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Short communication

eCTD today vs eCTD v4.0 tomorrow: the real-world shift from document type definition to regulated product submission

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Introduction

The electronic Common Technical Document (eCTD) has become the global standard for submitting regulatory information for pharmaceutical products, facilitating harmonized communication between industry sponsors and health authorities such as the Food and Drug Administration (FDA), European Medicines Agency (EMA) (ICH, 2020a). Since its widespread adoption in the early 2000s, eCTD—particularly version 3.2.2—has enabled structured electronic submissions organized into five standardized modules, significantly improving efficiency, consistency and transparency in regulatory review processes.

Despite its success, the traditional eCTD framework is inherently document-centric, relying heavily on predefined folder structures and static PDF documents linked via an Extensible Markup Language (XML) backbone defined by Document Type Definitions (DTD) (ICH, 2020a).

This approach, while effective for earlier regulatory needs, presents limitations in handling increasingly complex data types, lifecycle management requirements, and the need for greater interoperability across global regulatory systems (ICH, 2020b; FDA, 2026).

To address these limitations, the International Council for Harmonisation (ICH) developed eCTD version 4.0, a next-generation submission standard based on the Health Level Seven (HL7) Regulated Product Submission (RPS) model. This new framework introduces a fundamental paradigm shift—from static document management to structured, data-centric submissions, aimed at improving data reuse, automation and regulatory decision making (ICH, 2024; FDA, 2026).

This paper explores the differences between current eCTD practices and the emerging eCTD v4.0 standard, focusing on the transition from DTD-based XML structures to RPS-based submissions and its real-world implications for regulatory operations (ICH, 2020a; ICH, 2024).

eCTD today: document-centric and DTD-based structure

The current eCTD (v3.2.2) is built around a hierarchical folder structure that mirrors the CTD modules. Each submission is provided as a "sequence" with documents organized and linked through an XML backbone file (e.g., *index.xml*).

Key characteristics of eCTD today include:

Document-centric approach: Focus is placed on PDF documents rather than structured data (ICH, 2020a; FDA, 2026).

Rigid folder structure: Content must fit predefined module and section hierarchies (ICH, 2020a).

Lifecycle management via sequences: Updates are managed through "new", "replace" or "delete"

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operations within sequences (ICH, 2020a; ICH, 2020b).

Regional XML variations: Different regions may use specific XML structures or requirements (ICH, 2020a; FDA, 2026).

While this model has enabled consistent global submissions, it has notable limitations:

- Difficulty in *reusing documents* across multiple applications.

- Increased complexity in managing *cross-references and lifecycle updates.*

- Limited support for *structured data exchange and automation* (ICH, 2020b; FDA, 2026).

eCTD v4.0 tomorrow: transition to RPS and data-centric submissions

eCTD v4.0 introduces a fundamentally new approach based on the HL7 RPS standard. Unlike DTD-based XML structures, v4.0 uses modern XML schema definitions (XSD) and structured data models to enable more flexible, interoperable submissions.

Key transformational changes:

From DTD to RPS/XSD Architecture - The rigid DTD-based structure is replaced with a more flexible schema aligned with HL7 standards, supporting complex data relationships and validation rules.

Data-Centric Model - Instead of focusing solely on documents, eCTD v4.0 introduces structured metadata and data elements, allowing regulators to interpret submissions at a granular level (ICH, 2024; FDA, 2026).

Document Reuse via Unique Identifiers - Each document is assigned a unique identifier (UUID), allowing reuse across submissions without duplication (ICH, 2020b; FDA, 2026).

Controlled Vocabularies and Metadata Standardization - Standardized terminologies improve consistency and facilitate automated processing and review.

Enhanced Lifecycle and Flexibility - The concept of rigid "sequences" is replaced by more flexible submission units and lifecycle tracking mechanisms (ICH, 2024; FDA, 2026).

Bi-directional Communication (Future Capability) - eCTD v4.0 is designed to support two-way communication between regulators and sponsors, enabling more dynamic interactions (FDA, 2024).

Conclusion

The evolution from eCTD v3.2.2 to eCTD v4.0 represents a key step in the digital transformation of regulatory submissions. While the DTD-based model has standardized submissions for years, it is limited by its document-centric and rigid structure. eCTD v4.0, based on the HL7 RPS model, introduces a data-centric approach that improves interoperability, efficiency and lifecycle management, fundamentally changing how regulatory information is organized and reviewed (ICH, 2020a; ICH, 2024; FDA, 2026). This transition requires updates in technology, processes and skills, including better metadata management. In return, it enables faster reviews, greater transparency and improved global collaboration (ICH, 2020b; FDA, 2026). Overall, eCTD v4.0 points toward a more intelligent, data-driven future for regulatory submissions, positioning early adopters for success (ICH, 2024; FDA, 2024; FDA, 2026).

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