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Review Article

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The future of Regulatory Submissions: Transition to eCTD 4.0

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Abstract

As a global standard for regulatory submissions, the electronic Common Technical Document (eCTD) has improved efficiency among health authorities and streamlined procedures for pharmaceutical and biological products. The introduction of eCTD version 4.0 represents a significant digital leap with enhanced lifecycle management, interoperability, and message-based architecture. This transition supports more effective data handling and fosters cross-border regulatory cooperation. eCTD 4.0 offers advantages such as reduced redundancy, real-time communication, and increased submission flexibility by moving away from document-centric models to a modular, data-centric framework. Regulatory agencies including the FDA, EMA, PMDA, and Health Canada are at various implementation stages, signaling global commitment to submission modernization. This review examines the evolution, benefits, challenges, and strategic opportunities associated with the implementation of eCTD 4.0 in global regulatory systems.

Conclusion: The transition to eCTD 4.0 marks a major advancement in regulatory submissions, offering a more flexible, interoperable, and data-driven framework. By addressing the limitations of earlier versions, it enables improved efficiency, communication, and global harmonization.

Keywords: eCTD 4.0; regulatory submissions; lifecycle management; digital transformation; global harmonization; regulatory agencies; FDA; ICH

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1. Introduction

Regulatory submissions serve as the foundational mechanism through which pharmaceutical and biotechnology companies seek approval from global health authorities to initiate clinical trials, market new therapies, or modify existing product licenses. These submissions encompass a vast array of scientific, technical, and administrative documents including clinical trial protocols, manufacturing specifications, safety data, and efficacy outcomes. (1) Historically, such information was compiled and submitted in paper form or as static PDF files, often resulting in voluminous dossiers that were difficult to manage, update, or cross-reference. (2–4)

The introduction of the electronic Common Technical Document (eCTD) fundamentally transformed this paradigm. (5) As a structured and internationally harmonized format developed by the International Council for Harmonization (ICH), eCTD allowed sponsors to compile and submit regulatory information electronically to agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. (6) The transition from paper-based processes to eCTD significantly improved submission management by enabling modular organization, lifecycle tracking, and region-specific granularity, all while maintaining a consistent framework across jurisdictions. (7)

The most widely used version to date, eCTD version 3.2.2, became the global default standard and offered a major leap in terms of submission efficiency, transparency, and regulatory review timelines. (8) As the complexity of therapeutic products and regulatory expectations has grown, driven by adaptive clinical trials, real-world data (RWD), and the rise of personalized medicine, these limitations have become increasingly problematic. (9,10)

To address these gaps, ICH introduced eCTD version 4.0, developed under the ICH M8 guideline. (11) This version is built upon the Health Level Seven (HL7) Regulated Product Submission (RPS) standard, which enables more granular, metadata-rich, and interoperable submission practices. Unlike its predecessor, eCTD 4.0 supports modular content reuse, structured data exchange, bidirectional messaging, and dynamic lifecycle management, all of which enhance collaboration between sponsors and regulators and improve overall regulatory

agility. (12,13) This simplifies the submission formats and provides a consistent structure across submissions. With eCTD 4.0, documents can be reused without knowledge of the file path across or within an application or sequence. Rather, these documents are assigned a unique identifier (ID) across regulatory activities and applications for easy reference. The two parties can communicate and exchange information with one another via eCTD 4.0 throughout the entire application review process, which is a much-welcomed update. (14)

This paper offers a comprehensive examination of the transition from eCTD 3.2.2 to eCTD 4.0. It analyzes the historical evolution of regulatory submission practices, the technical innovations introduced by the new standard, and the strategic implications for stakeholders across the regulatory ecosystem. In doing so, it identifies the limitations of legacy systems, presents the benefits of adopting eCTD 4.0, and explores the challenges and opportunities associated with its global implementation.

2. Evolution of eCTD Standards

2.1 From CTD to eCTD 3.2.2 to eCTD 4.0

The ICH introduced the Common Technical Document (CTD) in 2000 to harmonize drug submissions across the USA, Europe, and Japan. It established a common structure for data related to quality, safety, and efficacy. In 2003, eCTD was launched to enable electronic submission of CTD content. eCTD version 3.2.2, finalized in 2008, became the prevailing standard, facilitating sequence-based document submission and lifecycle tracking. (15) Despite its success, eCTD v3.2.2 revealed critical shortcomings as regulatory environments evolved. Its reliance on region-specific XML schemas, lack of structured data exchange, and static document management made it increasingly unsuitable for modern regulatory demands such as cloud integration, digital review systems, and global collaboration. (16)

Recognizing the need for a future-ready system, ICH reconstituted its M8 Working Group in 2010 to develop eCTD version 4.0. (17) Finalized in 2015 and gradually adopted thereafter, eCTD 4.0 introduces a more modular and dynamic architecture based on the HL7 Regulated Product Submission (RPS) standard. (18) This enhanced model supports structured metadata tagging, document reusability, two-way messaging, and dynamic lifecycle management. By unifying submission formats across regions and enabling seamless data flow between sponsors and regulators, eCTD 4.0 represents a pivotal advancement toward fully digital and harmonized regulatory ecosystems. (15) **Figure 1** illustrates the transition from eCTD-to-eCTD v4.0 enabling enhanced data consistency and compliance through controlled vocabularies, reuse of documents, use of context, and documents lifecycle control.

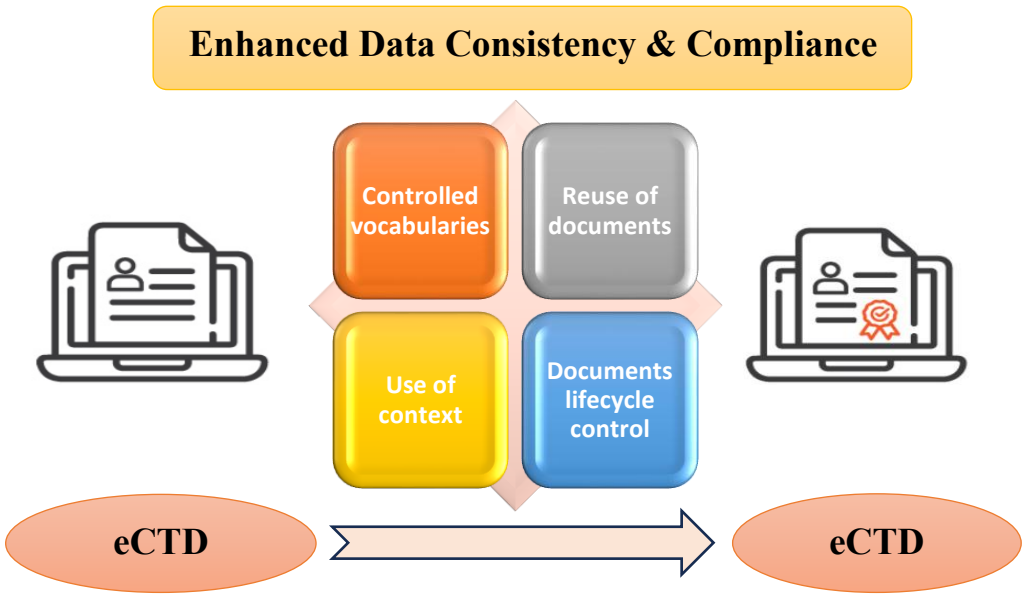

Figure 1. Transition to eCTD 4.0

2.2 ICH M8 Guideline

The ICH M8 guideline standardizes the technical and structural aspects of eCTD. It defines the XML schema, lifecycle rules, validation criteria, and implementation guidance for regions including the USA, Europe, Japan, and Canada. The guideline ensures harmonized communication across regulatory systems while accommodating regional requirements.

2.3 Limitations of eCTD v3.2.2

- Static XML Backbone: It imposes a rigid structure, making it difficult to adapt to new submission types or incorporate modular updates.
- Document-Centric Design: The system is document-centric, heavily reliant on PDF files, which limits the reuse of structured content and hampers integration with digital data systems.
- Cumbersome Lifecycle Tracking: Lifecycle management requires manual tracking of document replacements and deletions across

sequences an error-prone and resource-intensive process.

- One-Way Communication: eCTD v3.2.2 supports only one-way communication, offering no mechanism for real-time, bidirectional interaction between regulatory agencies and sponsors.

2.4 The Need for a Modern Lifecycle and Messaging System

As the pharmaceutical industry evolves with increasingly complex products, adaptive clinical trials, and globalized development strategies, the limitations of legacy submission systems particularly eCTD version 3.2.2 have become more pronounced. A central issue lies in its inability to support a dynamic, flexible, and interactive lifecycle management approach. In eCTD v3.2.2, managing updates such as replacing, deleting, or appending documents requires manual tracking of sequences and lacks standardization across regions. This static document lifecycle leads to inefficiencies, submission errors, and regulatory review delays. (20,21)

2.5 Benefits of eCTD 4.0

eCTD 4.0 modernizes regulatory submissions with improved data structure, process automation, and communication capabilities. This transition offers faster and more efficient submissions and reviews, less redundancy, easier management of complex application lifecycles, and better global interoperability a leap forward for regulatory affairs in the digital era. The transition to eCTD 4.0 brings numerous advantages to sponsors, regulators, and other stakeholders in the pharmaceutical industry as illustrated in **Figure 2**. (21,22)

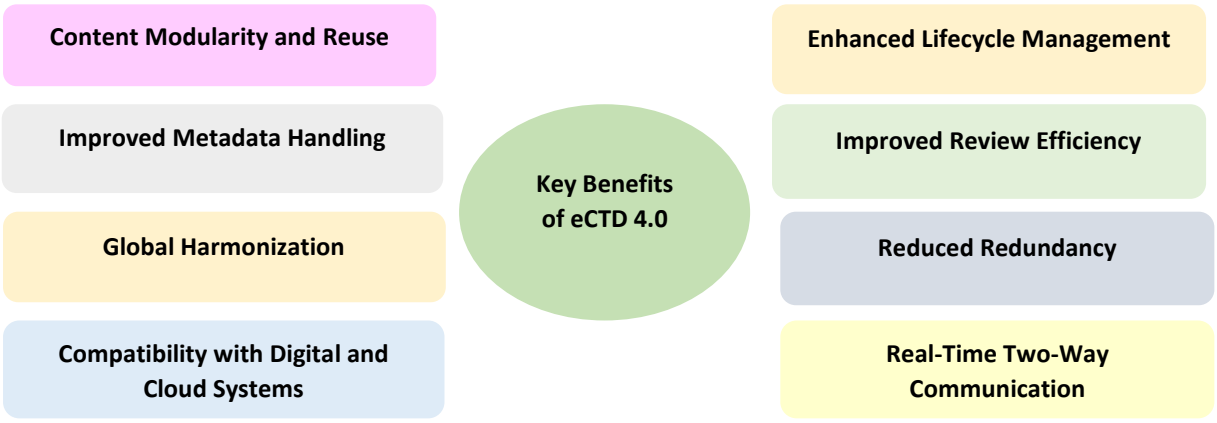

Figure 2. Key benefits of eCTD 4.0

- **Enhanced Lifecycle Management**: Enables more granular and automated control of submission updates and version history, reducing the manual burden of tracking document changes.
- **Improved Review Efficiency**: With better metadata and structured content, regulators can search, retrieve, and assess information more rapidly, leading to faster approvals and fewer clarifications.
- **Reduced Redundancy**: Documents can be reused across sequences and applications, minimizing repetitive submissions and improving consistency. Improves consistency and reduces the risk of submission errors.
- **Real-Time Two-Way Communication**: Bi-directional messaging supports dynamic interaction between sponsors and regulators, improving transparency and enables faster resolution of queries and immediate acknowledgements or updates.
- **Content Modularity and Reuse**: Through object identifiers (OIDs) and UUIDs, documents can be updated or referenced without re-uploading entire sequences, supporting efficient submission compilation.
- **Improved Metadata Handling**: eCTD 4.0 provides more precise classification and context for documents, allowing for better tracking, filtering, and automation. It eases the development of automated tools for regulatory tracking and compliance.
- **Global Harmonization**: It promotes regulatory convergence and easier cross-jurisdictional collaboration. It reduces the burden of reformatting for different global regions.
- **Compatibility with Digital and Cloud Systems**: eCTD 4.0 is well-positioned for integration with emerging technologies such as cloud-based repositories, AI-powered document review tools, and structured content authoring platforms.

2.6 Technical Features and Innovations

The release of eCTD 4.0 represents a substantial advance in regulatory submission technology, offering several key innovations designed to enhance efficiency, clarity, and global interoperability within the pharmaceutical regulatory environment. The following sections delineate the principal technical features that distinguish eCTD 4.0 from its predecessor, v3.2.2.

- **Message-Based Architecture**: eCTD 4.0 adopts a dynamic, message-based architecture built upon the HL7 Regulated Product Submission (RPS) standard which enables bi-directional communication between sponsors and regulatory authorities, thereby facilitating real-time exchanges of regulatory information, feedback, and queries.
- **Document Groups and Context of Use**: This mechanism allows sponsors to group, for instance, all documentation pertaining to a specific clinical study or regulatory response.
- **UUIDs and OIDs**: To ensure the unambiguous identification of documents and submission elements, eCTD 4.0 mandates the Universally Unique Identifiers (UUIDs) and Object Identifiers (OIDs). UUIDs provide persistent identification of submission objects across their entire lifecycle, supporting consistent referencing, reliable version control, and robust lifecycle tracking. The implementation of OIDs, which conform to international standards, further supports the classification and referencing of submission content, thereby facilitating global harmonization.
- **Content Reusability**: eCTD 4.0 is engineered to maximize content reusability. Sponsors can reference a single source document or content fragment across multiple applications, sequences, and even regulatory jurisdictions without the necessity of duplication.
- **Priority Control and Sequencing**: The new scheme introduces explicit mechanisms for establishing priority and sequencing of documents and document groups. Sponsors can now assign display priorities, thereby guiding reviewers to the most salient or time-sensitive content within a dossier.
- **Forward Compatibility**: A significant design consideration in eCTD 4.0 is its support for forward compatibility. The system is architected to ease the transition from eCTD v3.2.2 by accommodating legacy submission structures and allowing for the co-existence and even integration of earlier sequences.
- **Enhanced Validation Rules**: eCTD 4.0 incorporates a more stringent and comprehensive set of automated validation rules. These rules govern the accuracy and integrity of metadata, the structural correctness of submissions, and the completeness of submitted content.

To better understand the transformative impact of eCTD version 4.0, it is essential to compare it directly with its predecessor, eCTD v3.2.2, across key functional dimensions. **Table 1** outlines the major differences between the two standards, highlighting advancements in structure, metadata handling, lifecycle management, and interoperability. This side-by-side comparison illustrates how eCTD 4.0 addresses the limitations of the earlier version and introduces features that support greater efficiency, flexibility, and harmonization in global regulatory submissions. (14)

Table 1. Comparison of Key Features Between eCTD v3.2.2 and eCTD v4.0

Feature	eCTD 3.2.2	eCTD 4.0
Structure	Hierarchical, definition-based Table of Contents	Flat structure using keywords and context of use
XML Message	Every region has their own regional XML, index XML, and study XMLs.	Standardized and will have a single XML file (submissionuntil.xml).
Lifecycle Management	Basic (replace/delete documents	Granular, reusable, partial lifecycle updates.
Study Tagging Files	Used in this version	Replaced by Document Groups
Metadata	Less detailed	More detailed, including unique identifiers for documents
Communication	One-way communication (sponsor to agency)	Two-way communication (sponsor and agency) via sequences
Document Replacement	Difficult to replace multiple documents with a single approved version	Enables replacement of one document with many, and vice versa
Global Harmonization	Region-specific nuances	Harmonized for multi-region use
Regularity in the Format of the Document	Currently, there are more chances of irregularities as the process is a bit longer.	With the involvement of various bodies, including regional authorities, ICH, and other third parties, more content from the eCTD dossier via structured data can be provided in less time.
Priority Number	Not available	Allows controlling the display order of documents within a section
Technology Usage	Reliance on technology exists but only to a certain extent.	Much more reliance on technology by all parties to interpret the information being provided.
Searchability	Manual document review	Structured and metadata-supported search

As evident from the comparison, eCTD v4.0 significantly improves upon the static and document-centric limitations of v3.2.2 by adopting a more dynamic, data-rich, and globally harmonized architecture. The move toward standardized XML messaging, structured metadata, and two-way communication not only simplifies regulatory workflows but also positions eCTD 4.0 as a future-ready platform capable of supporting digital transformation initiatives across regulatory ecosystems.

3. Global Adoption Landscape

The global regulatory landscape is progressively shifting toward eCTD version 4.0, with regions at different stages of adoption. The FDA began accepting voluntary submissions in 2024, with mandatory compliance for certain types expected by 2029. (23) The EMA continues to use eCTD 3.2.2 but is running pilots to enable transition by 2027–2028, while Japan's PMDA plans to mandate eCTD 4.0 by 2026. (24) Health Canada is also targeting full implementation by 2026, (25) advancing from pilot to broader adoption. (26) Regulatory bodies in Australia and Switzerland are in pilot phases, while emerging markets like India and Brazil are building infrastructure, technical capacity, and training for future use. In India, the CDSCO has launched an eCTD pilot and upgraded the SUGAM portal, though nationwide adoption will require further investment and alignment with global standards. Its engagement in international forums such as the WHO and ICH underscores its intent to modernize in line with best practices. (27,28) The **figure 3** illustrates key milestones in the transition toward eCTD 4.0 across major regulatory regions.

The pace of eCTD 4.0 adoption varies significantly across regulatory regions, reflecting differences in technical readiness, policy priorities, and resource availability. While some agencies have already initiated structured pilot programs with defined transition timelines, others are still in the early stages of infrastructure development and capacity building. **Table 2** compares the current status, pilot activities, target implementation dates, and notable considerations for five key regulatory regions United States, European Union, Japan, Canada, and India providing a snapshot of the global adoption landscape.

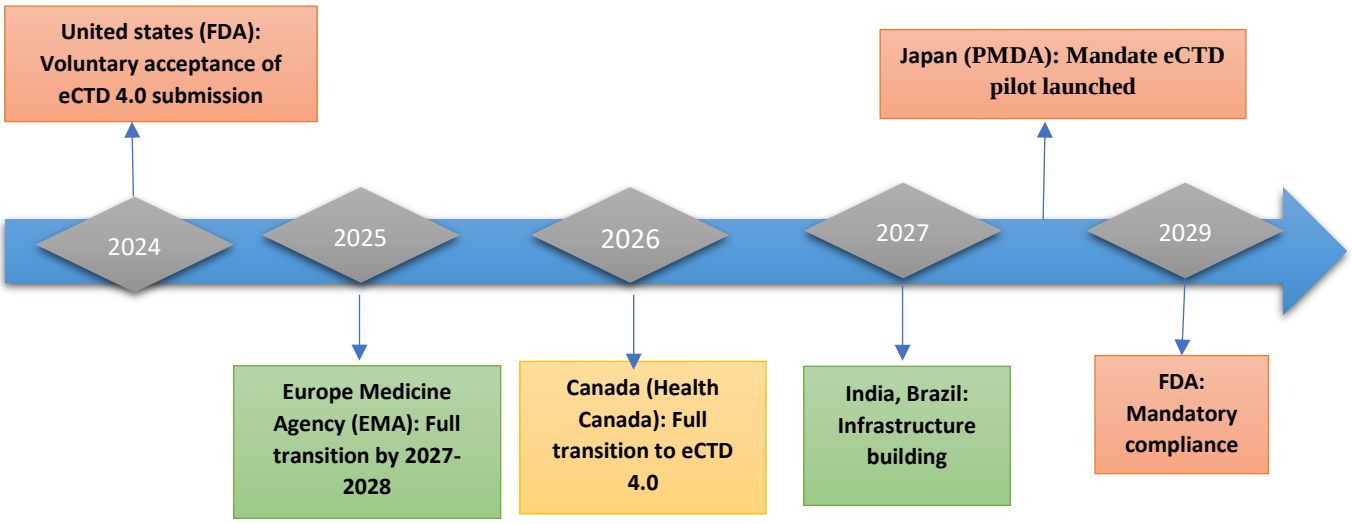

Figure 3. Global adoption timeline of eCTD 4.0

Table 2. Comparative status of eCTD 4.0 adoption across the United States, European Union, Japan, Canada, and India, highlighting current implementation stage, pilot activities, projected timelines, and key regional considerations

Region / Agency	Current Status	Pilot Programs	Target Full Implementation	Key Notes
United States (FDA)	Accepting voluntary eCTD 4.0 submissions since 2024	Ongoing technical and stakeholder pilots	Mandatory for certain submission types by 2029	Established guidance; gradual phased transition plan
European Union (EMA)	Still requires eCTD 3.2.2	Technical and business pilots underway	Targeted transition by 2027–2028	Harmonization across multiple member states; focus on interoperability
Japan (PMDA)	Transition in progress	Implementation guides and testing frameworks released	Mandatory by 2026	Proactive early adopter; strong industry engagement
Canada (Health Canada)	Moving from pilots to broader rollout	Completed pilot phase; scaling adoption	Full implementation by 2026	Close alignment with ICH guidelines

India (CDSCO)	eCTD not yet mandatory; pilot initiated	eCTD pilot via SUGAM portal	Timeline not finalized	Needs investment in training, interoperability, and alignment with international standards; engaged in WHO and ICH forums

4. Challenges in Implementation

While the transition to eCTD version 4.0 offers substantial strategic and operational advantages, its implementation is accompanied by several practical and systemic challenges. One of the foremost concerns is technical complexity. Moving from a document-centric model to a message-based, HL7 RPS-driven architecture requires extensive system upgrades, new submission tools, and the revalidation of existing regulatory workflows. This shift demands not only changes to backend infrastructure but also adaptations in document management practices and IT support systems. (29)

Equally important is the need for training and capacity building. Regulatory agency staff and industry professionals must be thoroughly trained on the structural and functional changes introduced by eCTD 4.0, including metadata management, lifecycle control, UUID/OID usage, and two-way messaging protocols. Without robust training programs, there is a risk of submission errors, increased rejection rates, and prolonged review timelines. (30)

Another major barrier is cost. The transition entails significant upfront investment in compliant software solutions, workforce training, and integration with regulatory portals. For small and mid-sized enterprises, and for regulators in low- and middle-income countries (LMICs), these costs can be prohibitive and may delay adoption.

Moreover, during the transitional phase, agencies and sponsors may need to support dual systems maintaining compatibility with both eCTD v3.2.2 and v4.0. This requirement introduces interoperability gaps and increases the operational burden on regulatory operations teams. Ensuring backward and forward compatibility while avoiding duplicative submissions is a key challenge during this overlapping period. (31)

Finally, the uneven pace of global harmonization poses a systemic risk to the core objective of eCTD 4.0: standardization. Variability in regional readiness, policy timelines, and implementation resources may create a fragmented regulatory environment, where sponsors are required to prepare multiple submission formats depending on jurisdiction. Without coordinated global alignment, the full benefits of eCTD 4.0 in reducing complexity and promoting harmonization may not be realized uniformly across regions. (32)

5. Strategic Outlook and Opportunities

The adoption of eCTD version 4.0 signifies far more than a routine technical upgrade and marks a pivotal step toward the digital transformation of global regulatory practices. As regulators and life sciences stakeholders grapple with escalating data complexity, evolving therapeutic innovations, and mounting pressure to expedite access to safe and effective treatments, eCTD 4.0 offers a scalable and interoperable framework to meet these demands. By enabling enhanced metadata granularity, lifecycle traceability, and bidirectional communication, eCTD 4.0 lays the groundwork for more agile, transparent, and harmonized regulatory ecosystems. (33–35)

Beyond its operational efficiencies, eCTD 4.0 opens strategic pathways for regulatory innovation and global alignment. Its broader potential can be summarized across five key opportunity areas:

- **Foundation for Digital Transformation:** eCTD 4.0 facilitates the integration of emerging technologies such as artificial intelligence (AI), real-world evidence (RWE), and advanced analytics into regulatory decision-making processes. It enables the transition from static document-based workflows to be structured, machine-readable content that can support dynamic, data-driven review models.
- **Regulatory Convergence:** By standardizing submission formats across jurisdictions, eCTD 4.0 promotes cross-border collaboration, joint reviews, and reliance models. This is particularly valuable for multi-region product launches and facilitates a more synchronized approach to global regulatory oversight.
- **Content Reuse Across Products and Regions:** The ability to reuse standardized documents and metadata across submissions and regions significantly improves operational efficiency. Sponsors can reduce duplication, ensure consistency, and accelerate the preparation of submissions for multiple indications or geographic markets.
- **Innovation Sandboxes:** eCTD 4.0 supports experimental regulatory frameworks such as innovation sandboxes and public-private partnerships. These initiatives allow agencies and industry to co-develop and test novel regulatory technologies, including cloud-based platforms, blockchain-enabled traceability, and structured content authoring.
- **Opportunities for LMICs:** Low- and middle-income countries (LMICs), such as India, Brazil, and ASEAN member states, have a unique opportunity to leapfrog legacy systems by adopting eCTD 4.0 as a digital-first standard. This can enable regulatory capacity building, streamline approvals, and align national systems with international norms from the outset.

Hence, eCTD 4.0 serves as a catalyst for modernization, fostering a regulatory environment that is not only more efficient and interoperable but also more inclusive and innovative. Its successful global implementation will require coordinated investment, capacity development, and policy alignment to fully realize its strategic promise.

6. Conclusion

The transition to eCTD 4.0 represents a pivotal moment in the evolution of global regulatory submissions. By addressing long-standing inefficiencies and introducing a scalable, interoperable framework, it empowers both regulators and sponsors to operate more efficiently in a data-driven, digital era. To fully realize the benefits of eCTD 4.0, strategic investments in infrastructure, workforce development, and harmonized implementation roadmaps are essential. As adoption continues to expand, eCTD 4.0 will play a central role in shaping the future of regulatory science and improving patient access to safe, effective therapies worldwide.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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