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STUDY ON THE ROLE OF ECTD SUBMISSIONS IN EXPEDITING DRUG APPROVALS IN INDIA

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Abstract:

This topic aims at reviewing the drug filing and different aspects of obtaining United States Food & Drug Administration (USFDA) and European Medicines Agency (EMA) approval for a drug in order to get a Marketing Authorization in US & Europe and their effective role in improving the standards laid down by them. All new / generic drug products must be approved by the respective regulatory agency governing the respective market before a particular product can be introduced into the market. By law, all new drugs must first be shown to be safe and effective before they can be approved by the respective regulatory agency for marketing. USFDA is the regulatory agency which is responsible for safety regulation of the food and drug products in US. EMA is the regulatory agency/ decentralized body which is responsible for safety regulation of the food and drug products in Europe. Drug approval process in USFDA involves submitting of an Investigational New Drug Application, followed by submission of New Drug Application. The applications are reviewed and agency officials examine the drug's safety and efficacy data and the drug is approved. EU establishes 4 different drug approval processes:

1) Centralized Procedure
2) Decentralized Procedure
3) National Procedure
4) Mutual Recognition Procedure

Keywords: *Drug Approval, EMA, USFDA.*

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INTRODUCTION:

In his article titled "The Evolution of eCTD", Tim Felgate, Senior Manager of TOPRA and Managing Director of Applied Regulatory Consulting, writes: As recently as the 1940s, submissions to support the marketing of medicines were small single-volume dossiers containing fewer than 100 pages of data, most of which were manufacturing information.1 Since then a number of serious adverse reactions associated with the use of medicines have led to an extensive review of the regulatory framework for medicines. The most notable example of this was the tragedy associated with the use of thalidomide during pregnancy. Following this, most developed countries around the world introduced a raft of legislation that requires an extensive review of the safety, quality and efficacy of a medicine before it can be granted approval for placing on the market. This resulted in a sudden and dramatic increase in the volume of data that need to be generated and submitted to the regulatory authorities. Whereas, at the end of the 1950s a typical dossier for a new medicine would comprise two volumes of data at the most, just 10 years later this had increased to nearly 200 volumes.

With this increase in volume of data came a need to build tables of contents and cross-referencing tools to facilitate the navigation of the dossier. The remainder of the millennium saw dossiers increase further in complexity and size, and this has been accelerated by the harmonization that has taken place both within regions, such as the European Union, and across regions, driven by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Felgate believes the extent and complexity of the data required today have meant that the development program for new drugs has become a lengthy and expensive process, involving substantial preclinical and clinical studies.

In Wendy Hamilton's article titled, "E-Ticket to Global Harmonization," she suggests there is a critical need to share compliant regulatory, not only within the pharmaceutical enterprise but also across the globe, and this is driving new submission formats and transport specifications.2 According to Hamilton, organizational compliance can be achieved when every employee in a company can access the most current marketing application, for every product, and in every region. It is more than a compliance issue: The ability to share intellectual assets globally can be a critical competitive advantage. Yet, despite the billions of dollars invested in content management products, few life sciences companies report that kind of access to product information. The common technical document (CTD) and other initiatives to standardize regulatory information processing worldwide can potentially reduce costs and accelerate time-tomarket opportunities. But emerging formats, such as the electronic version of the CTD (eCTD) may also result in internal competitive benefits, such as knowledge management and organizational compliance. Hamilton believes, the ultimate goal for most pharmaceutical companies' regulatory operations is to minimize time to marketing approval while ensuring compliance. The typical pharmaceutical company's regulatory department processes thousands of documents a month, all part of applications for new drug marketing approval. It must also keep approvals current in dozens, even hundreds, of regions. Changes in a regulation, manufacturing process, and/or product indications for use can trigger an update to the original application to maintain compliance. And due to drug discovery, technology advances, licensing agreements, and productive corporate partnerships, the volume of marketing applications that needs to be processed and maintained-with the same set of regulatory resources-is rapidly growing.

In a FDA presentation titled, "Transitioning to eCTDs" some statistics regarding regulatory agency review trends was revealed:

- The FDA receives hundreds of applications for new drugs and medical devices annually -- each containing about 500,000 pages of information.
- It costs the FDA $32.67/second to review new applications.
- The current approval process averages more than 400 days, over twice the statutory limit of 180 days (this is about a 100 percent improvement from just a few years ago).3

These rapidly growing challenges to the regulatory landscape create a need to update regulatory submission technologies. The regulatory industry and agencies are always seeking methods to make regulatory compliance tasks more efficient. Because of the industry's obligation to remain compliant and the FDA's obligation to protect the health of the citizens within the United States, regulatory submission technologies have evolved tremendously throughout the past ten years. The introduction of the current electronic submission technology, eCTD and emerging technologies such as RPS (Regulated Product Strategy) has a far greater effect on the processes and people involved. These changes can be beneficial in one area, but pose numerous challenges in others. This study will examine the changes in regulatory submissions trends and analyze the

opinions of regulatory professional on their benefits and challenges.

Regulatory Submissions within the pharmaceutical industry have evolved tremendously over the past 10 years. These changes require that the regulatory professional continually stay abreast of new technologies mandated by regulatory agencies. The last two decades of the previous millennium saw an explosive increase in the accessibility of information technology. This has been greatly accelerated by the emergence of personal computers together with their rapid decrease in cost. The increase in connectivity afforded by the advent of the Internet has also made a major impact. Together these have provided valuable tools to assist in the process of assembling submission dossiers, drawing together data from multiple authors and locations almost instantly. Prior to the information technology revolution, dossiers were prepared, often in one location by a dedicated registration department. They used such tools of the trade as typewriters, scissors, glue and photocopiers. The arrival of the newer technologies has greatly facilitated the process.

Figure 1 illustrates the evolution of regulatory submissions.

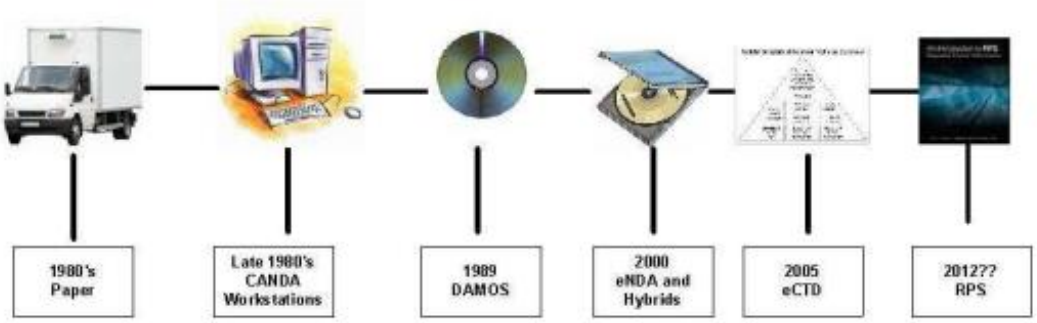

Figure 1: Regulatory Submissions Timelines

Paper

Regulatory submissions made to regulatory agencies, such as the FDA, have typically been prepared and submitted through a manual, paper-based process. Some the challenges with submitting in paper can include lifecycle management, tracking changes to documents, assembling the dossier and submitting the appropriate data. Oftentimes, paper submissions become so voluminous that they require cargo trucks for delivery to FDA. In an article written by Cathy Brode she writes:11 "The pure paper process of submitting a dossier to the FDA is undoubtedly a manual process." In most cases, regulatory affairs departments are responsible for the compilation and publishing of a submission. Often times they have little knowledge of the status of critical documents needed to make up the submission. Oftentimes it is the last hour before a deadline when a referenced document or report is turned into Regulatory Affairs by the clinical or pre-clinical departments. Once the document is delivered its format becomes an issue. How was it created? Will the section or volume of the submission have to be re-paginated due to the late inclusion or change? If so, will the table of contents have to be updated? After millions of dollars and human hours have been spent on developing a promising drug, it is hard to imagine that millions of dollars could be then be lost if there is a delay getting the submission into review. Brode believes the regulatory affairs department is ultimately responsible for piecing together years of related product documentation manually. Brode describes the paper compilation that takes place at her company. Many pharmaceutical products employ this same legacy process when compiling paper submissions. Brode describes the process as follows: First, documentation is received by Regulatory Affairs and sorted into volumes. Tabs and slip sheets are inserted and the volumes are paginated. Once paginated, the volumes are duplicated and each copy must go through a QC process. Cross references are inserted, tables of contents generated and each page must be hand stamped and signed by an authorized individual. Once all this is complete, each copy is bound and labeled. The headache of the inevitable last minute changes is immense as these must be cross-checked, page numbers and cross references must be updated and tables of contents retyped.

Figure 2 is a depiction of the tedious paper workflow, which can repeat itself multiple times, as documents, are changed.

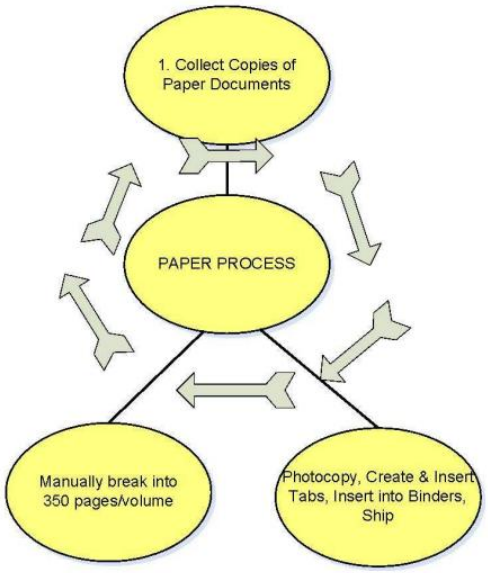

Figure 2 : Workflow for Paper Submissions

This process is resource intensive and costly when you factor in the copying of the thousands of pages and the binding into volumes. These then must be shipped to the agencies and stored for reference. Subsequently, submissions of the drug application to other agencies need to meet the individual agency regulatory requirements. This means that though most of the content will remain the same, the format of the content as well as the presentation will change.

If this is the case, this long manual process has to be repeated again. When the submission reaches the FDA, the key challenge is retrieval of information and navigation through the truckloads of paper. One of the major hurdles in the review process of a paper submission is cross references. For example, a reviewer may be reviewing a section that references another volume. If the reviewer needs to review the referenced volume, the volume must be physically retrieved. This referenced volume may not always be readily available as it may be in use by another reviewer.11 According to Brode, the FDA reported that for new drugs that gained marketing approval in 2002, the average time spent in review was about 18 months. For new biologics approved in 2002, it was about 30 months.11

DAMOS (Drug Application Methodology with Optical Storage)

The first standard for electronic submissions was DAMOS, Drug Application Methodology with Optical Storage, which began in 1989. This was primarily an image format (TIFF) for documents, delivered on optical discs (which predated CD-ROMs).12 The DAMOS standard solved the document exchange problem between pharmaceuticals manufacturers and health agencies successfully. First, it was accepted by the German health authority for a special case of the German health laws ("Vorlegung"), second it was accepted for general drug application submission in Germany, in Europe EMEA (European Medicines Agency) and in several European countries.13 The European Medicines Agency is a European agency for the evaluation of medicinal products.14 Unfortunately, DAMOS was never accepted by the Food and Drug Administration (FDA), reducing its overall impact. The US FDA did not accept the DAMOS standard because they developed their own electronic submission approach with a strong focus on the statistical data exchange. (The statistical data exchange is also part of DAMOS, but it was not the focus.) The FDA defined a document exchange standard, which was more practical for the then IT infrastructure.

CANDAs (Computer Aided New Drug Applications) and CAPLAs (Computer Aided Product Licensing Application)

According to an article written by Joel Finkle, an employee of Image Solutions titled “An Introduction to RPS, Regulated Product Submissions, starting in the late 1980’s, drug and biologics sponsors began delivering custom Computer Aided New Drug Applications (CANDAs) and Computer Aided Product Licensing Application (CAPLAs). These often included custom databases, document readers and imaging tools that required reviewer training for

each submission, and often a separate computer for each review of the Agency.13 This CANDA system consisted of a stand-alone personal computer running several commercial programs in Microsoft Windows to access both text and data. WordPerfect was used as the word processor that contained all the documents and data tables (in read-only format) that were submitted in hard copy, and Andyne GQL was used as a tool to query the data in an Oracle relational database. Microsoft Excel was provided as a spreadsheet for graphics and analysis of data. Documents appeared virtually identical to those in the hard copy NDA submission. Searching the text was facilitated by the use of buttons on the screen, which allowed the NDA to be searched for a particular term.15 Data could be located either in WordPerfect documents, or in an Oracle database (using Andyne GQL) by querying the data. The data queries could be performed ad hoc, in which the reviewer selected all the parameters for a search, or with predefined query buttons, which retrieved data for principal treatment-related changes. This type of system also could serve as a useful model for both in-house nonclinical review and the submission of INDs and IND amendments.

The custom built CANDA systems had the advantages of bringing up-to-date computing power while enabling close interaction between the sponsors and reviewers.15 The biggest disadvantage of CANDAs was the huge cost in training and IT support, not to mention the logistics of a single reviewer needing space for a large-screen monitor for each sponsor-delivered system. 15 The introduction of this technology was a starting point for the implementation of electronic submissions. However, there was still a need to refine this technology so that it was more cost-efficient and less labor intensive. Companies that had limited financial resources were unable to realize any advantages to implementing this technology.

eNDAs/Hybrid Submissions

Electronic New Drug Application is the predecessor for electronic common technical document. This submission type, also referred to as hybrid submissions, possesses a specialized folder structure. The Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – NDA" was finalized in January 1999.16 According to this guidance, applicants have the option to provide archival copies of the submission in electronic and/or paper. In this format, applicants were also required to provide a review copy of the technical sections.16 One of the advantages of this submission type was that applicants could reduce their usage of paper by providing the majority of documents in electronic format. One of the disadvantages of this format was the wide variances across review divisions and FDA regulatory project managers. According to the guidance, review divisions could use their discretion in their requirements for a review copy. Some review divisions may require all paper, while others require electronic.

eCTDs (Electronic Common Technical Document)

The electronic Common Technical Document (eCTD) is an interface for industry to Agency transfer of regulatory information, while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archiving of the electronic submission. The content is based on the Common Technical Document (CTD) format.17eCTD was developed by the International Conference on Harmonization (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). As of January 1, 2008, the U.S. Food and Drug Administration announced that the eCTD is the preferred format for electronic submissions.18 To date, over 80,000 eCTD sequences have been submitted to the FDA. Although the agency has not released an expected target date, the FDA revealed during the 2009 DIA Annual Meeting that it is looking at draft legislation to require eCTD for all data and file submissions.19 According to Nancy Smekanavich, Vice President, Global Regulatory Affairs for Octagon Solutions, the eCTD poses many benefits and challenges. Some benefits include document standards, the ability to easily navigate through dossiers and reduction of process time in the FDA document room. However, some challenges encountered include lifecycle management (the process of managing the entire lifecycle of a product from its conception, through design and manufacture to service and disposal), appropriate usage of leaf titles (names used to identify each document within the submission) and study tagging files (metadata that identifies all of the files associated with a study). Even though there are many challenges, Smekanavich believes that the benefits far outweigh the challenges.20 Analysis of previous work done and independent research in this study will further evaluate this opinion.

The eCTD is the first electronic submission format that is global and applies to both updates and original applications. The eCTD uses a unified format that works well for multiple marketing applications over time. It eliminates several barriers to reuse, including the need to format and present the same content in different ways for different regions. Also, it can manage small, reusable content components. The key

to those benefits is a small electronic data file included with the eCTD, called an XML backbone. That data file inventories the submission's contents and provides rich metadata about each physical file submitted. Anything is better than paper, says Nancy Smerkanich, VP Global Regulatory Affairs for Octagon Research who sums up a widely held opinion in industry. "Just being able to pull up a 3-year old investigational new drug (IND) application and look at it in a current view, as well as, a historical view with a couple of clicks is an enormous advance over spending hours in a file room looking through boxes, pulling out volume after volume – in some cases hundreds of volumes."21 As of January 1, 2008, eCTD standard is the only acceptable format for new electronic submissions to CDER.22 Paper submissions are still accepted by the Agency, but not preferred.23

eCTD Specifications

The eCTD essentially consists of an XML file (index.xml), a file structure, and a (rather large) number of PDF files (but also some other XML files). The XML file (the backbone) describes the file structure (so the location of all other files), checksums for these files (to guarantee integrity of the files) and meta-information about the files (version, operation status, role, keywords ...)24 The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

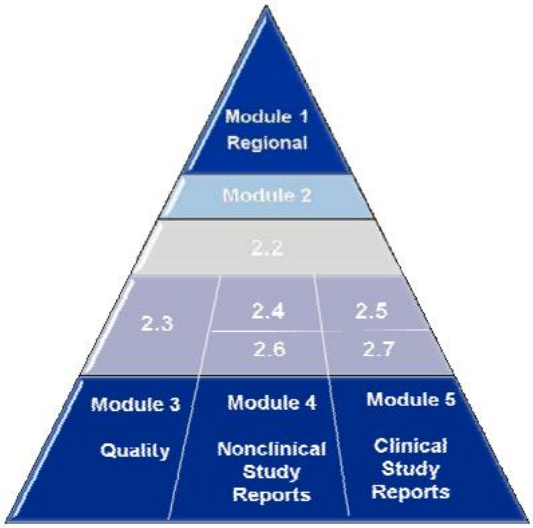

Figure 3: ICH CTD Structure

Module 1 contains Administrative and Prescribing Information. This module contains information specific to the region to which the dossier is being submitted. The relevant regulatory authorities specify the content and format of this module.20 Module 1 of the eCTD (regional information) further contains 3 additional XML files (for each region). These contain meta-information (e.g. applicant, product, submission date ...), and links to the files with the actual submission information.20

Module 2 contains summaries and overviews of the 3 CTD technical sections: Quality, Safety and Efficacy. The organization of these summaries is described in separate guidance documents for each discipline (Quality, Safety and Efficacy).20

Module 3 contains information pertinent to the Quality of the pharmaceutical (drug or biologic) substance and product. This consists of information concerning the Chemistry, Manufacturing and Controls of the drug/biologic substance and product.20

Module 4 contains information on the nonclinical (pharmacological, pharmacokinetic and toxicological) evaluation of the drug/biologic substance and product. This information is typically provided in the form of study reports and publications.20

Module 5 contains information on the clinical evaluation of the drug/biologic product. This module typically includes Clinical Study Reports describing each conducted clinical study. Supportive publications are also provided here. In addition, in U.S. submissions, datasets and Case Report Forms (CRFs) are provided in Module 5. Modules 4 and 5 are organized by study tagging files. In order to help identify all of the files associated with a study, information is needed for each document this includes the document title, subject matter (defined by the headings under which the documents are located in the table of contents), relationship to other documents (e.g., all documents for a specific study report are related to one another), revision information (i.e., new, replace, delete, append), the location of the document and information on the sequence that is included the document. The eCTD backbone files (e.g., index.xml and us-regional.xml) include many of those informational items. However, the eCTD backbone files do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory uses. This additional information is provided in the STF (Study Tagging File). An STF is to be provided with the submission of any file, or group of files belonging to a study in Modules 4 and 5. STFs are required by the United States; however, they are not required in Europe and are not allowed in Japan because their data tabulation dictionaries do not support the xml files. The STF provides for additional heading elements and heading attributes not currently provided by the eCTD DTD (Data Tabulation Dictionary). In the STF, heading elements are called file-tags and are included in the doc-content element. Heading attributes are included in the study-identifier element.

In a presentation by Virginia Ventura, Supervisor, Electronic Submission Support Team titled "Study Tagging Files: Their Vital Role in Submissions to the FDA", she explained the roles of the STF are to: 25

• Organize study information into meaningful, standardized headings
• Allow reviewer to quickly understand what has been submitted and what has not
• Guide reviewer to specific documents they are looking for
• Provide consistency over the lifecycle of the regulatory application

Advantages of Ectd

eCTD has many advantages to industry over paper submissions. They reduce the need for paper documentation. Hyperlinks and bookmarks make it easy to navigate through the dossier. Documents are submitted only once with future amendments cross-referring to information in previous eCTDs; and it is also much easier to copy sections of a dossier to adapt for specific country requirements. In an US eSubmissions update presentation by Gary Gensinger, he mentioned some of the advantages of transitioning to eCTD by FDA which includes support to complete more comprehensive reviews, provides reviewers a more efficient and effective review process, promotes standardization within the Agency and promotes operational efficiency.

A Global Solution

The eCTD is the first electronic submission format that is global and applies to both updates and original applications. The eCTD uses a unified format that works well for multiple marketing applications over time. It eliminates several barriers to reuse, including the need to format and present the same content in different ways for different regions. Also, it can manage small, reusable content components. The key to those benefits is a small electronic data file included with the eCTD, called an XML backbone. The XML file is a data file which provides an inventory of the submission's contents and provides rich metadata about each physical file submitted. eCTD provides a structure for simultaneous global drug marketing application submissions to the United States, the European Union, and Japanese regulatory authorities. In practice, companies adopting the CTD format have been able to create a second marketing application, months sooner than before. Thus, for a blockbuster product, that can mean bringing in revenues of $1 million a day that much sooner.2 In the Suchanek study, 5 out 8 experts agreed that an advantage of eCTD is the ability to reuse data.9

Cost Savings

Cost savings is one of the main items projected as a benefit in the business case for industry to switch from paper to eCTD submissions. The pictures below depict the cost savings associated with printing a paper submission. The picture to the left is a 664 volume paper submission prepared to submit to EMEA (European Medicines Agency). This submission equaled about 265,500 pages and printed costs equaled thousands of dollars. Shipping costs equaled thousands more dollars. On the other hand, the picture on the right depicts an eCTD submission containing the same 664 volume submission. Printing and shipping cost were virtually eliminated. The only cost for submitting this same application was the price for two DVDs (approximately $5.00) and 4 pieces of paper containing the cover letter (approximately $.04). In the Suchanek and

Ostermann study, 6 out of 8 experts agreed that one of the advantages of transitioning to eCTD was less paper, handling logistics and archiving costs. Karl HeinzLobel, Head of Regulatory Operations of Pharmalex, stated the reduction in paper, led to a reduction in costs for binding and assembling.

Figure 4 Before Photo (Paper Submission) After Photo (eCTD Submission)

Storage space has also been a growing concern for those at the FDA. If the average amount of pages of a typical new drug application is around 500,000 pages and there are hundreds of application received annually, storage issues are becoming more and more costly over the years. In a presentation by Virigina Ventura, she posts a picture of one of many FDA storage rooms. The room is overflowing with volumes of applications and this lack of space continues to be a growing problem for the FDA. In this presentation and many other FDA presentations, the FDA continues to stress their desire to receive electronic submissions over paper, with storage space being a major factor fueling this recommendation. In a presentation by the FDA, there were many benefits realized through the use of the FDA electronic submissions gateway by industry for regulatory submissions.

The Food and Drug Administration (FDA) Electronic Submissions Gateway (ESG) is an Agency-wide solution for accepting electronic regulatory submissions. The FDA ESG enables the secure submission of regulatory information for review. Most of the benefits realized were associated with cost savings. Some of these benefits include:

• Reduced hardware/software costs and resources associated with media creation
• Reduced costs associated to processing, tracking and archiving paper
• Eliminated paper output
• Obviated need to burn CDs/DVDs or to create tapes
• Eliminated courier and overnight shipping fees associated with regulatory submissions

• Eliminated need for Docutech printer

Michael Fauntleroy, from the FDA, performed a cost comparison which compared the usage of traditional media versus submitting through the electronic submissions gateway across 1500 submissions. This comparison shows a cost savings in operating cost by $80,184.23.

Time Savings

The depiction in Figure 4 represents a significant cost savings that can be realized when switching from paper to eCTD submissions. However, it's important to evaluate time savings to the industry. Although there may be significant savings on printing and shipping costs, are there time savings realized. Time can be a huge contributor to the overall costs of building a submission. Pharmaceutical, biotechnology and medical device companies that market blockbuster products can earn over $1 billion dollars per year once their products are approved for sale by the United States Food and Drug Administration (FDA). Approval by the FDA can result in rapid entry to market on a global level. Companies can invest $1 billion dollars or more over the course of the discovery, research, and development phases of their product candidates.2 Patent protection can be extended minimally by certain strategies of the developing company.

Once patents expire generic products can enter the market at a fraction of the development cost and receive the same reimbursement rates of the original products. These factors mean that speeding time to market results in both competitive and financial benefits to the company that reaches the market first. According to Terri Booth-Gene, Senior Director of Global Regulatory Submissions, Wyeth submits everything in eCTD that FDA is able to accept. She states, Wyeth set about converting all of its drug

applications into eCTD format. “By the end of 2007, all of our active U.S. files were in eCTD.” The following year, Wyeth converted all of its European marketing authorization applications (MAA) to eCTD format. That effort is paying dividends. Currently, there is just a 1-4 week lag between Wyeth's U.S. and EU submissions; prior to the eCTD initiative, Booth-Genthe says the gap between submissions was often 6-12 weeks.

Time savings is one of the biggest advantages to eCTD realized by the FDA. In the Suchanek and Ostermann study, 4 out 8 experts noted ease of dossier navigation as an advantage of eCTD. With paper submissions, multiple volumes of paper are submitted to the Agency. When cross references are made to other volumes, the reviewer must locate that particular volume to continue their review. If that volume is currently in use by another reviewer, others would have to wait until that reviewer is complete to continue. This created a huge issue in review times. With the adoption of eCTD, the application is uploaded to a central server. Each application contains electronic navigational aids such as bookmarks and hyperlinks which take the reviewer to the appropriate location at the touch of a button.

Reviewers can review the application concurrently and can even perform their reviews while telecommuting or away from the office. This can be done by logging into a central server and completing the review. This proves to be a significant time saver in the application review process.

Disadvantages to eCTD

Regulatory agency officials' assessments of the value of eCTD are mixed. Quoted in a recent issue of the Pink Sheet, John Jenkins, MD, director of FDA's office of new drugs, minimized the value of electronic submissions by suggesting they simply shift the cost burden of printing to the agency. He also noted that FDA carries additional costs because it currently must maintain both electronic and paper application processing systems.

On the other hand, agency presentations encourage the usage of eCTD and mentions very few disadvantages in the eCTD format. In the Suchanek and Ostermann study, there were several disadvantages identified. 5 out of 8 experts identified implementation/migration training costs as a challenge. 4 out of 8 experts mentioned insufficient eCTD standards as a disadvantage. According to Karl Heinz-Lobel, this is a disadvantage because there is a tendency for some agencies to make their own interpretation of eCTD specif cations. 3 out 8 experts agreed that one-way communication is a disadvantage of eCTD, Harv Martins of Extedo agreed that oneway communication is a disadvantage because it does not inherently support reviewer’s comments and annotations.9 The next couple of sections will explore more disadvantages in greater detail.

Granularity

Granularity refers to the level of hierarchy of the folders and files in the eCTD directory tree or the smallest unit of detail within the eCTD tree structure. 26 Companies are troubled by the effort to make documents more granular to support the eCTD format. The data file component is new, different, and requires a technology investment to produce. Companies must also make process changes to adapt to, and take advantage of, those new paradigms. All that adds up to an investment that many life sciences companies are hesitant to make when there were no time guarantees for reviewer acceptance of eCTDs.2 According to Karl-Heniz Lobel, the rather stringent eCTD specif cations do restrict f exibility in the organization of documents in certain cases (granularity aspects) and require a certain submission pattern (e.g. consecutive variations of different types, communication with agencies outside the eCTD, handling of national translations) that does not always f t regulatory requirements.

Lack of Experience

According to a description of regulatory training course offered by RAPS27, all regulatory authorities who receive eCTD submissions are reporting serious problems with lack of compliance with the electronic format and difficulty navigating the electronic files that comprise an eCTD. These issues are preventing reviewers from effectively conducting their reviews. This includes the correct usage of templates and document navigability. According to an article written by Shylendra Kumar of DataFarm, Inc, he states that knowledge plays an important role. Lack of understanding about CTD, eCTD, what it is and what it does makes it very difficult to appreciate the advantages. Some people are purely intimidated by the new technology and buzz words such as XML, XSL, DTD, and so on. The companies that have followed a ‘wait and see’ policy have, to some extent, benefited – they simply haven’t had to deal with the early implementation issues.28 According to Ted Hanenbach in the Suchanek and Ostermann study, there is a necessity to re-train existing staff, or acquire human resources with new set of skills. Antoinette Azevedo mentions, there is also a lack of qualified operators of eCTD publishing software.

Product Lifecycle

Dr. Andrew Marr, Director of electronic documentation in European regulatory affairs for GlaxoSmithKline, says, "Currently, one of the greatest obstacles to the eCTD is managing all of a product's lifecycle documents.2 According to the Suchanek and Ostermann study, one of the biggest disadvantages identified is the stringent eCTD format which does not provide much leverage in the product lifecycle and metadata. As changes occur across the product lifecycle, such as manufacturing changes, this is somewhat challenging to reflect in the eCTD structure. The granularity chosen at the beginning of the product lifecycle can prove to be a challenge throughout the product lifecycle.

THE FUTURE OF ELECTRONIC REGULATORY SUBMISSIONS

Regulated Product Submission (RPS) is a Health Level Seven (HL7) standard designed to facilitate the processing and review of regulated product information. RPS is being developed in response to performance goals that the U.S. Food and Drug Administration (FDA) are to achieve by 2012, as outlined in the Prescription Drug User Fee Act (PDUFA). The project to develop a regulated product submission standard was initiated on June 22, 2005.29 RPS is in many ways comparable to the electronic Common Technical Document. Ideally, the FDA would like to implement RPS as the next iteration of eCTD. The idea behind RPS and ICH's eCTD is the same—the use of a standardized format for regulatory submissions, including PDF documents and SAS datasets. Although document contents are the same for eCTD and RPS, the internal XML structures are very different.29 In addition to the U.S., regulatory agencies from Europe, Canada, and Japan are at varying levels of interest and participation. Currently, the second release of RPS is in development. RPS is being developed in response to performance goals by the FDA, however, one of the primary business cases for this initiative is due to the number of limitations within the eCTD specifications. One of the primary goals of RPS is to have a single submission format for all FDA divisions that require regulated product submissions. RPS will offer three obvious advantages over eCTD.13 The first advantage is the ability of the FDA to receive electronic submissions in most divisions that receive submissions. The FDA receives numerous submissions that address a variety of regulatory issues. The information contained in these submissions is divided into large numbers of files, both paper and electronic. Often, files in one submission are related to files in earlier submissions. Because the information is divided into numerous files sent over time, it can be difficult to efficiently process and review the information. eCTD is currently only specified for use in pharmaceutical submissions. RPS can be specified for multiple submission types.13 Secondly, RPS will establish two-way communication between the submitter and all FDA-regulated product centers within the agency.

Currently eCTD does not allow two-way communication. Sponsors can send information to the Agency electronically, but responses from the Agency are still received on paper. This proves to be difficult to a regulatory professional when attempting to track Agency responses to regulatory submissions. 13 Thirdly, RPS will manage the life cycle of submissions by allowing crossreferencing of previously submitted information. This means that for electronic Investigational New Drug (IND) applications, New Drug Applications (NDA), and biologics license applications (BLAs), information will need to only be submitted once and previously submitted electronic documents can be applied to marketing applications. With RPS, archived electronic IND, NDA, and BLA submissions will be retrievable through standardized automated links. eCTD lacks this cross-referencing capability.13 The updates outlined in the business case for RPS should alleviate some of the disadvantages associated with eCTDs. However, is eCTD and RPS advantageous as projected? And will RPS really improve the shortcomings of eCTD? Independent research conducted within this study will seek the answers to these questions.

Previous work conducted in the area of studying electronic regulatory submissions trends has been collected in a yearly quantitative survey conducted by Thomson Scientific This series of studies captures trend data on Technology usage, Document Management System usage, Regulatory Outsourcing, and use or future use of the eCTD and RPS standard5, ,6 7. The Thomson survey in 2007 concluded, three-fourths (76%) of respondents plan to migrate to eCTD, and those planning to migrate within 3 months increased significantly from 4% to 26%. However, this study failed to reveal why a significant number of respondents planned to move to eCTD. It also failed to capture qualitative data on the benefits and challenges of eCTD and the industry's opinions of the transition to eCTD.

The Suchanek and Ostermann study captured good qualitative data on the benefits and challenges of eCTD. The Suchanek and Ostermann Study showed consensuses among eight experts that the advantages outweigh the disadvantages. However, the survey

mechanism used was the Delphi method which gathered opinions from eCTD experts. The majority of respondents were self-employed eCTD consultants who were paid to train companies on eCTD specifications. There was a need to obtain additional qualitative and quantitative data from a larger population of regulatory professionals..

AIM AND OBJECTIVE

Aim:

To evaluate the role and impact of Electronic Common Technical Document (eCTD) submissions in expediting drug approval processes in India by assessing their contribution to regulatory efficiency, review timelines, submission quality, and overall effectiveness within the Central Drugs Standard Control Organization (CDSCO) framework.

Objectives

To examine the structure and regulatory framework governing eCTD submissions in India and their alignment with international standards such as ICH guidelines.

To analyze the influence of eCTD submissions on drug approval timelines, including dossier validation, review cycles, and communication efficiency between applicants and regulators.

To compare traditional paper-based or non-eCTD submissions with eCTD formats in terms of documentation accuracy, lifecycle management, and regulatory review efficiency.

To assess the benefits of eCTD implementation for stakeholders, including regulatory authorities, pharmaceutical companies, and patients in terms of transparency and faster access to medicines.

To identify key challenges and barriers faced by industry and regulators in adopting eCTD submissions in India, including technical, infrastructural, and training-related issues.

CONCLUSION:

The adoption of Electronic Common Technical Document (eCTD) submissions represents a significant step toward modernization and digital transformation of the drug regulatory system in India. By enabling structured, standardized, and fully electronic dossier submissions, eCTD has the potential to streamline regulatory workflows within the Central Drugs Standard Control Organization (CDSCO), reduce administrative burden, and improve the overall efficiency of the drug review process. Compared to traditional paper-based or non-standardized electronic submissions, eCTD facilitates faster dossier validation, improved document navigation, efficient lifecycle management, and enhanced communication between applicants and regulators.

The study indicates that eCTD submissions can contribute to expediting drug approvals by enabling parallel review processes, minimizing documentation errors, and enhancing transparency and traceability of regulatory information. The digital format supports more effective collaboration among reviewers and reduces delays associated with manual handling of documents. Additionally, alignment with internationally recognized ICH standards promotes regulatory harmonization, strengthens India's global competitiveness in pharmaceutical regulation, and facilitates smoother submissions for companies operating across multiple jurisdictions.

However, the effectiveness of eCTD implementation in India depends on several critical factors, including robust digital infrastructure, clear regulatory guidance, skilled human resources, and industry readiness. Challenges such as limited technical expertise, costs associated with transitioning to electronic systems, and the need for continuous training and system upgrades may slow widespread adoption. Addressing these challenges through capacity-building initiatives, standardized national policies, and stakeholder collaboration will be essential for maximizing the benefits of eCTD.

In conclusion, eCTD submissions hold substantial promise for expediting drug approvals in India by enhancing regulatory efficiency, reducing review timelines, and supporting a transparent and globally aligned regulatory environment. With sustained investment in digital capabilities and regulatory harmonization, eCTD can play a pivotal role in improving access to safe, effective, and high-quality medicines for patients while strengthening the efficiency and credibility of India's drug regulatory framework.

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