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Review Article

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A Review on Next Generation eCTD – eCTD v4.0

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Abstract

eCTD 4.0 is the first major upgrade of eCTD in over a decade, designed to meet the objective of using a single electronic message standard for exchange of regulatory information through internationally approved standards. It is based on the Health Level Seven (HL7) Standard called Regulatory Product Submissions (RPS). HL7 is an ISO-certified standards body that builds health standards, specifically for North America but has been adopted worldwide. With RPS, the regulatory information is transferred in the form of an xml message that is represented by the colour coded R-MIM (Refined Message Information Model) diagram which efficiently describes each content of the regulatory data to be processed and exchanged between sponsors and regulatory authorities. The International Council on Harmonisation (ICH) has adopted the RPS standard as basis for eCTD version 4.0, and implementation guides for this format have been issued by ICH, US FDA, Health Canada, Japan PMDA, and EU EMA. ICH has built requirements into RPS that significantly enhances the regulatory submission and review process for sponsors and regulatory officials in the eCTD v4.0 version. This review provides a brief outlook on the new eCTD v4.0 standard.

Keywords: eCTD, ISO, RPS, HL7, R-MIM, ICH, FDA, PMDA, EMA

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1. Introduction

A regulatory submission which is also known as a 'Dossier', is a collection of documents submitted to the drug regulatory authority for review and marketing approval. This is required to substantiate that a newly developed drug or a modified drug is safe and effective for use. The regulatory documents were initially shared with agencies in the form of paper copies; the submission consisted of stack of paperwork detailing complex administrative and study data. Due to the enormous information presented in huge volume of papers and different format of documentation adopted by different applicants, the review process was monotonous and less efficient for reviewers. In order to resolve the difficulties involved in the process of reviewing non-standard paper regulatory submissions, the ICH introduced Common Technical Document (CTD) format where all the Quality, Safety and Efficacy Information are assembled in a common format. Later, the industry progressed from CTD to the electronic version of CTD (eCTD). It permits electronic gateway for transmitting submission to minimize delay, error and effectively manage dossier life cycle operations.

The eCTD was defined as an "interface for Regulated Industry to Regulatory Authority transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission". In 2017, most of the regulatory agencies transitioned from accepting paper dossier to electronic format to bring standardization of data submitted. Now, the eCTD version 3.2.2 has been revolutionized into the next major version know as eCTD 4.0 which shall address the limitations experienced in the industry over the last decade and achieve long-term objective of having one globally used electronic message standard.

eCTD 4.0 is based on the HL7 standard which is a set of international rules for transferring admin and clinical information between software applications used by healthcare providers and regulatory officials. The standard has been implemented in Layer 7 of the OSI model which is the Application layer. Incorporating this standard offers global harmonization of CTD format, speeds up the regulatory submission process with greater accuracy and simplifies the agency review.(1-5)

ICH has published the draft version of technical specifications for implementing eCTD v4.0 in 2018, followed by minor updates to specifications in 2022.

2. eCTD v4.0 Objectives (2-4,6)

a) Documents reuse with UUID – Documents reused in multiple submissions can be tracked and further reused by assigning a unique identifier for each document. This UUID will be used a reference when a document is reused in different sequences in an application.

b) Restructuring TOC and Document Grouping – TOC in v4.0 is not defined by the XML structure. Files are delivered in a flat structure and use the concept of 'contextOfUse' & 'Keywords' to determine the location in the TOC. This combination functions to create a group of in a specific context which eliminates the need for STF.

c) Versatile Life Cycle operation Management – eCTD v4.0 allows replacing many documents in the application with one or replacing one document with many. It supports the existing operations 'New', 'Replace' and 'Delete'. The figure below depicts many documents replacing one or many documents from prior sequence within the same Context Group.

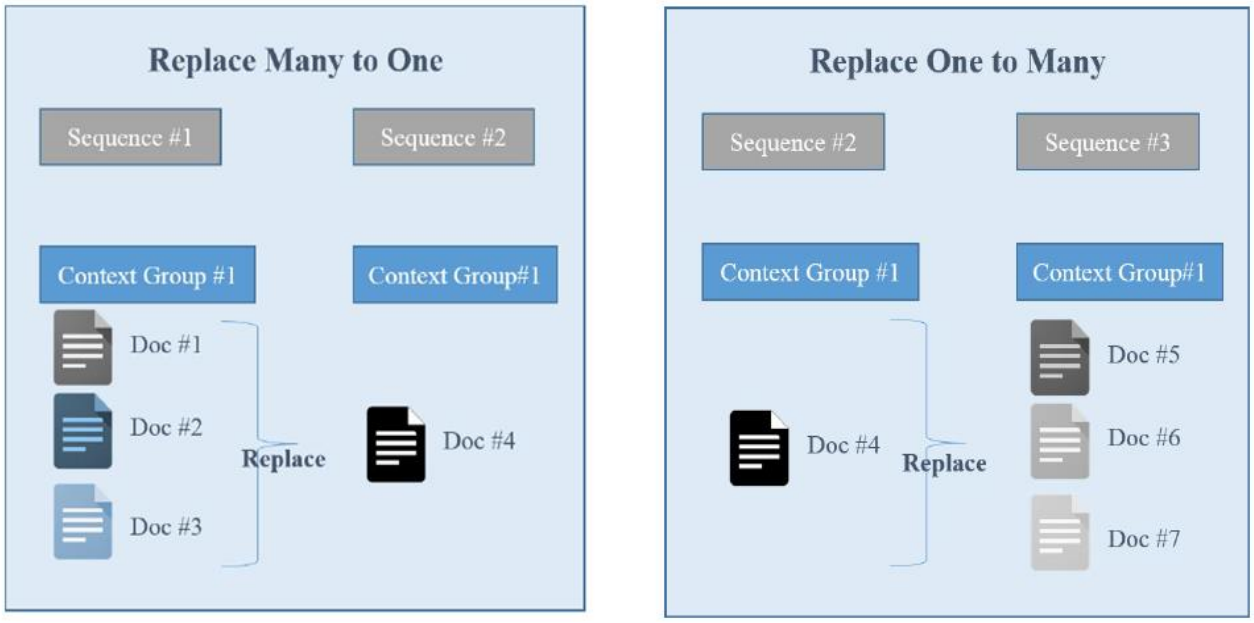

Figure 1. Life Cycle Replace Operation (7)

When using life cycle operations of delete or replace in a subsequent grouped submission, the life cycle operation will apply to all context of use in all submissions referenced in the grouped set of applications.

a) Harmonizing Submission – In eCTD 4.0, the regional (Module 1) and ICH content are consolidated into one exchange message i.e. one submission unit xml file, unlike the usage of two messages i.e. regional xml and index xml in eCTD v3.2.2. The schema for the exchange message is shared with agency, thus, it will not be required to be submitted with each submission unit.

b) Enhance/Establish communication between sender and receiver – eCTD 4.0 makes use of Controlled Vocabularies which defines the valid values to be used in xml messages by incorporating code identifiers.

c) Forward Compatibility (FC) – Enables seamless transition of an existing ICH 3.2 application into 4.0 without the need of creating new 4.0 application. For example, if the recent eCTD v3.2.2 message has a sequence number "0003", then the first eCTD v4.0 submission unit in the same application will be sequence number "4". This allows continuation of life cycle operations, regulatory activity, and metadata (keywords) from 3.2 to 4.0 within an application. FC concept is also considered for grouped submissions.

d) Two way Communication- Enables communication from sponsor to agency as well as responses from agency to sponsor on queries, information requests, whereas the existing eCTD v3.2.2 supports only interaction from sponsor to agency. This functionality has been planned to be implemented at a later phase.

3. eCTD 4.0 Features (7)

a) Priority Number – A section (i.e. either the CoU or a combination of CoU & Keyword) can have one or more documents placed under it. The document(s) in a section will be automatically assigned a priority number (in the backend) based on the sequential order. Hence, the priority number indicates the order in which the documents should be displayed.

b) CoU – The Context of Use is used to place documents under a CTD heading and associated keywords. The combination of the context of use and keywords create a context group under which one or more documents can be placed. It keeps the content organized and life cycle maintained

c) Keywords – Keywords replace the eCTD v3.2.2 metadata and valid values such as Product, Substance, Manufacturer, Study Title details. This information is more dynamic in the v4.0 message and certain rules need to be followed to ensure the required keywords are provided in the message. Only one keyword of each keyword type should be provided on a heading (i.e., context of use). The following are the types of keywords defined:

- Document Type Keywords – The document type keywords are a replacement for file-tags to organize study data into additional headings. Document types will continue to follow the same rules as previous file-tags; however, they are now provided as keywords.
- Sender Defined Keywords – This sender keywords are sent for each application, but it is recommended that the submitter manages the keyword definitions across applications to enable the use of grouped submissions. This can be sent only once for an application. Once the keyword definition is established, the value will be displayed for each Context of Use that references the sender-defined keyword.
- Group Title Keywords – Group Title is an alternative to node extension used in the legacy eCTD v3.2.2. This keyword allows the submitter to create further organization of documents under specified headings that allow for more than one document. Documents associated with a group title will be displayed separately under the eCTD heading and other associated keywords. The group title keyword will be applied to the lowest heading level

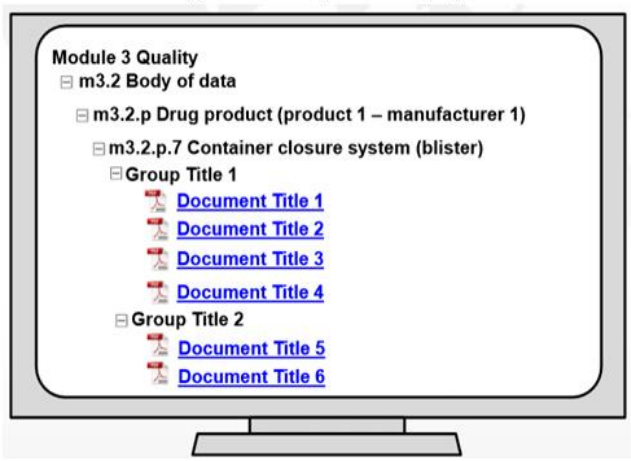

Figure 2. Group Title (7)

The group title keyword is not intended to replace other specified keywords – it is only intended to allow for the further organization of content where multiple documents are combined to provide information for a specific topic area. If the codes assigned to the sender-defined keywords are not shared across applications, the submitter will not be able to effectively use the grouped submission option.

4. Components of eCTD 4.0 (1-5)

a) ICH eCTD v4.0 XML Schema – Defines the basic XML elements and attributes used in eCTD 4.0 XML messages, developed by HL7. The schemas are organized by category and sub-categories in the figure 3.

b) Data Type – Defines the type of value per element or attribute. The data type for the elements and attributes could be text, alphanumeric, Boolean, null Flavors.

c) Controlled Vocabularies – Defines the valid values to be used for the information exchanged by the eCTD v4.0 XML messages. For the XML elements that have coded values, a controlled vocabulary will be required to indicate the value of concept.

d) A code is used as the identifier to convert the code value into the meaningful terms that will be used in any system that implements the viewing of the information sent in the XML message. Each code has a code system. The code system may be managed by ICH, Region, or the Applicant.

e) OID (Object Identifier) – OIDs are unique identifiers managed in a hierarchical fashion. In eCTD 4.0 they are used to identify the code lists on which the codes are defined. The code lists could be owned by ICH, a regional authority, or the applicant.

f) Universally Unique Identifiers (UUID) – A UUID (equivalent to a GUID in Microsoft terminology) is a

random, 128-bit number represented by hexadecimal text of 32 characters and 4 hyphens. Most of the identifiers in eCTD 4.0 use UUIDs; submission unit, submission, application, document, contextOfUse etc. are all submitted using a UUID. e.g. 25635f23-a3a4-4ce0-9994-99c5f074960f

g) Regional/Module 1 specification – Defines elements and business rules that are specific to regions.

h) Files and Folders – The files (i.e., documents referenced in the XML message) will be sent in addition to the XML message. Each document element within the eCTD v4.0 XML message will be given a specific directory location i.e., the folders that will be used to organize the physical files if the document is being sent for the first time.

	Major Category	Schema Files	
1	**Core Schemas:** A common schema set for all HL7 Version 3 messages	datatypes-rX-cs.xsd hl7-r2_datatypes.xsd infrastructureRoot-r2.xsd NarrativeBlock.xsd voc-r2.xsd	
2	**RPS Schema:** A schema set for the eCTD v4.0 – RPS compliant message	**Interactions:** PORP_IN000001UV.xsd **Message Type:** PORP_MT000001UV01.xsd	**Control Act:** MCAI_MT700201UV02.xsd **Transmission:** MCCI_MT000100UV02.xsd
		Referenced Schema Files	
3	**Common Message Elements Schema:** The CMETs referenced by the Common Product model or RPS Schemas	COCT_MT030203UV07.xsd COCT_MT040203UV09.xsd COCT_MT070000UV01.xsd COCT_MT090100UV01.xsd COCT_MT090108UV.xsd COCT_MT090300UV01.xsd COCT_MT090303UV01.xsd	COCT_MT150000UV02.xsd COCT_MT150003UV03.xsd COCT_MT150007UV.xsd COCT_MT710000UV07.xsd COCT_MT960000UV05.xsd

Figure 3. ICH eCTD 4.0 xml schema (8)

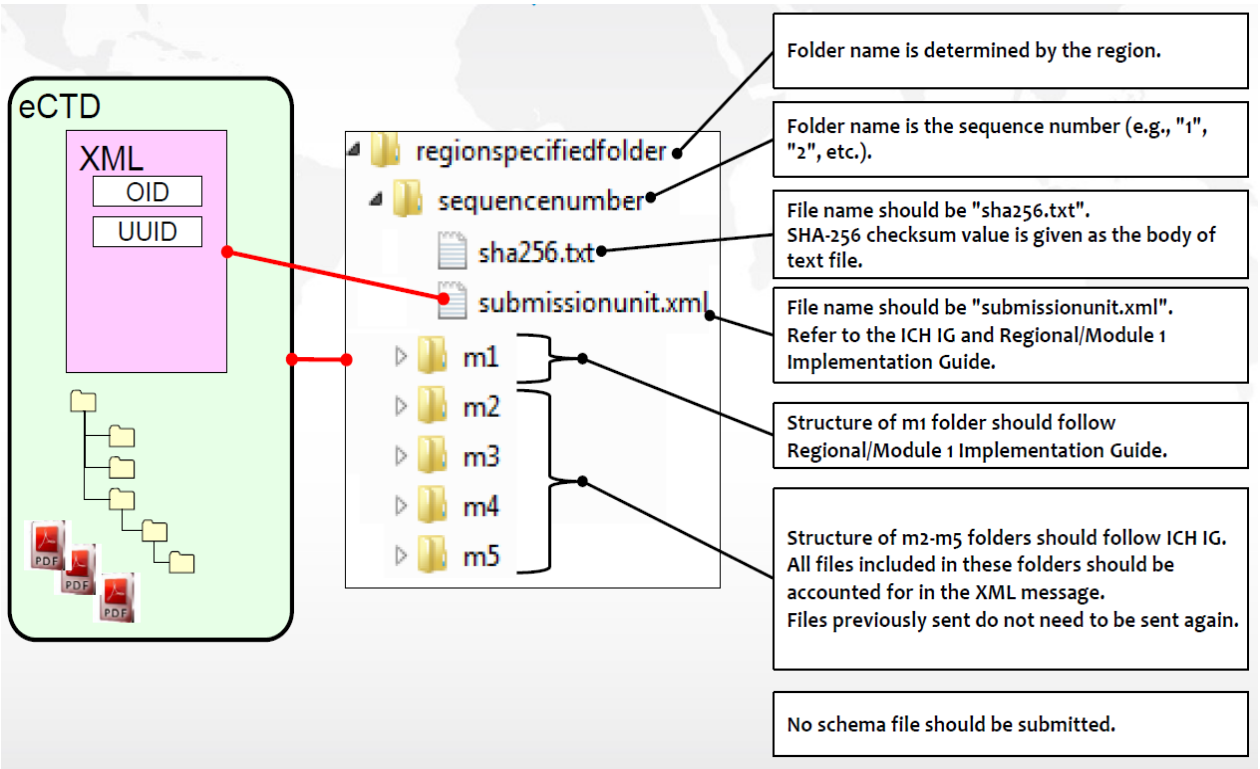

Figure 4. Submission Contents, File and Folder Structure (1)

5. XML Message Structure (1,2)

The eCTD v4.0 message is based on the ICH eCTD v4.0 schema and region-specific guidelines. The message components in the XML follow the HL7 standard. The XML consists of a message header and the payload message:

a) Message Header – This provides a set of elements that are needed to specify the sender and receiver and indicate the version of the ICH and Regional specification.

b) Payload Message – This contains the actual contents within a submission organized into different levels which include both ICH & Regional specific elements:

- Control Act Process (Starting point of the eCTD 4.0 message) – This is the initial message interaction that generally passes the application content which is the purpose of the message interaction sequence (triggering of an event process). So, the payload begins with identifying the subject element of the XML message i.e., the submission unit.
- Application – An application consists of one or more submissions (Regulatory Activity), where each submission can be associated with one or more submission units.

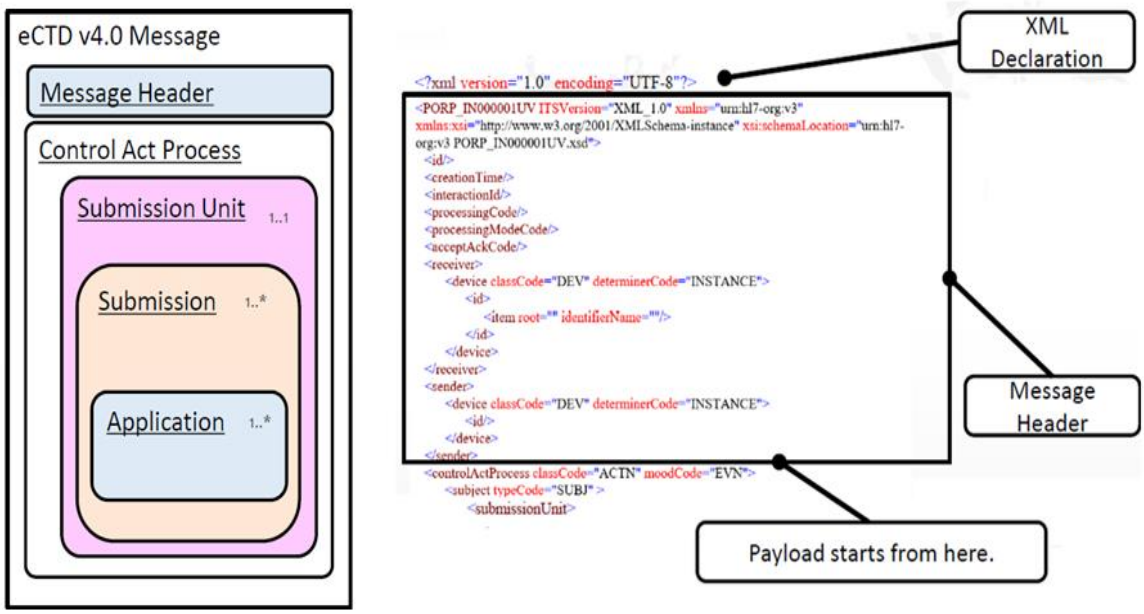

Figure 5. eCTD 4.0 xml Message Header and Payload (1)

a) Submission – The submission is the representation of a regulatory activity constituted by one or more submission units in an application. It defines the relationship between a submission unit, the Contexts of Use, and the application. (1,2,6,8)

b) Submission Unit – The 'Submission Unit' in eCTD 4.0 refers to the actual submission providing information about an individual eCTD v4.0 XML message. It contains the information about the submission and application which is submitted to the regulator.

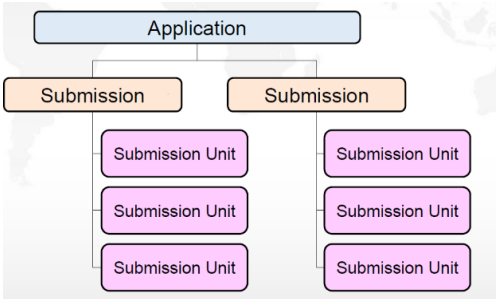

Figure 6. Three layered structure of an Application (2)

6. Regional Adoption of eCTD 4.0

US FDA

The window for technical pilot submissions of eCTD 4.0 to US FDA was opened between 2022 – 2023 Q2 and voluntary eCTD 4.0 submission from healthcare and pharma organizations are accepted from 2024. The center mandates the submission of dossier in eCTD 4.0 format from 2029.(6)

The submission must adhere to the ICH guidelines (M2-M5) and US regional guidelines which provides the details of region specific Controlled Vocabulary, OID listing that are described in the implementation package.(7,9)

Japan MHLW/PMDA

Pilot submissions began in 2021 and voluntary submission have been accepted from 2022. The agency

will mandate the submissions in eCTD 4.0 format from 2026.(6)

Japan(JP) submissions are accepted in both English and Japanese language. The following methods have been defined by the agency to submit a dossier:

- Method 1(a): Requires the submission to contain only the electronic study data or the data specified by the CTD notification may be included depending on the situation of submission and the type of the data.
- Method 2(b): The eCTD to be submitted will be referred to only the electronic study data from eCTD 4.0 xml message. This is required to be submitted prior to the submission of Method 2(c)
- Method 2 (c): The eCTD to be submitted by referring to the data specified by the CTD notification from eCTD v4.0 xml message.

In addition to the above methods defined, JP PMDA has also classified study datasets into various JP categories such as JP Terminology, JP Analysis which are listed in the regional Controlled Vocabulary.(10)

Health Canada

Canada has planned pilot eCTD 4.0 submissions in 2024 and voluntary submissions in 2025. The eCTD 4.0 format shall be mandated from 2027.(6)

The terms used in the ICH eCTD v4.0 messages differ from regulatory vocabulary regularly used at Health Canada, so the agency has provided mapping between common and Health Canada specific vocabulary as shown in the Table 1 below.

Table 1. Health Canada Regulatory Terminology Mapping (11)

eCTD v4.0 Term	Health Canada Term	Description
Submission Unit	Regulatory Transaction	The base message produced in eCTD 4.0. Each eCTD 4.0 message or Regulatory Transaction is considered a Submission Unit.
Submission	Regulatory Activity	A collection of Submission Units or Regulatory Transactions make up the content for a Submission or Regulatory Activity.
Application	Dossier	A collection of Submissions or Regulatory Activities through the life cycle of a product.

Europe

The European Commission will begin with pilot eCTD 4.0 submission in 2024 and shall later accept voluntary submissions in 2025 for CAPs and 2026 for MRP/DCP/NP respectively. The eCTD 4.0 format is likely to be mandated from 2027.(6)

Other Regions

Brazil, Australia, and Swissmedic will begin with pilot eCTD 4.0 submission in 2024 and voluntary submissions shall be accepted from 2025.(6)

Table 2. Regional Implementation of eCTD v4.0 Timeline (6)

Region	Technical Pilot	Implementation Dates	Implementation Documents
FDA, United States	2022-2Q 2023 (Completed)	2024 (Voluntary) 2029 (Mandatory)	FDA, United States regional implementation page
MHLW/PMDA, Japan	2Q 2021 (Completed)	2022 (Voluntary) 2026 (Mandatory)	MHLW/PMDA, Japan regional implementation page
Health Canada, Canada	2024 (Planned)	2025 (Voluntary) 2027 (Mandatory)	Health Canada, Canada regional implementation page
EC, Europe	2024 CAPs (Planned)	2025 (Voluntary for CAPs) 2026 (Voluntary for MRP/DCP/NP) 2027 (Mandatory for CAPs) TBC (Mandatory for MRP/DCP/NP)	EC, Europe regional implementation page
Swissmedic, Switzerland	2024 (Planned)	2025 (Voluntary) 2029 (Mandatory)	Swissmedic, Switzerland regional implementation page
TGA, Australia	4Q 2024 (Planned)	2025 (Voluntary) TBD (Mandatory)	2023 (In Progress)
ANVISA, Brazil	4Q 2024 (Planned)	1Q 2025 (Production Pilot) 2025 (Voluntary)	TBD
MFDS, Republic of Korea	TBD	2025 (Voluntary) 2029 (Mandatory)	TBD

7. Conclusion

eCTD 4.0 offers greater simplicity, flexibility, reliability, and error-free regulatory submission management process. Since this is the highly anticipated international submission standard which is ready-to-be implemented, various regulatory agencies across the globe have started adopting and mandating the 4.0 format. Through the

participation of few pharma organizations in submission of pilot dossiers in 4.0 format to agencies, the effectiveness in management of the regulatory submission process have been analyzed and it appears to outweigh any known limitations of 4.0. As this is soon going to be a reality, healthcare and pharma organizations must get on the bandwagon to be benefited by whole new revolutionary changes offered by eCTDv4.0. However, the adoption of eCTD 4.0 depends on vendor readiness in terms of using of publishing and validation tools that are capable of supporting eCTD 4.0 format, testing pilot submissions, exchanging feedback with agencies, and having increased collaboration with regulatory agencies on regular intervals.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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