European Federation of Pharmaceutical Industries and Associations

Global ICH eCTD Adoption



White Paper

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1 Executive Summary

Over the past decade, industry, technology solution vendors, and regulators have made tremendous advances in the evolution of the submission, review and approval process of regulatory data for medicinal products. Thanks to dossier content and format harmonization efforts by the International Council for Harmonisation (ICH) and advances in technological innovation, it became possible to support the entire process of submissions and reviewing regulatory dossiers and data exchanges via electronic systems throughout a product's registration and its entire lifecycle.

Thus, industry and many health authorities have made the transition to accepting digitized applications from drug manufacturers and phasing out their paper-based processes. The move away from paper has been greatly facilitated by the introduction of a common global electronic submission format that provided a means to accommodate the common technical document (CTD) structure for documents, defined by ICH, and the regional content requirements defined by each country/region in one electronic application; the electronic CTD (eCTD) format.

Today, the eCTD format remains the only globally approved and ICH-recommended standard. While it has been in use for more than 15 years, it is the mandated submission format for drug applications within Europe and the US, and adopted by many other health agencies as shown in Figure 5.

The recent experience with lockdowns during the Covid-19 pandemic has highlighted the need to speed up the global transition into digital formats to facilitate regulatory business continuity. As a result, more health authorities have expressed interest in eCTD adoption, collaborating with trade associations, companies, vendors and regulator networks to understand how to implement eCTD.

In this white paper, the European Federation of Pharmaceutical Industries and Associations (EFPIA) eCTD Subgroup introduce the concept of eCTD, what are some of the main advantages of adopting ICH eCTD as a submission and review standard, along with guidance and recommendations for how to adopt eCTD. This paper presents incremental options for switching to digital formats, and recommendations, depending on the resources and needs of health authorities. This paper is intended as an introduction to the topic, and an invitation for future dialogues with prospective health authorities where this content can be presented in more detail.

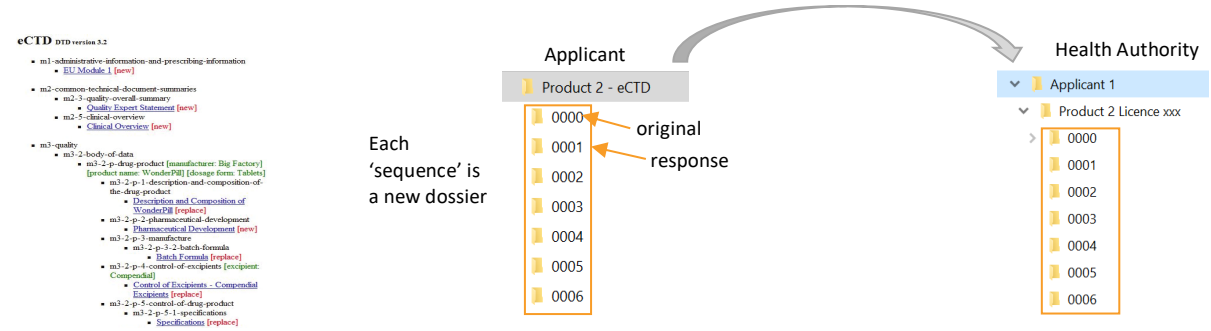
Target Audience

This white paper is targeted to decision-makers and budget holders in health authorities who are deciding to invest in implementing digital infrastructure to create a system where documents and data can be exchanged digitally, and a system that supports eCTD submissions and beyond (i.e., dynamic dossiers and data exchange in cloud-based platforms).

What is eCTD?

The eCTD is the electronic manifestation of the CTD, defined by ICH. It contains international specifications for organizing, structuring and submitting dossiers to health authorities who in turn can review them electronically. Each submission is made in an eCTD 'sequence' that is added to the product lifecycle, providing the ability to manage a dossier and its contents' lifecycle dynamically over time. eCTD is not just an electronic version of a CTD paper dossier but a different system altogether related to how the information is extensively organized and easily navigated and dynamic in nature, which is achieved through programming with eXtensible Markup Language (XML technology). The eCTD retains the same structure as CTD but allows for a greater flexibility and efficiency in use. All the elements in the CTD are represented in the XML backbone, which functions as the table of contents of the structure and also provides information about each physical file submitted (see Figure 1). The overall structure of the eCTD format is described in more detail in Section 9.2.

Figure 1. Illustrated view of an eCTD application



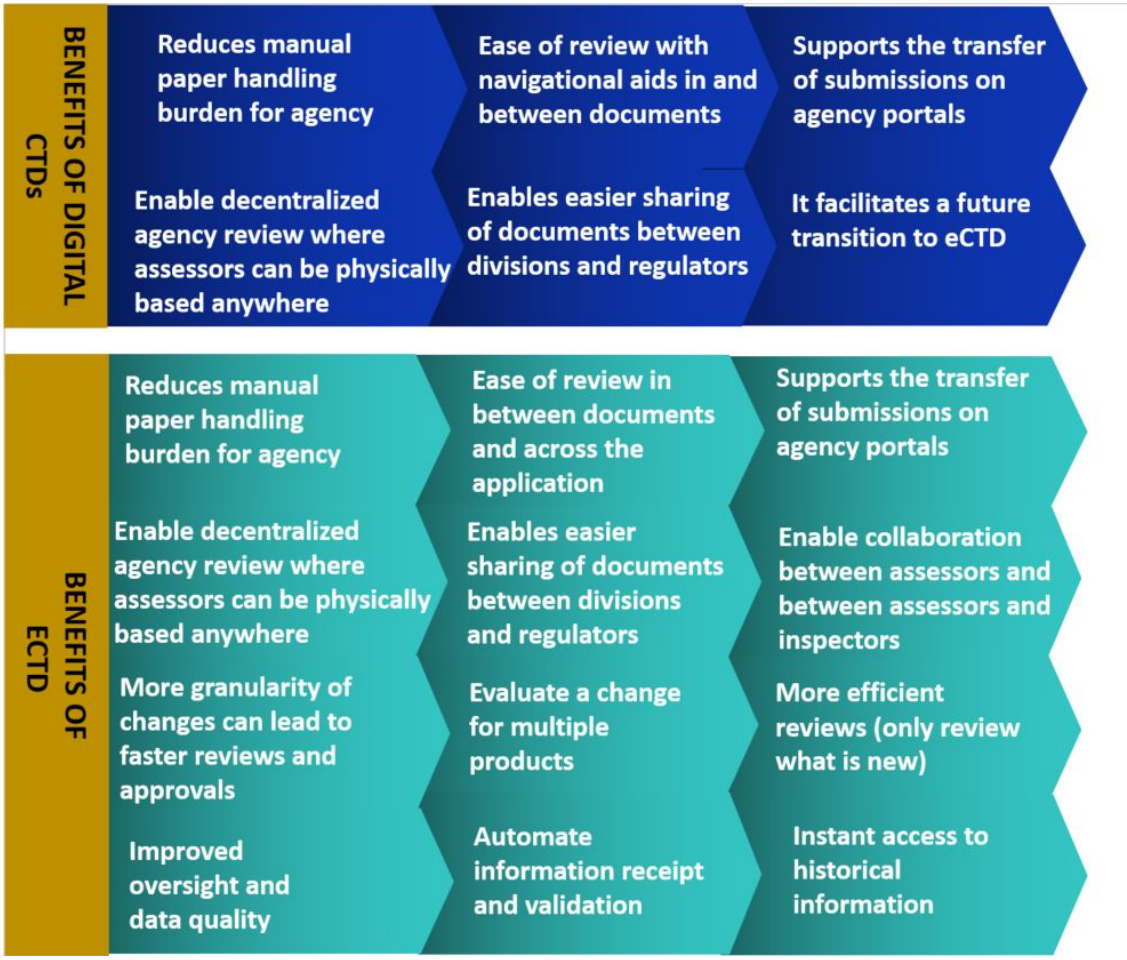
eCTD xml backbone as viewed in a browser

eCTD folder structure as viewed in file explorer

Opportunities and benefits of eCTD

There are numerous benefits to be realized for health authorities in the transition from static-based CTDs to dynamic eCTDs that improve information management and significantly increase the efficiency of reviewing the regulatory submissions. The adoption of eCTD also acts as a key foundation for digital transformation, allowing for broad efficiencies to be gained within the regulatory submission and review system and within the health authorities as a whole.

The graphic below highlights the benefits of digital CTDs plus the additional benefits of eCTDs and are further described in Section 5.



Incremental steps towards eCTD adoption

The approach that the various health authorities took/are taking to transition to eCTD depends on several factors, including resources, timing, industry and vendor readiness, and CTD adoption. The implementation of CTD/eCTD requires significant resources and planning. Health authorities may therefore decide on incremental steps, with the ultimate goal to develop digital infrastructure that is able to accept eCTD submissions, see Figure 3 .

In Section 6, the interim solutions of digitizing CTD, portal and gateways to facilitate eCTD transfers, as well as full transition to eCTD are discussed. Regulatory agencies may decide not to invest in implementing eCTD yet, but may choose to begin by converting their dossiers to CTD, and implementing infrastructure to accept digital versions of CTD as part of the longer-term strategy to adopt eCTD. This way regulators get familiar with navigating CTD sections, thereby easing the learning curve and effort required to transition to eCTD. It is worth noting that this option is also currently being accepted by countries that may not have adopted CTD as a standard yet, for example Hong Kong, Argentina, Mexico or may be using other formats such as ASEAN (Association of Southeast Asian Nations) CTD (ACTD), for example, Singapore.

Roadmap to Electronic Common Technical Document for Health Authorities

A roadmap to help guide the adoption of eCTD is essential. Adequate time is required to allow for budgeting financial capital, transition planning, drafting of system specifications and updated regulatory guidance, development or modification of software required, beta testing the system, pilot testing the system, encouraging voluntary submissions by eCTD, and then mandating submissions by eCTD. At least 12 months should be allocated for these important steps to adoption. The suggested EFPIA eCTD adoption timeline is shown in Section 6.3.

Regional specifications

The CTD and eCTD format allows for national and regional variances within non-common modules of the CTD (i.e., Module 1), and to comply with local review requirements. In order to achieve full convergence and speed up global dossier preparations and foster more collaborations with health authorities, it is recommended that national requirements should be kept to a minimum.

Transitioning to eCTD with Baselines

Many health authorities recommend “baselines” to be provided as a means to transition from paper to electronic dossiers. Baselines refer to where applicants provide part or all of the current registered submission documents that were previously provided in paper format, via an eCTD sequence (normally as an initial eCTD sequence but can be provided later in the lifecycle). The industry position and recommendation of EFPIA is that a baseline should not be mandated as some old products that have very little activity would not benefit from this. If baselines are required, flexibility for full versus partial baselines and the degree of formatting required of previously submitted legacy documents (e.g., those generated by scanning) should be given.

2 EFPIA Recommendations

EFPIA advocates for the adoption of ICH eCTD globally and recommends critical success factors to enable a smooth implementation, listed below:

- Move quickly to acceptance of digital CTD format as an interim solution while incrementally preparing for the switch to eCTD, see Section 6.1.
- Maximise use of technology through electronic submission gateways. Electronic transfer from applicant to regulator should be developed, preferably as an online submission portal.
- Allow sufficient time for each stage of eCTD adoption (minimum 12 months, see Section 6.3.)
- Develop a clear, transparent roadmap available for all partners that is carefully planned and aligned with industry, see suggested timeline for adoption in Section 6.3.
- Consistency with existing ICH M2 standards and national requirements kept to a minimum
- Baselines should not be mandated
- Early partnership and vendor engagement is critical
- Collaboration among regulators and between regulators and industry should be developed early in the adoption process in order to leverage experience of other health authorities and industry (advice, testing, pilots, and discussion)

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3 Introduction

The adoption of the Common Technical Document (CTD) format, developed by the International Council of Harmonisation (ICH), is an important step as it harmonises regulatory content across regions. The CTD assembles all the Quality, Safety, and Efficacy information in a common format, organized into five modules [1]. In the past, paper-based CTD was the standard for submission, but the enormous volumes of paper required and the inability to easily navigate the dossiers have led many Health Authorities (HAs) to electronic submissions of CTDs to try and minimize these shortcomings. By digitizing the CTD submission documents, usually to Adobe Portable Document Format (PDF), the paper burden is effectively eliminated and PDF-based hyperlinking and bookmarking allows for easier navigation within the submission dossier. However, with digital CTD format the dossier is static which leads to shortcomings in dossier lifecycle management. A dynamic version of the digital CTD has been developed by The ICH Multidisciplinary Expert Working Group 2 (ICH M2 EWG) and maintained by the ICH M8 eCTD Implementation Working Group, termed the electronic CTD (eCTD), current version 3.2.2 [2]. Electronic CTD format has all of the benefits of the digital CTD plus a number of other important benefits including enabling automated receipt and validation of submissions, immediate availability of dossiers for inspection, navigation improvements within and among dossiers, acceleration of collaboration among reviewers, improved collaboration among HAs and inspectors and dossier lifecycle management.

The adoption of eCTD is another important step in the modernization and digitalization of the regulatory process. In the future, cloud-based systems will allow for even greater capabilities and collaboration.

4 Background

4.1 Common Technical Document

The CTD format was recommended for adoption by the ICH in November 2000 [3], facilitating review both within and across HAs. As local guidelines (national/regional) for content requirements vary widely, the format of the CTD allows for national and regional variances within non-common modules of the CTD (i.e., Module 1).

The transition from non-CTD submissions to CTD submissions is an essential step towards a digitalized regulatory process. However, rigorous and extensive content requirements and an increase in the volume of data and complexity have resulted in submissions to HAs that often exceed half a million pages each. The volume of paper for review, storage, retrieval, and lifecycle management for paper-based CTD submissions is no longer sustainable. In addition, it strains the resources of HAs, often resulting in prolonged time required for review and consequent delays of new medicines reaching patients, not to mention the negative impact on the environment.

4.2 Digital Common Technical Document

While adoption of eCTD from paper-based CTD may be an eventual goal for HAs that want to digitalize their submission processes, there are numerous technical and infrastructure requirements that make this transition rather complex. Digital transformation may be best understood as an evolving process. Moving from a paper-based CTD to that of a CTD submission process that is digital, but without the technical requirements of eCTD, is often an attractive intermediary step for HAs. This approach of initial digitalization can be referred to as digital CTD format.

The first step in digitization is the conversion of existing and new documents into electronic documents, most commonly PDFs, to achieve a digital CTD. Each of these PDFs can have a hyperlinked table of contents (TOC) to facilitate navigation within the document and can also link among different PDFs to allow for navigation among related documents within a dossier [4]. PDFs do have to adhere to standard requirements, e.g., size limitations, security settings, and PDF version. Once all the dossier documents are digitized, they can be shared among many reviewers, negating the occurrence of reviewers waiting for a specific document while it is under review by another reviewer. This further facilitates joint assessment, reliance pathways, and worksharing initiatives, and as experienced during crises like the Covid-19 pandemic, supports adoption of common review platforms.

4.3 Electronic Common Technical Document

After HAs have made the decision to digitize their submission process, a decision needs to be made to either adopt a digital CTD format as interim solution before eCTD format adoption or proceed directly to eCTD.

The ICH first developed guidance for eCTD in October 2002 [5]. The ICH (ICH M2 EWG) defined the format and specifications to manage common documentation among dossiers for eCTD, the content itself defined within the CTD issued by ICH M4 EWG. Modules 2 through 5 are generally consistent across HAs, with regional/national document requirements submitted in Module 1, where specific programming allows for regional variances to be reflected.

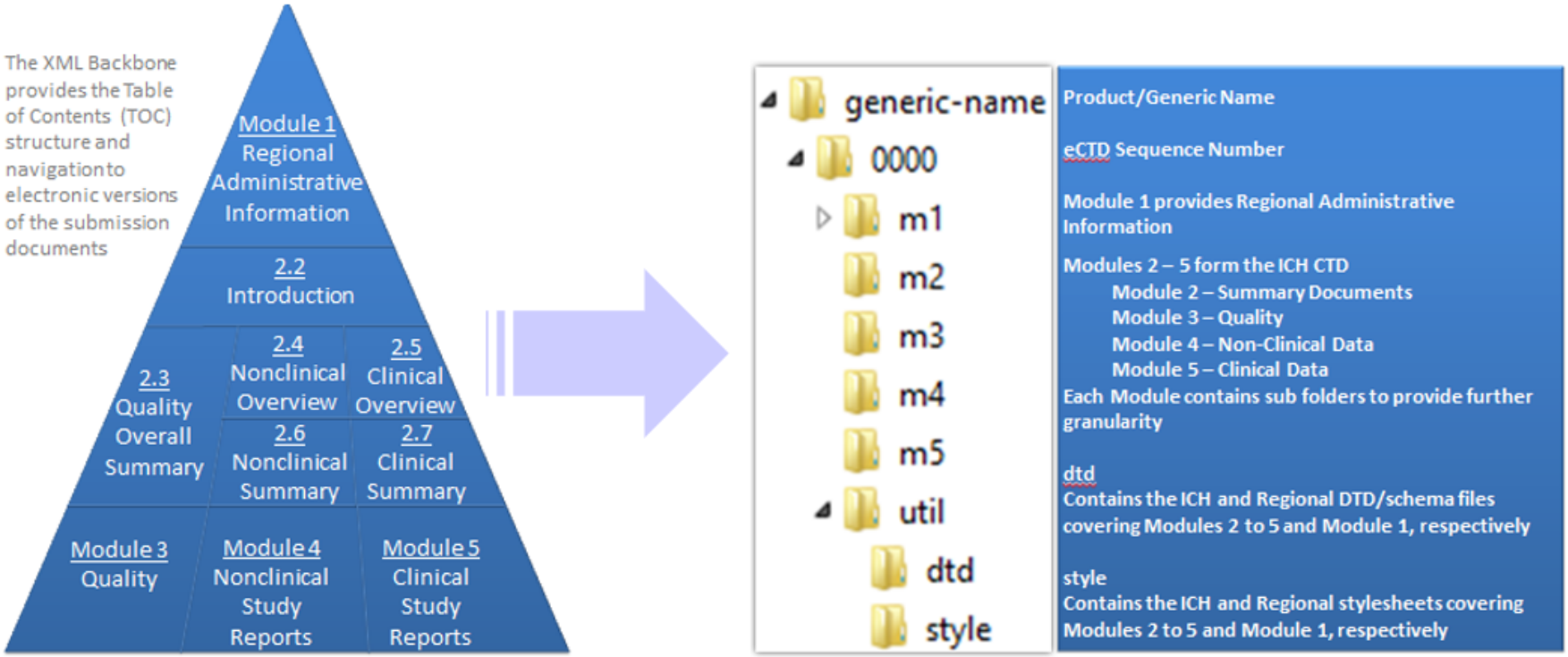
Since the implementation of eCTD v3.2.2 in various regions, there have been several change requests submitted to develop next versions. To address the requests and further enhancements to the eCTD specification, the M8 Expert Working Group was formed in November 2010, tasked to develop the next major version of eCTD, eCTD 4.0, more on this next version can be found in Section 9.3.

eCTD has been mandated in the EU (via the Centralised Procedure) since 2010 and by the FDA since 2017 (for Investigational New Drug Applications) [6]. Up until 2021, HAs in Canada, Europe, Japan, United States of America, Australia, Bahrain, Oman, Saudi Arabia, Jordan, United Arab Emirates, South Africa, Switzerland, Thailand, Chinese Taipei (Taiwan) and China have adopted eCTD. Health authorities in Brazil, Turkey, Singapore and Morocco and ECOWAS are in the process of implementing or considering future adoption of eCTD for regulatory submissions. It is important to note that, after the initial Marketing Authorisation Application (MAA) submission or baseline submission has been made in eCTD the following lifecycle submissions are to be in eCTD format too.

At the core of eCTD is its extensive organization that is easily navigated and dynamic in nature, which is achieved through programming with eXtensible Markup Language (XML), a structured data exchange standard that is both human and machine readable. The XML backbone provides the TOC structure that describes the location of every electronic document in the submission within the file structure and provides rich metadata about each physical file submitted. The overall structure of the eCTD format is described in more detail in Section 9.2.

The eCTD retains the same ‘pyramid’ structure as CTD but allows for a greater flexibility and efficiency in use (see Figure 2).

Figure 2. Electronic Common Technical Document Dossier Format



5 Advantages of Electronic Common Technical Document

There are numerous benefits in transitioning eCTDs that improve information management and document storage, review, retrieval, and archiving, listed below and elaborated further in this section.

- eCTD Transition becomes a key foundation for digital transformation
- Creates alignment with international ICH standards
- Minimization of paper burden and environmental waste
- Automated receipt and technical validation of dossier submissions
- Creates efficiencies with dossier assessment
    - Immediate availability of dossiers for inspection/evaluation
    - Navigation improvements within and across dossiers
    - eCTD Viewing software significantly improves viewing the lifecycle of the application (e.g., it offers various views and quick identification of new or replaced content, see Figure 7.
    - Accelerates collaboration among HA as well as assessors and inspectors
    - Facilitates joint assessment and regulatory reliance
- Creates efficiencies with dossier lifecycle management
- Paves the way for e-labelling thanks to structured information possibilities
- Updating of submissions simplified
- Utilization of existing documents among submissions possible
- Ready access to historical information
- Simplified support for different doses and form of a product

5.1 Key Foundation for Digital Transformation

One of the primary benefits for HAs that embark on a digital transformation is overall modernization of the regulatory process and simplification of the registration lifecycle. Developing digital platforms to automate a workflow that triages and routes inquiries and responses would significantly increase operational efficiencies and provide a better experience for the end user. Adopting eCTD allows HAs to be able to keep up to date with new advances in technology (i.e., move to mandatory data submissions for greater data integrity).

Adopting the eCTD format and undergoing a concurrent digital transformation also allows for leveraging of existing proven technologies. For example, innovative cloud technology can be used to simplify access to data and data sharing while providing industry-standard information security.

5.2 Alignment with ICH Standards

The adoption of eCTD aligns the HA with ICH standards to facilitate future membership. The adoption of eCTD is considered an added value for agencies contributing to qualification as a reference agency from the World Health Organization (and Pan-American Health Organization for the Americas), it leverages standard specifications from ICH, and can be an important stepping stone to implement further innovative standards.

5.3 Efficiencies with Initial Dossier Submission

There are numerous advantages with the eCTD format during the initial dossier submission. In sum, these efficiencies allow information to be found more easily by HAs as well as ensuring all required information is included (validation).

5.4 Automated Receipt and Technical Validation

Digitization through eCTD allows for automated information receipt and validation of submissions, which decreases personnel burden, increases the speed of filing, and minimizes filing errors. Using software to validate the submission minimizes the need for HA personnel to manually validate the submission and allows for rapid feedback to the submitter, significantly decreasing the time needed to correct any technical complications.

To initiate the submission process, applicants send the submission through a common portal to the HA where the eCTD sequences are immediately validated by specialized software that identifies naming conventions or other technical qualities that are incorrect before applicant dispatch. Most regions have the concepts of Pass/Fail and Best Practice defined in their validation criteria. Should there be a technical problem with a submission, the application will be rejected and the applicant will be notified of the specific error(s) immediately so that the appropriate corrections to the dossier can be made before resubmission.

After the submission has been technically validated as being correct and complete, the HA portal issues an automated receipt for the submitter of compliance to technical standards. If the submission is not technically valid, there is a resubmission under the same sequence number. This is the only time the same sequence number can be used. An eCTD submission must pass technical validation before it then undergoes content or business validation. Where technical validation involves an automated check of the format of the dossier against a common set of technical criteria using validation tools, content or business validation involves a check of the completeness of the dossier and that all the administrative and mandatory content is included. Any business / content validation issues will be handled in a related new sequence, they cannot be resolved by resubmitting an existing sequence.

5.5 Efficiencies with Dossier Assessment/Evaluation

There are numerous advantages with eCTD format during the HA dossier assessment. In sum, these efficiencies allow for dossiers to be assessed more rapidly, with less time spent on navigation and access of documents, leaving more time available for functional experts to review the content of the application.

5.5.1 Immediate Availability of Dossier for Inspections

With paper-based CTD, there is generally a time delay before assessors can begin their review as the dossier needs to be received by all reviewers, catalogued, and validated before any review work can commence. With eCTD, the application becomes immediately available for concurrent inspectors' assessments after successful automated submission, validation, and receipt. These time savings alone are substantial.

5.5.2 Navigation Improvements Within and Across Dossiers

The XML backbone format of eCTD streamlines HA assessments by facilitating navigation through the dossier and across products (in version 4 of eCTD for most countries [some do not allow lifecycle navigation], see Section 9.3). These increased efficiencies allow HA content experts to spend a greater proportion of their time reviewing dossiers.

5.5.3 Accelerates Collaboration Among Assessors, Health Authorities

With paper-based CTD, submissions are generally only available in a single copy, thwarting review of sections by more than 1 assessor at a time. In addition, paper forces all assessors to be based in a single physical location. With eCTD, documents can be shared and reviewed concurrently among numerous reviewers and/or HAs in different locations. Collaboration across HAs can be easier and more rapid, allowing for sharing of resources and faster reviews.

Further, eCTD adoption creates the possibility of participating in or developing worksharing or reliance schemes on a regional basis. The European Union procedures (Centralized, Mutual Recognition and Decentralized) are good examples on how eCTD can be leveraged for collaboration across agencies.

5.6 Efficiencies with Dossier Lifecycle Management

There are numerous advantages with eCTD format for dossier lifecycle management. In sum, these efficiencies allow for dossiers to be managed more thoroughly and efficiently than with what is possible with paper-based CTDs.

Another automated advantage of eCTD is the assurance of technical integrity through software (MD5 Checksum), which provides a unique calculated value of each submitted document that is used to determine if the document has been changed and assures robust document integrity within eCTD over its lifespan.

5.6.1 Updating Submissions

Once the submission has been accepted and is residing within its appropriate locations within the XML backbone, electronic navigation, searching, and cross-referencing are improved and dynamic in nature.

When documents are uploaded to the eCTD, users are required to assign a lifecycle operation to each document. Lifecycle operations assigned to documents include 1 of 4 possibilities: new, a document that has never been submitted before for this particular product; replace, replace a previous version of a document with a newer version; delete, hide from current view a document that is no longer relevant to the review or has been submitted in error; and append, associate a document with another document that has already been submitted (this lifecycle operation is generally not recommended as it can lead to lifecycle problems over time).

5.6.2 Utilization of Existing Documents among Submissions

Within an eCTD submission, every document is contained within a ‘leaf’. A sequence can contain multiple ‘leafs’, each referencing the same physical document within the XML backbone. Since the application path is specific, content can be shared across different eCTD sequences such that content

already supplied in one sequence does not need to be provided again in the future; the relevant document can be cross-referenced with a hyperlink to the intended document in a previous sequence without having to re-submit.

5.6.3 Ready Access to Historical Information

With eCTD, historical information is more readily accessible than with paper-based CTD. The ability for reviewers to quickly look back into the history of a submission to gather perspective is an important tool, given new reviewers may be assigned to a dossier long after the initial submission. Further, regulators may also need access to previous versions of the dossier for monitoring or auditing purposes.

5.6.4 Different Doses and Forms of a Product

Another advantage of eCTD is that there is essentially 1 XML backbone per product, with the initial submission acting as the base, and subsequent submissions adding to that base, much like chapters in a book that fully describes the product. With eCTD, an application can cover all dosage forms and strengths of a product under one application. This approach of merging strengths and dosage forms under a common application has numerous advantages including: documents that are common to all strengths and doses are presented once and reviewed once by the assessor.

Best practice includes merging strengths and dosage forms where possible to reduce workload for industry and HAs, and inclusion of regional and ICH metadata (drug substance, manufacturer, drug product, dosage form, manufacturer) to clearly describe what the eCTD application covers.

6 Transitioning from a Paper-based Common Technical Document to a Digital Common Technical Document

6.1 Transitional formats based on Digitized CTD

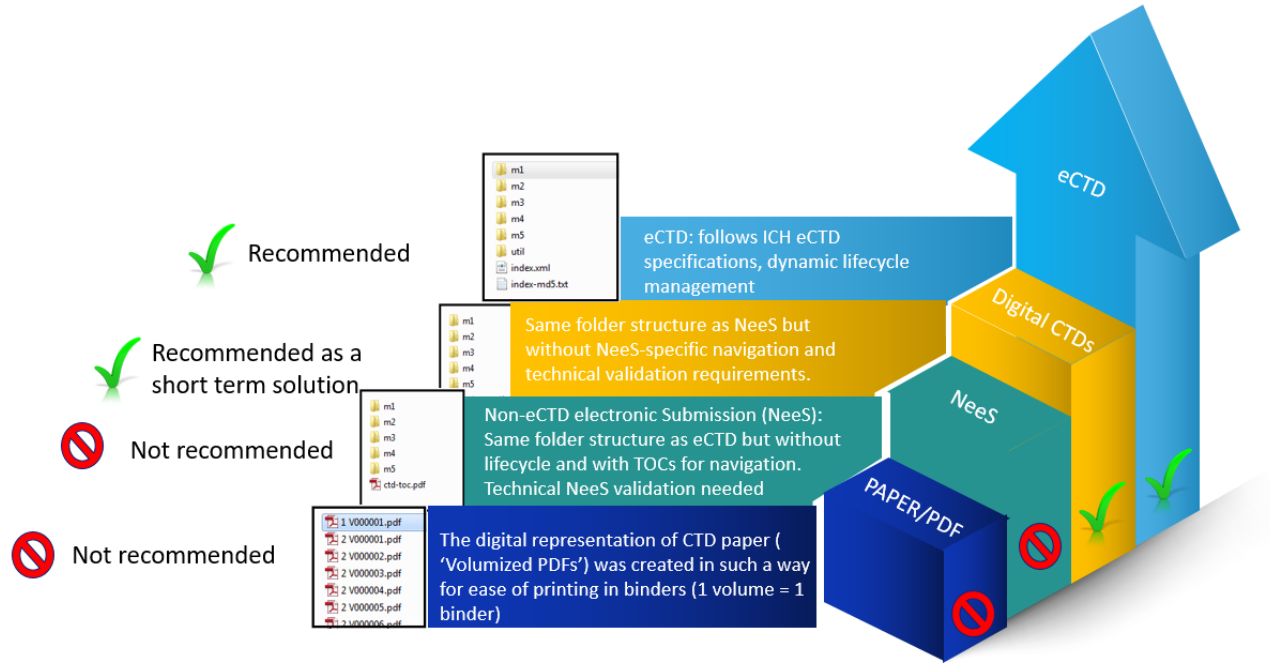
Many of the early adopters of eCTD were also involved in defining and testing the emerging standard itself and the global and regional requirements. In order to adequately prepare internally and externally for eCTD they also developed transitory or hybrid digital formats as a bridge to full transition to eCTD. The digital representation of CTD paper dossiers (known as ‘Volumized PDFs’ or ‘Paper publishing’) was created in such a way for ease of printing in binders (1 volume = 1 ring binder). While this format allowed for a digitized representation of the CTD submission, it continues to follow paper-based processes and is not sustainable.

Other examples of transitional formats include the Non-eCTD electronic Submission (NeeS) format, developed in Europe and adopted in other countries like Australia. This format is essentially a collection of files organized in a series of folders matching the CTD modules, with its own set of technical specifications and requirements to maintain. Although the NeeS format provided significant benefits, it is still lacking many of the advantages of eCTD format (e.g., the ability to lifecycle documents from one submission to the next, or to include additional metadata for each document) and today NeeS is considered ‘legacy’ and is not recommended as a long-term option for submission format.

Acceptance of other digital versions of CTD dossiers (with ‘NeeS-like’ folder structures, but without the NeeS-specific navigational and technical validation criteria) emerged as the most viable and low complexity option towards a longer-term strategy to adopt eCTD. These are simplified versions of

NeeS and allow the regulators to get familiar with navigating CTD sections, thereby easing the learning curve and effort required to transition to eCTD. It is worth noting that this option is also currently being accepted by countries that may not have adopted CTD as a standard yet, such as Mexico and Argentina, and may be using other formats such as ACTD for Asean countries, including Hong Kong, Singapore, Chinese Taipei (Taiwan).

Figure 3. Transitional Formats towards eCTD adoption



6.2 Portals and Gateways to facilitate digital and eCTD submissions

6.2.1 Electronic submission portals for digital CTD format dossiers

The HA creates a portal, with industry collaboration, that serves as a common digital platform between sponsors and agencies for receipt, parallel distribution, and assessment of applications. These portals enable a central transmission point with the possibility for automating the routing of documents and dossiers to respective divisions, which can be particularly useful during the review process. Some global software providers of regulatory systems provide functionality in this area. Examples of secure transfer exchanges and portals used by European HAs include Eudralink, IRIS, and CESP for the receipt of non-eCTD submissions.

6.2.2 Portals for eCTD receipt

The ultimate goal is the development of a digital infrastructure that is able to accept eCTD submissions. This requires the development of eCTD specifications to allow dossiers to be technically valid for transmission over a portal. This portal can have built in automated technical validation and acknowledgement. This system requires a multi-year investment of funds, people, process, and technology. HAs can utilise commercially available eCTD validation, viewing and storing tools.

For some HAs (e.g., TGA Australia), portal development is part of a longer-term strategy, and in order to progress with eCTD, sponsors submit eCTD applications as a single zipped file by email or in a USB or non-rewritable CD or DVD as an interim measure. To minimize costs and leverage the experience of HAs, Health Canada opted to collaborate with the US FDA by creating a Health Canada space on the US FDA's ESG Gateway. Through this agreement, sponsors have the ability to send electronic submissions to both Health Canada and the FDA. Access is secured only for the respective HA and reviews and approvals are done separately. Other examples of European portals developed for this purpose are the eSubmission Gateway and eSubmission WebClient for EMA and the Common Repository for National Competent Authorities.

6.3 Roadmap to Adopting Electronic Common Technical Document for Health Authorities

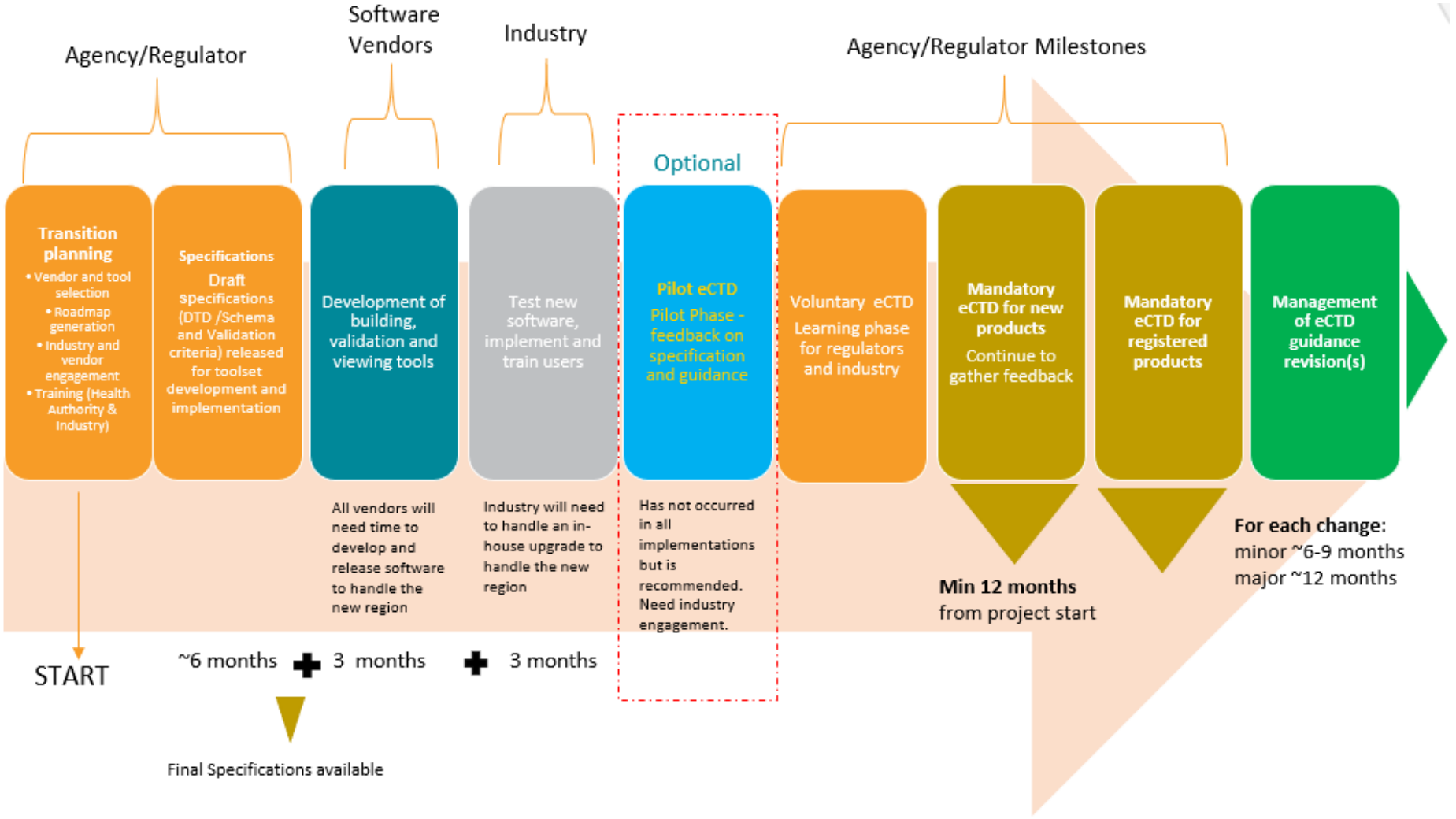
In order for a successful migration of CTD or digital CTD to eCTD format to occur, a clear roadmap needs to be established that is agreed to by all parties.

Software and IT infrastructure and vendor selection and contracts needs to take place on both the HA and industry side. Material to aid the transition needs to be readily available on the HA website and transparent communication between the HA and industry needs to occur early and often to minimize adoption errors. Clear timelines and advance notices of changes need to be provided with sufficient time to comply.

After any vendor selection activities, the HA should develop a roadmap that outlines the path towards full eCTD adoption. This roadmap usually takes into consideration tool selection and testing, training for HA reviewers and technical processing teams (industry authors, submission groups), a staged new and registered product implementation that moves from optional to mandatory timelines, management of eCTD guidance revision(s), consideration of benefits associated with the establishment of a secure and stable gateway/portal for submission delivery enabling large sized (>1GB) filings to be made from virtual support locations, and establishment of a service desk in support of technical questions and/or issues.

The suggested EFPIA eCTD adoption timeline is shown in Figure 4.

Figure 4. Suggested Timelines to eCTD Adoption



During eCTD transition planning, appropriate selection of vendors and tools is critical. HAs need to engage with established vendor(s) to develop timelines and infrastructure needs in order to implement software solutions that are fit-for-purpose. HAs and applicants use these vendor-supplied technologies (tools) to build, validate, and view and review eCTD submissions.

Six months should be allocated for transition planning and for the development of the draft of specifications for eCTD. Draft specifications (DTD/schema and validation criteria[1]) should be released for toolset development and implementation.

Three months should be allocated for developing the validation and viewing tools. All vendors will need time to develop and release software to handle the new region. It is essential that common standards (e.g., HL7 preferred) and criteria are set for all of these functions. While validation tools differ among vendors, there needs to be clear criteria provided to ensure consistency of results. When interpretation differs between vendors, there needs to be a mechanism to work with the HAs to bridge these interpretations. As with validation tools, HAs and applicants do not always buy the same vendor viewing/reviewing tool, therefore, it is essential to plan in a coordinated fashion and to get assurances on cross-compatibility among systems. Specialized software and tools need to be developed in order to effectively implement the XML structure; while some of these are already available, some will need to be built to the needs of each HA. Numerous tools are already available to match the needs of all classes of manufacturers (i.e., generics, innovative, local, and global) and can save substantial time and effort through their adoption.

In addition to validation and viewing tools, HAs need to assess the most optimal platform for bi-directional receipt, distribution and assessment of drug applications. If creating a HA gateway or portal, or collaborating across HAs for one common portal, sufficient time needs to be allocated for this effort to develop and test.

After the tools have been chosen, developed, and tested, there is a further 3 months required for the end users to test and implement the new software, and train users as to best practices. Industry will need to handle an in-house upgrade to handle the new region that has adopted eCTD. Vendor webinars for new releases have helped applicants with adoption of eCTD.

After the planning phase is complete, a pilot eCTD phase can occur where feedback on specification and guidance can be collected. This step is optional, but is recommended.

It is recommended that mandatory eCTD for new submissions should not begin until a minimum of 12 months after the start of the project, and each revision to the eCTD guidance should allow 6 to 9 months for a minor revision and 12 months for a major revision. A phased and careful approach to eCTD adoption is the preferred option for both HAs and industry. Adopting a new product in a staged manner allows for learnings across both HAs and industry. Lead times are typically introduced and move from optional eCTDs to mandatory eCTDs that encourages use while allowing phasing for pilots, learnings, HA transition, and applicant preparation.

6.4 Regional Electronic Common Technical Document Specifications

When beginning to plan for eCTD adoption, there needs to be clearly written eCTD specifications that detail where regional dossier materials should be located and how they should be structured within the regional module 1, rules on mandatory versus optional content, the submission process, and dossier maintenance. Further, technical files need to be developed to support the eCTD such as

[1] Please refer to glossary on page 23 for more information on DTD/schema

templates and validation criteria. As far as possible, the specifications should be aligned with other regions to facilitate international dossier production and speed up submissions. Many countries have leveraged regional module 1 eCTD specifications from other established regions/countries and re-used standards or content, when possible and appropriate to avoid needing to create everything new.

Several international vendors have experience with developing the various components that make up an eCTD in other countries/regions. The majority of countries/regions have worked with a vendor to implement the adoption of eCTD from paper-based or digital CTD.

6.5 Electronic Common Technical Document Version

Consideration of which version of eCTD to adopt is important; either ICH v3.2.2 or ICH v4.0. eCTD v4.0 is the newest version and was a collaboration with ISO and HL7 in order to leverage a standards foundation that is used in other health contexts (e.g., Electronic Health Records). The new eCTD version will address several business scenarios that v3.2.2 had difficulties with such as sharing/referencing documents across applications/products, changes to attributes for individual documents, and enabling two-way communication, see Section 9.3 for more information on eCTD v4.0 and its benefits compared to 3.2.2.

Currently, most regions that have adopted eCTD are planning their implementation roadmap to transition to eCTD v4.0. For more information on regional implementation dates refer to ICH eCTD v4.0 page [7].

Countries that are planning to adopt eCTD need to consider various aspects in deciding which version of eCTD to implement. A company or health authority's internal advantages and disadvantages need to be carefully weighed against industry's overall learning curve between eCTD v3.2.2 to eCTD v4.0, the timelines, and expertise within the companies and health authorities.

6.6 Electronic Common Technical Document for New Products

A phased and careful approach to eCTD adoption, which allows for learnings and feedback to implement improvement during the phasing in period, is the preferred option for both HA and industry. With this approach, lead times are typically introduced with encouragement for initial optional eCTD submissions which over time transitions to mandatory eCTD submissions. This timeline encourages use of eCTD while allowing phasing for pilots, learnings, HA transition, and applicant preparation. This approach reduces time, minimizes wasted effort, and achieves an overall smoother transition for both industry and HAs.

Some HAs in the ICH region have adopted eCTD for new products only (i.e., The Swiss Agency for Therapeutic Products, Therapeutic Goods Administration Australia, United Arab Emirates, Thai Food and Drug Administration).

6.7 Electronic Common Technical Document for Registered Products

Introducing eCTD for registered products also means deciding how to handle non-eCTD history. In the European Union, US, and Japan, the use of eCTD format for lifecycle dossiers without resubmission of original content is possible, although baseline submissions (summarizing the most up-to-date information for the product) are recommended. In Saudi Arabia, Oman, and Bahrain there is the requirement for a baseline of current approved information. In these countries, the baseline is not a full baseline, but the CMC part of the dossier, i.e., Module 2 Quality Overall Summary and

Module 3. If an eCTD base line submission for registered products is required, it is recommended to introduce a sufficiently long transition period to avoid excess administrative work for HA and applicants . This phase-in time also allows for HA transition, applicant conversion of existing content to CTD, and selection of appropriate lifecycle dossiers. A recent best practice example of a phased approach is with the conversion of EMA Centralized Procedures (CP) products to National UK licenses for MHRA post separation of UK from EU. The approach taken was to stagger eCTD baselines for all products over a 12-month period.

7 The Future – Dynamic Dossier Cloud Platforms

In the future, many HAs and industry partners may be able to work together to create robust, secure platforms for the submission and management of eCTD. In this system dossiers and data would be uploaded (or shared) by the sponsor via a cloud-based platform, allowing multiple organizations to securely share information . With this strategy HAs worldwide would have access to the same dossier version at the same time, creating convergence among HAs. With digital transformation HAs access to submissions and related information would occur via a cloud environment in a 'pull' process as opposed to the 'push' process that is currently implemented. This new strategy for gathering requisite information allows a higher degree of control to the HAs in the information received and when to receive it [8].

Clinical trial data as well as other data types, including real world data, would be evaluated on an ongoing basis in order to adapt the license. Leverage of artificial intelligence and advanced analytics for decision support would further strengthen the platform. For example, experiments are ongoing for dynamic dossiers in the cloud with the US FDA, European Medicines Agency and others through Accumulus Synergy [9]. Many large pharmaceutical companies are moving to cloud-based systems for Regulatory Information Management.

Sharing an application such as this across many partners drives convergence of processes, facilitates real-time reviews and reduces overall costs and time for initial implementation and for continuous update of information. Several technology vendors are currently considering developing cloud platforms for regulators (including eCTD).

Full implementation of dynamic dossiers is still some years away and EFPIA's recommendation is to move forward with adoption of the established CTD structure and eCTD format in the meantime.

8 References

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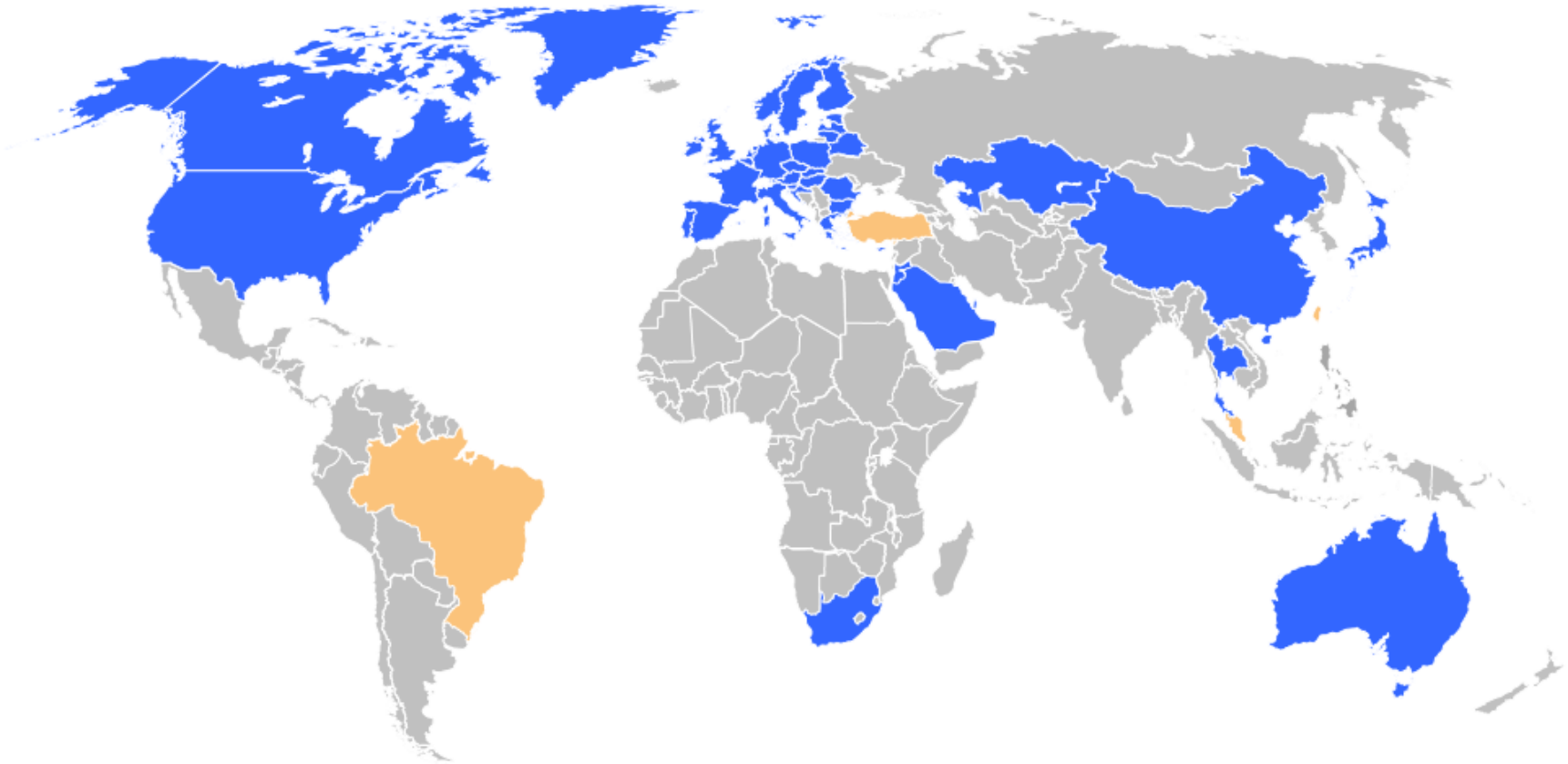
9 Appendix

9.1 Health Authorities Currently accepting eCTD

Numerous HAs across the globe are currently accepting eCTD format and there many that are in the planning stage of eCTD adoption. Figure 5 provides a visual representation of the adoption of eCTD up until 2021.

Figure 5. Global ICH eCTD Adoption per 7 December 2021



eCTD adopted – Australia, Bahrain, Canada, China (2021), Europe, Great Britain, Japan, Jordan, Oman, Qatar, Saudi Arabia, South Africa, Switzerland, Thailand, United Arab Emirates, USA

eCTD planned – Brazil, Turkey, Chinese Taipei, Singapore

9.2 Structure of Electronic Common Technical Document

At the core of eCTD is its extensive organization that is easily navigated and dynamic in nature, which is achieved through programming with XML, a structured data exchange standard that is both human and machine readable. The XML backbone (see Figure 6 below) provides the TOC structure that describes the location of every electronic document in the submission within the file structure and provides rich metadata about each physical file submitted. Each eCTD primarily relies on 2 XML files which provide the TOC, metadata detailing the submission, documents, and the structure of eCTD (1 XML file for Module 1 and 1 XML file for Modules 2 to 5).

Figure 6. Example of an XML backbone

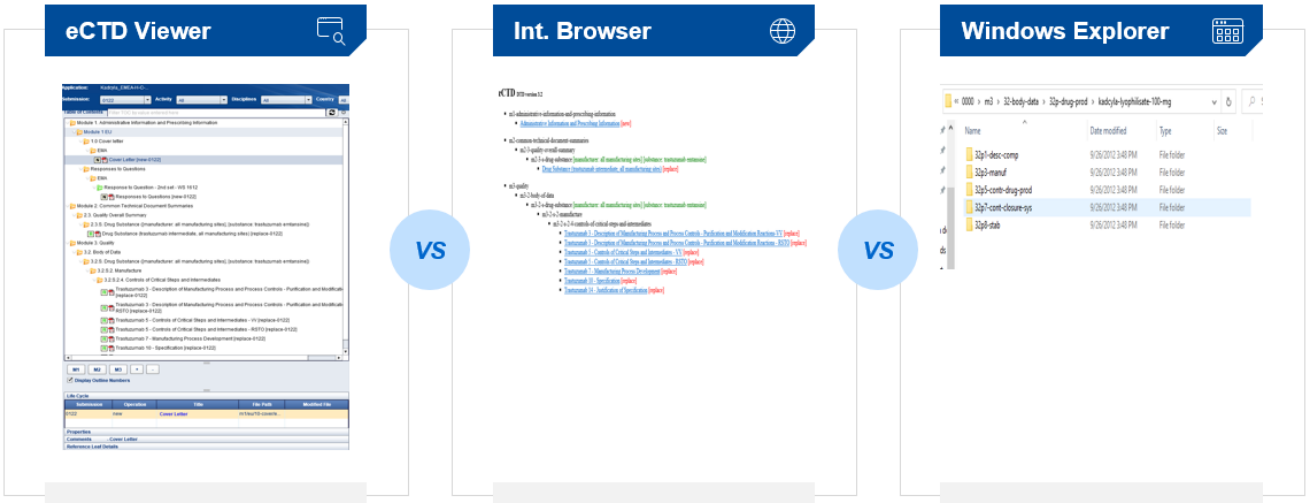
```
<leaf ID="Int235" modified-file="../0002/index.xml#Int206"
operation="replace" checksum="1fbda9ba62a53a85660e9c5dd980089d"
checksum-type="MD5"xlink:href="m2/22-intro/introduction.pdf"
xml:lang="en">
<title>introduction</title>
</leaf>

<leaf ID="Int20" operation="new"
checksum="3322da9078b95fe4af63811aa23452d6" checksum-type="MD5"
xlink:href="m2/23-qos/qos-introduction.pdf" xml:lang="en">
<title>qos-introduction</title>
</leaf>
```

The XML backbone provides the TOC structure that is used to facilitate the upload of all of the required documents, typically in PDF format, that together constitute an application. Each uploaded document is paired with a file termed a leaf document that contains pertinent information about the document and references the actual physical file location in the eCTD file system. The eCTD filename is the physical filename that is linked from the TOC page by including the file path (i.e., 0000\m1\eu\10-cover\ema\em-cover.pdf). The leaf title, or eCTD title, is the document name that is displayed to the reviewer (i.e., 'Cover Letter'). The XML can be viewed with a stylesheet. Viewing software allows a user friendly view of the eCTD, see Figure 7 below.

The most optimal way to view an eCTD sequence is via an eCTD viewing software. Reviewing in different ways (Windows Explorer or Internet Browsers) will not allow for dynamic reviews.

Figure 7. Viewing eCTDs



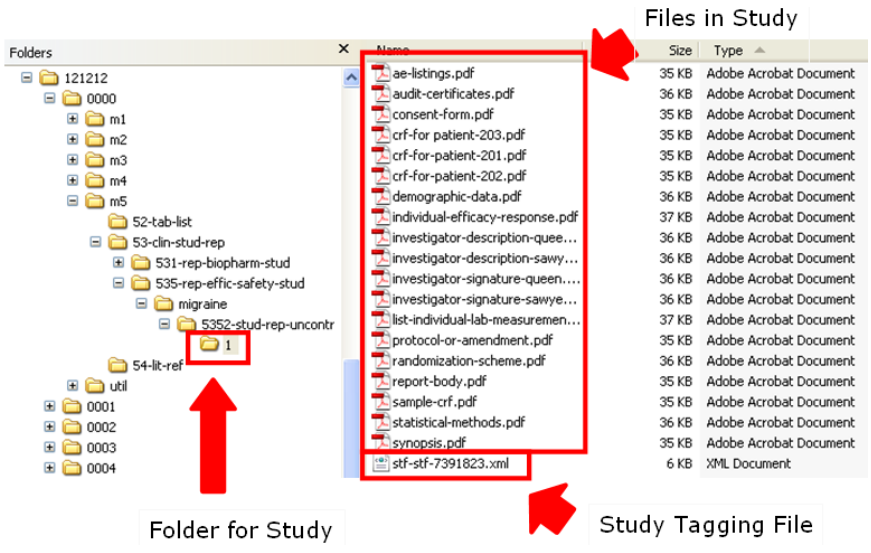
When documents are uploaded to the eCTD, users are required to assign a lifecycle operation to each document, allowing for dynamic, robust lifecycle management of the dossier, a key advantage of eCTD as compared to paper-based CTD. Section 5.5.1 contains a description of the eCTD lifecycle operations.

The XML backbone is arranged in a logical order that is easily understood and readily navigated (as shown in Figure 1). At the highest level of the XML backbone is a folder that contains all of the pertinent sub folders and documents for either the product (industry) or the applicant (HAs).

Immediately below the product/applicant name folder are folders that are labelled with the eCTD sequence, a unique 4-digit sequential number used to identify a submission (i.e., 0000). The initial submission submitted is generally 0000 (0001 in the US) and subsequent responses and lifecycle maintenance submissions are sequentially numbered 0001, 0002, etc. with each forming their own submission packages. This structure allows new sequences and therefore, new dossiers (for variations, new indications, etc.), to be added to the overall application. The file 'index.xml' also resides in this folder and provides the XML backbone for Modules 2 to 5 for that particular submission or sequence.

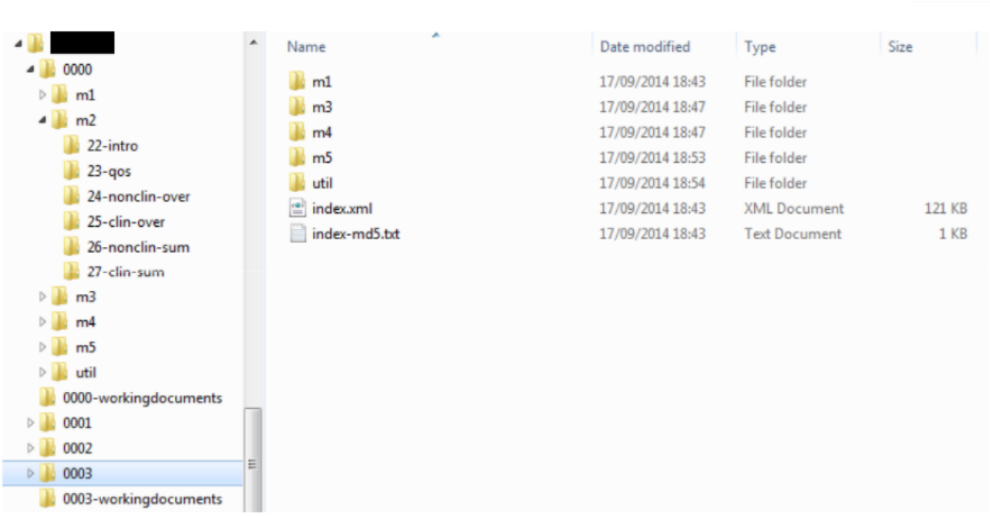
Within the eCTD sequence folder are module folders designed to mirror Modules 1 through 5 of the CTD. Each of these module folders contains sub folders that provide further granularity and allow each document within a module to be easily located and accessed. Module 1 contains administrative and prescribing information as specified by the HA for the region or regions of submission. Within this folder resides another XML file 'xx-regional.xml' that is specific to each region and resides in the \nnnn\m1\xx\ folder (where xx is the 2-letter country/region code). Modules 4 and 5 can also be further organized by study tagging files (STFs) as the XML backbone file does not contain enough information for several document types (e.g., study report documents) as required for regulatory use in some regions. These STFs include metadata that provides information regarding document title, subject matter, relationship to other documents, revision information, the location of the document, and information on the sequence that is included the document (see Figure 8 below). The STFs are required in US and China, encouraged in Canada, not permitted in Japan, and not required in other HAs to date). In Europe, further organization is provided through the use of node extensions.

Figure 8. Example of Study Tagging Files



At the same level as the module folders, and following them on the XML backbone, is a utility folder, with sub-folders for document type definition (DTD), which contains the ICH and regional DTD/schema files (contains rules on how the XML must be structured) covering Modules 2 to 5 and Module 1, and a style folder, which contains the ICH and regional stylesheets (used to display the eCTD XML in a user-friendly manner) covering Modules 2 to 5 and Module 1. Refer to the graphic below.

Figure 10. Example of Folder structure including backbone Files and XML util



9.3 The next major version of eCTD, eCTD 4.0

In 2015, ICH reached Step 4 [7] on the next major version of eCTD, eCTD 4.0. Step 4 is an ICH step where the Assembly agrees that there is sufficient consensus on the Guideline to move to implementation. Once Step 4 is reached, the Harmonised Guideline moves to the final step of the process and is implemented by each of the Regulatory Members in their respective regions. The harmonised Guideline is implemented according to the same national/regional procedures that apply to other regional, scientific or regulatory Guidelines and requirements.

The ICH M8 Working Group on electronic submission has drafted the documents based on the Regulated Product Submission (RPS) standard established by Health Level Seven (HL7) in September 2014. This standard defines the message for exchanging regulatory submission information electronically between applicants and HAs and will be developed jointly with eCTD 4.0.

eCTD 4.0 aims to improve robustness, flexibility and long-term stability of the message. Currently, all regions that have adopted eCTD are planning their pilot and transition period. For more information on regional implementation dates, refer to ICH eCTD 4.0 page [7].

Benefits of eCTD 4.0 compared to 3.2.2 include:

- Lifecycle improvements
- Globally unique identifiers (UUID) for documents that will allow more reuse
- Granularity changes supported while maintaining life cycle relationships, e.g., replace 2 documents with 1 and replace 1 documents with 2, previously not possible

- "Priority" number provides sort order for viewers
- Attributes and metadata can be corrected easily
- Potential for 2-way communication (agency to applicant as well)
- Paves the way for additional metadata to be included in future.

10 Glossary and Definitions

Abbreviation or Term	Definition
Backbone	Table of contents in XML format
Baseline	Providing part or all of the current registered submission documents (normally as an initial eCTD sequence, but can be provided later in the lifecycle) Many HAs recommend baselines are provided - the industry position is that they should not be mandated as some old products would have very little activity so would not benefit from this. If baselines are required, flexibility for full versus partial baselines and formatting of previously submitted legacy documents (e.g., those generated by scanning, non-text searchable) should be given.
Current view	Displaying just those documents across all sequences that are current (i.e., not Deleted/Replaced)
Document reuse	Ability to reference a document previously submitted by linking to it It is possible to re-introduce documents from another section or another eCTD sequence or application without physically re-submitting the file through the use of eCTD reference leafs
eCTD sequence	A 4-digit sequential number that identifies a particular submission (i.e., 0000)
eCTD filename	Physical filename linked to contents page by including the file path (i.e., 0000\m1\eu\10-cover\ema\ema-cover.pdf)
HL7 RPS	Health Level Seven Regulated Product Submission standard
ICH eCTD metadata	Information used to define the contents of submission sections (i.e. indication, substance, manufacturer)
Leaf	Contains information about a document in the eCTD Will reference to a physical file on the file system
Leaf title or eCTD title	Document name that will be displayed to the reviewer (i.e., 'Cover Letter')

Lifecycle	Submission lifecycle – relationship between eCTD sequences using the related sequence metadata Document lifecycle – relationship between document versions using lifecycle operations (new, replace, delete, and append)
MD5 checksum	Unique calculated value of a document used to determine if it has been changed
Node	A section of the eCTD (i.e., 3.2.S.4.1) that contains leaf documents
Node extension	Provides ability to create a node at the lowest level of the eCTD only, to help keep content together. Used in many regions as an alternative to STF
Regional Metadata	Information in the XML that describes the submission
Regulatory activity	A collection of eCTD sequences related to the same regulatory step (i.e., a variation sequence and associated response sequences)
Schema/Document Type Definition (DTD)	Provides rules on how the XML must be structured
STF (study tagging file)	Provides metadata to categorise study reports in Module 4 and 5 (required by US and China, encouraged in Canada) Not allowed in Japan and not required by other HAs, but if included STF will be validated
Stylesheet	Used to display the eCTD XML in a user-friendly manner within a browser
XML	eXtensible Markup Language – a structured data exchange standard that is both human and machine readable