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A COMPARATIVE STUDY OF eCTD IMPLEMENTATION, LIFECYCLE MANAGEMENT AND TECHNICAL REQUIREMENTS ACROSS MAJOR REGULATORY AUTHORITIES

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Abstract:

The electronic Common Technical Document (eCTD) is the principal standard for electronic exchange of pharmaceutical regulatory information between applicants and health authorities. Although the scientific organization of Modules 2–5 is broadly harmonized through the International Council for Harmonisation (ICH), implementation remains regionally differentiated through Module 1, validation criteria, controlled vocabularies, submission gateways, lifecycle conventions and transition schedules. This review compares eCTD implementation, lifecycle management and technical requirements across the US Food and Drug Administration (FDA), European Union/European Medicines Agency (EU/EMA), Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, Health Canada and the Therapeutic Goods Administration (TGA) of Australia. Particular emphasis is placed on the transition from eCTD v3.2.2 to eCTD v4.0, including metadata-driven regulatory information exchange, Universally Unique Identifiers (UUIDs), controlled vocabulary, document reuse, forward compatibility and two-way communication. The latest ICH eCTD v4.0 Implementation Guide version 1.7 was endorsed in June 2026. Japan has entered mandatory v4.0 implementation, while FDA and EU adoption are progressing through phased transition. The review concludes that efficient multinational submissions require a harmonized scientific core combined with strong regional publishing governance, current validation rules and integrated regulatory information management.

Keywords: *eCTD; eCTD v4.0; CTD; regulatory submissions; lifecycle management; FDA; EMA; PMDA; Health Canada; TGA; regulatory information management.*

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1. INTRODUCTION[1-3]:

Pharmaceutical development generates large volumes of quality, nonclinical and clinical information that must be assessed by regulatory authorities before and after marketing authorization. Paper-based dossiers created logistical and review difficulties because applications were difficult to transport, copy, archive, navigate and update. The Common Technical Document (CTD) established a harmonized scientific organization for regulatory dossiers, while the electronic Common Technical Document added a standardized electronic structure and lifecycle mechanism.

The eCTD is not simply a collection of electronic files. It is a controlled regulatory information architecture that combines documents, metadata, technical specifications and lifecycle relationships. FDA identifies eCTD as the standard format for applications, amendments, supplements and reports submitted to CDER and CBER [6]. In Europe, eCTD has long supported centralized and other procedures, with regional implementation rules maintained through the EU eSubmission framework.

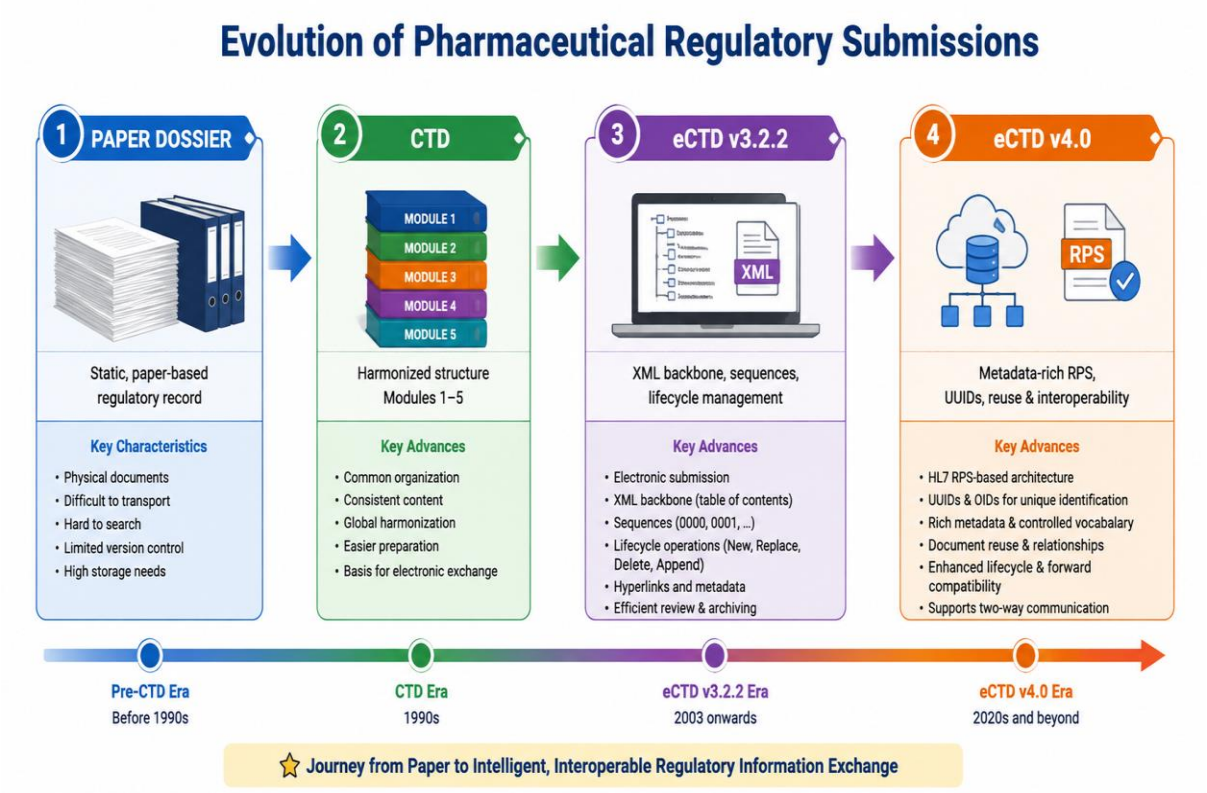

Figure 1. Evolution from paper dossiers to metadata-driven eCTD v4.0 regulatory exchange.

2. Objectives and Scope[4]

This review evaluates the harmonized and region-specific elements of eCTD implementation, with emphasis on dossier architecture, Module 1, technical validation, lifecycle operations, sequence management, quality-data maintenance and the transition to eCTD v4.0. The authorities compared are FDA, EU/EMA, PMDA/MHLW, Health Canada and TGA. The analysis reflects regulatory information available through August 2026.

3. CTD and eCTD Architecture[5,6]

The CTD is organized into five modules. Module 1 is regional and administrative, while Modules 2–5 contain the harmonized scientific summaries, quality information, nonclinical reports and clinical study reports. eCTD overlays this scientific structure with an electronic backbone, metadata, document references and lifecycle relationships.

3.1 Core Dossier Structure and Regionalization

The division between a harmonized scientific core and a regional administrative layer is fundamental to global publishing. It permits substantial reuse of Modules 2–5 while preserving legal, labeling and procedural requirements in Module 1. In practice, however, regional expectations can still influence the granularity, placement and timing of scientific documents.

Table 1. Comparative eCTD environment across major regulatory authorities.

Region	Core Modules 2–5	Module 1	Submission infrastructure	2026 v4.0 position
US FDA	ICH	US-specific	FDA electronic submission infrastructure / ESG	New applications accepted; phased implementation
EU/EMA	ICH	EU-specific	eSubmission Gateway / EU systems	Optional new CAP MAAs; transition in progress
Japan PMDA	ICH	Japan-specific	Japanese electronic submission systems	Mandatory implementation from Apr 2026
Health Canada	ICH	Canadian-specific	Health Canada electronic transaction framework	Roadmap / future implementation
Australia TGA	ICH	Australian-specific	TGA electronic submission infrastructure	Pilot / staged preparation

3.2 eCTD v3.2.2 Technical Model

eCTD v3.2.2 uses an XML backbone, defined directory structures, leaf elements, document hyperlinks, sequence numbers, lifecycle operators and checksums. Each submission is delivered as a sequence, and the cumulative sequence history forms the regulatory lifecycle. The reviewer therefore receives both a historical record and an actionable current view.

3.3 Sequence-Based Lifecycle

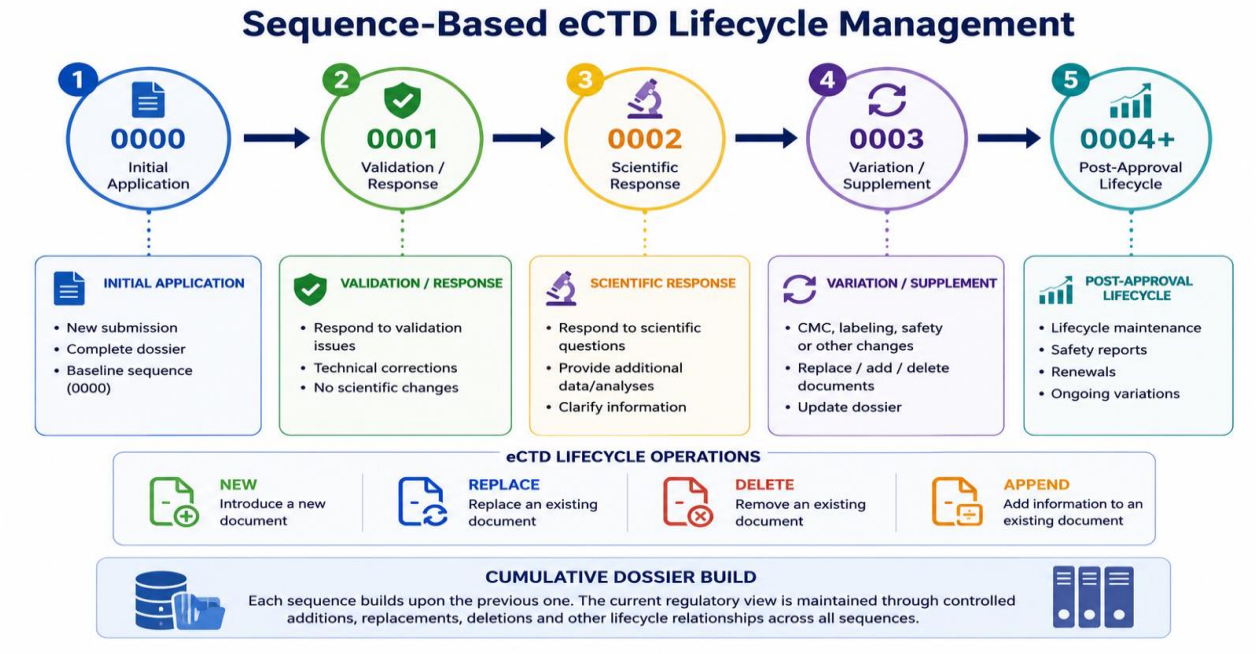

Figure 2. Simplified sequence-based lifecycle of an eCTD application.

A sequence may represent an initial application, amendment, response, supplement, variation, annual report, safety update or other regulatory activity. Sequence governance is critical because incorrect numbering or lifecycle targeting can disrupt the authority's current view of the dossier.

4. Lifecycle Management in eCTD v3.2.2[7-9]

Lifecycle management is the defining operational advantage of eCTD. Rather than retransmitting an entire dossier whenever information changes, applicants submit only the new regulatory unit and define its relationship to information already submitted. The conventional v3.2.2 model uses operations such as new, replace and delete, while append is regionally constrained and should not be treated as universally interchangeable.

Table 2. Comparative lifecycle-management characteristics.

Lifecycle element	FDA	EU/EMA	PMDA	Health Canada	TGA
Sequential submission history	Yes	Yes	Yes	Yes	Yes
Replacement of current documents	Supported	Supported	Supported	Supported	Supported
Removal of obsolete content	Per regional rules	Per EU rules	Per JP rules	Per CA rules	Per AU rules
Regional metadata	US	EU	Japan	Canada	Australia
Technical validation	Critical	Critical	Critical	Critical	Critical
v4 forward compatibility	Phased / testing	Pilots ongoing	Advanced	Future	Future

4.1 Regulatory Activity and Sequence Governance

A robust submission register should link sequence number, regulatory activity, transmission date, lifecycle purpose, documents affected, validation outcome, gateway acknowledgement, authority correspondence and approval status. This information becomes especially important in global portfolios where a single manufacturing or labeling change can create different regulatory activities in several regions.

4.2 Lifecycle Risks

Common lifecycle risks include replacing the wrong document, deleting information that remains legally relevant, using a sequence number that does not follow the accepted history, assigning incorrect metadata and failing to reconcile technical acknowledgements. Such errors may not alter the underlying science but can impair reviewability, create ambiguity regarding the current approved state and trigger technical rejection or requests for correction.

5. Transition from eCTD v3.2.2 to eCTD v4.0[10-12]

eCTD v4.0 is a structural modernization rather than a cosmetic version update. It is based on the HL7 Regulated Product Submission model and expands the role of structured metadata, persistent identifiers and controlled terminology. The result is a move away from strong dependence on document paths and leaf placement toward information objects and relationships.

Table 3. Principal differences between eCTD v3.2.2 and eCTD v4.0

Feature	eCTD v3.2.2	eCTD v4.0
Technical foundation	XML/DTD-oriented eCTD backbone	HL7 RPS-based message architecture
Primary organization	Folder/leaf and path dependent	Metadata-rich information model
Identification	Leaf/path relationships	Persistent UUID/OID-based identification
Controlled terminology	Regional / more limited	Expanded controlled vocabularies
Document reuse	Limited	Enhanced reuse and referencing
Lifecycle model	Leaf lifecycle operations	Context- and relationship-oriented lifecycle
Forward compatibility	Not a migration concept	Designed for transition of legacy lifecycles
Two-way communication	Limited	Architecture supports future structured exchange

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5.1 Key Technical Innovations

The v4.0 model introduces persistent UUIDs for regulatory objects, use of OIDs, richer controlled vocabulary and a more structured context for submission units. These features enable more reliable machine processing and provide a technical foundation for document reuse, more sophisticated lifecycle handling and potential two-way structured communication.

5.2 Forward Compatibility

Forward compatibility is strategically important because sponsors cannot realistically rebuild every legacy eCTD v3.2.2 dossier. The transition mechanism must preserve historical regulatory relationships while allowing future submissions to use the v4.0 model. FDA and EU implementation programs therefore include dedicated forward-compatibility work [7,11].

6. Comparative eCTD v4.0 Implementation Status[13-15]

Implementation is intentionally staggered among regions. Consequently, global regulatory organizations must maintain dual capability for v3.2.2 and v4.0 during the transition period. The status below is based on authority information available through August 2026 and should be rechecked before an actual submission.

Table 4. Comparative eCTD v4.0 implementation position across major authorities.

Authority / Region	Key implementation position as of Aug 2026	Operational implication
ICH	Implementation Guide v1.7 and Controlled Vocabulary Package v1.0.3 endorsed June 2026	Global harmonized technical baseline updated
FDA	Accepting new NDA, BLA, ANDA, IND and MF applications in v4.0 since 16 Sep 2024; forward compatibility is a future phase	Sponsors can use v4.0 for eligible new applications; legacy transition requires current FDA guidance
EU/EMA	Optional v4.0 for new CAP MAAs since 22 Dec 2025; strongly recommended from Q1 2027; mandatory for new CAP MAAs planned Q1 2028	Transition planning and pilot participation remain important
Japan PMDA/MHLW	Mandatory eCTD v4.0 implementation from Apr 2026	Mature operational reference for v4.0 publishing
Health Canada	Implementation roadmap remains phased / future-oriented	Maintain Canadian v3.2.2 capability while monitoring v4.0 notices
TGA Australia	Regional v4.0 specification and pilot framework published; staged adoption	Pilot readiness and Australian Module 1 governance required

FDA updated its regional eCTD v4.0 controlled vocabulary, Module 1 implementation material and validation criteria on 28 August 2026 [8]. The EU published v4.0 validation criteria v1.1 in March 2026, applicable from 15 July 2026, while forward-compatibility pilots continued during 2026 [11].

6.1 Implication for Global Sponsors

A single global cutover date is not feasible. Organizations need authority-specific readiness matrices covering accepted versions, supported application types, regional Module 1 releases, controlled vocabularies, validation rules and gateway requirements. Change control for publishing tools must be coordinated with regulatory intelligence so that software configuration does not lag behind authority specifications.

7. Regional Module 1: The Main Source of Divergence[16-18]

Module 1 contains administrative, legal, procedural and product-information content that is intentionally region specific. Even when Modules 2–5 are identical, a complete sequence cannot generally be transmitted unchanged to several authorities because Module 1 structures, metadata and validation rules differ.

Table 5. Major regional Module 1 differences affecting global publishing.

Area	FDA	EU/EMA	PMDA	Health Canada	TGA
Application forms	US forms / forms and cover materials	EU procedure-specific forms	Japanese forms	Canadian forms / enrolment data	Australian forms
Product	US	SmPC,	Japanese	Product	Australian

information	prescribing/labeling information	labeling, package leaflet	labeling	monograph / labels	Product Information / labels
Administrative metadata	FDA-specific	Procedure-specific EU metadata	Japan-specific	Canadian transaction metadata	Australian metadata
Regional XML / M1	FDA M1	EU M1	Japan M1	Canadian M1	AU M1
Validation rules	FDA criteria	EU criteria	PMDA criteria	Health Canada rules	TGA rules

7

.1 FDA

FDA maintains separate eCTD submission standards for v3.2.2 and v4.0, together with a US Regional Module 1 implementation package, controlled vocabulary, technical conformance guidance and validation criteria [6–8]. FDA's 2026 technical conformance material reflects active refinement of the v4.0 implementation.

7.2 European Union

EU submissions require EU-specific Module 1 organization and procedure metadata. The centralized, decentralized, mutual-recognition and national environments make European lifecycle planning particularly dependent on procedure context. During the v4.0 transition, EU eSubmission guidance and validation criteria should be treated as primary operational sources [10,11].

7.3 Japan, Canada and Australia

Japan, Canada and Australia similarly combine the harmonized ICH core with regional Module 1 structures. TGA explicitly directs applicants to Australian Module 1 specifications while using ICH specifications for harmonized modules [14].

8. Technical Requirements and Submission Quality[19-22]

Successful eCTD publishing requires document engineering, metadata control and automated validation in addition to scientific authoring. PDF remains the dominant presentation format for narrative documents, while structured datasets and XML or other formats are used where specified. Regulatory PDFs should be searchable, readable, correctly oriented and efficiently navigable.

8.1 Document and PDF Quality

- Generate PDFs directly from source documents whenever possible; avoid unnecessary scanning.
- Use accurate bookmarks and internal hyperlinks to support reviewer navigation.
- Ensure fonts, symbols, tables and figures render correctly without clipping or substitution.
- Apply regionally accepted file formats, file names and security settings.
- Confirm that hyperlinks resolve to the intended regulatory content and not to local file paths.

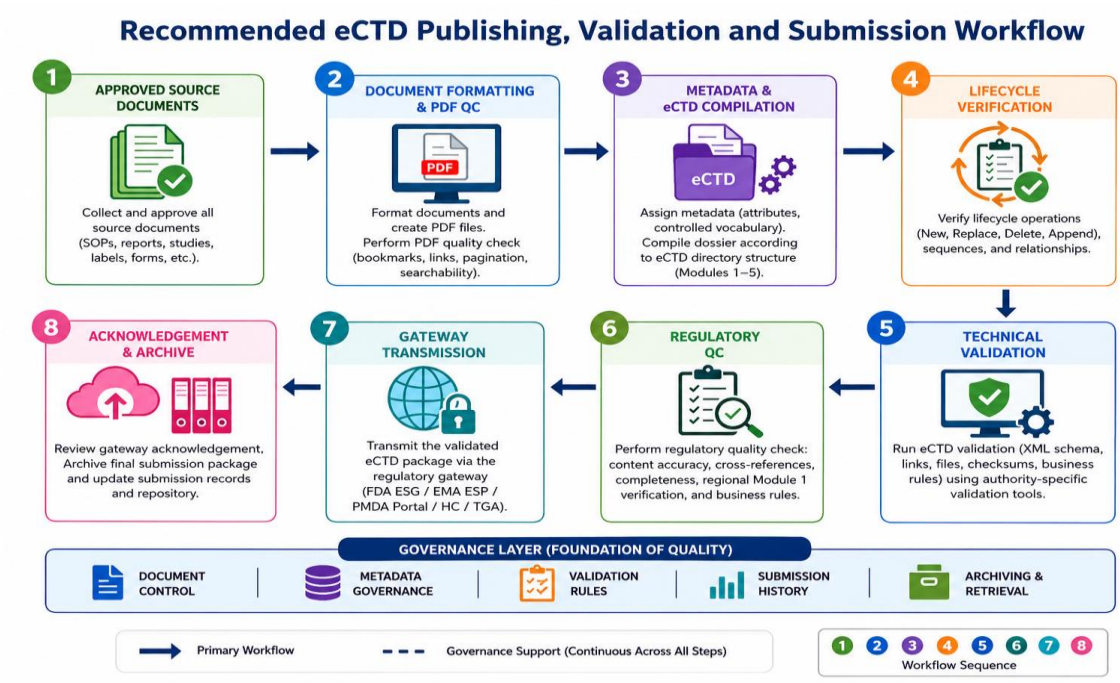

Figure 3. Recommended end-to-end publishing, validation and transmission workflow.

8.2 Validation

Validation checks whether the electronic package conforms to the applicable technical specification. Typical checks address XML or schema validity, file and folder requirements, metadata, controlled terms, identifiers, lifecycle relationships, file formats and integrity checks. A technically valid sequence can still be poor for review; therefore regulatory publishing QC should additionally verify document version, placement, bookmarks, hyperlinks, titles and consistency with the approved submission plan.

9. Quality/CMC Data in the eCTD Lifecycle[23]

Module 3 contains most Chemistry, Manufacturing and Controls information and is frequently affected by post-approval change. The harmonized CTD organization supports global reuse, but change classification and submission timing remain region dependent.

Table 6. Representative quality data maintained through Module 3 lifecycle.

CTD section	Representative quality information
3.2.S	Drug substance: general information, manufacture, characterization, controls, reference standards, container closure and stability
3.2.P.1–P.2	Drug product description/composition and pharmaceutical development
3.2.P.3	Manufacturing process, controls, process validation / evaluation
3.2.P.4–P.5	Control of excipients and control of drug product
3.2.P.6–P.8	Reference standards, container-closure system and stability

9.1 Typical Post-Approval Quality Changes

Common lifecycle changes include manufacturing-site changes, batch-size changes, process optimization, specification revisions, analytical-method updates, packaging changes, supplier changes, shelf-life extensions and new stability data. The regulatory publishing strategy must ensure that each approved change is reflected in the correct current document without destroying historical traceability.

9.2 Quality Data Governance

For multinational products, the same CMC change may be approved at different times and under different reporting categories. A global dossier therefore needs market-specific status control. Regulatory information management should link the change-control record with affected documents, applications, commitments, submission sequences and approval dates.

9.3 Data Integrity and Reviewability

Publishing quality is part of regulatory quality. A correct scientific dataset can become difficult to assess if the electronic presentation contains broken links, illegible scans, incomplete metadata or inconsistent versions. Therefore, CMC authorship, document management and eCTD publishing should be governed as connected processes rather than isolated activities.

10. Regulatory Information Management and eCTD[23]

The shift to v4.0 increases the strategic importance of regulatory information management because persistent identifiers, controlled vocabulary and reusable information objects require governance beyond the publishing tool itself. A mature operating model integrates source systems, document management, regulatory information management, publishing, validation and authority transmission.

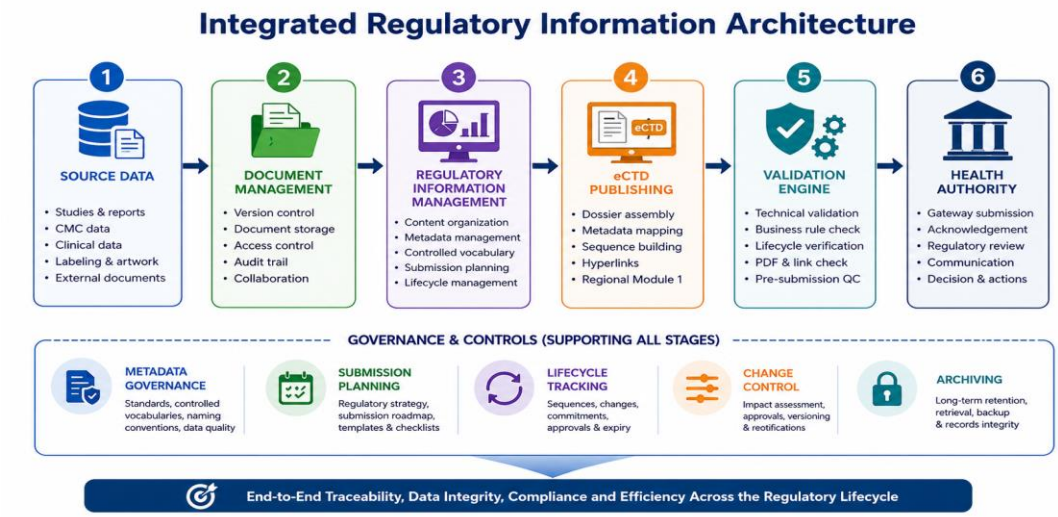

Figure 4. Integrated regulatory information architecture supporting eCTD lifecycle management.

10.1 Metadata Governance

Metadata should be treated as controlled regulatory data. Organizations need defined ownership for application identifiers, submission-unit attributes, document titles, controlled terminology, sequence or message relationships and regional classifications. Incorrect metadata can impair automated ingestion even when the underlying document is scientifically correct.

10.2 Document Reuse

One of the principal opportunities in eCTD v4.0 is improved reuse of previously submitted information. Reuse can reduce duplication and support consistent references across applications, but it also increases the need for persistent identifiers, controlled versioning and clear rules governing when a document remains valid for reuse.

10.3 Technology Readiness

Readiness assessments should cover publishing software, validation engines, gateway configuration, archival systems, UUID generation and persistence, controlled vocabulary updates, user roles, training, SOPs and disaster recovery. Tool validation should demonstrate that configured outputs remain compliant with the authority's current implementation package.

11. Operational Challenges and Risk-Control Strategy[24]

The global eCTD environment combines harmonization with persistent regional divergence. The principal operational challenge is therefore not dossier structure alone but controlled synchronization of science, metadata, regulatory commitments and local technical rules.

11.1 Major Challenges

- Regional Module 1 differences and changing controlled vocabularies.
- Parallel support for long-lived v3.2.2 applications and new v4.0 applications.
- Forward compatibility of historical lifecycles.
- Different authority implementation dates and supported regulatory activities.
- Validation-rule changes that require publishing-tool configuration updates.
- Global CMC changes approved at different times across markets.
- Management of reusable documents and persistent identifiers under v4.0.

11.2 Recommended Global Operating Model

A practical multinational strategy is to maintain a global scientific core for Modules 2–5 and generate controlled regional adaptations through a regulatory requirements matrix. Module 1 should be maintained by region, while metadata governance and submission history should be centralized enough to preserve consistency.

Every submission should pass two gates: technical validation against the current authority rules and regulatory QC against the approved submission plan. Gateway acknowledgements must be reconciled, archived and linked to the regulatory activity. For v4.0 transition, organizations should establish dedicated readiness governance covering system capability, metadata, UUID persistence, controlled vocabulary, forward compatibility, document reuse and staff competence.

11.3 Risk-Based Publishing Controls

Risk-based QC can focus additional scrutiny on high-impact lifecycle operations such as replacement of approved product information, quality changes affecting multiple sections, cross-application document reuse and migration from v3.2.2. Routine automated checks should be supplemented by manual review of reviewer navigation and the resulting current view.

12. Discussion

The comparative analysis shows that eCTD has achieved substantial global convergence in scientific dossier organization, but not complete technical uniformity. ICH harmonization is strongest in Modules 2–5, whereas Module 1, validation rules, submission infrastructure and implementation schedules remain regionally governed. These differences are not accidental; they reflect distinct legal systems, application types and regulatory workflows.

The transition to eCTD v4.0 further changes the nature of regulatory publishing. Under v3.2.2, publishing organizations often focused primarily on document preparation, leaf metadata and sequence lifecycle operations. Under v4.0, persistent identifiers, richer controlled terminology and information relationships move the function closer to enterprise regulatory data management. The most successful implementation model will therefore combine regulatory affairs, publishing, information management, quality and technology governance.

Implementation timing is a major source of complexity. Japan entered mandatory v4.0 implementation in April 2026, FDA has accepted eligible new v4.0 applications since September 2024, and the EU began optional production use for new centrally authorized product marketing authorization applications in December 2025, with mandatory use for new CAP MAAs planned from Q1 2028 [7,11,12]. Other authorities remain at earlier stages. Sponsors therefore need a deliberate hybrid operating model.

13. CONCLUSION:

The eCTD has transformed pharmaceutical registration from static dossier delivery into controlled electronic lifecycle management. eCTD v3.2.2 established the global sequence-based model, while eCTD v4.0 introduces a more metadata-driven architecture based on HL7 RPS,

persistent identifiers, controlled vocabulary, document reuse and forward compatibility.

For global pharmaceutical companies, the optimal strategy is not to create independent dossiers for every market. Instead, organizations should maintain a harmonized scientific core, manage regional Module 1 content separately, apply authority-specific validation rules and maintain a centralized record of submission history and regulatory commitments. This approach supports efficiency without compromising regional compliance.

The transition to v4.0 should be treated as a regulatory operating-model transformation rather than merely a publishing-software upgrade. Effective adoption will depend on integrated regulatory information management, strong metadata governance, validated tools, lifecycle traceability and continued surveillance of authority implementation updates.

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