RECENT ADVANCES AND CHALLENGES FACED BY PHARMACUETICAL COMPANIES IN FILING DOSSIERS WITH NATIONAL DRUG REGULATORY AUTHORITIES

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ABSTRACT:

Now a days in order to market any drug product need to get approval from concerned regulatory authorities by submitting the dossier via., CTD or eCTD formats. CTD is the agreement to compile all the facts on Quality, Safety, and Efficacy in a uniform format. Using the Electronic Common Technical Document (eCTD), CTD can be electronically submitted from the applicant to the regulator, such as the USFDA or EMA. The eCTD software underwent a lot of changes. Extedo/IABG Life Sciences are the companies that provide eCTD validator solutions. Data and information included in a regulatory submission must be gathered and managed for thoroughness, correctness, and integrity in accordance with agency criteria. The typical stages in the submission process flow are submission management, document level publishing, submission level publishing, validation and verification, and dispatch to agency. Based on the requirement of eCTD format in major market places companies must provide an uniform infrastructure that supports the lifecycle of every type of intrinsic submission. Under Industrial perspective, The static, PDF-locked documents provide particular difficulties for automation, dynamic data access, review, and analysis. Challenges faced by the companies from Health Authorities because the turnaround time for responses varies by region and can, in many cases be as little as a few days.

Keywords: Non-eCTD electronic submission (NeeS), parallel importation, data exclusivity, patents, compulsory licensing.

INTRODUCTION:

A Common Technical Document (CTD) is a list of leaflets that must be sent to the regulatory body with pharmaceutical registration applications in order to get market authorisation. The data format is primarily described by CTD. It is common for RA experts to be aware of the paperwork required for product approval. Contrarily, the organised structure of information is what CTD is most interested in. CTD documentation must be clear, uncomplicated, and transparent.[1] CTD is an ICH-defined format that has been agreed upon and accepted by regulatory agencies in Europe, Japan, and the United States. The FDA defines the CTD as an information package containing clinical, non-clinical, manufacturing, and technical data that would be submitted for registration of novel pharmaceuticals in all three ICH regions, namely the United States, the European Union, and Japan. [2] The CTD triangle is shown in Figure 1, it having five modules. The electronic submission equivalent of the CTD is the eCTD. The

eCTD serves as a conduit between industry and government agencies for the exchange of regulatory data, facilitating the development, review, lifecycle management, and archiving of electronic submissions. All CTD information is included in the eCTD submissions. Using the Electronic Common Technical Document (eCTD), the Common Technical Document (CTD) is sent online in electronic form to the drug regulator by the Dossier filing Company. CTD includes three parts viz., Directory structure, XML eCTD instance and content file as shown in the Figure 2. Formats that are commonly used for submission of eCTD are: Graphic, Structured: Extensible Markup Language (XML), and Narrative: Portable Document Format (PDF): Whenever possible, use PDF.[3] The recent updates in the eCTD software are given in Table 1. Two vendors provide to regulatory organisations with eCTD validator solutions. In EMEA, there are two companies: Extedo and IABG Life Sciences. The US refers to it as Global Submit. Businesses in the pharmaceutical and biotech industries should think about methods that allow them to have their eCTD submissions' content and structure assessed before submission. It is very crucial in ensuring that the software's and tools utilized for creation, administration, and publication of the eCTD are capable of meeting internal technological and procedural requirements. It is obvious that all software developers can produce legitimate eCTD structures, but it is less obvious whether the tools and methods they provide are equally capable or useful. Choose a vendor carefully, then pay them.[4] A list of Tools and Software's is shown in Table 2. The amount of Regulatory information for building the dossier for each drug product differs from country to country based on requirements of the importing country regulations. Applications, modifications, supplements, and reports can all be sent to different regulatory agencies using the eCTD standard format. Several nations in the European Union and Gulf Cooperation Council still use the Non-eCTD Electronic Submissions (NeeS) format.

Depending on the local agency, many nations around the world have different regulatory standards. Developing and filing information for pharmaceutical products in accordance with the drug regulations of a specific country is one of the main concerns for authorities. Data and information included in a regulatory submission must be gathered and managed for thoroughness, correctness, and integrity in accordance with agency criteria. To decide whether a product may move on to clinical testing and to confirm that it is efficient and secure for commercialization, regulatory bodies need these. The typical stages in the submission process flow are given below. They are;

- **Submission Management**
- **Document Level Publishing**
- **Submission Level Publishing**
- **Verification and Validation**
- **Dispatch to Agency**[5]

Table 1: Updates in the eCTD software

Version	Date	Summary of Changes
1.0	08-05-2015	Initial Version
2.0	21-09-2016	Modifications to the PDF Specifications and the M1 v2.3 eCTD Validation Criteria Specifications
2.1	29-09-2016	eCTD Technical Conformance Guide update
2.2	07-11-2016	The M1 Specifications for eCTD Validation Criteria have been updated.
2.3	02-03-2017	Update to the M1 Specifications for eCTD Validation Criteria, the Technical Rejection Criteria for Study Data, and the Specifications

		for File Format Types Using eCTD Specifications.
2.4	29-03-2017	Update to the Study Data Technical Rejection Criteria
2.5	05-04-2017	eCTD Validation PDF version has been updated. standards for evaluating errors
2.6	22-06-2017	The Transmission Specifications, Specifications for eCTD Validation Criteria, and both versions of the eCTD CTOC have all been updated (see M1 v. 1.3 and Supportive Files and M1 v. 2.3 and Supportive Files sections for more information).
2.7	15-11-2017	Technical Conformance Guide and File Format Type Specifications Both the eCTD Specifications and their use have been upgraded. Valid Valus xml was added and the ICH STF Stylesheet was updated. Pinnacle 21 and GS Validate are further validation tools.
2.8	21-06-2018	The eCTD Validation Criteria have been updated.
2.9	30-11-2018	Updates have been made to the Technical Conformance Guide v1.3, M1 v2.4 Specifications, eCTD CTOC, and Submission-type (M1 Attribute List).
3.0	22-01-2019	Updates to the eCTD Validation Criteria and the addition of eCTD Q&A and Change Requests
3.1	01-04-2019	The Transmission Specifications have been updated
3.2	12-07-2019	An update was made to the M1 v. 2.4 Attribute List for promotional materials.
3.3	15-08-2019	Updates were made to the M1 v. 2.4 Attribute List and the File Format Specification for advertising materials.
3.4	12-12-2019	Technical Conformance Guide v1.4 has been updated.
3.5	27-07-2020	Updates were made to the REMS Supplement submission-type.xml and the eCTD Validation Tool.
3.6	09-09-2020	Versions 2.2 and 3 of valid-values.xml have support end dates stated.
3.7	01-10-2020	Form 3988 form-type.xml update
3.8	09-11-2020	The M1 v2.4 Specification and CTOC have been updated, and M1 v. 1.3 and its supporting files will no longer be supported on that date.
3.9	15-03-2021	The eCTD Validation Criteria, form-type.xml, and File Format Specification have all been updated. Versions 2.2 and 3.0 of valid-values have also been removed because they are no longer supported.
4.0	28-05-2021	Updates to the eCTD Validation Criteria and the File Format Specification
4.1	24-06-2021	Transmission Specification and eCTD Validation Criteria revisions
4.2	16-08-2021	The eCTD Validation Criteria have been updated, and the M1 v. 2.5 Attribute List, Supporting Files, and Date Requirement Begins have been listed.
4.3	01-10-2021	Updates to the File Format Specification and Technical Conformance Guide
4.4	15-03-2022	Updates to the eCTD Technical Conformance Guide and eCTD Validation Criteria; Removal of the M1 v1.3 and Supportive Files section (M1 Specification v1.3, eCTD CTOC v1.2.2, US Regional

		DTD 2.01, US Regional Stylesheet v1.1)
4.5	11-05-2022	eCTD Validation Criteria revisions
4.6	12-08-2022	File Format Specification updates
4.7	04-11-2022	Updates to the Lorenz docuBridge tool version and the eCTD Technical Conformance Guide

Table 2: List of Products and Vendors

Product	Vendor	Vendor Description
eCTD Builder	Datafarm	The intricate directory structure and XML backbone are abstracted by eCTDBuilder. It offers a straightforward and user-friendly user interface with compatibility for several locations, including Canada, the EU, Japan, and the US.
eCTD Viewer	Datafarm	All eCTD applications developed in accordance with ICH and local DTD criteria are supported by the all-inclusive evaluation programme known as eCTDViewer. The capability to receive, validate, review, and archive eCTD submissions is provided by this programme, which was created based on the specifications shared by numerous agencies and our industry partners.
Gatekeeper	Datafarm	The ability to validate the accuracy and integrity of the eCTD submission based on ICH and local criteria and specifications is provided by the GateKeeper module.
pCTD	Datafarm	The dossier needs would be fulfilled by the pCTD (paper CTD) With the help of Volume Table of Contents and Tab separators, this application can produce paper volumes.
eCTD Bridge for Documentum	DoubleBridge	The Documentum WDK or Webtop environment can be used by users to check and navigate eCTD submissions when using the DoubleBridge eCTD Viewer for Documentum.
eCTD Manager	Extedo (USA) IABG LSS	The commercial submission management tool eCTDmanager is great and effective. It supports the eCTD operations of building, viewing, validating, and publishing (electronic and print) as well as the straightforward generation of compliant electronic dossiers based on CTD, eCTD, and other dossier formats.
eCTDView	Extedo (USA) IABG LSS	Users can examine and comment on all Dossier attributes and eCTD material using the "reader-only" version of eCTDmanager, eCTDview, which incorporates all of eCTDmanager's viewing features. In contrast to other eCTD viewers, eCTDview acts inside the context of the live, in-progress eCTD while displaying only the findings of the final eCTD submission

		output.
Study Manager	Extedo (USA) IABG LSS	It is common practise to develop an eCTD over time and/or by different teams. StudyManager was developed with the intention of enabling the production of studies with speed and accuracy, including Study Tagging Files (STF), independent of and prior to the creation of an eCTD that incorporates the study. The entire study can be added to the eCTD at any time throughout development with just one simple "drag and drop" operation.
eCTDauthority	Extedo (USA) IABG LSS	The application that reviewers in the EMEA and across 38 EMEA nations will use to assess and validate eCTD submissions has been chosen by the EMEA from EXTEDO/IABG-LSS as the supplier. Extedo provides this software to both the industry and the national regulatory organizations. In the EMEA region, the product is known as EURS is Yours, while in North America, it is known as eCTDauthority.
Global Submit Review	Global Submit	GlobalSubmit REVIEW^{TM}'s sole function is to expedite the collaborative review procedure for eCTD-based electronic submissions. It provides a wide range of features and options to facilitate the quick assessment of electronic submissions.
Global Submit Validate	Global Submit	Only GlobalSubmit VALIDATE^{TM} is used by the U.S. FDA to validate and verify eCTD dossiers. Leading companies use GlobalSubmit VALIDATETM to make sure their dossier satisfies the exacting eCTD requirements before submitting it to regulatory agencies.
eCTDXpress	Image Solutions	The newest web-based tool from ISI for developing, overseeing eCTD lifecycles, and evaluating eCTD submissions is called eCTDXPress. The programme serves the needs of industry sponsors and regulatory authorities for multi-region eCTD submission assessment, compilation, publication, and archiving. The ability to decouple technology from content with eCTDXPress increases productivity and shortens time-to-market.
docuBridge Express	Lorenz	The most recent web-based tool from ISI for developing, controlling eCTD submission lifecycles, and reviewing eCTD submissions is called eCTDXPress. The application complies with regulatory agencies' and industry sponsors' criteria for multi-region eCTD submission assessment, compilation, publication, and archiving. To increase productivity and shorten time-to-market, eCTDXPress enables users to

		isolate technology from content.
docuBridge Validator	Lorenz	docuBridge.The validation programme, known as Validator, is a free standalone software that may be downloaded from the LORENZ website. The tool is a part of the docuBridge.com applications & services and will be updated as part of the yearly service package, according to any docuBridge.com subscribers.
eCTD Composer	MedXView	Without a tool, creating a proper eCTD submission takes effort and is prone to mistakes. Companies may lose millions of dollars as a result of these potential delays and mistakes, which also reduces their competitive advantage. Our eCTDcomposer guarantees that competitive edge by assisting our users in submitting eCTDs quickly and accurately in accordance with the requirements set forth by the government.
eCTD Auditor	MedXView	The most robust and functional tool available for validating, reviewing, and tracking eCTD is MedXview eCTDauditor™. Additionally, eCTDauditor™ includes built-in reporting capabilities for producing the Audit-Trail Summary Report, Submission-Details Report, and Error-Summary Reports.
TAKE Solutions	PharmaReady eCTD	A web-based electronic Common Technical Document solution called PharmaReady eCTD was created with regulatory affairs departments at health science organisations in mind, where ease of installation, convenience of use, regulatory compliance, and affordability are the key business drivers.
Submission Accelerator for eCTD	Thomson Liquent	Assembling and publishing compliant eCTD dossiers, including the XML foundations for regional information, are automated by Submission Accelerator™, a companion module for CoreDossier®. Drag & drop your files into CoreDossier with Submission Accelerator to publish compliant output for regulatory agencies to assess anywhere in the world.
<virtx:eCTD/>	Virtify	Virtify's <virtx:Ectd/> A single solution for authoring, compiling, reviewing, QCing, publishing, and transmitting Electronic Common Technical Documents (eCTD) is the Electronic Submissions Management solution. It does away with the requirement to maintain and deploy various solutions for eCTD submissions.

Table 3: Implementation Timeline

Region	Technical Pilot	Implementation Dates	Implementation Documents
ANVISA, Brazil	2Q 2023 (Planned)	3Q 2023 (Production Pilot) 2023 (Voluntary)	TBD
EC, Europe	2024 CAPs (Planned)	2024 (Voluntary for CAPs) 2025 (Voluntary for MRP/DCP) 2026 (Voluntary for NAPs) 2026 (Mandatory for CAPs) TBC (Mandatory for MRP/DCP)	EC, Europe regional implementation page
FDA, United States	2022 - IQ 2023 (In Progress)	2023 (Voluntary) 2028 (Mandatory)	FDA, United States regional implementation page
Health Canada, Canada	2023 (Planned)	2024 (Voluntary) 2027 (Mandatory)	Health Canada, Canada regional implementation page
MHLW/PMDA, Japan	2Q 2021 (Completed)	2022 (Voluntary) 2026 (Mandatory)	MHLW/PMDA, Japan regional implementation page
Swissmedic, Switzerland	2024 (Planned)	2024 (Voluntary) 2028 (Mandatory)	Swissmedic, Switzerland regional implementation page
TGA, Australia	TBD	2023 (Voluntary)	2023 (Planned)

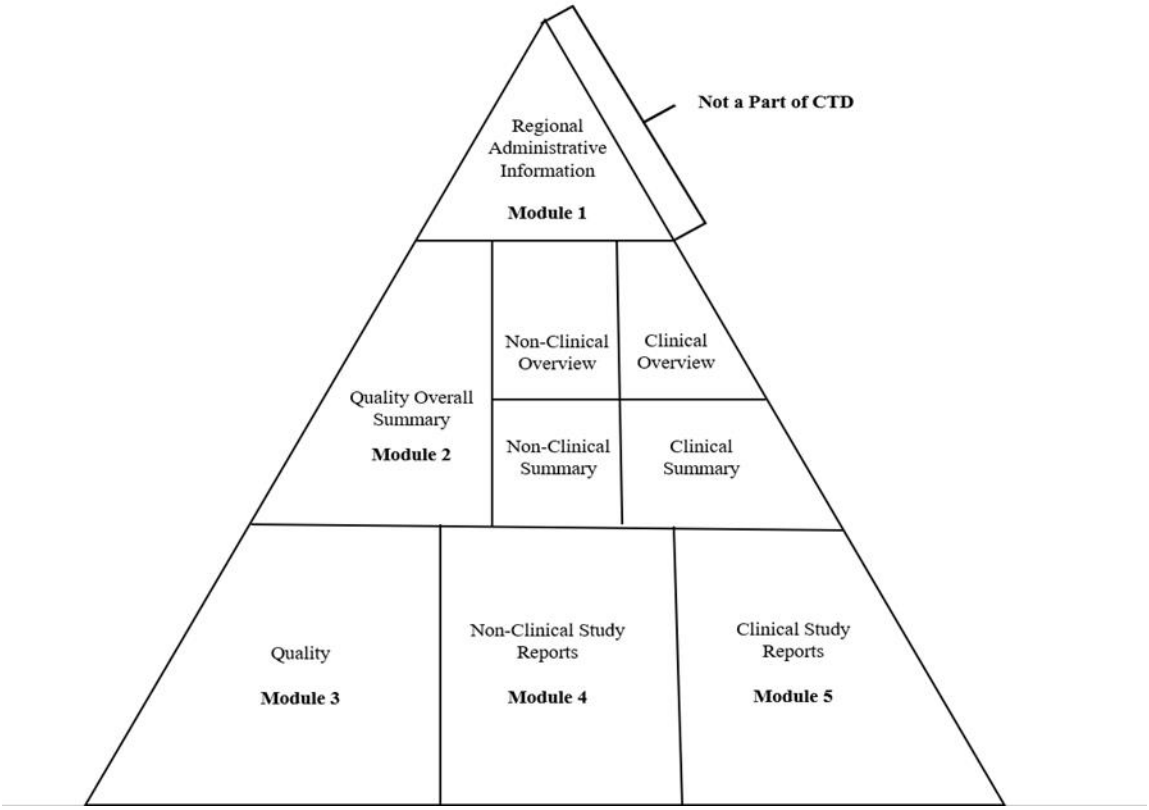

Figure 1: CTD Triangle

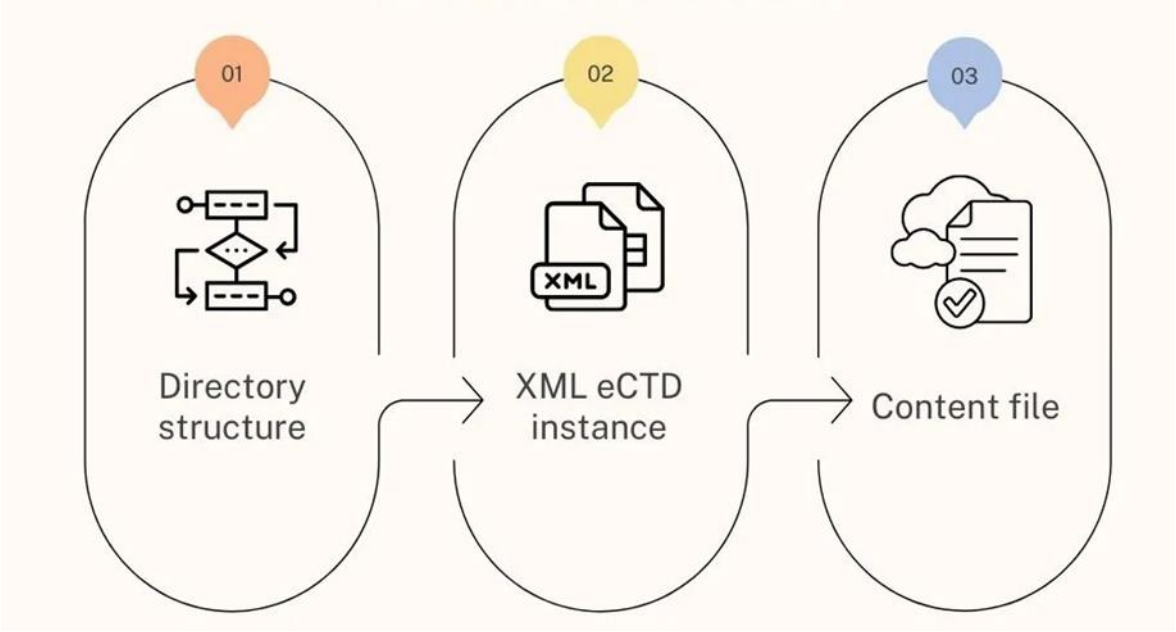

Figure 2: Parts of eCTD Submission

Digitized CTD as a basis for Transitional formats

The creation and testing of the new standard, as well as the regional and global requirements, involved many of the early eCTD adopters. To properly prepare for eCTD both internally and internationally, they developed temporary or semi hybrid digital formats to act as paving path prior to full implementation of eCTD. To make it simpler to print in binders (1 volume = 1 ring binder), the CTD paper dossiers' also known as "Volumized PDFs" or "Paper

publishing" was developed in this way. Another example of a transitional format is the non-eCTD electronic Submission (NeeS) format, which was established in Europe and is used in nations like Australia. The main part of this format is a group of documents arranged into a number of folders that correspond to the CTD modules, each of which has a specific set of technical specifications. Even though the NeeS format had many advantages over eCTD (such as the capacity to transfer documents from one submission to another or to provide additional metadata for each document), it is currently regarded as "legacy" and is not advised as a long-term replacement for submission formats.

l and eCTD submissions

With the help of the industry, the HA develops a portal that acts as a standard digital platform for sponsors and agencies to receive, distribute, and evaluate applications. These portals allow for a single point of transmission with the potential for automating the routing of papers and dossiers to the appropriate departments, which can be very helpful when conducting reviews. Functionality in this area is provided by some international software developers of regulatory systems. Eudralink, IRIS, and CESP are a few instances of secure transfer exchanges and portals that European HAs utilise to receive non-eCTD submissions. The creation of a digital infrastructure that can handle eCTD submissions is the ultimate objective. To enable dossiers to be technically legitimate for transmission over a portal, this necessitates the development of eCTD requirements. This portal may have automated technological validation and acknowledgment features. This system demands a multi-year investment of resources, including cash, labour, technology, and other resources. Commercially accessible eCTD validation, viewing, and storing tools can be used by HAs. eCTD applications must be sent as a single zipped file through email or in a USB or non-rewritable CD or DVD as a temporary step in order to move forward with the programme for some HAs (such as TGA Australia), where portal development is a longer-term goal.

Roadmap for Electronic Common Technical Document Adoption

clear roadmap that is accepted by all parties must be established in order for CTD or digital CTD to successfully transition to eCTD format. Both the HA and industry sides need to pick and sign contracts with vendors for software, IT infrastructure, and related services. To reduce adaptation errors, there needs to be easy access to transitional materials on the HA website and frequent, open communication between the HA and industry. Ample time must be allowed for compliance with clear deadlines and early notices of changes. The HA should develop a roadmap describing the actions required to complete full eCTD implementation following any vendor selection efforts. The choice of providers and technologies during the planning phase of the eCTD transition is crucial. To execute software solutions that are appropriate for their intended use, HAs must collaborate with reputable vendors to set deadlines and infrastructure requirements. These vendor-supplied technologies (tools) are used by HAs and applicants to create, validate, view, and evaluate eCTD submissions. Planning the transition and creating the first draught of the eCTD requirements should take six months. For the creation and use of toolsets, draught specifications (DTD/schema and validation criteria1) should be made available. The creation of the validation and viewing tools should take three months. It will take time for all vendors to create and publish software to manage the new region. Common standards (HL7 is ideal) and criteria must be established for each of these functions. While vendors' validation methods vary, consistent outcomes must be guaranteed by providing defined standards. There needs to be a way to work with the HAs to overcome interpretation gaps when there are discrepancies between vendors' views. As with validation tools, HAs and applicants may not always purchase the same vendor viewing/reviewing tool, thus it is crucial to plan together and obtain guarantees on system

interoperability. Tools and software that are specialised must be created. While some of these are currently available, others will need to be customised for each HA in order to apply the XML format in an efficient manner. All types of manufacturers (generic, innovative, local, and worldwide) can use a variety of tools that are currently available to them, which can save a lot of time and work. HAs must evaluate the best platform for the bi-directional receipt, delivery, and evaluation of drug applications in addition to validation and viewing tools. Ample time must be set aside for this effort to construct and test if a HA gateway or portal is being created, or if HAs are working together for one common portal. The end users must test, implement, and test again the new software after it has been built and tested for three months. They must also train users on best practises. In order to handle the new region that has adopted eCTD, industry will need to undertake an internal upgrade. Vendor webinars for fresh releases have facilitated eCTD uptake for applicants. After the planning stage is finished, a pilot eCTD phase may be conducted to get input on the specification and instructions. Although optional, this step is advised. The eCTD advice should be revised every 6 to 9 months for minor revisions and every 12 months for substantial revisions. It is advised that mandatory eCTD for new submissions not start until at least 12 months from the project's start date. Both HAs and industry want a gradual and cautious approach to eCTD deployment. A new product can be adopted gradually, allowing for industry-wide and HA-specific learning. Lead times are often added, and the transition from voluntary to required eCTDs promotes utilisation while enabling phasing for pilots, lessons learned, the move to HA, and applicant preparedness.[6]

Upgradation in eCTD software.

The most recent edition of the Electronic Common Technical Document (eCTD) has been finalized and is being distributed globally. By 2028 (before in many regions), all major regulatory agencies will require compliance with the significant advances offered by eCTD v4.0 in the way that sponsors and regulatory bodies manage submissions. [7] The Health Level Seven (HL7) standard known as RPS (Regulated Product Submission) is the foundation of eCTD 4.0. The actual content, which will continue to evolve with each iteration of the eCTD, is not the primary focus of this standard; rather, it focuses on streamlining the processing and evaluation of regulated product information. In order to obtain approval for future regulated products including medical devices, animal health, and others, RPS was also created to be applied in other industries. The main objectives are to implement modifications that quicken the regulatory filing procedure; improve communication between sponsors and agencies and the format should be more uniformly used worldwide. The main features are

- **Document re-use -** Throughout an application's lifecycle, it is typical for the same material to be required more than once. Currently, to do this, one must submit the identical document in each order in which it is needed. Each document in eCTD 4.0 will receive a Universal Unique Identifier (UUID). In order to prevent having to submit the content again, this identification can be used in subsequent sequences.
- **Lifecycle enhancements -** It will be possible to replace numerous documents in the application with one document or one document with many documents in order to optimise the management of information over longer periods of time. In eCTD 4.0, the legacy "append" process will be completely removed, and documents and metadata can be renamed (for example, to change the trade name).
- **Tables of Content -** In eCTD 4.0, the hierarchy outlined in v3.2.2 will be replaced by a flat structure. Instead, the placement of the content inside any eCTD tables of content produced by the viewing tools will be determined by its context of use and keywords.
- **Study Tagging Files (STFs) -** Study Tagging Files will no longer be required in eCTD 4.0; Document Groups will take their place.

- **Enhance how agencies and sponsors communicate -** Two-way communication between sponsor and agency: Only one-way communication from the sponsor to the agency via individual sequences is permitted under the current specification of the eCTD. It is not included in the eCTD itself and all agency-to-sponsor communication is done independently. In addition, eCTD 4.0 will give the agency the ability to react to the sponsor in a sequence, giving the sponsor a complete picture of the application's whole lifespan, including all inquiries and information requests, in one location. The use of controlled vocabularies is an important step in establishing consistent communication between sponsors and agencies is the greater usage of agreed regulated lists. Regional authorities, the ICH, as well as other organisations will have jurisdiction over these listings. These must be put into practise by the publishing systems.
- **Improve global harmonization of the format -** A variety of Standards Organisations are involved in format standardisation. eCTD was created based on the HL7 RPS (Regulated Product Submissions) project as well as the ICH with the goal of becoming an ISO standard. Sponsors and agencies' long-term goal is to supply additional content from the eCTD dossier via structured data (such that described in the IDMP standard), in addition to including Health Authorities and other third parties for controlled vocabularies. Given that there are currently more variations than intended in the way the eCTD is applied across various health authorities, this should all result in increased harmonisation. Fresh XML schema, it is created to support the new standard's upgraded features and to be more adaptable in the long run.[8]
- **Implementation Timelines -** The FDA is in charge of the eCTD v4.0 technical pilot, which sponsors are using to submit samples and test results, as of April 2023. By 2028, all sponsors in the US will be forced to adopt eCTD v4.0, and the agency will start accepting applications from any sponsors who desire to do so in Q1 of 2024. Reviewing the ICH and applicable areas' implementation kits will help sponsors get ready. It is shown in Table 3.[9]

Procedure:

Now, Companies must provide an uniform infrastructure that supports the lifecycle of every type of intrinsic submission because eCTD format is now required in the major marketplaces. They are able to manage the complex process of compiling, approving, releasing, and documenting new drug and medical device applications with ease in this way. Needs experienced employees and cutting-edge technologies Standard Format Not necessarily required for all the content therefore, Standardization required.

- Regional variations in the PDF version, bookmarking, and hyperlinking
- Difficult to make last minute changes
- Life-cycle management is difficult.
- Regional variations in validation requirements
- Local affiliates have limited access to create or customize
- Differences seen in authentication of different regions
- Consolidated approach to drafting of dossier
- Baseline submissions have limited value and costly.[10]

Despite all the advantages provided by the standardized eCTD framework, there are still some drawbacks with this submission format that make it difficult for the life sciences industry. Finding the regulatory tools that support the software supporting the eCTD submission requirements is the main challenge. Pharmaceutical companies must have access to all documentation, including collections, questions and answers, updates, and restorations,

in a uniform electronic format in order to complete the eCTD submission effectively. To manage the integrated regulatory data and regulatory filings process, pharmaceutical companies should employ a core software product.[11]

Emerging challenges and opportunities for drug registration

Compulsory licensing - South Africa is one of the few nations that has come close to issuing a compulsory licence, hence the issue of registration requirements for pharmaceuticals with a compulsory licence has been taken into consideration there. According to the DRA, the product would need data to demonstrate that it is of appropriate quality, safety, and efficacy – presumably the prerequisites for registration of an NCE. The regular registration requirements would then apply in this case. In conversations with the DRA chief, it was made clear that any compulsory licences would be issued by the Patent Office, not the Regulatory Authority, and that a registration application would be treated equally regardless of whether or not a compulsory licence was involved. Due to the fact that by 2005 all nations besides the least developed ones must be TRIPs compliant, their options for obtaining affordable, high-quality vital medications will be even more limited. Again, there are no specific instances of this having been used effectively to date, but it is difficult to see how this will be a viable option for nations who are in desperate need of a treatment to explore.

Parallel importation - The idea of parallel importation has also been put out as a way to increase access to important medications. In this arrangement, a supplier in country B provides nation A with a (legally marketed) version of the product of interest in addition to, or in instead of, the identical product from the primary source since the drug is more reasonably priced there than it is elsewhere. The rights of nations to pursue this option are expressly acknowledged in Article 6 of TRIPs and Paragraph 5(d) of the Doha Agreement. Oxfam has proposed a two-tier structure with separate parallel import rules for wealthy and poor nations, but this idea has encountered both political and practical opposition. Regarding the registration of goods acquired for supply through parallel imports, there may be two strategies.

Data exclusivity and patents - The problem of data exclusivity has surfaced as another possible obstacle to expanding access to vital medications. It is addressed in TRIPs (Article 39.3) and results in a five-year ban on using innovator dossier information on an NCE for generic applications in the US and between eight and eleven years in Europe35. This restriction is applicable regardless of the patent's status, therefore these applications cannot rely on innovator data regarding bioavailability, efficacy, or safety (since it cannot be accessed legally). This restriction may require a generic manufacturer to do bioavailability studies using the original manufacturer as a comparator and clinical trials proving the efficacy and safety of the generic version of a product. The US and Europe will increasingly employ this method, notably through bilateral trade agreements, to completely avoid the application of TRIPs flexibilities, according to a number of experts during the past year. Alternative methods for trial design and drug registration should be further considered in this regard.[12]

Challenges related to Industrial Perspective - A study on digital innovation in regulatory submissions in the pharmaceutical industry was recently examined and released in May 2021. The authors emphasized a variety of opportunities and challenges in the regulatory submission process, focusing on the premise that static, PDF-locked papers provide specific difficulties for automation, dynamic access and review of data, and intelligent analysis of data. This article builds on previous discussions and promotes the use of technology to

modernize the conventional methods for organizing and obtaining the crucial data from the enormous amount of data generated and examined while making regulatory judgments. The potential and developments for automating CMC data for pharmaceutical regulatory submissions to health authorities are particularly underlined. Due to the fact that CMC data can be automated, this article will present guidelines and procedures that can later be used with different datasets, such as pre-clinical and clinical data. In the parts that follow, an industry perspective on the structure and challenges of these regulatory submissions will be presented.

Challenges in Responses to Questions from Health Authorities[13]

Obtaining health authority clearances adds another layer of complication, and sponsors and health authorities alike face new obstacles as a result of information requests. After an initial submission, it can be challenging to obtain responses to a health authority's information requests because the turnaround time for responses varies by area and is typically only a few days. Lastly, because the embedded raw data is not readily available for additional analysis, the static PDF format of the CTD is ineffective for data mining and information exchange between the sponsor and reviewers. This causes a complicated array of submissions for each region and makes it more difficult to track specific CMC commitments with each health authority. Subsequent change controls including agency information requests and modifications to Module 3 are also made more difficult. Throughout the product lifetime, interactions with sponsors and health authorities and assessments call for quick access to data that is discoverable, accessible, interoperable, and reusable (FAIR).

Challenges in CMC Data Management

Narratives written by a big group of subject matter experts are highly relied upon to convey the volume of data that is there inside the hundreds of pages being generated for regulatory submissions. For narrative-based submissions, there may be a large number of authors, reviewers, and data verifiers.[13] This can increase subjectivity and cause inconsistency even within a single company's portfolio of products. Manual data translation, aggregation, verification, and mistake correction require a substantial amount of resources due to the data's inconsistent structure. It would be difficult to achieve the ultimate goal of submitting a single, unified worldwide filing with parallel evaluations because it depends on sponsors and authorities putting automated systems and data standardisation in place. The actions taken by health authorities to increase the effectiveness of their review procedures are discussed in the sections that follow. [13]

CONCLUSION:

The electronic submission equivalent of the CTD is the eCTD. The eCTD serves as a conduit between industry and government agencies for the exchange of regulatory data, facilitating the development, review, lifecycle management, and archiving of electronic submissions. All CTD information is included in the eCTD submissions. The Common Technical Document (CTD) may be electronically submitted from the applicant to the regulator, such as the USFDA or EMA, using the Electronic Common Technical Document (eCTD). The FDA defines the CTD as an information package containing clinical, non-clinical, manufacturing, and technical data that would be submitted for registration of novel pharmaceuticals in all three ICH regions, namely the United States, the European Union, and Japan. Compulsory license has been considered for drug registration requirements in South Africa. By 2005, there were fewer possibilities for obtaining affordable, high-quality necessary medications, yet industrialised nations were still required to comply with TRIPS. This article, which was mostly based on earlier discussions, recommends the use of technology to modernize the

current methods for organizing and extracting the pertinent data from the vast amount of data generated and analyzed during the regulatory decision-making process. The main emphasis is on the possibilities for and developments in automated data for CMC sections of pharmaceutical regulatory filings to health authorities. Sponsors and health authorities have additional challenges as a result of information requests, which make it challenging to obtain authorization from health authorities. Throughout the product lifecycle, quick access to data that is discoverable, accessible, interoperable, and reusable is required for discussions and evaluations between the sponsor and health authority.

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REFERENCE:

1. Sahitya, K. et al. (2020) 'Regulatory Pathway for Registration and Approval of Indian Drug Products in Overseas Market.' Journal of Pharmaceutical Science and Research., 12 (0975-1459), 1150- 1161. Available from: www. Just. Pharma info. In.
2. [Internet], (11), 1759-1768. Available from: www.wjpps.com. [28 October 2015].
3. Chowdary, K., and Ravi Shankar, K. (2015) 'CTD - A Critical Document for Dossier Submission: An Overview.' World Journal of Pharmacy and Pharmaceutical Science.
4. https://laszloletter.typepad.com/the_laszlo_letter/2007/02/ectd_software_v.html
5. https://www.appliedclinicaltrialsonline.com/view/global-regulatory-publishing-trends
6. eCTD Executive Paper FINAL 20-Dec-21 (efpia.eu)
7. https://premierconsulting.com/resources/blog/transitioning-to-ectd-v4-0/
8. https://www.docshifter.com/blog/what-is-ectd-4-0/
9. https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v40
10. https://www.freyrsolutions.com/blog/challenges-faced-by-life-sciences-companies-in-ectd-submissions
11. https://regulatoryinfo.org/challenges-faced-by-life-sciences-companies-in-ectd-submissions/
12. http://heart-resources.org/wp-content/uploads/2012/10/Emerging-challenges-and-opportunities-in-Drug-registration-and-regulation.pdf
13. KabirAhluwalia, Michael J.Abernathy, Jill Beierle, Nina S.Cauchon, DavidCronin, SheetalGaiki, AndrewLennard, PradeepMady, MikeMcGorry, Kathleen Sugrue-Richards GangXue The Future of CMC Regulatory Submissions: Streamlining Activities Using Structured Content and Data Management Journal of Pharmaceutical Sciences Volume 111, Issue 5, May 2022, Pages 1232-1244