

eCTD Sequence Management: A Guide to Regulatory Submissions

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Executive Summary

This report provides a comprehensive examination of **eCTD sequence management**, an essential aspect of modern pharmaceutical regulatory submissions. The Electronic Common Technical Document (eCTD) has become the global standard for submitting **drug dossiers** to authorities. Under eCTD, regulatory submissions evolve as a series of numbered “sequences,” each building on prior content. Effective sequence management involves correct numbering, linkage, and lifecycle operations (such as **new**, **replace**, **delete**, or **append** on individual dossier files) to ensure that regulators see an accurate, cumulative “current view” of a product’s data (^[1] www.linkedin.com) (www.pharmaregulatory.in).

Regulatory authorities worldwide have mandated or strongly encouraged eCTD usage, with specific timeline requirements (for example, the FDA required all new NDAs/ANDAs/BLAs to be eCTD by May 5, 2017 (^[2] www.linkedin.com), and INDs/DMFs by May 5, 2018 (^[3] www.linkedin.com)). The EU’s EMA has similarly phased in eCTD use, and new requirements are emerging globally. With the advent of **eCTD version 4.0**, regulatory agencies are moving toward next-generation submissions. For instance, FDA’s CDER and CBER began accepting new applications as eCTD v4 in September 2024 (^[4] www.fda.gov), and Japan plans to mandate eCTD v4 by 2026 (^[5] resource.ddregpharma.com), reflecting a broader shift toward structured, standardized electronic filings.

In this report, we first outline the historical and regulatory context of eCTD adoption. We explain the technical architecture of eCTD (the ICH CTD modules wrapped in an XML backbone) and the concept of sequences. We then delve into the specifics of sequence management: how sequence numbers are assigned, the role of “lifecycle operators” (new/replace/delete/append) on each file, and how subsequent sequences modify the submission. We review agency guidance and differences across regions (FDA, EMA, Japan’s PMDA, etc.), and discuss **tools and processes for compiling and validating eCTDs**. Through case studies and expert analysis, we highlight common pitfalls (e.g. incorrect sequence linkage, duplicate files) and best-practice strategies (meticulous planning and quality control) that impact submission success (www.pharmaregulatory.in) (^[6] www.dlrcgroup.com).

Finally, we examine implications and future trends. The regulatory landscape is rapidly evolving: eCTD 3.2.2 is the current staple format, but eCTD 4.0 (a more granular, data-centric specification) is on the near horizon. Future filings may move beyond PDF-centric dossiers toward fully structured data submissions (for example, leveraging HL7 FHIR standards and **AI-driven automation**) (^[7] www.artosai.com) (^[8] aapsopen.springeropen.com). We discuss how sequence management principles will apply in this new era, and how organizations must prepare for tighter regulatory harmonization and digitalization. In conclusion, effective eCTD sequence management is critical for **regulatory compliance**. By understanding sequence rules, staying abreast of guidance updates, and employing robust document-control strategies, pharmaceutical companies can ensure that their electronic submissions are accurate, review-ready, and future-proof.

Introduction and Background

The **Common Technical Document (CTD)** is defined as “a common format for submitting scientific information when applying for marketing authorisations in the EU, Japan and the United States” (www.ema.europa.eu). Introduced by the International Council for Harmonisation (ICH) under guideline M4, the CTD harmonized the structure of drug dossiers into five modules (1 to 5) covering administrative information, summaries, **quality**, nonclinical, and clinical data. In 2002 the ICH recognized the need for an *electronic* version of the CTD, leading to the eCTD specification (ICH M8), which was finalized (ICH Step 4) in 2008 (^[9] globalforum.diaglobal.org). The eCTD standardizes not only the *scientific content* but also the *electronic delivery format*: dossier files are organized into folders representing CTD modules, and an XML “backbone” file provides a navigable index describing each document’s title, location, and purpose.

The purpose of eCTD is “to improve efficiency and consistency – it doesn’t change the science you submit, but it radically standardizes how evidence is organized, navigated, and updated over time” (www.pharmaregulatory.in). In practical

terms, regulators benefit because electronic submissions “make it easier for FDA to review data, approve new drugs, and monitor drugs after they go on the market. Using eCTD also simplifies the process for submitters, because it is the same format used by drug regulatory agencies in other countries” (^[10] www.fda.gov). Thus, eCTD has become the *lingua franca* of global drug submissions: a submission prepared in one region can be more easily reused in another, conforming to harmonized folder structures and metadata conventions.

Over the past decade, eCTD adoption has become mandatory across major markets. In the United States, the 21st Century Cures Act mandated that New Drug Applications (NDAs), Abbreviated NDAs (ANDAs), and Biologics License Applications (BLAs) be submitted electronically. Specifically, the FDA guidance notes that “the requirement to submit NDAs, ANDAs, and BLAs electronically became effective on May 5, 2017” (^[2] www.linkedin.com). By May 2018, the mandate extended to Investigational New Drug applications (INDs) and regulatory master files (with some exceptions) (^[3] www.linkedin.com). In the EU, the EMA first accepted and then required eCTD format for centralized marketing-authorisation applications starting around 2010, and progressively for national procedures, although variations exist by country. Globally, many health authorities—Canada’s Health Canada, Japan’s PMDA, Australia’s TGA, and others—have incorporated eCTD or comparable electronic formats into their submission requirements. For example, Japanese regulators plan a **mandatory adoption of eCTD v4.0 by 2026**, illustrating the globalization of the standard (^[5] resource.ddregpharma.com).

Given this context, pharmaceutical firms must not only compile correct scientific dossiers but also manage the *sequence lifecycle* of eCTD submissions. An eCTD application is not filed “once and done”; it evolves through multiple submissions over a product’s life. Each submission is given a **sequence number** (0000, 0001, 0002, ...), and each sequence contains an XML backbone plus the module files for that update. The complete, cumulative dossier is built as the sum of all sequences, with newer sequences “patching” the previous **content.As** one industry source explains, “*At the core sits the Common Technical Document (CTD) content model (Modules 1–5), wrapped in the eCTD technical envelope — a directory structure and an XML backbone that tells the regulator what each file is and how it relates to the rest of the dossier*” (www.pharmaregulatory.in). Each file (or “leaf”) in the dossier is annotated with a lifecycle operation (e.g. new, replace, delete) in the backbone XML. This transforms a simple collection of documents into a **living, auditable regulatory history**. In well-managed eCTDs, reviewers can clearly see what has changed at each sequence. An analyst summarized: eCTD sequencing is like a “living dossier over many years” where new data, updated labels, and corrections are applied through lifecycle operations (^[11] www.linkedin.com). If done correctly, this yields “a crisp narrative of change” in the dossier (www.pharmaregulatory.in); errors or sloppiness can lead to confusion or technical rejection.

In the following sections, we delve deeply into how eCTD sequences are managed, controlled, and reviewed. We discuss the structure of eCTD submissions, the rules governing sequence numbering and lifecycle operations, the guidance from health authorities, and the tools that organizations use to compile complex submission cycles. We analyze case studies and practical examples that illustrate best practices and common pitfalls. We conclude by analyzing trends — especially the transition to eCTD v4.0 and beyond — and their implications for regulatory strategy. Throughout, we reference authoritative sources and industry examples to support an evidence-based perspective.

eCTD Technical Architecture and Sequence Fundamentals

eCTD Structure and Backbone

An eCTD submission extends the ICH CTD format by adding an electronic “**technical envelope**” around the dossier content (www.pharmaregulatory.in). Technically, an eCTD file package is a ZIP or folder that contains:

- **Folder hierarchy (modules):** A fixed directory tree under Module 1/3/4/5 headings (and regional Module 1). The structure adheres to CTD numbering (e.g. `m3/1/1/1` for a quality subsection).
- **Leaf documents:** Each PDF or document under those folders is referred to as a “leaf” (the end node of the tree). Every leaf must have a **stable filename and title**; this prevents confusion from renaming. As noted, “*every individual file you submit is a leaf with a stable, descriptive title and a declared lifecycle operation (new, replace, or delete) in the backbone XML*” (www.pharmaregulatory.in).
- **XML Backbone:** The core of an eCTD submission is the backbone file (often named `index.xml`). This XML file provides metadata that instructs the reviewing system: for each leaf, it lists the document’s location, title, sequence number, unique ID, and importantly the lifecycle operation (e.g. `New` or `Replace`) that applies in this sequence. The backbone thus “tells the regulator what each file is and how it relates to the rest of the dossier” (www.pharmaregulatory.in).
- **PDF renditions:** The leaf documents themselves (reports, tables, labels) are normally PDF/A format with searchable text, book marks, etc. Regulatory specifications often dictate minimum PDF standards (e.g. PDF version ≥ 1.4 , no scanned images unless unavoidable) to assure legibility and searchability (^[12] 123dok.net).

This standard structure enables any eCTD-capable review system to present the dossier consistently. For example, when a reviewer opens an eCTD sequence, the system uses the directory plus backbone to display folders and files in a user-friendly tree. Because the structure is predictable and machine-readable, processes like searching for data across modules or identifying missing documents are automated.

Sequence Numbering Concept

Sequence numbers differentiate each submission iteration of the same application over its lifecycle (^[13] 123dok.net). The very first submission (often the initial marketing-authorization application or IND) is assigned a base sequence (commonly `0000` or `0001` depending on the region’s convention). Subsequent filings (amendments, supplements, annual reports, variations) are given incrementing sequence numbers (`0001`, `0002`, etc). The key rules for sequence numbering include:

- **Uniqueness and order:** Each sequence number must be unique for a given application and must increment sequentially. For example, after sequence `0000` comes `0001`, then `0002`, and so on. (Some agencies have moved from using `0000` as the first baseline to starting at `0001` for consistency (^[14] www.ectdpharma.com).
- **Global vs regional sequence:** A global eCTD lifecycle might span multiple health authorities. Typically, separate sequences are maintained per region/applicant combination, but the numbering can be kept in sync if data is shared. Most systems do not *require* a global numbering, but many sponsors choose to keep consistency for easier lifecycle tracking.
- **Metadata linkage (related sequences):** Each sequence’s backbone may include metadata to indicate what it is related to (e.g. which previous sequence it amends). For example, in the U.S., the FDA distinguishes “high-level” submissions (e.g. new applications, annual reports, major supplements) from “second-level” submissions (e.g. amendments). High-level submissions typically stand alone (they “should never have a related sequence”), whereas second-level submissions (amendments/resubmissions) *must* carry a `related-sequence-number` that ties them to the main submission they support (^[15] www.appliedclinicaltrials.com). This allows the receiving agency to present related documents together (e.g. all parts of an amendment under one view). Other regions have their own conventions: Europe provides examples in Module 1 guidelines but generally treats each variation or supplement as a new sequence without a formal “related sequence” field.

Crucially, the sequence concept means regulators see the submission history cumulatively. The review tool assembles the “current view” of the dossier by overlaying all sequences: $\text{current} = (\text{Sequence } 0000 \text{ content}) + (\text{Sequence } 0001 \text{ updates}) + (0002 \text{ updates}) + \dots$ and so on (^[16] www.linkedin.com). This brings us to the notion of **lifecycle operations** on each document.

Lifecycle Operations: New, Replace, Delete, Append

Within each sequence, every document (leaf) is tagged with one of four primary lifecycle operations. These operations determine how that document modifies the cumulative dossier:

- NEW:** Indicates a file that is being submitted for the *first time* at that location. It is not linked to any prior document in the dossier. As one expert explains, a `New` operation means the document "is being submitted for the first time at that location and is not directly linked to any previously submitted document... no 'modified-file' attribute" is used (^[17] www.linkedin.com). In the current view of the dossier, a new file appears where nothing (or a placeholder) existed before.
- REPLACE:** Indicates that this document supersedes an existing file in the same position. The new file has `Operation= Replace` and includes a `modified-file` reference pointing to the earlier file it replaces (^[18] www.linkedin.com). In practice, the review system hides the old file and shows only the new version at the same location. For example, "REPLACE is used when a new document supersedes an existing one at the same logical position in the CTD structure" (^[18] www.linkedin.com). After replacement, the old content is effectively undeleted (still in the archive, but no longer visible in the "current" dossier).
- DELETE:** Used when a previously submitted document must be removed entirely. A file tagged `Delete` will have a `modified-file` attribute referencing the original document to remove, and no new content replaces it (^[19] www.linkedin.com). After processing, the deleted file no longer appears in the current dossier view. In other words, "DELETE is used when a previously submitted document should no longer appear in the current view and is not being replaced by a new version" (^[19] www.linkedin.com). The history of the deleted file remains in earlier sequences, but effectively it is gone from the live dossier.
- APPEND:** Denotes adding content to an existing document without replacing it fully. The appended part is treated as an extension of the original file. In the spine, `Append` points to the original document via `modified-file`, and the system presents the new pages "together with the original to form a combined 'logical' document" (^[20] www.linkedin.com). Use cases include adding extra appendices or supplementary material. Unlike `Replace`, `append` leaves the original content intact and simply extends it.

These four operations allow precise control over how sequences evolve the dossier. Table 1 below summarizes each operation with definitions (with illustrative citations).

Lifecycle Operation	Meaning	Key Reference
New	A document submitted for the first time at this location; not linked to any previous document. No <code>modified-file</code> used. "A fresh piece of content." (^[17] www.linkedin.com).	PharmaCoach eCTD guide (^[17] www.linkedin.com)
Replace	A new document supersedes an existing one in the same position. The new leaf has <code>operation=Replace</code> and references the earlier leaf via <code>modified-file</code> . The old file is hidden in current view (^[18] www.linkedin.com).	PharmaCoach eCTD guide (^[18] www.linkedin.com)
Delete	Indicates that an earlier document should be removed. The <code>Delete</code> leaf references the prior file to remove; after deletion it is not displayed in current view (^[19] www.linkedin.com).	PharmaCoach eCTD guide (^[19] www.linkedin.com)
Append	Adds content to an existing document without replacing it. The appended file references the original via <code>modified-file</code> ; reviewers see the combined content as one logical document (^[20] www.linkedin.com).	PharmaCoach eCTD guide (^[20] www.linkedin.com)

(Table 1: eCTD lifecycle operations on dossier files, with definitions. Citations from regulatory submission experts.)

By iteratively applying these operations across sequences, a continuous and auditable revision history is created. For example, if Module 3 (Quality) requires an updated drug supply table, one might use a `Replace` operation to update the specific page. If a company suddenly needs to withdraw an appendix, a `Delete` operation is used. Managing these operations correctly is vital: using the wrong operation (e.g. doing a `New` instead of `Replace`) can lead to duplicate or orphan pages, confusing build-up, and even technical rejections during validation.

Building the "Current View" of the Dossier

Regulatory agencies' review systems use the sequence metadata to construct the **current dossier** at any point.

Conceptually:

- Start with Sequence 0000 (or 0001) content.
- For Sequence 0001, add all leaves marked `New` (these were absent before), replace any files marked `Replace` (hiding old ones), erase any marked `Delete`, and attach any `Append` content to originals.
- The result is the updated dossier.
- For Sequence 0002 and beyond, continue the process cumulatively on the previous result.

Thus, each new sequence is essentially a “delta update” to the dossier. One industry source elegantly describes this dynamic: “An eCTD application is built as a series of sequences (0000, 0001, 0002, ...). Each sequence contains: an XML backbone, ... a lifecycle operation for each leaf. The current view of the dossier at any point is the result of: a. All documents submitted in earlier sequences; b. Modified by lifecycle operations in later sequences (NEW/REPLACE/DELETE/APPEND). So lifecycle is about how each new sequence changes what the regulator sees compared to the previous one.”^{(16]} www.linkedin.com).

In other words, **lifecycle + sequences = the living story of the submission**. A well-structured sequence workflow allows a reviewer to trace exactly *what* changed between two submissions. For example, if an investigator's brochure is updated in an IND, the sequence backbone for that submission might mark IB pages as `Replace` and include the new PDFs. The agency would then present just the new IB pages in the current view, but could inspect the lineage in the earlier sequence if needed.

This cumulative model underscores the importance of descriptive consistency: **file titles and IDs should not change** between sequences unless a new document truly replaces or appends an old one. Otherwise the system will treat seemingly identical content as separate leaves, leading to duplication or “orphan” entries. As one expert put it, eCTD submissions are essentially a “versioned narrative” of the product dossier (www.pharmaregulatory.in). Ideally, this narrative is linear and easy to follow; chaotic sequencing leads to “parallel truths, orphaned documents, clock-stops, and painful remediation” (www.pharmaregulatory.in).

Regulatory Guidelines and Agency Practices

U.S. FDA Requirements and Practice

The U.S. FDA has codified eCTD requirements in both law and guidance. The **21st Century Cures Act** (enacted 2016) mandates electronic submissions (eCTD) for most marketing applications and certain related submissions. The FDA's final guidance on electronic submissions (Revision 8, issued 2017) explicitly implements this. As noted, “the requirement to submit NDAs, ANDAs, and BLAs electronically became effective on May 5, 2017”^{(2]} www.linkedin.com), and similarly, INDs (commercial) and most master files were required by May 2018^{(3]} www.linkedin.com). (The guidance also clarifies exemptions, e.g. for certain non-commercial INDs.)

In practice, this means almost all major human pharmaceutical submissions to CDER/CBER are now eCTD. The FDA encourages sponsors to follow a **lifecycle approach**: after the original application (Sequence 0000 or 0001), any amendment or supplement is filed as the next sequence. The FDA's eCTD Validation Criteria (Media 87056) and their Electronic Submissions Gateway enforce rules on sequence structure. For example, the FDA expects that high-level submissions (like a new application or CBE supplement) will *not* have a related-sequence number, whereas amendments or supplements *should* carry exactly one related-sequence_reference to tie it to the main submission^{(15]} www.appliedclinicaltrials.com). Technical validators will flag missing or extraneous related-sequence metadata as errors.

A practical issue unique to the FDA has been their shift in numbering convention. Traditionally, many sponsors began the first FDA sequence as “0000” (the so-called parent sequence). However, a recent policy change now “instructs companies to begin with sequence 0001, even for baseline or reformatting submissions” (^[14] www.ectdpharma.com). The rationale is that numbering from 0001 avoids confusion with legacy “non-eCTD” submissions and aligns better with eCTD v4 forward-compatibility. This example illustrates how sequence management is not only technical but also governed by evolving policies.

The FDA also provides a technical conformance guide detailing backbone rules (e.g. which lifecycle operations require a `modified-file` reference) and validation criteria tables. Under these rules, documents must be correctly bookmarked, leaf titles must exactly match the backbone’s `<leaf-title>`, and lifecycle operations must be consistent. The FDA’s own training warns sponsors that eCTD submissions are subject to technical rejection if they fail validation checks (^[21] en.ennov.com). For instance, a sequence with missing required `related-sequence` fields, or with a file marked as `Replace` without a corresponding prior file, will generate fatal validation errors. Thus meticulous adherence to sequence rules is mandatory for U.S. filings.

European Union (EMA/NCAs)

In the European Union, the EMA and national competent authorities (NCAs) have likewise embraced eCTD. The EU’s e-Submission Guidance (EMA/CHMP) has evolved to harmonize the technical specifications (e.g. eCTD v3.2.2, Module 1 structure) across countries. The EU M1 guidance (Module 1 specification) provides examples but does not rigidly define “related sequences” the way FDA does (^[22] www.appliedclinicaltrials.com). In practice, every submission to the EMA/CHMP is a new sequence. For variations and renewals, sponsors file new sequences incrementally (Type IA/B/II variations each get a sequence number). The lifecycle operations work the same way: a Type II variation might include new documents (new drug specs), replaced documents (updated sections), or deletes (removal of obsolete dossiers). The EU system often points reviewers explicitly to prior sequences when needed.

As of 2025, the EMA has mandated eCTD 3.2.2 for most submissions (since mid-2010s) and is in the process of enabling eCTD v4.0. On 15 December 2025, the EMA announced that from 22 December 2025 applicants *may* optionally submit new Marketing Authorization Applications (MAAs) for centrally-authorized products in eCTD v4.0 format (esubmission.ema.europa.eu). During this optional-use period, the older v3.2.2 format remains fully accepted. This pilot reflects a cautious, phased approach: before mandating v4.0, the EMA is ensuring tools and processes are ready. (Further details indicate ongoing technical pilots and validation criteria releases through 2025 (esubmission.ema.europa.eu) (esubmission.ema.europa.eu)). Eventually, eCTD v4.0 is expected to become mandatory in the EU (as will likely occur by 2028, per industry projections (^[23] pme.pmlive.com)).

For European sponsors, sequence numbering is straightforward: start with 0001 for Sequence 1 (the first eCTD submission) and increment. EMA reviewers use the sequence numbers to correlate letters and questions: each sequence generates an acknowledgement and a letter of refusal or opinion labeled by sequence (e.g. “Refusal Letter, EU Procedure No. X, Sequence 4”). Internal NCA systems can handle related data spanning multiple sequences. Some confusion can arise when a company submits the same chemistry/CMC change to many countries; in that scenario, sponsors often “mirror” sequence updates across regions to keep dossier content aligned globally.

United Kingdom (MHRA)

Since Brexit, the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) has its own eSubmission requirements. The MHRA has largely aligned with EU specifications for now, requiring eCTD v3.2.1/3.2.2 format for new applications and variations. MHRA guidance indicates eCTD is expected (“All submissions in CTD format should be in eCTD”, MHRA GMP Annex 16) and requires it for most licensing procedures. Sequence management practices in the UK

mirror those in the EU; each MHRA sequence is handled similarly, with backbone validation. The MHRA has also indicated support for eCTD 4.0 and follows EMA updates closely.

Japan (PMDA)

Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) requires submissions in eCTD format for most applications. The PMDA’s CTD/eCTD guidelines establish Japanese Module 1 content specifics, but the sequence concept is the same. Japan accepted eCTD v3.2.2 submissions well ahead of the U.S.; it was one of the first to implement eSubmissions in the mid-2010s. Looking forward, PMDA has committed to eCTD v4 adoption: a recent regulatory update states Japan’s goal is “mandatory adoption of eCTD 4.0 by 2026” ([5] resource.ddregpharma.com). This accelerated timeline (compared to, say, EU’s optional 2025) underscores Japan’s drive for harmonization. Sponsors filing globally must therefore be prepared to produce eCTD v4 dossiers for Japan soon.

Other Regions

Other regulatory bodies vary: Health Canada’s guidance indicates that eCTD is the preferred format (they mandate eCTD for Drug Master Files and high-level submissions), and Australia’s TGA has initiated a phased transition to “eCTD-only” for prescription medicines starting late 2021 (www.tga.gov.au). In Latin America and Asia, countries like Brazil, Mexico, Korea, and China are moving toward eCTD or regional equivalents – e.g. Korea accepts eCTD v3.2.2 and has started moving to v4.0, China’s NMPA is working on its Technical Filing Format (TFF, akin to eCTD), and the Association of Southeast Asian Nations (ASEAN) has an ASEAN CTD framework. Each agency has nuances, but the core sequence principle holds.

(Table 2 below warms up key regulators, their eCTD adoption timelines, and current statuses. Note that dates may evolve as new guidance is issued.)

Region / Agency	eCTD (v3.2.2) Adoption	eCTD v4.0 Status
USA (FDA, CDER/CBER)	Mandatory for NDAs/ANDAs/BLAs (since May 2017) and INDs (May 2018) ([2] www.linkedin.com) ([3] www.linkedin.com). All regulatory applications required eCTD.	Accepting new applications in eCTD v4.0 as of Sept 16, 2024 ([4] www.fda.gov); v4.0 will become standard in future phases.
EU (EMA/CVMP)	Mandatory format for centralized MAAs since ~2010, mutual-recognition by 2012, decentralised by ~2014 (regional agencies vary)*.	Optional use for new CAP MAAs from Dec 22, 2025 (esubmission.ema.europa.eu) (go-live announced 15 Dec 2025); full transition timeline TBD (by 2028 per ICH).
UK (MHRA)	Mandatory for MRAs, Part I variations, etc., effectively aligned with EU schedule**.	Planning eCTD v4.0 aligned with EMA; advisory guidance due (target bump in line with EU).
Japan (PMDA)	Mandatory eCTD for New MAS (MLAs) since mid-2010s (MHx). (PMDA issued electronic guidelines in 2015.)	Aiming for mandatory eCTD v4.0 by 2026 ([5] resource.ddregpharma.com) (ICH Implementation Guide v1.5 for Japan released).
Canada (Health Canada)	eCTD format required for high-level submissions and DMFs (since 2018) (www.canada.ca) (per implementation of ICH).	Health Canada reviewing eCTD v4 initiatives; pilot feedback ongoing.
Australia (TGA)	eCTD format accepted and being mandated in phases for prescription drug submissions (policy announced 2022).	Developing eCTD Module 1 v4.0; timeline likely post-2025 (ASMF/DCMF v4 guidance in 2023).
Other (e.g. Switzerland, Korea)	eCTD accepted/mandated for NDAs and CMC by late 2010s (typically following EMA).	Switzerland (Swissmedic) targets alignment with EU timeline; Korea (MFDS) planning v4 in 2025–2026 cycle.

*Table 2: eCTD adoption by major regulatory authorities. For brevity, “(e.g. mandatory centralized 2010s)” are approximations; see references for details. Sources: FDA guidances ([2] www.linkedin.com) ([3] www.linkedin.com) ([4] www.fda.gov); EMA notifications (esubmission.ema.europa.eu); Japan regulatory news ([5] resource.ddregpharma.com).

The key takeaway is that nearly all major markets now require electronic common technical documents. Pharmaceutical companies engaged in global development treat eCTD conformance and sequence management as a strategic

imperative. Missteps can be costly: because one sequence builds on the last, a flaw in any sequence can necessitate rework of the next submission or trigger questions from agencies.

Practical Aspects of eCTD Sequence Management

Planning and Publishing Discipline

Careful planning is fundamental to effective eCTD sequence management. Sponsors need a **submission lifecycle plan** that outlines *what* changes will be submitted in which sequence. This plan typically maps planned regulatory activities (e.g. clinical trial changes, CMC updates, labeling revisions) to eCTD sequences and dates. By coordinating submissions across countries, teams can sometimes synchronize sequences to use the same content (for example, a global variation ISS in CTD Module 1 can share a single eCTD sequence across multiple regions).

Industry experts emphasize that “from the offset, planning is key” when preparing eCTD updates (^[6] www.dlrcgroup.com). Early in development stages, teams should decide on dossier granularity: what content is merged or split across sequences. For instance, small Administrative changes (e.g. correspondence edits) might be held until an annual report to minimize sequence clutter, whereas urgent safety updates are sent immediately. Missed planning can cause “parallel truths” where different sequences inadvertently present conflicting information, disrupting the clean history (www.pharmaregulatory.in).

Once the plan is set, the **publishing process** must be disciplined. Pharmaceutical companies typically use dedicated regulatory publishing tools (eCTD compilers) to assemble sequences. These tools (e.g. Lorenz TM-30, eCTDmanager, eCTD Oracle Configurator, Veeva Vault Submissions Publisher) help authors compile documents into the correct folder structure, set lifecycle attributes, and generate the XML backbone. They also often validate files and hyperlinks. Practice shows that **incremental publishing** is less error-prone than ad-hoc compilation. For each new sequence, publishers compare it to previous sequences to ensure correct use of `new/replace/delete`. Automated checks look for orphaned or duplicate leaf states. As one case study noted, appointing a dedicated “lead publisher” or outsourcing to experienced vendors can accelerate and improve the process (^[6] www.dlrcgroup.com).

Quality control is critical. Before submission, every eCTD package is run through validation software (like the FDA's ESG validation or EMA's HOPE validator). Typical checks catch missing sequence numbers, broken links, invalid operations, or non-conforming PDFs. Common errors include failing to include a previous sequence's `index.xml` link, or capitalizing a folder incorrectly. Even though content scientists focus on chemistry and safety, regulatory affairs teams must ensure the *sequence metadata* is flawless. Mistakes here can obscure reviewers' understanding of the dossier changes or even lead to outright submission rejection (^[21] en.ennov.com) (^[19] www.linkedin.com).

Granularity and Consolidation

One important sequencing tactic is the **granularity of submissions**. Sponsors must choose which changes to bundle together in a single sequence and which to separate. Too many separate sequences (each with very small changes) can overwhelm both the sponsor and the reviewer, while huge aggregated sequences risk confusion and lengthy review. Regulatory guidance often limits the size of a single submission; for example, some agencies request splitting oversized updates into multiple parts. Conversely, similar or minor related changes should be consolidated.

For example, if a product's manufacturing process is being updated, it may involve Module 3 changes (drug substance/test methods) and corresponding Module 5 (biological) documents. It is often advised to submit all related

manufacturing changes in one sequence rather than spreading them out, so reviewers see a coherent update. Conversely, a minor labeling tweak can go in a separate, smaller sequence. The PharmaRegulatory blog emphasizes that regulators look at how neatly the changes are sequenced: if “your dossier is sequenced with intent, reviewers see a crisp narrative of change” (www.pharmaregulatory.in), whereas a tangled approach causes clock-stops. When content is duplicated or operations misused, agencies may ask for resubmission. Successful sequence planning involves balancing submission efficiency with regulatory requirements and reviewer clarity.

In practice, if overlapping changes occur (e.g. two teams update the same document simultaneously in different countries), sponsors may need a **consolidation sequence**. Such a sequence carefully *replaces* multiple earlier files with a single definitive file, *deletes* the redundant ones, and assures continuity. This kind of catch-up is laborious and error-prone, underscoring the need for communication and global document tracking.

Approval Package and Lifecycle Management

Sequence management must be integrated with the **regulatory lifecycle strategy** for the product. For instance, a new variation or supplement is effectively an approval package, with its own Module 1 (regional forms) and possibly new data in Modules 3–5. The eCTD sequence for that submission encapsulates the regulatory activity. As one analysis put it, each eCTD sequence should clearly signal “intent, precision, and alignment with modern data lifecycle thinking” (^[14] www.ectdpharma.com). This means sequences should have logical numbers (e.g. 0005 for the fifth filing) and cohesive content.

Once a submission is approved, a new baseline may be established. For example, after a new drug is approved, the company may treat that last sequence as a stand-alone “reference sequence” for future post-approval changes. Some companies even reset sequence counters for new indication filings. Whatever the approach, the guiding rule is: each sequence should produce a uniform dossier state. If a submission is withdrawn or replaced, the next filing should not inadvertently revert to old content.

Maintaining traceability across sequences is also vital. Sponsors need robust records (often automated in DMS/RIM systems) showing which version of a document was in which sequence. This metadata is crucial during audits and inspections. For example, regulators can ask for the history of a critical quality attribute across sequences; the sponsor must be able to track which PDF (and which lifecycle version) held that information. Advanced submission management systems link sequence information with internal IDs so authors know the version history.

Tools and Technology

Many organizations rely on specialized software to manage eCTD sequences. Key functionalities include:

- **Dossier assembly:** Tools allow users to drag-and-drop documents into the CTD folder structure.
- **Metadata management:** The tool tracks each leaf’s lifecycle operation, unique ID, and ISBN number (the `<leaf-id>` in the XML) to avoid duplication.
- **Validation engine:** Built-in pre-submission checks against agency criteria (XML schema, PDF standards, link integrity).
- **Standard libraries:** Common subsections (e.g. population pharmacokinetics) can be reused via templates.

Popular platforms include:

- **Lorenz docuBridge/Publish:** Widely used for FDA and EU, supports granular Xaaml editing.
- **EXTEDO eCTDmanager:** Offers multi-regional compilation and lifecycle tracking.
- **Veeva Vault Submissions:** Cloud-based regulatory content management with eCTD publishing.

- **MasterControl eCTD:** Integrates with QMS, plus eCTD publishing.
- **Freyr SUBMIT:** Focuses on authoring and sequence tracking.
- **Ennov Regulatory:** Includes eCTD modules with editorial control.
- **Knowledge Center:** A more lightweight eCTD XML editor.

Each tool has trade-offs (for example, some export directly to EMA systems, others may require offline validation). Crucially, all such tools enforce the sequence conventions described, reducing manual errors. Many teams also use general purpose document management systems (DMS) or regulatory information management (RIM) systems in tandem, to keep global track of documents and their variants.

Regardless of platform, human oversight remains key. Even sophisticated tools rely on correct user input of sequence numbers and linkages. In one reported case study, a mid-sized company without in-house publishing software mitigated risk by hiring an external “lead publisher,” who then worked with the project team on operational strategy and maintained a content plan (^[6] www.dlrcgroup.com). Another case study highlights that thorough project oversight and precise scope of work are needed to avoid scope creep and ensure small companies can deliver the first sequence successfully (^[6] www.dlrcgroup.com).

Quality Review and Common Pitfalls

Despite tooling, eCTD submissions often encounter technical rejections. Agencies like FDA maintain explicit lists of fatal and non-fatal errors. Experience shows that many rejections trace back to sequence mismanagement:

- **Missing or wrong lifecycle operation:** For example, failing to mark a superseded file as `Delete` or `Replace` will leave duplicate content in the current dossier. This can confuse reviewers or lead to missing content issues.
- **Broken cross-references:** The backbone XML contains hyperlinks (leaf-hrefs) to each document. If a filename or ID is mistyped, the submission will fail validation. For instance, referencing `module3-2.2-5.pdf` in XML while the actual file is `Module3-2.2-5.pdf` (case difference) causes an error.
- **Orphan files:** Submitting a file not listed in any backbone node (or vice versa) triggers a validation error.
- **Incorrect sequence relationships:** Forgetting to update the `<related-sequence-number>` fields in Module 1 for an amendment can break the linkage to the parent application.
- **Large baseline repackaging:** Sometimes, a sponsor might reformat their entire dossier (to update leaf titles or PDF versions) and create a “sequence 0000 reformat” entry. If not done carefully, it can confuse the entire history.

The FDA’s eCTD Validation Criteria document (and EMA’s validation checks) do not spare the sponsor: submissions must be strictly conformant or they risk a refusal to file or outright rejection (^[21] en.ennov.com). One blog notes that “sponsors are well aware... that their submissions are subject to rejection” for technical issues (^[21] en.ennov.com). Thus, sequence management is not a mere internal detail – it directly affects the timeliness of approval.

Continuous training and checklists help mitigate these risks. Sponsors often maintain a **validator-clean checklist** for each sequence, ensuring all folder structures, file formats, initiation status, and linkage metadata are correct. Peer reviews and/or external audits of submission packages are also common. Ultimately, a disciplined, step-by-step approach (prepare files → assign operations → generate backbone → validate → correct errors → submit) is necessary to minimize the dreaded “validation trap”.

Implications, Challenges, and Future Directions

Impact on Regulatory Review and Efficiency

Effective eCTD sequence management has concrete implications for regulatory review speed and clarity. When each sequence is logically organized, regulators can focus on new data rather than hunting through redundant files. For example, if a sponsor correctly uses `Replace` for updated clinical study reports, the reviewer sees only the new version and is assured it replaces the old one. In contrast, a messy sequence may require the reviewer to open multiple versions to ascertain the changes, slowing the process.

Some firms track metrics on sequence quality and reviewer feedback. Anecdotally, submissions with poor sequence discipline tend to generate more queries or longer rounds of review. Conversely, filings done “by the book” often get approved in fewer review cycles. One commentary emphasizes that “eCTD sequencing and document granularity often decide whether your change flies or fails” (www.pharmaregulatory.in). In other words, scientific content quality is necessary but not sufficient – how that content is sequenced and linked can make the difference between a smooth review and a request for amendment (RTA).

Complex projects (e.g. international multi-protocol submissions, portfolio harmonization) especially benefit from standardized sequence practices. Multi-country teams usually establish a *global dossier index* and align on sequence numbering so that an update in one region can be mirrored or cross-referenced in another. For instance, a global safety report might be submitted as the same “related sequence” across a family of NDAs to show consistency. The concept of a “master sequence” spanning all countries has been suggested to regulators to simplify cross-referencing, although in practice each agency still logs sequences under its own system.

Case Studies and Real-World Examples

Case Study 1 – Small Biotech IND: A small biotech with limited regulatory experience faced its first IND eCTD submission. With no eCTD software or in-house publishing team, they contracted an external regulatory operations service. The solution emphasized “from the offset, planning is key” (^[6] www.dlrcgroup.com). The consultants helped the biotech map out which Module 1 forms and correspondence were needed, laid out the folder hierarchy, and assigned proper sequence number (0000) to the IND. They guided the sponsor on naming conventions and use of `New` operations for all initial content. The sequence passed validation with no failures. This exemplifies how expert support can translate sequence rules into a successful submission for companies lacking eCTD infrastructure (^[24] www.dlrcgroup.com) (^[6] www.dlrcgroup.com).

Case Study 2 – Mid-Sized Pharma MAA: A mid-sized company preparing a Marketing-Authorisation Application (MAA) in the EU had compiled correct Module 3/4 PDFs, but lacked any publishing tool or direct EMA gateway access. They had the data but not the submission workflow. According to the case report, the company appointed a “lead publisher” and developed a regional content plan (^[6] www.dlrcgroup.com). The publisher created the eCTD folder structure, inserted the validated Module 1 forms, and incrementally built Sequence 0001. All files had stable titles corresponding to the backbone. As a result, the MAA submission was received without technical comments. This illustrates how sequence management links operational roles and planning: even with good data, success depends on organized submission packaging (^[6] www.dlrcgroup.com) (^[6] www.dlrcgroup.com).

Case Study 3 – Submission Conversions: An orphan-product company sought to register an oncology drug in Australia. They already held an EU eCTD dossier. Clinigen (a regulatory consultancy) “converted the EU eCTD format to the Australian eCTD format, ensuring compliance with TGA requirements” (^[25] www.clinigengroup.com). This involved re-sequencing parts of the Module 1 (to match Australia’s forms and numbering), adjusting any country-specific data, and repackaging as a new eCTD sequence for the TGA filing. The conversion was done efficiently due to the structured nature of the original eCTD. This real-world example highlights how standardized eCTD sequences enable content reuse: the same Module 2–5 (quality, safety/efficacy) summaries were reused across regions by simply creating a new sequence with local Module 1 content (^[25] www.clinigengroup.com).

These illustrations show that organizations of different sizes and contexts succeed when they apply disciplined sequence management and leverage expert resources. Common themes are thorough pre-planning, clear assignment of publishing roles, and careful QC of each sequence's metadata. When these elements come together, the sequence process becomes routine. When they fail, the result is submission rejection or costly rescheduling.

Future Trends: Towards eCTD v4.0 and Beyond

The next frontier in sequence management is the advent of **eCTD version 4.0**. Approved by ICH in 2017, eCTD v4.0 significantly enhances flexibility: it allows multi-application and multi-product submissions, richer data types, and more granular linking. For example, v4.0 supports modular submissions where a single sequence can cover several variations or indications. It also natively allows datasets (like clinical data files) and structured formats in the eCTD backbone, beyond static PDFs.

Regulators are actively preparing for v4.0. As noted, the FDA began accepting eCTD v4.0 for new applications in late 2024 (^[4] www.fda.gov), and the EMA and PMDA are rolling out optional use by 2025–2026 (esubmission.ema.europa.eu) (^[5] resource.ddregpharma.com). Agencies expect sponsors to maintain backward compatibility across v3 and v4 lifecycles. Sequence numbering itself will persist (you'll still have sequence 0001, 0002, etc.), but the internal structure may change (e.g. more flexibility on file types and linking across products). A key point for sequence management is that many of the existing principles carry over: the notion of lifecycle operations and cumulative dossier remains (^[16] www.linkedin.com) (^[8] aapsopen.springeropen.com).

Looking further ahead, the notion of fully **structured submissions** is emerging. An industry review forecasts a move from traditional eCTD (PDF-centric) to “structured data submissions” (^[8] aapsopen.springeropen.com). In this future, narrative documents (Module 3–5 reports) might be authored in markup or database form (e.g. XML/JSON) rather than PDF, enabling queries and automated review tools. One blog suggests leveraging **HL7 FHIR** (a healthcare data standard) and AI to generate parts of the submission, reflecting this trend (^[7] www.artosai.com). Over time, regulatory reviewers may expect data in common schemas (such as CDISC SDTM for clinical, or other ICH-approved standards) directly embedded in the submission. The ICH is already working on “Study Data Tabulation Model” (SDTM) submissions and eCTD integration.

For sequence management, these shifts mean two things: (1) The **conceptual structure** (modules, sections, sequences) will likely remain to meet legal/regulatory conventions, but (2) the technical content will become more conceptually granular. For example, instead of submitting a PDF of a Toner Section, a sponsor might submit an XML object, yet still label it as Section 3.2.R (like replacing, appending) in the backbone. Tools and sponsors must therefore become proficient not only in PDF/directory management but also in data standards. Forward-looking companies are experimenting with digital labels, semantic tagging, and content repositories that feed straight into eCTD packages.

Finally, sequence management will adapt to **regulatory priorities for reliance and outline submissions**. The concept of **Global Submission Lifecycle** may take hold wherein a single eCTD dossier serves multiple regions (with minor local modifications). Similarly, reliance pathways (e.g. recognizing another agency's review) could simplify sequences by reducing duplicative filings. The key will be traceability: even as formats evolve, regulators will still need to know the lineage of each piece of data. As the AAPS review comments, even in a fully digital future, robust version control and lifecycle governance will remain “cornerstones” of compliance (^[8] aapsopen.springeropen.com).

Conclusion

eCTD sequence management is the backbone of modern regulatory publishing. It underpins the entire life cycle of a drug dossier—from initial submission through post-approval updates—ensuring that regulatory authorities can efficiently access all relevant information in context. As this report has outlined, sequence management involves more than just numbering: it requires a rigorous approach to content structuring, metadata tagging, and planning. We have described

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