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A Review on: Electronic Submission Standards RPS Vs. eCTD

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Abstract: *The implementation of digital submission standards is crucial for keeping uniformity, and gratifying regulatory neces-sities inside streamlining strategies, the submission documentation. full-size in this discipline are of pharmaceutical and healthcare product the electronic not Regulatory Product Submission unusual Technical document (eCTD) and the (RPS). and realistic use of those factors The eCTD, created by the International Council for Harmonisation (ICH) This abstract highlights the mutual significance, organization, eCTD version 3, section 2.2. This is the commonly accepted file format and container used for sending the Common Technical Document (CTD). It uses PDF files linked via an XML table of contents to convert the paper dossier into a digital version.*

ECTD (version 3). 2. 2): The widely acknowledged file format and container used for submitting the Common Technical Document (CTD). By utilizing PDF files connected through an XML ToC, the paper dossier was digitized. The HL7-developed RPS specifies the technical protocol for electronic sharing of regulated product data. The XML framework serves as the foundation for eCTD version 4. Certainly, here's a version: Unlike RPS, which is created by Health Level Seven (HL7) and focuses on a data-centric and flexible strategy, it facilitates improved metadata management and accommodates intricate regulatory processes. Using RPS changes how submissions are made, moving from a format that focuses on documents (like the eCTD v3) to a more flexible and updated way 2) to a data-driven ecosystem (eCTD v4).

Sure This is achieved by using UUIDs and specific metadata from Controlled Vocabularies, which allows machines to better understand the information. Version 4 of the RPS/eCTD system was released. In 2015, the ICH approved this change. The rollout of this approval is happening gradually across the world. The US FDA started accepting new regulatory submissions in eCTD version 4. As of September 16, 2024, the format has been updated. The EMA still uses eCTD version 3.2. The plan is to move to version 4.0 through a step-by-step approach. PMDA in Japan has approved eCTD version 4. Since the academic year 2016/2017, no voluntary submissions have been made.The sector is currently undergoing a period of change, making it a crucial subject for any academic review paper.

The electronic common technical document (eCTD) allows for the electronic submission of content is consistent with the harmonised CTD, the eCTD also provides a harmonised of the Comorin Technical. Document (CTD) from applicant to regulator. While the table of technical solution to implementing the CTD electronically. The specification is based on the Common Technical Document (CTD) format and was developed by the International Council Gtor Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG).

Version 2.0 of eCTD, an upgrade over the original CTD was finalised on February 12, 2002, and version 3.0 was finalised on October 8 of the same year. As of August 2016, the most current version is 3.2.2. released on July, 2008..

Keywords*:* Electronic Common Technical Document (eCTD), Common Technical Document (CTD), ICH Harmonization, Regulatory Submissions, Pharmaceutical Applications, Modular Structure

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I. INTRODUCTION

History:

The idea of submitting drug applications electronically is not a modern fad; it is an evolution that began decades ago in the late 1980s. The goal was simple: to replace literal pallets of paper with a system that allowed regulators to review crucial data efficiently.

The path to today's standardized electronic submissions was anything but steady. The format of a drug submission was as unstable as a house of cards: in just two decades, the industry saw a flurry of competing standards (including SEDAMM, MERS, MANSEV, CANDA, DAMOS), proving that the permanence of the old "paper submission" no longer applied in the digital age.

The history of the electronic Common Technical Document (eCTD) began with a need to move from paper to a standardized in 2003 and formalized between 2003 and 2008. It became the required standard for major regulatory bodies like the FDA and EMA and is now a global standard that streamlines the submission process through an XML backbone, enabling efficient lifecycle management and review.

DAMOS-Drug Application Methodology with Optical Storage; Initiated by European regulatory Europe in 1989.

SEDAMM - Submission electro Nique de Dossiers d 'Authorisation de Mise sur le Marché; Initiated by France in 1993.

Key Difference (RPS vs. eCTD):

Feature	RPS(Regulated Product Submission)	eCTD (Electronic Common Technical Document)
Concept	XML message standard for two-way communication.	XML envelope with PDF documents inside, structured into 5 modules.
Flexibility	More flexible; designed to cover all regulated products.	Structured based on the CTD (Common Technical Document) for human medicines.
Structure	Flat structure; uses a single XML file to manage content links	Hierarchical/Modular structure (5 modules) with multiple XML files
Goal	Advanced data exchange; manage submissions across the entire product lifecycle with ease of cross-referencing.	Standardized organization of documents for initial submission and maintenance

Table:01

INTRODUCTIONOF (eCTD):(Electronic Common Technical Document)

Concept XML message standard for two-way communication. XML envelope with PDF documents inside, structured into 5 modules.

Flexibility More flexible; designed to cover all regulated products. Structured based on the CTD (Common Technical Document) for human medicines.

Structure Flat structure; uses a single XML file to manage content links. Hierarchical/Modular structure (5 modules) with multiple XML files.

Goal Advanced data exchange; manage submissions across the entire product lifecycle with ease of cross-referencing. Standardized organization of documents for initial submission and maintenance.

MERS- Multiagency Electronic Regulatory Submission Project; Initiated by USA, Newzea land, and Australia in 1994.

MANSEV - Market Authorisation by Network Submission and Evaluation; Initiated by UK, Denmark, France, Italy and EMEA in 1997.

Specifications:

The specifications describe the way the files should be constructed for the inclusion in the eCTD. The commonly used formats in the electronic submission are as follows, any other formats could be used according to the guidance published in each region.

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1. PDF:

Standardization (ISO) standard ISO 32000-1:2008.

The files must not contain Java Script, Portable Document Format (PDF) is a published format compliant to the International Organisation for dynamic content (e.g., audio, video or special effects), attachments or 3D content.

Current versions of PDF recommended by ICH website must be referred.

The size of the file must on exceed 500 MB.

2. XML Files:

The working group at the World Wide Web Consortium (W3C) developed the Extensible Markup Language (XML) It is a non-proprietary language developed to improve on previous markup languages.

XML is currently used for some content of the eCTD.

3. Study Dataset Files:

Specific regions include; study datasets and may have different rules regarding the following topics:

Allowable file formats

Dataset files sizes

Dataset filenames arid allowable characters

eCTD submissions are accepted for the following applications:

Investigational New Drug (INDs)

New Drug Applications (NDAs)

Abbreviated New Drug Applications (ANDAS)

Biological License Application : All the master files which are part of any above-mentioned applications The eCTD is based on the original Common Technical Document (CTD) format developed by the International Conference on Harmonisation (ICH). The structure provides a uniform way to organize the five modules of a submission dossier.

The Core Methodology of eCTD

The eCTD methodology can be broken down into five key pillars:

1. The Common Technical Document (CTD) Structure

This is the foundational "table of contents." The CTD, established by the ICH (International Council for Harmonisation), organizes the vast amount of data required for a marketing application into five standardized modules.

Module 1: Region-Specific Information

This is not harmonized and contains documents specific to each region (e.g., FDA Form 356h, Product Labelling, Patent Information, Environmental Assessment).

Module 2: Summaries

Contains high-level summaries of the application: Quality Overall Summary (QOS), Nonclinical Overview, and Clinical Overview, along with written summaries.

Module 3: Quality (Chemistry, Manufacturing, and Controls - CMC)

Detailed information about the drug substance and drug product, including manufacture, characterization, and specifications.

Module 4: Nonclinical Study Reports

Full report from toxicology and pharmacology studies.

Module 5: Clinical Study Reports

Full reports from human clinical trials.

Methodological Impact: This structure ensures that a regulator, anywhere in the world, knows exactly where to find specific information, streamlining the review process.

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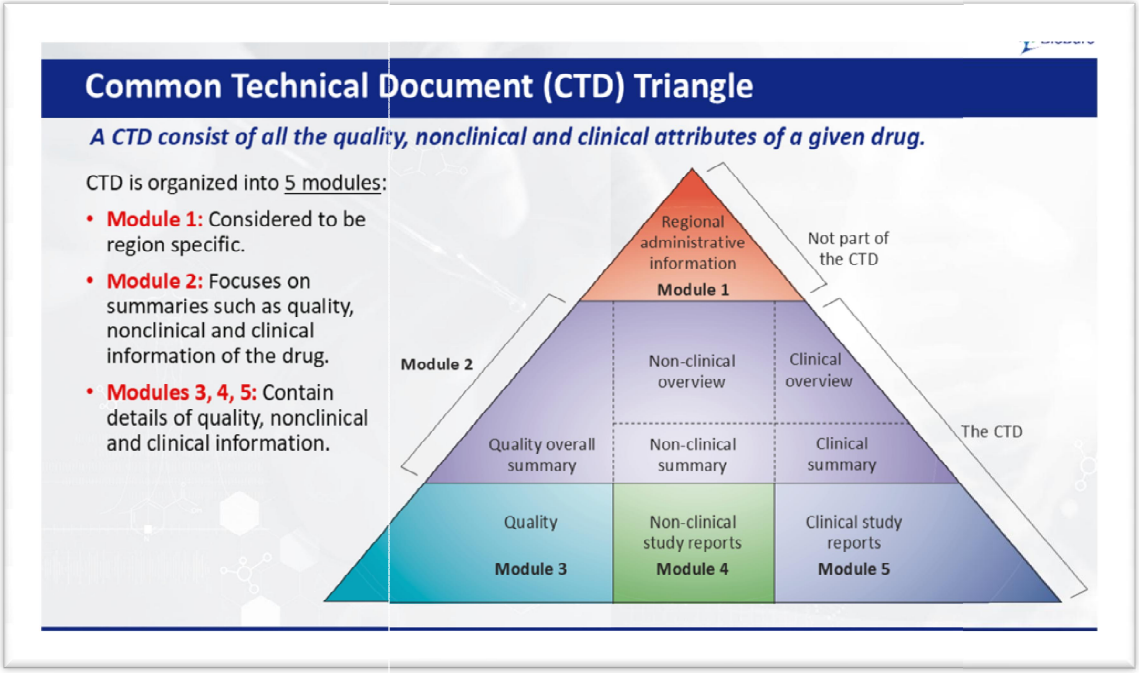

Fig.01

2. The Electronic Backbone: XML (Extensible Markup Language)

The "e" in eCTD is powered by a specialized XML file called the backbone file or index file (index.xml). This file is the digital map of the entire submission.

It defines the hierarchy: It replicates the CTD structure (Modules 1-5).

It links to documents: Every individual file (PDF, Word, SAS dataset, etc.) in the submission is referenced by a hyperlink in the backbone.

It contains metadata: For each document, it stores critical metadata like:

leaf title (e.g., "Study Report C123")

operation (New, Replace, Delete, Append)

Regulatory context (e.g., application-number, sequence-number)

Methodology Impact:

The XML backbone allows for automated processing and validation by regulatory agency systems. Its “brain that tells the reviewer's system how to assemble and display the dossier.

3. The Lifecycle Management System: Sequences and Operations

This is a core methodological innovation of eCTD. A regulatory application is not a single, static submission; it evolves over time. eCTD manages this through sequences.

· Sequence 0000: The initial submission (e.g., the original NDA or MAA).

· Sequence 0001: The first regulatory activity (e.g., responses to information requests).

· Sequence 0002: The next activity (e.g., a CMC change, a new safety report, a labelling update).

For each new sequence, you only submit the changed documents. The backbone file uses "operations" to tell the system what to do with these documents:

· New (new): Adding a document for the first time.

· Replace (replace): Submitting a new version of an existing document. The old version is archived but remains accessible for audit trails.

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· Delete (delete): Marking a document as deleted (it is not physically removed from the history).
· Append (append): Adding information to an existing document without replacing it (less common).
Methodological Impact: This creates a complete, searchable, and transparent history of the product's regulatory lifecycle. A reviewer can easily see what changed, when, and why.

4. Strict Technical Specifications and File Formats
The methodology is enforced by strict technical rules to ensure consistency and interoperability.
File Formats: Primarily PDF for documents, but also allows for other formats like Word, XML (for study data using SEND), and SAS transport files for clinical datasets.
PDF Requirements: Specifics like PDF/A for long-term archiving, bookmarks, hyperlinks, and security settings are mandated.
Naming Conventions: Files must follow strict naming rules (e.g., m5-csr-clin-study-01.pdf).
File Size Limits: Individual files must often be under a certain size (e.g., 100 MB), requiring large documents to be split.
Methodological Impact: Standardization prevents technical errors upon submission and ensures the dossier renders correctly on the regulator's system.

5. Regional Implementation Guides (RIGs)
While the eCTD is a global standard, Module 1 and some technical details are region-specific. Each major health authority publishes its own Regional Implementation Guide (RIG).
· FDA: Provides the eCTD Technical Conformance Guide.
· EMA: Provides the EU eCTD Module 1 Specification.
· Health Canada: Provides the Canadian eCTD Guidance.
Methodological Impact: Applicants must tailor their eCTD submissions to the specific requirements of the target health authority, even while using the same global standard.

The eCTD Workflow Methodology
The process of creating an eCTD submission typically follows these steps:
1. Authoring & Document Preparation: Content is created in appropriate software, ensuring it meets format and style guidelines.

Paper CTD	Paper eCTD
1. Well organized in format with Tabs, Volumes and sheets then printed to paper.	1.Compiled electronically with e-documents in folder.
2. Paper volumes must be A4.	2.e-documents can be A4 or US letter size.
3.CTD navigation by TOCs and volume.	3.eCTD navigation by XML backbone.
4.Cross-references includes target CTD Section number	4. Cross-references are hyperlinked to targets.
5. Submitted in binders in boxes.	5.Submitted in CD or DVD and email.

2. Document Management: Documents are checked into a specialized eCTD publishing software system.
3. Publishing:
· The publisher assigns documents to their correct location in the eCTD structure.
· Metadata (leaf titles, operations) are assigned.
· The XML backbone file is automatically generated.
· The system creates the necessary folder structure.

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4. Validation: The publisher's validation tool checks the submission against the technical requirements of the target health authority's RIG. This catches errors before submission.
5. Review and Export: The final submission is reviewed by the regulatory team and then exported as a compressed folder (e.g., a ZIP file).
6. Submission: The compressed eCTD is transmitted to the health authority via their designated electronic gateway (e.g., FDA's ESG, EMA's Submission Gateway/Common Repository).
7.Acknowledgment & Lifecycle Management: The health authority's system validatesthe submission and sends an acknowledgment. The sequence number is incremented for the next submission.

Comparison between paper CTD and paper eCTD:

Why is the eCTD essential ?

The adoption of the eCTD was driven by three primary needs:

- Efficiency and Review Speed: The eCTD allows agency reviewers to navigate effortlessly via hyperlinks, instantly jumping between summaries in Module 2 and the raw study data in Modules 4 or 5. This dramatically reduces the time spent searching for information, helping accelerate the overall drug review process.
- Harmonization: By standardizing the format across major regulatory regions, the eCTD allows pharmaceutical companies to compile one single master dossier that meets the technical requirements of multiple agencies simultaneously, saving enormous time and resource costs.
- Lifecycle Management: Perhaps most critically, the eCTD excels at managing the product lifecycle. Every new submission (an update, an amendment, or a safety report) is treated as a subsequent "sequence." The eCTD system intelligently tracks all changes, allowing reviewers to see instantly which document was added, replaced, or deleted since the last submission, creating a complete and traceable audit trail from development through post-market monitoring.

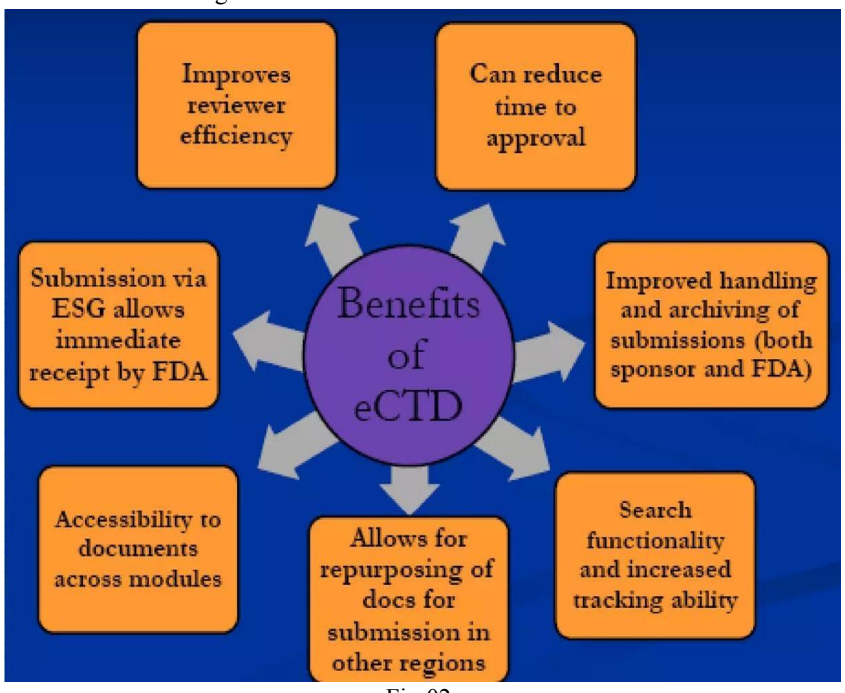

Fig:02

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Key Benefits of eCTD v4.0

1. Content Reusability

The introduction of unique identifiers (UUIDs) enables sponsors to submit a document once and reference it in future submissions without resending the physical file. With unique IDs, documents can be reused/referenced across a sequence (referred to now as 'Submission Unit'), across regulatory activities within an application, or even across different applications.

This advancement underscores the need for lean authoring practices to ensure content is written for reusability across various registrations and jurisdictions. describer™ supports this principle by offering templates that separate content from context. Describer™ benefits include:

Streamlined updates and lifecycle management

Reduced inconsistencies and compliance risksFaster submission preparation with fewer variations (e.g., manufacturers only mentioned in relevant sections like S.2.1 and P.3.1)

Elimination of redundancies during writing, review, approval, and publishing

2. Enhanced Lifecycle Management

eCTD 4.0 introduces the "Context of Use" (CoU) concept, which organizes documents based on their purpose/context or CTD section. Coupled with keywords, CoU facilitates lifecycle management at the contextual rather than the document level.

A single document can now replace multiple documents or vice versa while maintaining lifecycle traceability. This structured approach ensures precise content placement and easier updates over time.

Describe™ templates accommodate varying levels of document granularity, empowering businesses to align content strategies with regulatory requirements effectively.

3. Improved Metadata Correction

With the introduction of Keywords, eCTD 4.0 allows sponsors to apply changes to the metadata (now called keyword definition display names) without resubmitting the physical files. Sponsors can easily correct a typo in the manufacturer name or substance name or align them to the controlled vocabulary by submitting a new display name value.

This feature enhances efficiency and improves data accuracy while reducing administrative burden.

4. Context Groups and Simplification

As described above, the CoU concept and Keywords are used to group documents in a specific context. This approach makes Study Tagging Files (STFs) obsolete. In modules 4 and 5, STFs were implemented to organize or group the documents associated with a particular study. In v3.2.2, they are required in the US, not required in the EU, and not allowed in Japan. eCTD 4.0 uses context groups to organize this content and harmonize the requirements.

5. Improved Content Organization

Using a priority number system, sponsors can now prioritize and order documents within each CTD section, allowing for better control over how submissions are presented to health authorities. This flexibility extends to future submissions, where the order can be modified or new content added.

6. Harmonized Submission Unit

eCTD 4.0 consolidates content from Modules 1 to 5 into a single exchange message schema, eliminating the need for multiple schemas and reducing submission complexity.

7. Standardized Terminology

eCTD 4.0 introduces new terminology and concepts while providing clear definitions and relationships between them (e.g., Application, Submission, Submission Unit). It eliminates ambiguity, ensuring consistent communication and understanding across global stakeholders.

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8. Controlled Vocabularies

The adoption of controlled vocabularies from authoritative sources (e.g., ICH, HL7, ISO) ensures structured, traceable, and reusable regulatory information. Controlled vocabularies are a vital component of eCTD 4.0. Sponsors can also define their own vocabulary, standardize values across products and registrations, and improve overall data governance.

9. Flexibility for future updates

As noted, eCTD 4.0 relies heavily on controlled vocabularies, which is a step towards data-centric submissions. This means that changes to the CTD structure can be updated more quickly, eliminating expensive and time-consuming system upgrades.

10. Two-Way Communication

In the initial stages of eCTD 4.0 development, the working group proposed two-way communication, where health authority responses would become part of the eCTD lifecycle, as a significant enhancement. However, they ultimately omitted this feature, and it is not currently supported. The feature remains a possibility for future updates, offering further potential to streamline regulatory interactions.

Key reported industry challenges include:

30–45% of submissions rejected due to non-compliance

20–35% increase in regulatory queries arising from formatting defects

60%+ of delays linked to dossier quality gaps, not scientific content

Lifecycle management failure in sequence updates and backbone xml errors

With the regulatory environment evolving toward real-world evidence (RWE), automated compliance verification, and structured data governance, readiness assessments must move beyond traditional checklists to intelligence-driven quality scoring using:

eCTD XML backbone integrity

Module completeness mapping

Hyperlink & leaf validation

Metadata accuracy and version control

Hash value authentication

Clinical evidence quality metrics

Labelling alignment to CCDS/SmPC/PI fields

eCTD Submission

eCTD management software. This compiled submission is then validated to ensure technical compliance, and finally transmitted through the designated electronic portal, such as the FDA's Electronic Submissions The eCTD submission process involves organizing documents into the five modules, preparing them in the correct format, and assembling them into a structured dossier using

1. Prepare eCTD ready submissions

Develop content using standard templates and style guides to create submission ready documents

Manage and process source documents

Provision various eCTD templates for different types of submissions (initial, reports, and amendments)

Process and format documents to ensure high-quality submissions

2. Compile, publish, and validate submissions

Create submission modules in industry-leading eCTD software

Set up submission specific attributes

Render PDF of final hyperlinked documents

Review and assemble modules for submission

Assign documents to a location within the eCTD modular structure

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Organize PDF files containing metadata and lifecycle instructions to ensure data is properly transferred to agency reviewers and is easy to navigate

Run validation tool to ensure technical requirements are met

Perform quality control on documents to ensure agency validation criteria are met

3.Submit to agency and perform lifecycle management

Submit applications through FDA's secure electronic submission gateway

Manage complete life-cycle for submissions

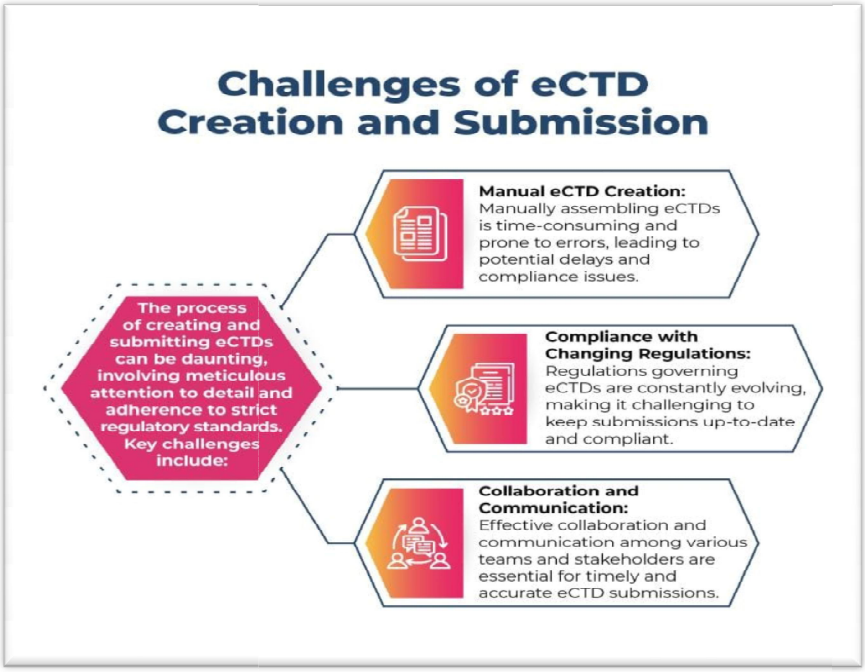

Fig:03

Structure of submissions

This document provides guidance on how to organise application information for electronic submission using the eCTD specifications. Guidance on the detailed information to be included is described in the Common Technical Document (CTD), and relevant ICH and EU Q&A documents. The structure and organisation of an eCTD submission is defined by the following standards:

* ICH M2 eCTD Specification
* EU Module 1 Specification
* Relevant ICH and EU Q&A docs

Annex 1 contains links to the currently approved version of these documents.

Typically, an eCTD application will cover all dosage forms and strengths of a product with any one invented name. In the centralised procedure, this will be equivalent to all dosage forms and strengths covered by an EMEA application number (e.g. EMEA/H/123).

In MRP/DCP, a single eCTD application should preferably be used for the procedure. However, if an applicant decides not to apply for all strengths and dosage forms in every member state in the procedure, the possibility of having one eCTD application per strength should be considered. Applicants should carefully consider what an eCTD application should cover before submitting the first sequence, as the choice could have implications for workload for the lifespan of the product. For example, if the applicant decides to have one eCTD per strength or dosage form, it is expected that each of these eCTD applications will be maintained individually, such that submission of a single sequence that covers

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more than one strength or dosage form will no longer be possible if very good reasons are not presented for a change over. Inthese rare cases, please contact the NCA/RMS/EMEA concerned at an early planning stage. For further details on the pros and cons of the different approaches to dossier structure, see Annex 3, Table 1.

Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD Applications version 1.0 May 2009 please check the specific NCA guidance when preparing national e CTD s

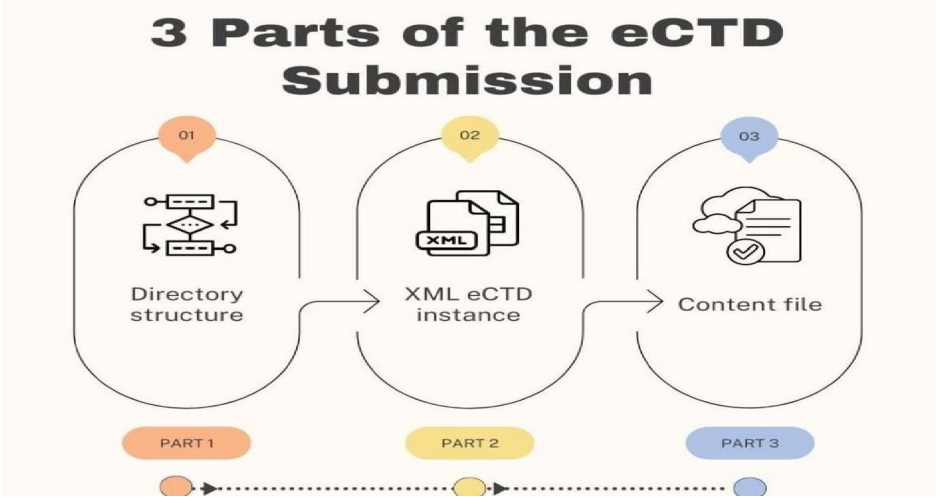

Fig:04

INTRODUCTION OF RPS:

Regulated Product Submission (RPS) is a Health Level Seven (HL7) standard designed to help the processing and review of regulated product information. Initiated on June 22nd, 2005, RPS is created for the registration of pharmaceutical products for human use. The purpose of RPS is to meet the goals set by the FDA under the Prescription Drug User Fee Act (PDUFA). RPS is the primary aspect of PDUFA's five-year plan.

RPS is a global, standardized, data-centric model for submitting regulatory information for any regulated product (drugs, biologics, devices, veterinary products). It was developed by the International Council for Harmonisation (ICH) to replace and improve upon the region-specific eCTD standards.

RPS and eCTD share the same ideology of a standardized format for Regulatory submissions including PDF documents and SAS datasets. Though the document structure is same for both RPS and eCTD, the internal XML structures are very different. RPS involves only a single file of XML but due to the complexities of the standard, it is difficult to generate the XML manually.

Think of it as:

eCTD 1.0: A standardized filing cabinet (the structure) with paper files inside (the PDFs).

RPS 2.0: A standardized database where the information itself is structured, computable;

Core Methodology Shifts: Frome CTD to RPS:

The methodology of RPS is built on several fundamental shifts.

Features	e CTD Methodology	RPS Methodology	Impact of shift
1.core standards	Region-Centric (ICH M2 eCTD Spec, but implemented via Regional Implementation Guides - RIGs).	Truly Global (A single, universal ICH RPS standard)	Harmonization: One standard for all regions (US, EU, Japan, etc.). Reduces complexity and need for regional customization.
2.Data structure	Document-Centric. The primary unit is a PDF file. The XML backbone is a	Data-Centric / Content-Centric. The primary unit is structured data (XML,	2. Computability: Data can be automatically processed, analysed, and compared by

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	"table of contents" pointing to these files	FHIR resources). Documents are just one type of content.	AI/ML tools. Enables advanced analytics and faster review.
3.Lifecycle Management	Operation-Based. Uses "New," "Replace," "Delete" in the XML to manage changes to documents.	State-Based. Each piece of content has a "status" (e.g., Active, Inactive, Superseded). The system infers the lifecycle from the current state	Simplification & Clarity: Eliminates complex "operation" logic. The current approved state of the application is always clear.
4.Technical foundation	Custom DTD (Document Type Definition) for XML	HL7 FHIR (Fast Healthcare Interoperability Resources). A modern, web-based standard widely used in healthcare	Interoperability: FHIR allows seamless data exchange with other healthcare systems (e.g., electronic health records, clinical registries).
5.Scope	Primarily for Human Pharmaceuticals (though adapted for Vet, Devices)	Any Regulated Product. The model is flexible enough to cover drugs, biologics, devices, combination products, and veterinary medicines	Unified Process: A company can use the same system and process for all its product types.

Table:03

Objective of RPS:

FDA receives many applications addressing a variety of Regulatory issues every year. As the information is divided into various files, the information of one file should always be correlated to the information in another file to efficiently review and process the information. Though the general data is same across all the files for regulated products, different products require different topics tobe covered within the submission.

To streamline this issue, RPS has been introduced as an HL7 XML message standard for submitting information to the Regulatory authorities. Each message has Regulatory information which is necessary for the submission. The structure of the message is in a colour coded diagram which is represented by R-MIM (Refined Message Information Model). The R-MIM diagrams are designed to capture the necessary information for efficient processing and Regulatory submissions review to explain the information of each message.Regulatory Product Submissions are crucial and challenging to manage. To know more about them for successful submissions, contact a publishing and submission expert at

RPS Methodology in Detail

1.The Universal Standard and Structure

RPS defines a single, global structure for organizing submission content. While it maps to the familiar CTD modules (1-5), it is not bound by a rigid folder-based hierarchy like eCTD. It uses a more flexible, object-oriented model.

2. The Shift to a Content-Centric Model

In RPS, everything is a "piece of content" with rich metadata. This content can be:

An unstructured document (e.g., a PDF of a study report).

Structured data (e.g., an SEND dataset for toxicology, a FHIR resource for a clinical trial protocol, or structured product labelling (SPL)).

A defined term (e.g., a product name, substance).

The RPS "backbone" is a comprehensive manifest that describes all these content pieces, their relationships, and their current status.

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3.State-Based Lifecycle Management

This is a key methodological improvement. Instead of telling the system what to do (Replace a file), you tell it what is (This is the new, approved version).

Example: eCTD: In Sequence 0002, you submit a replace operation for fileXYZ.pdf.

RPS: You submit a new version of the content. The system automatically updates the status of the old version to "Superseded" and the new version to "Active." The complete history is preserved, but the current state is unambiguous.

4. Built on HL7 FHIR

Using FHIR means RPS is built for the modern digital world. FHIR uses:

APIs (Application Programming Interfaces) for system-to-system communication.

RESTful principles, making it web-native.

Standardized Resources to represent clinical and administrative data.

This allows for real-time data exchange and integration far beyond the "package-and-send" model of eCTD.

Real-World Implementation: FDA's PRS and EMA's DARWIN

RPS is not just a theoretical standard. It is being implemented now.

FDA: Project Prime RTA / RPS Portal (PRS)

The FDA is actively developing its RPS-based system. The goal is to receive submissions as structured data from the outset, enabling:

· Automated data validation and analysis.

· Instant integration of submission data into review tools.

· Significant reduction in pre-review processing time.

EMA & FHIR Use Cases

The EMA is exploring the use of FHIR for specific submission components, such as clinical trial data (as part of the Data Analysis and Real-World Interrogation Network (DARWIN) initiative). This aligns with the RPS philosophy of using structured,computable data

Regulatory Absorption Status:eCTD (electronic Common Technical Document) is the current mandatory standard for regulatory submissions in major regions like the US (FDA) and EU (EMA). RPS (Regulated Product Submission), often referred to as eCTD v4.0, is an emerging, more advanced standard that is being actively implemented in the US but has not yet fully replaced eCTD v3.2.2 as the sole mandatory format globally.eCTD (version 3.2.2) is currently the mandatory standard for most human pharmaceutical product submissions to major global regulatory agencies, including the US FDA, European Medicines Agency (EMA), and Health Canada.

RPS, known as eCTD v4.0, is the next-generation standard that is in varying stages of implementation or piloting across different region RPS (HL7 RPS Release 1) is a more modern, XML-based messaging standard developed to cover all regulated products, including medical devices, and is often referred to as eCTD v4.0

eCTD VS. RPS (e CTD V4.0):

Features	eCTD (v3.2.2)	RPS (eCTD v4.0)
Standards	International Conference on Harmonisation (ICH) M2 standard	Health Level Seven (HL7) XML message standard (ICH M4)
Backbone	Uses a proprietary DTD (Document Type Definition) backbone	Uses a single, more advanced XML backbone for smarter submissions and potentially two-way communication (though two-way is removed from initial FDA implementation)
Scope	Primarily for pharmaceutical products for human use	Covers all regulated products/medical devices, expanding beyond pharmaceuticals
Status	Mandatory standard in most major regions	In early adoption/piloting phase in some regions; not yet mandatory globally

Table No.04

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Data Reuse and Interoperability:

eCTD: Enables Document Reuse. Its interoperability is limited to the package level—ensuring a standard structure for submission and review.

RPS: Enables Data Reuse. Its interoperability is at the content level—allowing individual data points to be understood, exchanged, and processed by machines across different systems.

Data Reuse and Interoperability in eCTD

1. Data Reuse in eCTD

eCTD is fundamentally document-centric. Therefore, "data reuse" is primarily document reuse.

How it Works:

A company can create a master document (e.g., a Quality Overall Summary or a core stability study report).

This master document can be slightly modified and submitted across multiple applications in different regions (e.g., an NDA in the US and an MAA in Europe).

The content inside the PDF is reused by humans (regulators) reading it, but the system itself only sees a file to be stored and displayed.

Limitations: Static and Manual: The data within the PDF is "trapped." To extract a specific data point (e.g., the results of a particular clinical endpoint), a regulator must manually read, find, and transcribe it.

No Machine-Actionability: The system cannot automatically validate, compare, or analyse data across different submissions. Reuse is a manual, human-driven process.

2. Interoperability in eCTD:

eCTD's interoperability is structural, not semantic.

How it Works:

System-to-System (Limited): The eCTD package, with its XML backbone, provides a standard that allows a regulator's system to receive, validate, and unpack a submission from any sponsor. This is a form of technical interoperability.

Cross-Region (Fragmented): While the CTD structure (Modules 2-5) is harmonized, the implementation is not. Regional Implementation Guides (RIGs) for Module 1 create friction, meaning a submission must be "re-published" for each target region application. It is incredibly difficult to pool data from multiple eCTD sequences or different products for a broader analysis (e.g., a safety signal across a drug class). High Cost of Integration: To get data out of an eCTD for analysis, it often requires manual extraction or complex, custom-built text-mining tool

Data Reuse and Interoperability in RPS

RPS is designed from the ground up to be data-centric, fundamentally changing the game for reuse and interoperability.

1. Data Reuse in RPS

RPS enables true data-level reuse, where individual data points are structured, identifiable, and machine-readable.

How it Works:

Structured Content: Information is submitted as structured data using standards like HL7 FHIR. For example, a clinical trial participant's demographics, lab results, and adverse events can be submitted as discrete, coded data elements instead of a block of text in a PDF.

Reusable Data Elements: A single, master data element (e.g., a defined product substance) can be created once in a database and then referenced in multiple submissions. If it's updated, all references can be updated.

"Submit Once, Use Many Times": Data submitted for one purpose (e.g., an original marketing application) can be easily queried and reused for another purpose (e.g., a post-market study, a labelling update, or a new indication) without manual re-entry.

Benefits:

Efficiency: Eliminates redundant data entry and manual copying.

Consistency: Ensures data integrity across the product lifecycle.

Automation: Enables automated report generation and data validation.

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2. Interoperability in RPS

RPS provides both technical and semantic interoperability.

How it Works:

Technical Interoperability (APIs): Built on modern web standards like HL7 FHIR and REST ful APIs, RPS systems can communicate directly with other systems. This allows for real-time data exchange, not just batch submission of packages.

Semantic Interoperability (Standardized Meaning): RPS uses controlled terminologies, ontologies, and codes (e.g., LOINC for lab tests, SNOMED CT for medical terms). This ensures that a data point like "headache" means the same thing to the sponsor's system, the regulator's system, and a hospital's electronic health record (EHR).

Cross-Platform and Cross-Product Analysis: Because data is structured and semantically consistent, regulators can pool and analyse data across:

Multiple submissions for the same product.

Submissions for different products from the same company.

Even different products from different companies to identify class-wide safety signals or efficacy trends.

Benefits:

Advanced Analytics: Powers the use of AI/ML for predictive safety, subgroup analysis, and real-world evidence (RWE) generation.

Regulatory Agility: Facilitates faster safety reporting and more dynamic label updates.

Advantages and Challenges:

Advantages of eCTD

Maturity and Stability:

Well-Understood: The standard, its regional variations (RIGs), and the validation

criteria are well-defined and stable. Regulatory affairs professionals and publishing teams have decades of experience.

Proven Track Record: It has successfully managed the lifecycle of thousands of products globally, proving its effectiveness over paper.

2. Standardized Global Structure:

Harmonized Review: The CTD format (Modules 2-5) ensures that regulators in any region know exactly where to find specific information, significantly streamlining the review process.

Predictable Workflows: Both industry and agencies have established, efficient workflows for submitting, receiving, and reviewing eCTD sequences.

3.Efficient Lifecycle Management:

Clear Audit Trail: The "sequence" model with "New," "Replace," and "Delete" operations creates a perfect historical record of all regulatory changes, which is invaluable for audits and inspections

4. Robust Vendor Ecosystem:

Specialized Tools: A mature market exists for eCTD publishing, validation, and document management software. This creates competition and choice for sponsors.

Expert Services: Many consulting and outsourcing firms offer deep expertise in eCTD submission management.

Challenges of eCTD

1. Document-Centric Limitation:

Trapped Data: The primary challenge. Information is locked in PDFs, making it inaccessible for automated analysis, comparison, or reuse. Regulators must manually read and re-key data.

No Computability: Hinders the use of advanced analytics, AI, and cross-submission data mining.

2. Regional Fragmentation:

Implementation Guides (RIGs): While the core is harmonized, Module 1 and technical specifics differ by region (FDA, EMA, PMDA, etc.). This requires sponsors to create and maintain region-specific versions of submissions, increasing cost and complexity.

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3.Technical Complexity and Cost:

"Publishing" Burden: The process of compiling, hyperlinking, validating, and generating the eCTD package is highly technical and requires specialized staff and software.

High Overhead: Maintaining in-house eCTD capabilities and ensuring compliance with evolving RIGs is a significant ongoing investment.

4. Limited Future-Proofing:

Struggles with Modern Data Types: It is not well-suited for integrating large, structured datasets (e.g., from genomics, real-world evidence, or complex clinical trials) in a meaningful way beyond simply attaching the files.

RPS (Regulated Product Submission)

RPS is the next-generation standard designed to address eCTD's limitations. Its advantages are transformative, but its challenges are tied to its ongoing implementation and paradigm shift.

Advantages of RPS

1. Data-Centricity and Computability:

Unlocks Data Value: Information is submitted as structured, coded data (using HL7 FHIR). This allows for machine-to-machine processing, automated validation, and advanced analytics.

Enables AI/ML: Regulators can use tools to automatically analyse safety signals, compare efficacy across products, and generate insights from pooled data.

2. True Global Harmonization:

Single Standard: RPS is designed as one universal standard for all regions and all product types (drugs, devices, biologics, vet). This eliminates the need for regional republishing.

3. Enhanced Interoperability:

Connects to Healthcare Ecosystem: Built on HL7 FHIR, RPS can seamlessly exchange data with Electronic Health Records (EHRs), clinical registries, and other health IT systems. This facilitates the use of Real-World Evidence (RWE).

API-Driven: Enables real-time data exchange and system integration, moving beyond the "package-and-send" model.

4.Streamlined Lifecycle Management:

State-Based Simplicity: The "state-based" model (Active, Superseded) is more intuitive than eCTD's "operation-based" model, reducing complexity and potential for errors.

5. "Submit Once, Use Many Times":

Reusable Data Elements: Core data (e.g., product substance details) can be defined once and referenced across multiple applications, ensuring consistency and reducing redundancy.

Challenges of RPS

1. Implementation and Transition:

Immature Ecosystem: The standard is still being rolled out. Tooling for sponsors is less mature and widespread than for eCTD. The FDA's PRS and other agency systems are in active development.

Complex Transition: Migrating existing eCTD product portfolios to RPS is a massive, complex undertaking for both industry and regulators. The long-term coexistence of eCTD and RPS is a challenge.

2. Steep Learning Curve and Cultural Shift:

New Skillsets Required: Moving from document management to data management requires new expertise in data science, FHIR, and ontology management within regulatory teams.

Paradigm Shift: It requires a fundamental change in mindset from creating narratives for human readers to structuring data for machine consumption.

3. Upfront Cost and Resource Investment:

New Systems: Companies will need to invest in new software systems capable of handling RPS and FHIR-based authoring.

Data Transformation: The cost of converting legacy data and establishing new, structured data workflows is significant.

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4. Standardization and Governance:

Developing Ontologies: Achieving global agreement on the controlled terminologies and value sets for every data point is a massive, ongoing effort. Inconsistencies here could undermine interoperability.

Data Governance: Companies must establish rigorous internal data governance to ensure the quality and consistency of the structured data they submit.

II. CONCLUSION

The comparative analysis of the electronic Common Technical Document (eCTD) and the Regulated Product Submission (RPS) standards reveal a clear and necessary evolutionary pathway for global regulatory operations. The eCTD standard has been, and for the immediate future remains, the indispensable workhorse of regulatory submissions. Its profound contribution lies in its successful transition from paper-based chaos to a structured, predictable, and harmonized digital framework. By establishing a universal dossier structure and efficient lifecycle management model, eCTD has brought order, efficiency, and a foundation of global trust to the regulatory process for the past two decades.

However, the inherent limitations of its document-centric architecture are now the primary constraint on regulatory innovation. The "trapped data" paradigm, regional fragmentation, and inability to support automated computation prevent regulatory science from fully leveraging advanced analytics, real-world evidence, and the potential of artificial intelligence. eCTD optimized the submission of documents but failed to unlock the value of the data within them.

The RPS model emerges as the definitive response to this challenge. It represents a fundamental paradigm shift from managing documents to exchanging intelligent, structured data. Its core advantages—true global harmonization, inherent computability, and seamless interoperability via modern standards like HL7 FHIR—are not merely incremental improvements but are transformative. RPS lays the groundwork for a future regulatory ecosystem that is proactive, evidence-based, and integrated into the broader healthcare landscape, enabling capabilities from automated safety surveillance to personalized medicine applications.

Nevertheless, the transition from eCTD to RPS is arguably as challenging as the initial shift from paper to electronic submissions. The path forward is fraught with significant hurdles: the immense cost and complexity of transitioning legacy systems, the need for a mature vendor ecosystem, the critical development of global data standards, and a fundamental cultural shift within regulatory organizations and the industry from document management to data governance.

In conclusion, while eCTD provided the critical foundation for the digitalization of regulatory submissions, RPS is poised to enable their true transformation. The journey ahead is complex and will require sustained collaboration, investment, and vision from both regulators and industry. Yet, the imperative is clear: embracing the RPS standard is essential for building a more agile, knowledgeable, and effective global regulatory system capable of meeting the demands of 21st-century public health. The era of the document is passing; the era of intelligent, actionable data has begun.

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