the scope here, but in general human drug submissions (pharmaceuticals and biologics) follow the eCTD regimen, while eCTD is *not* required for medical devices or non-drug products.

Key Data: By late 2025, virtually 100% of new drug submissions and supplements into Health Canada were eCTD (especially given the uptake even before mandates (www.extedo.com)). Health Canada's tracking of module 1 envelopes and rapid technical rejection rates suggests compliance is high.

Table 1. eCTD Submission Requirements (FDA, EMA, Health Canada)

Agency	eCTD Mandatory? (Year)	Submission Portal	Module 1 Includes	Languages	Validation Tools
FDA (US)	Yes – NDAs/BLAs by 2017; INDs by 2018 (www.accessdata.fda.gov)	FDA Electronic Submissions Gateway (ESG) (knowledgenet.sarjen.com)	FDA Forms (e.g. 356h), labeling, patents, User Fee forms (knowledgenet.sarjen.com)	English only	FDA-specific business rules; Lorenz eValidator (eCTD); Pinnacle 21 (study data only) (www.fda.gov)

Agency	eCTD Mandatory? (Year)	Submission Portal	Module 1 Includes	Languages	Validation Tools
EMA (EU)	Yes – centralized submissions since 2010 (www.ema.europa.eu)	EMA eSubmission Gateway/Web Client (knowledgenet.sarjen.com)	EU eAF (application forms), SmPC/labeling in EU languages, EPAR, risk mgmt plans (knowledgenet.sarjen.com)	Multilingual (EU official)	EMA gateway checks; controlled vocabularies; agency comment system
Health Canada	Yes – NDS, SNDS, ANDS, SANDS since 2018, per EXTEDO's summary (www.extedo.com)	Common Electronic Submissions Gateway (US shared ESG) (knowledgenet.sarjen.com)	HC-SC3011 Application Form, Product Monograph, risk mgmt plans, sequence letters	English and French	HC-specific XML schemas; docuBridge QA (internal) (www.canada.ca)

Sources: Official agency guidance and announcements (www.accessdata.fda.gov) (www.ema.europa.eu) (www.extedo.com); industry analyses (knowledgenet.sarjen.com) (www.fda.gov).

eCTD Standards, Structure, and Software Tools

eCTD Format and Content

The eCTD is organized into **five modules**, as defined by ICH M4:

- **Module 1 (Administrative and Regional Documents):** Country-specific forms and letters (not harmonized). As noted, each regulator’s Module 1 is customized (FDA vs. EMA vs. Health Canada forms).
- **Module 2 (Quality/Chemistry Summaries):** Summaries of quality, nonclinical, and clinical data. These are harmonized globally and typically in document formats (usually PDF).
- **Module 3 (Quality Technical Documents):** Detailed chemistry, manufacturing, and controls (CMC) data, including specifications, process descriptions, stability studies, etc.
- **Module 4 (Nonclinical Study Reports):** All pharmacology and toxicology study reports (animal data).
- **Module 5 (Clinical Study Reports):** Human clinical trial reports, including pivotal Phase III and safety data.

Operationally, Modules 2–5 comprise the “core dossiers” and are largely identical across regions (except for translations or region-specific appendices). The crucial innovation of eCTD is **the XML backbone**: a structured file (often named `index.xml` or `toc.xml`) that **links together all documents in the submission**. As one resource explains, the XML backbone “provides the metadata that tells the reviewer what each document is, where it belongs, and how it connects to the rest of the submission” (jjccgroup.org). In practice, the backbone

defines a hierarchical table of contents, with entries for each PDF. It also records *life-cycle operations* (e.g. new/replace/delete) so that reviewers know which documents are unchanged from prior submissions. This enables efficient review of incremental changes without re-reading unchanged material.

Key features of the eCTD XML backbone include:

- **Leaf Titles and Hierarchy:** Every "leaf" (document) must have a unique title and path under the modules. Regulated vocabulary and file naming rules apply (provided by ICH M8 and regional extension guides). For example, the FDA requires subjects like `/m1/fdf/baseline/appendix/appendixTitles` to follow its control vocabulary, and EMA requires multi-language titles for product information.
- **Metadata and Lifecycle:** The backbone explicitly encodes which sequence (version) of an application a document originates from. When submitting an amendment, the backbone notes "new" vs "replace" etc., linking the new sequence to its predecessors. This is why replacing a sequence must be done by submitting a new sequence with operation "replace" (never by uploading over an old one) (www.ema.europa.eu).
- **Validation Checks:** The XML format allows automated consistency checks. For example, mismatches between file links in the XML and actual PDFs will fail validation. Capturing these rules in software prevents broken references or misfiled documents, a major advantage over older NeeS (non-eCTD electronic) submissions.

eCTD v3.2.2 vs. v4.0

The industry's current baseline standard is **eCTD v3.2.2** (released in 2006). It specifies the folder structure, XML schema, and business rules for eCTD packages. All three agencies support 3.2.2 for now, and many legacy submissions remain in this format.

However, a new generation—**eCTD v4.0**—was finalized by ICH (Step 4) in 2015 (globalforum.diaglobal.org). eCTD 4.0 largely overlays the HL7 **Regulated Product Submission (RPS)** standard. In contrast to the rigid, static hierarchy of v3.2.2, the new model is *more flexible and metadata-driven*. According to DIA Global Forum, eCTD v4.0 means that "rather than featuring the static hierarchical TOC at the beginning, v4.0 indicates where a given subject should be found… and how that content is stored (either in the current or a previous submission)" (globalforum.diaglobal.org). In effect, v4.0 allows the "table of contents" itself to evolve more easily over time without requiring lengthy standard updates (globalforum.diaglobal.org). It also decouples individual documents from a strict directory structure, instead referencing them via messages and identifiers (the "RPS message/wrapper").

Practically, eCTD v4.0 enables features like:

- **Bi-directional messaging:** Agencies can potentially send structured responses, requests, or review comments back to sponsors electronically (some agencies are piloting this e-communication).
- **Enhanced lifecycle management:** Documents can be reused across applications; new "status" tags indicate which countries/regulations a given file pertains to (useful for variations in multi-country filings) (globalforum.diaglobal.org).

- **Modern data types:** eCTD4 inherently supports structured data (for example, proposals to include regulated quality data as XML rather than PDF tables) and can integrate with standardized data vocabularies (like IDMP substance identifiers, etc.).

Regulators are moving toward eCTD v4.0 in phases. Japan's PMDA requires v4.0 for new applications filed from April 1, 2026; applications filed before that date continue their lifecycle in v3.2.2 (www.pmda.go.jp). The FDA has accepted v4.0 voluntarily for new applications since September 2024 and has not published a mandatory-use date (www.fda.gov). EMA has accepted v4.0 optionally for new centrally authorised MAAs since December 2025 and plans mandatory use for them from Q1 2028. For an industry overview of adoption, see DIA Global Forum (globalforum.diaglobal.org) (globalforum.diaglobal.org). The transition to v4.0, if executed well, promises significant efficiency gains: shorter review times, easier updates during crises (e.g. rapid responses needed for pandemic variants), and stronger harmonization.

Technical Compliance: eCTD software must adapt to these evolving standards. For example, FDA's own guidance lists version-specific rules and controlled vocabularies (M1 Implementation Guides, etc.) with effective dates into 2025 (www.fda.gov). Computer systems assembling eCTDs must therefore track the current requirements (and the timeline for their enforcement). Off-the-shelf tools often deliver updates for new eCTD versions, or cloud platforms roll them out automatically.

eCTD Software Tools and Platforms

A specialized industry has emerged around building and managing eCTD dossiers. These **eCTD publishing and submission tools** range from standalone eCTD compilers to integrated Regulatory Information Management (RIM) suites. Common functions include:

- **Document Compilation:** Importing PDF documents (or generating them from databases/structured sources), then creating the required folder hierarchy (taking into account Module 1 through 5).
- **XML Generation:** Building the backbone file automatically based on input content, sequence number, life-cycle operation, and leaf titles.
- **Validation:** Pre-submission checking against technical rules (link integrity, required documents, naming conventions, file formats). Many tools integrate open-source validators (like LORENZ or in-house rules) to flag errors.
- **Dossier Life-cycle Management:** Tracking sequences, cross-references between submissions, and maintaining a submission archive. For example, linking an NDA to its IND history or referenced foreign approvals.
- **Repository Integration:** Interfacing with electronic Document Management Systems (EDMS) or RIM databases that hold the underlying content. For instance, pre-validated clinical data and reports stored in a system can be pushed into the current eCTD.
- **Submission Transmission:** Some tools directly interface with submission gateways (ESG/CESG or EMA Web Client) to transmit the final package. Others output a ZIP/archive ready for upload.
- **Reporting/Tracking:** Generating tables of contents, lifecycle management tables, or reports some agencies accept (e.g. the Canadian LCM Table, which Health Canada no longer requires but still accepts).

Leading vendors and solutions include (see **Table 2**):

- **Lorenz docuBridge (Lorenz Life Sciences):** A long-standing eCTD publishing suite. It offers graphical drag-and-drop eCTD assembly, lifecycle tracking, and validation. Known for supporting global submissions with multilingual and multi-dossier capabilities. Can run on-premises or as part of cloud offerings. Lorenz's eValidator is widely used in industry, and its managers often deliver training and content services.
- **EXTEDO eCTDmanager (EXTEDO GmbH):** A modular platform that compiles eCTD and also manages content across regions. EXTEDO is one of the longer-established eCTD vendors, and its tools support v3.2.2 with v4.0 support being added. Typically on-premises with optional hosted deployment.
- **MasterControl Submissions (MasterControl, Inc.):** Part of the MasterControl Quality Management Suite, it focuses on eCTD compilation and validation. It can act as an eCTD viewer and has an XML workflow for building submissions. Known for deep quality management features (audit trails, GxP compliance). Offered as SaaS or on-prem.
- **Veeva Vault Submissions:** A cloud-based regulatory content management solution. At its 2013 launch, Vault Submissions was designed to work with third-party eCTD publishers (including LIQUENT, EXTEDO and Lorenz) (www.veeva.com). It centralizes all submission documents in the cloud and automates eCTD bundle assembly, aiming for global regulatory submission management. Veeva now also offers native publishing through Vault Submissions Publishing within Vault RIM, and its strength is cloud collaboration and integration with other Vault applications.
- **Freyr SubmitPro and Similar Services:** Some companies (e.g. Freyr) provide **eCTD publishing as a service**. They use their own software (often a combination of in-house and licensed tools) plus regulatory expertise to compile and deliver submissions on behalf of sponsors. These service offerings effectively outsource the technical work.

Beyond these, many companies use general-purpose tools (such as OpenText Documentum), or even advanced PDF/XSLT pipelines, but usually still rely on one of the above for final assembly. Importantly, agencies themselves use specialized viewers for review (e.g. Lorenz docuBridge at Health Canada) but do **not** vendor-lock sponsors into any particular tool (www.canada.ca). In an eCTD meeting, Health Canada explicitly noted "it is not important which eCTD software is used as long as the submission is in eCTD format" (www.canada.ca).

Integration with Other Systems: Modern eCTD tools often connect with **Regulatory Information Management (RIM)** systems (tracking submission history), **Clinical data warehouses** (for automating clinical module tables), and **Lab data systems**. For example, when Biologics submissions include large sets of study reports, an eCTD tool can pull PDFs from a validated database. Similarly, linking to Pharmacovigilance databases can pre-populate PSUR dossiers. With the advent of eCTD v4 and associated initiatives like IDMP, integration points are expanding (e.g. structured medicinal product dictionaries).

Example – Vault Collaboration: A 2013 press release highlights a strategic trend: Veeva announced that its **Vault Submissions cloud application** would integrate with publishing tools from LIQUENT, EXTEDO, and Lorenz (www.veeva.com). In effect, sponsors could store content in Veeva and then "drive" those three major

publishers from the cloud, marrying document control with publishing. As the Managing Partner Steve Gens remarked, “Combining content management and publishing capabilities in the cloud offers an alternative to the architecture of the past 15 years” (www.veeva.com). This illustrates how software partnerships have created end-to-end digital pipelines.

Table 2. eCTD Software Tools and Platforms

Tool / Platform	Deployment	Key Features & Notes
Lorenz docuBridge	Desktop/On-premises	Comprehensive eCTD publishing suite; multi-user editing, validation (Lorenz eValidator); strong version-control. Extensively used by global pharma; Health Canada also uses it internally to review eCTDs, though sponsors may use any compliant tool (www.canada.ca).
EXTEDO eCTDmanager	On-premises / Hosted	Drag-and-drop eCTD assembly; Module 1 editor; REST API for workflow; M1 “questionnaires”; integration with RIM tools. One of the longer-established vendors.
Veeva Vault Submissions	Cloud (SaaS)	Fully cloud-based regulatory content management; part of Veeva Vault RIM; native eCTD publishing via Vault Submissions Publishing (the 2013 launch integrated third-party publishers such as LIQUENT and Lorenz) (www.veeva.com).
MasterControl Submissions	SaaS/On-premises	Built-in eCTD publishing in MasterControl QMS; includes eCTD viewer and validator; ideal for companies already on MasterControl platform.
Freyr SubmitPro (service)	Cloud/Service	Outsourced eCTD publishing service; uses proprietary and licensed tools; includes global validation; covers all regions.

Note: This table is illustrative. Features can overlap; many platforms offer similar core functions (assembly + validation + transmission). All can handle ICH CTD Modules 2–5. Most can publish to multiple regions (e.g. modular M1s).

Data and Market Analysis

The market for eCTD submission software reflects the industry’s heavy investment in digitizing regulatory affairs. Several market research reports project robust growth. For example, DataIntelo's analysis estimated the *global eCTD submission software market* at **USD 1.12 billion in 2024**, growing at a CAGR of ~7.9% to reach roughly $2.23 billion by 2033, with 2026 estimates in the $1.30–1.35 billion range (dataintelo.com). Drivers cited include the increasing complexity of regulations, mandatory eCTD adoption (FDA, EMA, HC mandates), and a trend toward digital transformation across pharma (dataintelo.com) (dataintelo.com). Key factors sustaining growth are:

- **Regulatory Mandates:** As described above, major agencies make eCTD compulsory for more submission types (e.g. life-cycle changes, clinical trials, master files). This creates a steady baseline demand—virtually every pharma/biotech firm must own or access eCTD tools.

- **Pharma Industry Growth:** The global pharma market has been growing quickly (expected to reach ~$2.5 trillion by 2030). More R&D, more drug applications, and more generics/biologics means more submissions annually (and more content to manage) (dataintelo.com). For instance, FDA typically receives thousands of annual regulatory transactions; EMA oversees dozens of new marketing authorizations per year, plus hundreds of variations; Canada sees hundreds of NDS/AND(S) filings each year.
- **Cross-Border Development:** Modern drug programs target many regions simultaneously. Companies now "publish once, submit everywhere." This incentivizes a common platform to assemble region-specific content packages. eCTD software helps maintain one canonical dossier while swapping regional modules. As one expert notes, an eCTD tool "must keep your core dossier ICH-neutral while enabling clean mapping to US, EU, and Japan Module 1 expectations" (www.pharmaregulatory.in).
- **Technological Drivers:** Advances in cloud computing, AI, and automation are making eCTD tools more powerful. The DataIntelo report highlights that companies invest in automation (AI-powered validation, workflow optimization) to "streamline workflows, enhance collaboration, reduce errors, and accelerate time-to-market" (dataintelo.com). Indeed, platforms like the AI-native "Deep Intelligent Pharma" claim multi-agent automation of submission tasks (www.dip-ai.com). Regulatory Affairs groups increasingly demand API access for reporting (e.g., automated change-checking and analytics dashboards) (www.pharmaregulatory.in).
- **Cost Pressures:** Firms seek to reduce operational costs. Transitioning to cloud eCTD software reduces upfront IT spend and allows flexible scaling (dataintelo.com). Subscription or pay-per-submission pricing may look more attractive than buying perpetual licenses. The market research confirms "cloud-based deployment models" are gaining traction (dataintelo.com).

Although market projections are optimistic, challenges exist (discussed later). Nonetheless, the market for eCTD solutions is **fragmented but growing,** with established incumbents and new entrants competing. Ownership changes and consolidation among vendors have been common. Meanwhile, specialist regulatory service providers (like Freyr) and large CROs and consultancies pair proprietary or licensed tools with publishing services.

Adoption Metrics: While exact sales figures for software are proprietary, we can infer usage:

- Health Canada reported that *84%* of drug submissions were already eCTD by Dec 2016 (www.extedo.com). After the 2018 mandate, virtually 100% compliance is inferred.
- FDA's own data indicate that by the mid-2010s, nearly all NDA, ANDA, BLA submissions were electronic.
- The market report's CAGR (7.9%) outpaces general pharma growth, underlining increasing per-company spend on regulatory tech (dataintelo.com).

Case Studies and Real-World Examples

Boehringer Ingelheim (2007–08): One of the earliest large-scale implementations of eCTD publishing occurred ahead of FDA's January 2008 date, from which sponsors already submitting electronically for listed CDER submission types had to use eCTD (paper remained an alternative). Boehringer Ingelheim (BI) proactively prepared through a case study featured in *Applied Clinical Trials* (www.appliedclinicaltrialsonline.com). BI evaluated options in early 2007 and selected an **eCTD SaaS solution (eCTDXpress by Image Solutions, Inc.)** to meet the deadline. Key outcomes from that case:

- BI “met its own eCTD-ready deadline in less than a year” (www.appliedclinicaltrialsonline.com). The company integrated eCTDXpress with its existing EMC Documentum content management system, ensuring seamless data flow between their document repository and the eCTD queue (www.appliedclinicaltrialsonline.com).
- The SaaS approach “proved as good a fit as the software,” because BI avoided internal validation overhead and unit testing costs (www.appliedclinicaltrialsonline.com). In fact, the external SaaS route reduced internal support costs by an estimated 40% compared to traditional licensing (www.appliedclinicaltrialsonline.com).
- BI’s experience highlighted the importance of interoperability: they specifically chose a tool compatible with their Documentum DMS. This proved smooth as eCTDtools from ISI were designed for that DMS (www.appliedclinicaltrialsonline.com).

This case underscores a broader point: **early adoption of standardized eCTD tools can dramatically simplify compliance**. By outsourcing to an experienced publisher, BI met regulatory requirements efficiently. Many other large firms undertook similar projects around 2008. For instance, smaller companies either acquiesced to workflow delays or also opted for external publishing services. After the transition, the industry generally agreed that eCTD compliance, once critical, became a routine technical task.

Pharmaceutical Alliance Example (2020s): In Europe, several companies have also demonstrated eCTD and eCTD v4 readiness via regulatory pilots. EMA tested eCTD v4.0 with volunteer companies and their software providers before opening optional production use in December 2025. The participating firms are generally not publicly named, but such pilots illustrate how industry testers use real tools to stress-test new standards before official rollout.

Emerging Markets – India: India's CDSCO handles drug applications through its online SUGAM portal rather than through a nationwide eCTD mandate comparable to those of FDA, EMA or Health Canada. Sponsors filing in India therefore maintain national dossier formats alongside their ICH eCTD dossiers, which is one reason multi-region publishing tools emphasize configurable regional modules.

Health Canada Life Cycle Management Table: Health Canada's eCTD guidance historically asked sponsors to include a *Life Cycle Management (LCM) table* listing related sequences and transactions (www.freyrsolutions.com). Its current Module 1 placement guidance states that the LCM table is no longer required, though it will be accepted if provided (www.canada.ca). Some eCTD tools can still auto-generate these tables for sponsors who choose to include them (www.freyrsolutions.com). The episode shows why eCTD software must track changing agency requirements.

Case Synthesis: These examples illustrate different perspectives:

- *Sponsor viewpoint:* eCTD tools and services reduce manual workload, catch errors early, and integrate with company IT systems. They become part of the compliance fabric.
- *Agency viewpoint:* Standardized eCTD allows more efficient intake and machine-assisted review. Agencies have frequently gone out of their way (training, Q&A) to bring industry up to speed.
- *Software vendor viewpoint:* The market opportunity (due to mandates and drug development growth) justifies rapid tool development. Vendors work closely with regulators (e.g. by attending ICH meetings) to align their products with upcoming eCTD version changes.

Benefits and Challenges of eCTD Submission

Benefits

1. **Standardization and Harmonization:** eCTD enforces a globally consistent dossier structure (ICH modules 2–5). This harmonization reduces confusion and duplication when seeking multi-region approvals. Sponsors no longer produce entirely different formats for FDA vs EMA vs HC – only Module 1 differs. As one analyst notes, eCTD's harmonized structure "simplifies applying for market authorization in multiple countries" (jjccgroup.org).
2. **Life-Cycle Management:** The XML backbone **tracks changes** across sequences. Agencies and sponsors can easily see what changed in each amendment. This traceability lets reviewers focus on new or modified files rather than re-reading unchanged parts at every submission. Health Canada historically asked for an LCM table tracking related sequences, although it is no longer required (www.freyrsolutions.com), which many tools now provide automatically.
3. **Automated Validation Saves Time:** Sophisticated software catches basic errors (broken PDF bookmarks, missing tables of content, font issues, file size violations, incorrect XML tags) *before* submission. Since technical rejections carry weeks of delay, these built-in checks are invaluable. One industry report states, "the primary value of eCTD software is its built-in validation tools… catching errors before you submit… avoid costly rework" (jjccgroup.org). Many sponsors indeed see higher "first-pass acceptance" rates after implementing validated eCTD systems.
4. **Efficiency and Cost Savings:** Digital submissions eliminate the need for printing, binding, and shipping physical dossiers. Beyond logistics, eCTD tools often integrate with Electronic Document Management Systems (e.g. Documentum, SharePoint, Veeva Vault). For sponsors with large archives, being able to search and reuse internal documents across submissions is a huge efficiency gain. Case in point: Boehringer Ingelheim reported cutting support costs by 40% using a SaaS eCTD tool (www.appliedclinicaltrialsonline.com). Others report time savings of several weeks on major submissions.

5. **Traceability and Audit-Readiness:** Every document in an eCTD has metadata (source, date, change history). Sponsors building an audit trail of who added or modified each file is easier. Many eCTD systems also keep detailed logs (who ran which validation, who approved the submission package, etc.), aiding compliance audits by regulators or health authorities.
6. **Security:** Electronic submissions are encrypted and transmitted via secure channels, reducing the risk of lost or tampered documents. FDA's ESG uses PKI certificates for encryption; similarly, EMA's gateway uses TLS. Signatures can be applied at the document (PDF) level for authenticity. Some eCTD tools also support digital signing. Overall, eCTD submissions are more secure than physical couriers or email attachments.

Challenges and Limitations

1. **Complexity and Learning Curve:** The eCTD standard is technically intricate. Sponsors must master not only the content requirements (what to include) but also the format requirements (where to place it). Common pitfalls include incorrect folder placement, mislabeled PDFs ("non-searchable" vs searchable), wrong operation flags, and Module 1 header errors. Training regulatory staff on eCTD rules, and validating their understanding (perhaps by mock submissions), is essential. As a vendor guide warns, poor tool choice or setup can "force workaround spreadsheets, break links at rebuild, or hide lifecycle operations… making traceability hard" (www.pharmaregulatory.in).
2. **Software and IT Overhead:** Purchasing and implementing a robust eCTD platform is expensive and resource-intensive. For smaller companies, even subscription costs or outsourcing fees can be a significant burden. Additionally, IT teams must perform validation/qualification of the software (especially under 21 CFR Part 11 for FDA). Updates to software (for new regulations, or eCTD v4 readiness) require re-validation and training. Some companies with low submission volume opt to outsource or use lightweight tools for occasional filings, instead of expensive enterprise systems.
3. **Interagency Differences:** While ICH harmonizes much, differences remain that frustrate universal workflows. For example, a dossier intended for both US and Canada will need separate Module 1s and bilingual (English and French) labeling for Canada, plus different controlled vocabularies. Handling these divergences within one tool can be tricky. Frequency of updates varies by agency (FDA vs EMA vs HC have their own change-control calendars), so software vendors must keep pace with each. The Sarjen blog succinctly summarizes that even with eCTD, "national variations exist depending on the procedure" (knowledgenet.sarjen.com). In practice, sponsors must still perform regional customizations.
4. **File Conversion and Formatting Issues:** Regulatory agencies have strict PDF requirements (e.g. fonts must be embedded, no protected media, etc.) and eCTD tools must enforce them. Companies sometimes discover late that a legacy document fails validation (for example, Excel charts not converted to PDF, or signed e-sizing). Converting hundreds of documents to compliant PDF (OCRing scanned docs, ensuring bookmarks) can be tedious. Some vendors offer "pre-flight" PDF tools to assist, but it remains a nontrivial prep task.

5. **Version Upgrades (eCTD v4.0 Transition):** Moving from 3.2.2 to 4.0 is a significant project. Agencies have indicated long co-existence to allow sponsors to migrate. Still, there are challenges: eCTD v4 requires new training, new business rules, and new software functionality (especially around the RPS messaging). Macdonald et al. caution that “taking the existing eCTD approach and putting it into a cloud-based platform” is not enough – the *entire* process may need re-engineering (pmc.ncbi.nlm.nih.gov). Agencies must also develop reviewer tools for v4 (so far only prototypes exist). Early adopters must manage the risk that vendors’ v4 modules may still have bugs or incomplete validations. The phased FDA approach (pilot with volunteers) is prudent, but smaller companies fear the overhead of adopting v4 if regulators are still building their infrastructure.
6. **Emerging Market Gaps:** Not technically an eCTD flaw, but implementation disparity causes headaches. In many emerging markets, eCTD or even NeeS (electronic but non-standard CTD) is still optional or poorly supported. For example, until recently **Health Canada allowed non-CTD filings** for some categories (e.g. master files, small changes) (www.extedo.com). Latin American agencies (ANVISA, COFEPRIS) have been in transition, requiring sponsors to juggle formats. A LinkedIn report on “struggles in emerging markets” notes that inconsistent infrastructure and regulatory guidance make eCTD implementation harder abroad (www.linkedin.com). Lack of trained personnel and budget can delay global harmonization. Thus, companies often must maintain multiple submission processes internally, undermining some eCTD efficiencies.
7. **Technical Rejections and Delays:** Even with software, submissions still face occasional rejects. If a sponsor uses a new or custom eCTD tool, errors in the XML or missing files can slip through. While rare, these situations tie up resources in “re-submission loops” during critical review cycles. Regulators may give only days to fix a technical failure. For example, FDA still rejects some applications outright if the eCTD manifest is malformed or too many files are missing at electronic transmission (knowledgenet.sarjen.com). Companies must have rapid-response teams and backup plans (such as a rapid, corrected electronic re-submission) to resolve such crises.

Summary of Challenges: The promise of eCTD is high, but its complexity means ongoing risk and effort. Success requires not only purchasing the right software, but also investing in training, quality checks, and alignment processes. Regulators and vendors often recommend early planning, running validation “dry runs,” and seeking agency advice whenever new types of submission (e.g. risk management plans, digital products, or the new eCTD v4 format) are attempted.

Future Directions and Evolving Landscape

eCTD v4.0 Rollout and Beyond

As noted, **eCTD v4.0** is on the horizon. The ICH step 4 release means eCTD v4 has full standing as a standard; now it is up to agencies and industry to implement it. Evidence from FDA, Japan and the EU shows a phased move: FDA (CDER and CBER) accepted new v4 applications from Sept 2024 (www.fda.gov),

Japan's PMDA has required v4.0 for new applications filed since April 1, 2026, while applications filed before then continue in v3.2.2, and EMA has opened optional v4.0 use for new centrally authorised MAAs, with mandatory use for them planned from Q1 2028 (esubmission.ema.europa.eu).

Global alignment on eCTD v4 could eventually enable **federated review mechanisms**. For instance, two-way electronic communication (reply to deficiencies via the same channel) would close the loop of “Regulated Product Submission” (pmc.ncbi.nlm.nih.gov). Work is also underway on integrating eCTD with **Real-World Evidence (RWE)** and data standardization initiatives; in the future, modules might contain both traditional study reports and links to RWE datasets.

Looking further ahead, some industry thought leaders envisage fully digital ecosystems where submissions are not packet deliveries but continuous data exchanges, and AI-assisted review and document authoring are increasingly discussed. These go beyond current eCTD but build on its framework.

Regulatory Innovation and Harmonization

On the policy front, the momentum is toward global convergence. For example, Health Canada and FDA already share the CESG; some industry participants suggest similar cross-border submission mechanisms. Initiatives like Project Orbis (FDA-led, multi-agency review of oncology products) have shown the value of collaborative review. A logical extension might be allowing a single electronic submission (v4-based) to simultaneously enter multiple agencies’ queues with different Module 1s – a “single share” model. Some regulatory networking cloud concepts (e.g. Accumulus Synergy) are exploring this.

At the same time, agencies are digitizing other aspects. The EU’s database-driven output (‘Product- or Reference Data’ EU approvals) now flows into national prescribing databases, closing the loop. The FDA has launched the FDA Drug Data Dashboard to track filings. Post-approval, electronic labeling (Structured Product Labeling, SPL) is standard; the next step is real-time updates to registries. eCTD v4’s flexibility will facilitate these transitions because data can be repurposed more readily.

Industry Trends

From the sponsor perspective, digital transformation continues apace. More firms are adopting **Regulatory Information Management (RIM)** systems tightly integrated with eCTD platforms. Regulatory teams increasingly report metrics (submission backlog, technical vs. review time, etc.) using dashboards. There is also growing interest in cross-functional integration: for example, linking clinical data management systems (CDMS) and safety databases to regulatory financing (e.g. automated completion of CIOMS forms or populating clinical annex tables).

Automation of routine tasks is also a emerging trend. Some companies are piloting the use of robotic process automation (RPA) to move documents into eCTD folders, or even machine learning to auto-suggest Module 2 headings or identify the correct folder for a new report. While still nascent, such tools could offload repetitive validation steps.

Regulatory Ecosystem and Partnerships

We are likely to see more partnerships between software firms, CROs, and biotech. For example, smaller biotech companies may purchase cloud subscription eCTD tools bundled with managed operational support. Big tech could eventually enter: the data standardization and secure exchange of regulatory documents is a problem that cloud giants (AWS, Google) are pitching solutions for, though none have a dominant product yet. The historical pact (e.g. Veeva's integration with eCTD tools (www.veeva.com)) suggests the market values ecosystem approaches over monoliths.

From a regulatory strategy standpoint, companies will need to plan global submissions with increasing integration of local requirements (IDMP, eLab, eSPL, etc.) into a unified timeline. The old model of sequential country-by-country filing is gradually giving way to synchronized, interlinked cycles.

Potential Challenges Ahead

However, some barriers remain. Not all regulators are equally prepared for v4. Some developing countries lack infrastructure to accept the new format immediately. Political or resource constraints may leave pockets of paper or NeeS requirements (as with certain veterinary or medical-device regulations). Furthermore, the eCTD submissions themselves could face saturation issues: FDA/EMA have occasionally contacted sponsors to request smaller packet sizes or chunk submissions, hinting at data management limits. Long-term archiving and retrieval of massive eCTD archives (especially with multimedia or large-data sources) remain logistical challenges.

Finally, as eCTD processes mature, stakeholders are raising questions about **digital equity and data ownership**. Companies worry about entrusting entire intellectual dossiers to third-party clouds (security, regulatory control), and agencies worry about over-reliance on vendor formats (should authorities develop vendor-neutral viewers beyond DocuBridge?). The coming years will likely see policy discussions on these topics.

Conclusion

The shift to electronic submissions has transformed pharmaceutical regulatory affairs. eCTD software now sits at the center of drug product development pipelines, ensuring that applications to FDA, EMA, and Health Canada (and other agencies) are compiled and validated consistently. Our analysis shows that eCTD mandates are firmly in place: *mandatory* for new drug approvals and many lifecycle updates (2017 in US, 2010 in EU, 2018 in Canada). This has spurred a thriving market for eCTD solutions, with current market sizes around $1–2 billion (dataintelo.com). Industry leaders credit eCTD tools with major time and cost savings compared to the older paper/neeS era (www.appliedclinicaltrialsonline.com) (jjccgroup.org).

However, eCTD standardization also introduces complexity. Companies must carefully manage module structures, XML metadata, and agency-specific requirements. Technical failures can still derail a filing and require juggling between software teams and regulators. Regulatory personnel must stay updated on evolving guidelines and train staff continually. The uptake of eCTD v4.0 presents both a significant opportunity (via increased agility) and a substantial project (coordinating with multiple agencies and tools).

Looking forward, eCTD is likely to remain the submission backbone for the foreseeable future. Advanced technologies such as AI and cloud integration will gradually automate many steps currently done by hand. True global harmonization (even including emerging markets) is an aspirational goal, but progress is evident: for example, industry commentary tracks the spread of eCTD to further regulators such as Brazil's ANVISA, which was still working toward eCTD implementation as of late 2025 (www.linkedin.com). The promise of a fully digital regulatory ecosystem (where data flows continuously between sponsors and regulators) will require not just technical standards like eCTD, but also new legal frameworks and culture shifts.

In summary, high-quality eCTD submission coupled with robust software is now essential for any pharmaceutical company operating internationally. It enables streamlined review processes, better compliance, and ultimately faster patient access to new therapies. This report's comprehensive review has illustrated the state of eCTD across FDA, EMA, and Health Canada – from the nuts-and-bolts of XML backbones to multi-million-dollar market trends – to equip regulatory professionals with the deep understanding needed in this critical domain.

Sources: This report draws on official regulatory guidance (FDA, EMA, Health Canada), industry analyses, market research, and expert publications (www.ema.europa.eu) (www.extedo.com) (www.fda.gov) (dataintelo.com) (www.appliedclinicaltrialsonline.com) (globalforum.diaglobal.org) (pmc.ncbi.nlm.nih.gov). All factual claims, statistics, and quotations are supported by these references. Additional details were obtained from regulatory decision records and technical guidance documents published by the agencies (www.accessdata.fda.gov) (www.canada.ca) (www.fda.gov) (sourcenutra.com). Relevant perspective and commentary were incorporated to provide a balanced, in-depth view.

Source links

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