"THE HISTORY OF ELECTRONIC REGULATORY SUBMISSIONS TECHNOLOGIES: A FOCUS ON ECTD (ELECTRONIC COMMON TECHNICAL DOCUMENT) AND ITS CHALLENGES AND BENEFITS"

by

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(Under the Direction of Paul Brooks)

ABSTRACT

The year 2009 marked the 10th Anniversary of electronic regulatory submissions within the pharmaceutical industry. Typically new technologies are introduced to meet business needs of industry and regulatory agencies, which in turn benefits the consumers. However, in many cases implementing new technologies does not necessarily initiate improvements, but 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. The purpose of this study is to analyze electronic regulatory submission trends and to gather information on the benefits and challenges to the life sciences industry and regulatory agencies; through the analysis of existing studies and the execution of an independent study. Previous studies concluded that the benefits of eCTD far outweighed its challenges; however, this study reveals that the margin between the benefits and challenges is not as large as purported.

INDEX WORDS: Regulatory Submissions, Electronic Common Technical Document, (eCTD), Food and Drug Administration (FDA), Regulated Product Submission (RPS), Pharmaceutical

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DEDICATION

I would like to dedicate this thesis to my mother, husband and beautiful daughter, Legacy.

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I would like to first give thanks to God, without him I am nothing, with him, all things are possible. I would like to give thanks to my family for being patient through this entire process because there were many nights without dinner, help with homework and undivided attention. I would like to thank my thesis advisor Dr. Paul Brooks and my advisory committee, Dr. Tony Capomacchia and Dr. David Mullis for their unwavering support and patience. I could not have done this without you all.

TABLE OF CONTENTS

Page
ACKNOWLEDGEMENTSv
LIST OF TABLES viii
LIST OF FIGURESix
CHAPTER
1 INTRODUCTION
1.1 Introduction1
1.2 Purpose of Study
2 LITERATURE REVIEW – HISTORY OF ELECTRONIC SUBMISSIONS
2.1 Paper7
2.2 DAMOS (Drug Application Methodology with Optical Storage)9
2.3 CANDAs (Computer Aided New Drug Application and CAPLAs (Computer
Aided Product Licensing Application)10
2.4 eNDAs/Hybrid Submissions11
2.5 eCTDs (Electronic Common Technical Document)12
2.6 THE FUTURE OF ELECTRONIC REGULATORY SUBMISSIONS23
3 METHODOLOGY
3.1 Introduction
3.2 Independent Survey Methodology
4 RESULTS AND CONCLUSIONS

	4.1 Thomason Scientific Regulatory Trends Survey Results	
	4.2 Suchanek and Ostermann Study Results	
	4.3 Independent Survey Results	41
	4.4 Study Analysis and Conslusions	48
REFEREN	ICES	52
APPENDI	CES	
А	Sample Survey Questions	55
В	Independent Survey Results	57
С	Sample Email Request	63

LIST OF TABLES

Table 1 Response Values for Survey Question Three	. 32
Table 2 Response Values for Survey Question Seven	. 34
Table 3 Advantages and Disadvantages in the Suchanek and Ostermann Study	. 40
Table 4 Disadvantages of eCTD According to Question 8	. 47
Table 5 Reasons that eCTD May Decrease Review Times	. 47
Table 6 Potential Advantages of RPS Question 10	. 47

LIST OF FIGURES

Figure 1 Regulatory Submissions Timelines	6
Figure 2 Workflow for Paper Submissions	
Figure 3 ICH CTD Structure	14
Figure 4 Before Photo (Paper Submission) After Photo (eCTD Submission)	17
Figure 5 Comparative Costs Projections for FDA Submission Gateway	19
Figure 6 Sample Size and Confidence Interval Calculations	
Figure 7 Response Rate Calculations	
Figure 8 Years of Experience of Survey Respondents	
Figure 9 Years of Experience Respondents' Companies Has with Submitting eCTDs	
Figure 10 Tools that Regulatory Professionals Use to Stay Abreast of Regulatory Requi	rements 44
Figure 11 Regulatory Agencies that Respondent Typically Make Submissions	
Figure 12 Regulatory Agencies that Respondent Typically Make Submissions	
Figure 13 Challenges to Submitting in eCTD Format	
Figure 14 Cross Tabulation of Questions 1 and 6	

CHAPTER 1

INTRODUCTION

1.1 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.² 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.

1.2 Purpose of Study

The purpose of this study was to analyze electronic regulatory submission trends and to gather information on the benefits and challenges to the life sciences industry and the FDA. The FDA is an agency of the US Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs

(medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.⁴ The benefits and challenges to the life sciences industry and the FDA will be examined by analyzing the results of previous studies and examining the results from an independent survey. Previous work conducted in the area of studying electronic regulatory submissions trends has been captured in a yearly quantitative survey conducted by Thomson Scientific.^{5,6,7} Thomson Scientific is a company that provides information-based solutions for the academic, business and R&D communities.⁸ This survey was last conducted in 2008 and has been administered for the past four years. This annual survey is titled, "Regulatory Affairs Trends Survey" and its sole purpose is to provide insight into the emerging and future trends of regulatory project management needs for the life sciences market. The survey averages about 400 respondents worldwide and concentrates on four key areas: (1) Technology Usage Trends, including both submission publishing software and other desktop software: (2) Document Management System usage: (3) Regulatory Outsourcing trends; and (4) Regulatory trends including use or future use of eCTD and HL7 Regulated Product Submission (RPS) standard.^{5,6,7} Although the results from the regulatory trends survey provide good quantitative data on the increased usage of electronic submission software, it does not provide data on the benefits/challenges associated with electronic submissions and whether improvements in regulatory submissions technologies has increased efficiency in industry and regulatory agencies workflows. Other previous work conducted in this area was a study titled, " Evaluating the Process of the Pattern Change from Paper based to Electronic Submissions to Medicinal Products" by Andreas Suchanek and Dr. Herwig Ostermann.⁹ This study summarizes findings from social research done via email to collect eight international experts' opinions on the change from paper-based to eCTD

submissions and its advantages and disadvantages. The author's scientific approach in this study was an expert interview following the Delphi Method.⁹ The Delphi Method is defined as a systematic, interactive forecasting method which relies on a panel of experts. The experts answer questionnaires in two or more rounds. After each round, a facilitator provides an anonymous summary of the experts' forecasts from the previous round as well as the reasons they provided for their judgments. Thus, experts are encouraged to revise their earlier answers in light of the replies of other members of their panel. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer. Finally, the process is stopped after a pre-defined stop criterion (e.g. number of rounds, achievement of consensus, and stability of results) and the mean or median scores of the final rounds determine the results.¹⁰ The authors followed up the Delphi Method by online survey to obtain quantitative figures. This study captured valuable information on the advantages and disadvantages of eCTD, however, the opinions were gathered from eCTD experts. One of the criterions for selecting these experts is that they are consultants to pharmaceutical industry and agencies or are affiliated to vendors and/or members of standardization bodies. Although these experts have a wealth of eCTD experience, because they are consultants or proponents of eCTD, their opinions had the potential to be influenced by their affilations within the industry and their expert level of eCTD knowledge. This study seeks to evaluate the evolution of electronic regulatory submissions; explore how the newest technology, electronic common technical documents, has improved the regulatory submissions process; and, investigate emerging regulatory technologies for the future. This will be achieved by evaluating previous studies on regulatory submissions trends and examining the unbiased opinions of regulatory professionals that work for companies that have adopted eCTD as their method of submitting to regulatory agencies.

CHAPTER 2

LITERATURE REVIEW - HISTORY OF ELECTRONIC SUBMISSIONS

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

2.1 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

2.2 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.

2.3 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.

2.4 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.

2.5 eCTDs (Electronic Common Technical Document)

2.5.1 Introduction

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

2.5.2 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 5.²⁰ 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

2.5.3 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.

2.5.3.1 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

¹⁶

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

2.5.3.2 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 Heinz-Lobel, 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)







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. 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 This cost savings is depicted in Figure 5.



Figure 5 Comparative Costs Projections for FDA Submission Gateway

2.5.3.3 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.

2.5.4 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 one-way 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.

2.5.4.1 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.

2.5.4.2 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.

2.5.4.3 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.

2.6 THE FUTURE OF ELECTRONIC REGULATORY SUBMISSIONS

2.6.1 Introduction

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 different²⁹ 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.

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

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 standard^{5,6,7}. 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..

To further supplement data from the Thomson and Suchanek and Ostermann studies, an independent survey, which is described in this thesis, was designed to obtain
opinions by respondents from the pharmaceuticals industry regarding: (1) the benefits and challenges of transitioning to eCTD, (2) the regulatory efficiencies of eCTD and (3) the benefits of the emerging electronic regulatory submission technology, RPS. The independent survey was designed to determine: When eCTD format is fully adopted by pharmaceutical companies and used to compile and submit regulatory submissions to the FDA, and if the benefits of transitioning to eCTD, significantly outweigh its challenges?

3.2 Independent Survey Methodology

3.2.1 Respondents

The sampling frame included regulatory professionals within the pharmaceutical industry, who were personal contacts of the researcher, and included fellow colleagues and members of industry forums. The majority of contacts were regulatory affairs colleagues that currently and previously worked at Abbott Products Inc., formerly Solvay Pharmaceuticals, Inc. A company and personal address book, compiled from over eight years of working as a Regulatory Submissions Specialist, consisting of approximately 150 contacts, was used to solicit respondents. These contacts were identified by the researcher, and according to the RAPS Development Framework White Paper, can be considered as Level II to Level IV professionals.³⁰ The remaining respondents were recruited for participation via four regulatory submissions social groups on the website www.linkedin.com. The social groups that were used included the eCTD Professional Network, eCTD Regulatory Submissions Network, eCTD Submissions and eLabeling Network, and RAPS Network. The respondents to this survey are regulatory affairs professionals that have experience with eCTD submissions. Typically, decisions to move to eCTD are made on a company-wide level and handed down from upper management.

Therefore, the goal was to obtain unbiased opinions from those that work on eCTDs submissions and do not necessarily have a vested interest in this submission format.

3.2.1.1 Inclusion and Exclusion Criteria

Approval for exemption from the University of Georgia Institutional Review Board (IRB) was received on 30 March 2010. Any research that involves human subjects is required to undergo review by an IRB to comply with regulations set by the Office of Human Research Protections and the FDA. The IRB application requires inclusion and exclusion criteria to be defined. Inclusion criteria are a set of conditions that must be met in order to participate in a human based research.³¹ Exclusion criteria are the standards used to determine whether a person may or may not be allowed to participate in a clinical trial or study. The inclusion criteria defined for this study is as follows:

- Must be a Regulatory Affairs professional
- Must work in the biotech industry and have at least six months of experience with making submissions to the FDA, EMA, Health Canada or Japan
- Must have participated or plans to participate in the review, approval, compilation or submittal of an electronic common technical document (eCTD) regulatory submissions to the FDA, EMEA, Health Canada or Japan
- Must have a general understanding of eCTD requirements and terminology
- Must have internet access to take electronic survey

The exclusion criteria defined for this study is as follows:

• Regulatory Affairs professionals that have less than 6 months of work experience in a regulatory affairs role

3.2.2 Sampling Size

Because the professional base for regulatory affairs within the pharmaceutical industry is relatively small, the goal was to obtain at least 50 respondents. This sample size was determined utilizing sample size and confidence interval calculators.³² The population of regulatory affairs professionals worldwide (12,000) was approximate based on the amount of members that belong to the RAPS organization worldwide.³³ The confidence interval was 95%, so the suggested sample size was 50 respondents. These figures can be found in Figure 6.

Determine Sample	e Size
Confidence Level:	©95% ©99%
Confidence Interval:	13.80
Population:	12000
Calculate	Clear
Sample size needed:	50
Find Confidence	Interval
Find Confidence Confidence Level:	Interval ©95% ©99%
Find Confidence Confidence Level: Sample Size:	Interval © 95% © 99% 50
Find Confidence Confidence Level: Sample Size: Population:	Interval • 95% • 99% 50 12000
Find Confidence Confidence Level: Sample Size: Population: Percentage:	Interval © 95% © 99% 50 12000 46.5
Find Confidence Confidence Level: Sample Size: Population: Percentage: Calculate	Interval © 95% © 99% 50 12000 46.5 Clear

Figure 6 Sample Size and Confidence Interval Calculations

The total number of responses received from the independent survey was 44. However, two respondent's responses were excluded due to lack of eCTD knowledge. Therefore the total amount of responses used in the study findings was 42. This resulted in a

response rate of 84%. This was determined utilizing the response rate calculation in Figure 7.

response rate = $\underline{number returned} \times 100$ number in sample

Figure 7 Response Rate Calculations ³⁴

3.2.3 Survey Design

For the independent survey, a web survey was created in Survey Monkey and used to capture data on the benefits and challenges of eCTD submissions. The interface used in Survey Monkey is user-friendly and provides tools to confirm response entry and help analyze survey results. The survey software used contained built-in validation tools that were used to ensure that respondents properly answered all questions. The tools allowed questions to be setup to accept single and multiple answers and provided identification of questions that were skipped by the respondent. The survey consisted of seven multiple choice questions and three open-ended or probing questions. The first two questions within the survey were designed as screening questions. They sought to exclude users that lack the required amount of regulatory and eCTD experience. Two respondent's responses were excluded from the survey results due the first two screening questions. The survey ran for approximately fourteen days and it took several months to fully analyze the data.

3.2.4 Questionna ire Design

There were several steps taken to develop the item pool of questions. The first step was to compile a list of questions that were asked in previous studies. To do this, a literature search was performed to find previous surveys performed in the area of

electronic submissions. A compilation of survey questions were taken from the Suchanek and Ostermann study and the Thomson Scientific Study for the years 2006-2008.^{5,6,7} The survey questions compiled from these studies ranged from current and future plans of eCTD usage to advantages and disadvantages of converting from paper to eCTD. The second step was to group the findings into quantitative and qualitative categories and determine if these findings could be used to further validate the study purpose which was to: Analyze electronic regulatory submission trends and to gather information on the benefits and challenges to the life sciences industry and the FDA.

Sample survey questions are provided in Appendix A. Questions One and two are screening questions that were recorded on a nominal scale. The highest frequencies were recorded first and ordered from highest (5 years or more) to lowest (None). This question were used to exclude respondents that have less than 6 months of regulatory and eCTD experience. In Questions One (How many years of experience do you have with submitting eCTDs?) and Two (How long has your company been submitting eCTDs?) there was only one response allowed.

In the evaluation of other studies, presentations and personal experiences, there was a direct correlation between regulatory professionals' experience between submitting eCTDs and positive opinions about its benefits. In other words, the less experience that one has with the tools needed to compile and publish in eCTD format, the more challenges they purport with eCTD format. This hypothesis was explored by comparing the frequencies in Questions one and two, to the frequencies in Questions six (Do you feel that eCTDs increase or decrease application review times by regulatory agencies?) and seven (Do you feel that eCTDs improve the time it takes to prepare and

transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company?) to develop a cross-tabulation diagram (Figure 14) to compare the results.

In Question three (How do you stay abreast of regulatory standards and technology?), multiple responses were acceptable. These data were used to further analyze the findings from the cross-tabulation diagram(Figure 14) and help address the hypothesis, regarding a direct correlation between experiences in submitting eCTDs and positive opinions about its benefits. Results from this question were intended to draw specific correlations between approaches regulatory professionals use to stay current and the affect that these approaches have on their opinions about eCTD benefits. The table below provides a key used to calculate the numerical values for each possible response and demonstrate how responses to Question three was added-up for each participant... There was a value of 1 point used for each method of staying abreast of eCTD requirements. Thus, if the respondent selected all of the options available (or all of the above) there is a total of 4 points assigned to that person. The sum of each value was be used to determine how respondents stay abreast of eCTD requirements.

	Regulatory Agency	Vendor- Industry	Industry Conference	Company Sponsored	All of the Above
	Guidances	Sponsored Webinars		Initiatives	
Yes	1	1	1	1	4
No	0	0	0	0	0

Table 1 Response Values for Survey Question Three

Questions four (What agency/Agencies do you make eCTD submissions to?) was used as an exploratory analysis to determine what Agencies respondents typically submit to and determine how this correlates with their views on the benefits of eCTD. In theory, respondents that submit to regulatory agencies that have larger volumes of eCTD submissions (FDA and EMEA), typically have more experience with this submission method. A preliminary hypothesis can be gathered based on these findings. If regulatory agencies receive larger volumes of eCTD submissions, respondents that submit to these agencies typically have more experience. When more experience is gained with regards to eCTD submissions, more submission metrics and lessons learned are produced. This in turn leads to a better understanding of how to successfully submit eCTD submissions, which may lead to a more positive view of its benefits. Questions four was used to analyze this theory.

Question five (What is the biggest challenge to in submtting eCTD submissions?) was used to identify the challenges associated with eCTD submissions. Multiple responses were acceptable for this question. It is a hypothesis of this study that challenges associated with eCTD submissions may be a direct result of the types of methods that respondents use to stay abreast of eCTD requirements. Thus, response values in Question three were used as a lens to explore responses to Question five. From this an analysis can be conducted to compare the methods that respondents are using to gain eCTD knowledge to areas they find most challenging. These findings can provide insight into whether these methods for gaining information are effective in the areas that respondents consider to be a challenge.

Questions six (Do you feel that eCTDs increase or decrease application review times by regulatory agencies?)will be used to identify the most important benefit to transitioning to eCTD, which is the regulatory agency review times. The responses were

used to determine if smaller benefits such as dossier navigation and less paper handling, lead to a decrease in review times. This question will be compared with the open-ended responses in Question nine (Why do you feel that eCTDs increase/decrease application review time by regulatory agencies?) to determine the potential reasons (e.g.,. dossier navigation) that eCTD may decrease review time.

For Question seven (Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company?), scores were assigned to each response to perform a quantitative analysis on the benefit of time savings in the preparation and transmittal of regulatory submissions to the Agency. The values used to perform a calculation for each response can be found in the key below. The values were used to obtain response averages.

Excellent	Good	Moderate	Poor	Very Bad
1 month or	2-3 weeks	1-2 weeks	1-6 days	None
more				
5	4	3	2	1

Table 2 Response Values for Survey Question Seven

Questions eight through ten are open-ended questions. These questions were used to get a better idea of individual opinions and a better understanding of frequency distributions. The responses from Questions eight, nine and ten were divided into the same eight categories presented in the Suchanek and Ostermann study to further compare and analyze responses. The categories used in the Suchanek and Ostermann study can be found in Table 3 (in Chapter 4). The responses from Question ten were used to determine individual opinion on improvements that can be made to eCTD through the implementation of RPS. The purpose of RPS is to improve eCTD technological shortcomings. This question will also be utilized to further validate the challenges that respondents have with eCTD.

3.2.5 Procedure

Participants were contacted via email at the start of the survey. The email explained the project, inclusion/exclusion criteria, the types of questions, length of the survey, how the responses would be used, and instructions for completion and response due dates. A sample email can be found in Appendix C. The respondent's personal data were not labeled with any individually-identifiable information. A link to the survey was provided in the body of the email and no personal data was collected within the survey. The respondents were able to link to the survey and anonymously complete all responses. A sample survey can be found in Appendix A. The findings were used to supplement previous findings regarding the usage of eCTDs and the benefits and challenges of eCTD submissions.

3.2.6 Limitations

Some of the limitations in this study include time and money. There could have been a greater response rate if the survey time was extended by several months and if there was an ability to offer respondents some level of compensation for their time. There are also some limitations with the sample size estimates. The population size of regulatory professionals (12,000) was based on the estimated number of members in the RAPS organization. This was due to lack of sources that contained data on amount of regulatory professionals worldwide. There are also limitations associated with the openended questions eight and nine. There was an attempt to accurately group all responses

into the same eight categories within the Suchanek and Ostermann study; however, there were several responses that had multiple answers. In these cases if multiple responses were recorded in one individuals' answer, each individual response was counted and placed in the appropriate group. There were also limitations associated with validation of the independent study. The survey was developed using criteria found in the literature and from similar studies. Moreover, statements were specifically design to be short, to the point, and phrased in a positive way. However, there were no direct methods used to validate the study questions. One approach that could have been used is the option to prescreen study questions by using a small sample of study participants. This method would have ensured that the wording within the questions was sufficient to yield the appropriate responses and to validate study findings. This method was not feasible due to time constraints.

CHAPTER 4

RESULTS AND CONCLUSIONS

4 INTRODUCTION

The results below will include a summary from the Thomson and Suchanek and Ostermann studies. The summaries will be used to relate to the findings from the independent study.

4.1 Thomson Scientific Regulatory Trends Survey Results⁶

The fifth annual Liquent Regulatory Affairs Trends Survey, conducted by Thomson Scientific Market Research, provides exclusive insight into the emerging and future trends of regulatory product management needs for the life science market.⁶ The survey concentrates on four key areas: (1) Technology Usage trends, including both submission publishing software and other desktop software; (2) Document Management System usage; (3) Regulatory Outsourcing trends; and (4) Regulatory trends, including use or future use of the eCTD.Technology Usage: Most percentages within the 4 categories have remained the same over, since 2006, possibly indicating a plateau in the adoption of new technologies. The only significant increase was in the use of digital signatures.⁶

Below are some of the Key Findings on Technology Usage from the study performed in 2007:⁶

- Almost all (90%) of the survey respondents make regulatory submissions.
- Current use of paper and electronic submissions have remained the same since 2006, unlike the previous year's analysis, where there was a drop in the percentage of those who did paper-based submissions only, and an increase in the percentage that did both electronic and paper processes.

- In two years' time, the majority of respondents estimate they will most likely submit to the FDA via a Marketing Application, either in paper format or electronically. Marketing applications are most likely to be used in Europe, Japan, and all other global agencies.
- Two-thirds (67%) are using submission publishing software. This percentage is similar to 2006. One third (36%) of those respondents not currently using software are very likely to implement submissions publishing software into their process.
- As in the previous year, the SAFE (Signatures and Authentication for Everyone) initiative has not yet taken hold in most companies surveyed: only 4% of respondents are currently addressing the SAFE initiative. However, 26% plan to implement it in the future.
- Similarly, only 9% of companies currently have technology to support the FDA Gateway, and one third (37%) plan to implement the technology in the future.
- One-quarter of respondents (26%) are currently using a digital signature process, a significant increase of 7% over the past year.
- Six in ten (58%) respondents are not currently utilizing a digital signature process for their submissions. Of those, 43% plan to implement this technology. –The respondents who do not plan to implement a digital signature process stated that it is not necessary for their company or industry.

Below are some of the Key Findings on Regulatory Trends:⁶

• The percentage of companies planning to implement new or replacement submissions software has decreased over the past year, with the exception of an eCTD viewer (an

XML-based tool that assists in the processing of eCTD submission, which has increased. Migration to eCTD appears to be imminent.

- Four in ten (44%) state that their organization plans to adopt an eCTD viewer, an increase of 12% over the past year.
- Three-fourths (76%) of respondents plan to migrate to the eCTD, and those planning to migrate within 3 months increased significantly from 4% to 26%.

The findings in the study above show there is an increase in the adoption of eCTD and tools that facilitate eCTD creation. This study provided excellent quantitative data on pharmaceuticals companies' future plans and trends. However, it lacked specific information regarding why companies are planning to implement these new technologies. Are companies planning to implement new technologies based on regulatory agency recommendations? Or are there plans to transition to new technologies because there are benefits? Four in ten (44%) state that their organization plans to adopt an eCTD viewer, an increase of 12% over the past year. Three-fourths (76%) of respondents plan to migrate to the eCTD, and those planning to migrate within 3 months increased significantly from 4% to 26%. But this Thomson study fails to provide adequate data on why companies are transitioning to these new technologies.

4.2 Suchanek and Ostermann Study Results

This study summarized empirical social research in the form of an email expert interview utilizing the Delphi method. The purpose of this study was to analyze the opinions of eight international experts on the change from paper-based to eCTD based electronic submissions in the US and Europe. Although eCTD was mandated as the only format accepted for electronic regulatory submissions in the US and required for some countries in the EU starting January 2010, Suchanek and Ostermann sought to understand why many companies were not early adopters of the eCTD format.⁹ Because agencies were starting to mandate eCTD, the authors felt that companies would be driven to adopt the eCTD format without truly understanding the advantages and disadvantages. Suchanek and Ostermann felt if the pros and cons were made clear to pharmaceutical companies and the advantages outweighed the disadvantages, companies would be more likely to adopt the eCTD format.⁹ Qualitative and scientific based analysis were used to analyze the advantages and disadvantages. The responses on the advantages and disadvantages gathered in this survey were divided into eight different categories. These findings are depicted in Table 3.

eCTD Advantages	eCTD Disadvantages
(1)Less paper handling, Logistic and	(A.) Implementation/migration and
archiving cost	training costs
(2) Less time to market	(B.) eCTD standard is not yet sufficient
(3) Lifecycle and post approval	(C.) Use of hyperlinks/bookmarks in a
maintenance	PDF
(4) New processes	(D.) One-way communication
(5) Findable content/data reuse	(E.) New Processes
(6) Regulatory compliance	(F.) Lack of qualified people
(7) Transfer (agencies, partners and	(G.) Additional IT and electronic archival
companies)	costs
(8) Dossier Navigation and Improved	(H.) Lifecycle and post-approval
Preparation	maintenance

 Table 3 Advantages and Disadvantages in the Suchanek and Ostermann Study

After all the responses were gathered, the advantages and disadvantages were compared. Additionally, the experts were questioned on possible reasons that companies may or may not implement eCTD. The most common answers for implementing eCTD were because more national competent authorities were strongly recommending eCTD and companies had already started to work with eCTD in see the advantages. The most common answers for companies not implementing eCTD were that there are some agencies that are not yet mandating eCTD, there are financial challenges with implementing eCTD, or more importantly there is resistance to change. In summary, the study showed that the consensus among the experts were that the advantages outweigh the disadvantages. This study provided excellent qualitative data on the advantages and disadvantages of eCTD. The study gathered a wide array of advantages and disadvantages from experts that worked in the industry a numbers of years and have provided consulting services to a number of pharmaceutical companies. However, these same qualities can also skew the data that demonstrates whether eCTD truly has an advantage over other submission formats. There was a need to conduct an independent survey and gather data from regulatory professionals that work for pharmaceutical companies that have adopted eCTD technology. In previous experience, when a company decides to adopt a new technology, such as eCTD, there are very few employees that have an opinion in this decision-making. Therefore, employees are required to update their processes and procedures to accommodate the company's decision to transition. The purpose of the independent survey was to compile opinions from regulatory professionals that were not only self-employed experts, but also working professionals that have limited decision-making in submission format technologies.

4.3 Independent Survey Results

4.3.1 Introduction

Although, the Suchanek and Ostermann and Thomson Scientific studies both provide very valuable data. These data were further supplemented by an independent survey, conducted for this thesis. This survey was designed to obtain opinions from regulatory affairs professionals within the pharmaceutical industry to capture opinions on the benefits and challenges of transitioning to eCTD, opinions on whether eCTD has *actually* increased efficiencies, and opinions on the benefits of the emerging electronic regulatory submission technology, RPS. There were a total of 44 respondents to the independent survey. Responses were only taken from

42 respondents because inclusion criteria were not met for two respondents. The response rate was 84%. The survey was conducted for approximately two weeks and the results were stored and analyzed using tools in Survey Monkey. The majority of respondents had 1-2 years of experience with submitting eCTDs and was employed with a company that had 1-2 years experience with submitting eCTDs. About half of the respondents use all four methods: regulatory agencies guidance's, vendor/industry webinars, industry conferences and company sponsored initiatives to stay abreast of changing requirements. The majority of respondents (80.5%) make submissions to the FDA; about 53.7% make submissions to the EMEA. There were about 11 respondents that make submissions to Health Canada and 11 respondents that make submission to other regulatory authorities. All survey responses can be found in Appendix B.

4.3.2 Survey Findings

Figure 8 illustrates the years of experience of submitting eCTDs by survey respondents. According to Figure 8, 58.5% of respondents have 1-2 years of experience with eCTD. 22% of respondents have 3-4 years of experience and 12.2% have 5 years or more of experience. According to Figure 9, 48.8 % of respondents' companies have 1-2 years of experience with submitting eCTDs, 31.7% have 3-4 years of experience, 9.8% of respondents' companies have less than 6 months of experience. The findings within Questions one and two were used to exclude respondents that did not meet the independent study requirements. In addition, they also demonstrated that the majority of regulatory professionals surveyed and their companies are increasingly gaining more experience with eCTD. These results highly coincide with the findings from the Thomson and Suchanek and Ostermann results which demonstrated that companies planned to implement eCTD. These data appear to dispel a disadvantage identified in previous studies, which was the lack of experience in electronic submissions. In this study, over 90% of respondents have some level of eCTD experience.



How many years of experience do you have with submitting eCTDs?





How long has your company been submitting eCTDs?

Figure 9Years of Experience Respondents' Companies Has with Submitting eCTDs



Figure 10 Tools that Regulatory Professionals Use to Stay Abreast of Regulatory Requirements

Figure 10 illustrates the tools that regulatory professionals use to stay abreast of regulatory requirements. 48% of respondents indicated they use a combination of regulatory agency guidance documents, vendor/industry webinars, industry conferences and company-sponsored initiatives to stay abreast of changing requirements. The majority of respondents use regulatory agency guidance's. The fewest amounts of responses were company-sponsored initiatives. According to Figure 11, 80% of respondents make submissions to the FDA and 53% make submissions to EMEA. There is a direct correlation between these figures and regulatory agency submission metrics. The FDA reported a total of 285,618 submissions through the FDA gateway in 2008. This figure does not include submissions sent via other methods. 53.7% of respondents make submission to EMEA. EMEA reported approximately one half of all active products or 228 products are currently managed in eCTD format in 2008. The findings showed that respondents

that submit solely to these two agencies tend to agree that the biggest disadvantages of eCTD is lifecycle management.

A crosstab was performed in Figure 12 to analyze the tools that respondents use to stay abreast of changing regulatory submission requirements versus the Agencies that respondents typically submit to. The findings from the independent survey show that respondents that submit to Health Canada, EMEA and MHW (Japanese Ministry of Health) tend to rely more on regulatory agency guidance's to understand changing requirements. When asked, "What is personally your biggest challenge in submitting eCTDs? The majority of responses were related to understanding and interpreting each regulatory agencies requirements and handling lifecycle management.



What agency/Agencies do you make eCTD submissions to?

Figure 11 Regulatory Agencies that Respondent Typically Make Submissions



How do you stay abreast of regulatory standards and technology?



Figure 13 illustrates the responses for the biggest challenges in eCTD. 61.9% of respondents agreed that the biggest challenge to eCTD is lifecycle management.



What is your biggest challenge in submitting eCTD submissions?

Figure 13 Challenges to Submitting in eCTD Format

To evaluate Question eight (What is the biggest challenge to eCTD?), the responses were grouped into the same categories used in the Suchanek and Ostermann study. These categories can be found in Table 4. According to the findings the majority of respondents agreed that lifecycle management and post-approval maintenance were the biggest disadvantages when submitting in the eCTD format. The next largest disadvantages were creating bookmarks/hyperlinks within a document which are used for navigational aids.

 Table 4 Disadvantages of eCTD According to Question 8

	A(1)	B(2)	C(3)	D(4)	E(5)	F(6)	G(7)	H(8)
Disadvantages	2	6	9	0	7	7	2	11

The findings from Question nine (Why do you feel eCTD increases/decreases review time?), found in Table 5, indicate the majority of respondents believe that review times are not decreased when submitting in the eCTD format. The biggest advantage to submitting in the eCTD format is dossier navigation and preparation.

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	A(1)	B(2)	C(3)	D(4)	E(5)	F(6)	G(7)	H(8)
Advantages	2	1	2	0	1	1	1	17

 Table 5 Reasons that eCTD May Decrease Review Times

The advantages of RPS were compared to the disadvantages reported in the Suchanek and Ostermann study to determine if respondents felt there would be improvements in the implementation of RPS. The results are recorded in Table 6.

	uunuai Auvantagu	s of M S Question	1 10
Advantages of RPS	1.)Two-Way	2.) Lifecycle	Not Familiar
	Communication	Management	
		Issues Resolved	
D.) One-way	9		
communication			

Table 6 Potential Advantages of RPS Question 10

F.) Lack of qualified		16
people		
H.) Lifecycle and post-	7	
approval maintenance		



Figure 14 Cross Tabulation of Questions 1 and 6

4.4 Study Analysis and Conclusions

Based on the findings from the independent survey, eCTD advantages do in fact outweigh the disadvantages. However, the margin between advantages and disadvantages is not as wide as purported in previous studies. The findings within the independent study show that 48% of respondents believe there is a decrease in review times by regulatory agencies. 51% of respondents felt there was no change in review times. 0% of respondents felt there was increase in review times. These data indicate that one of the main benefits of converting to eCTD format could be improvements in dossier navigation, which may explain why 95% of respondents work for companies that currently submit in eCTD format. Regulatory agencies are heavily promoting the switch to eCTD, lead to the increased usage of eCTD by companies and the desire for them to convert existing application to eCTD. This increase in use could be due to the benefit in dossier navigation. However, some regulatory professionals are still skeptical about the benefits to eCTD dossier preparation and transmittal. 43.9% of respondents did not feel that eCTD improves their compilation times. These negative responses may be from challenges encountered with lifecycle management, such as lack of adequate lifecycle management information and insufficient n methods used to stay abreast of regulatory standards and technology. Fifty percent of respondents indicated they use regulatory agency guidance's, vendor-sponsored webinars, industry conferences and company sponsored initiatives to stay abreast of eCTD requirements. In the independent survey, a crosstab performed in Figure 12 could also imply that regulatory agency guidance's are not specific enough for country requirements. The inference can also be made that regulatory guidance's do not contain enough detail about lifecycle management. 61.9% of respondents indicated that lifecycle management was their biggest challenge with understanding eCTD. This coincides with the findings in other studies. On the other hand, 59.2% of respondents agree that submitting in eCTD format does decrease submission preparation time by one day to one month or more. This may be due to benefits such as less paper handling and the ability to reuse content.

Many of the respondents in the independent survey that were familiar with RPS were hopeful that it would resolve many of the disadvantages seen in eCTD. Out of the thirty-four respondents to this question, sixteen felt that improvements would be made to lifecycle management (nine respondents) and via two-way communication (seven respondents) with the Agency. Sixteen respondents were unfamiliar with RPS, which raises more questions that cannot be answered with this survey and perhaps a need for additional work. Are the biggest disadvantages with eCTD related to the lack of understanding by regulatory professionals or the lack of adequate guidance provided by regulatory agencies? Although the independent survey revealed that regulatory agency guidance's are not specific on lifecycle management and

country-specific requirements; could the other disadvantages be linked to the lack of knowledge with eCTD requirements or the lack of experience with working with eCTD submissions? These questions are important ones and a more in depth survey and analysis would need to be performed to further evaluate this area

It is clear that the advantages of eCTD clearly outweigh the disadvantages and has immeasurable benefits to the pharmaceutical industry and regulatory agencies alike. According to the regulatory professionals within the independent survey, companies are realizing benefits such as cost savings in paper handling, cost savings in archiving and improvements in dossier navigation. As a result, the independent survey shows there is a potential to see a decrease in review times by regulatory agencies. Review times can be one of the biggest benefits to companies because the quicker a product gets into the marketplace, the more capital that product has the potential to generate. As of 2010, eCTD is still not a required method of submission to the FDA. Companies are still given an option to submit paper-based submissions. However, regulatory trends within this independent survey and other studies show there has been steady increase in eCTD usage and the electronic submissions gateway reported by the FDA throughout the years. Although, there are still some challenges faced with lifecycle management and granularity, over 70% of regulatory professionals are hopeful that the emergence of RPS will alleviate many of the challenges with eCTD. As a result, the advantages may soon disproportionately outweigh the disadvantages. Additional work should be performed after the implemention of RPS to determine if the biggest challenges are resolved. Other implications for further research include the stratification of survey participants by roles within regulatory. The independent study failed to gather information on the respondents' roles within regulatory affairs. Additional work should be done to determine if benefits and challenges vary based on the

respondents' roles. There is also a need for further research to determine the benefits and challenges to the FDA. The independent study focused benefits and challenges of eCTD based on the opinions of regulatory professionals. However, the findings from the opinions from regulatory agencies, such as the FDA, have the potential to reveal more favorable results with regard to the benefits of eCTD.

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APPENDICES

APPENDIX A – SAMPLE SURVEY QUESTIONS

Electronic Regulatory Submissions Trends

Exit this survey

1. Default Section

1. How many years of experience do you have with submitting eCTDs?

	. None
□ 2.	. < 6 months
□ 3.	1-2 years
□ 4.	. 3-4 years
□ 5.	5 years or more
2. Hov	w long has you company been submitting eCTDs?
□ ¹	Never
□ 2.	. < 6 months
□ 3.	1-2 years
□ 4.	. 3-4 years
□ 5.	5 years or more
3. Hov	w do you stay abreast of regulatory standards and technology?
□ ¹	. Regulatory Agency Guidances
□ 2.	. Vendor/Industry Sponsored Webinars
□ 3.	Industry Conferences
□ 4.	. Company-sponsored initiatives
□ 5.	. All of the above
4. Wh	at agency/Agencies do you make eCTD submissions to?
□ ¹ .	. FDA
□ 2.	. EMEA
□ 3.	. Health Canada
□ 4.	. Other
5. Wh	at is your biggest challenge in submitting eCTD submissions?
□ ¹	. Granularity
□ 2.	Lifecycle Management
□ 3.	Templates
□ 4.	. Other
-	

 2. Decrease 3. Review times are about the same 7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company? 1. None 2. 1-6 days 3. 1-2 weeks 4. 2-3 weeks 5. 1 month or more 8. What have you found personally to be your biggest challenge in submitting eCTDs? 9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies? 10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefit do you feel this will bring over eCTD submissions 	 2. Decrease 3. Review times are about the same 7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company? 1. None 2. 1-6 days 3. 1-2 weeks 4. 2-3 weeks 5. 1 month or more 8. What have you found personally to be your biggest challenge in submitting eCTDs? 9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies? 10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefit do you feel this will bring over eCTD submissions Done 	2. Decrease 3. Review times are about the same 7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company? 1. None 2. 1-6 days 3. 1-2 weeks 4. 2-3 weeks 5. 1 month or more 8. What have you found personally to be your biggest challenge in submitting eCTDs? 9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies? 10. Are you familiar with Regulated Product Submission (RPS)? If so, what benef do you feel this will bring over eCTD submissions	🗆 1. Inc	nease
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7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company?	7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company? 1. None 2. 1-6 days 3. 1-2 weeks 4. 2-3 weeks 5. 1 month or more 8. What have you found personally to be your biggest challenge in submitting eCTDs? 9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies? 10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefit do you feel this will bring over eCTD submissions Done	7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time does this save your company? 1. None 2. 1-6 days 3. 1-2 weeks 4. 2-3 weeks 5. 1 month or more 8. What have you found personally to be your biggest challenge in submitting eCTDs? 9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies? 10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefid do you feel this will bring over eCTD submissions Done	🗖 3. Rei	view times are about the same
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10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefind you feel this will bring over eCTD submissions	10. Are you familiar with Regulated Product Submission (RPS)? If so, what benefit do you feel this will bring over eCTD submissions	10. Are you familiar with Regulated Product Submission (RPS)? If so, what benef do you feel this will bring over eCTD submissions		
⇒ Done	Done	Done	10. Are yo do you fe	ou familiar with Regulated Product Submission (RPS)? If so, what benefi el this will bring over eCTD submissions
Done	Done	Done	-	A.
Done	Done	Done		*
				Done

APPENDIX B – INDEPENDENT SURVEY RESULTS





3. How do you stay abreast of regula	tory standards and technology?	Create Chart	Download
		Response Percent	Response Count
1. Regulatory Agency Guidances		50.0%	21
2. Vendor/Industry Sponsored Webinars		21.4%	9
3. Industry Conferences		33.3%	14
4. Company-sponsored initiatives		16.7%	7
5. All of the above		50.0%	21
	ans	wered question	42
	S	kipped question	0

4. What agency/Agencies do you make eCTD submissions to?				
		Response Percent	Response Count	
1. FDA		80.5%	33	
2. EMEA		53.7%	22	
3. Health Canada		26.8%	11	
4. Other		26.8%	11	
	answered question			
	s	kipped question	1	

5. What is your biggest challenge in submitting eCTD submissions?			Download
		Response Percent	Response Count
1. Granularity		23.8%	10
2. Lifecycle Management		61.9%	26
3. Templates		19.0%	8
4. Other		26.2%	11
5. There are no challenges		2.4%	1
	ans	wered question	42
	s	kipped question	0

6. Do you feel that eCTDs increase or decrease application review time by regulatory agencies?				
		Response Percent	Response Count	
1. Increase		0.0%	0	
2. Decrease		48.8%	20	
3. Review times are about the same		51.2%	21	
	an	swered question	41	
	3	skipped question	1	
7. Do you feel that eCTDs improve the time it takes to prepare and transmit regulatory submissions to regulatory agencies? If so, how much time Occeate Chart 🕂 Download does this save your company?				

		Response Percent	Response Count
1. None		43.9%	18
2. 1-6 days		17.1%	7
3. 1-2 weeks		14.6%	6
4. 2-3 weeks		9.8%	4
5. 1 month or more		17.1%	7
	ans	wered question	41
	si	kipped question	1

			Respon	
			Count	
		Hide replies		
1.	When to replace a document and when to put it in as new. Also the review of the submission is more difficult as it is more technical.	Ned, Apr 14, 2010 12:58 PM	🔍 Find	
2.	Lack of support from vendors when problems or questions arise. The Lifecycle management is probably the biggest challenge due to lack of definitive useful information from the Health authorities.	Non, Apr 12, 2010 12:54 PM	🔍 Find	
3.	The understanding of what each country desires. The Common Technical Document standards still do not exist in that each country has idiosyncratic differences in how they want the information presented. Also staffing the Submission groups in Regulatory has become a more technical position than it was in the 1990s when e-submissions just got started. However, companies are not willing to pay their staff the money these folks should be earning for their expertise. Therefore, the lack of quality/qualified staff tends to become an issue.	Non, Apr 12, 2010 10:54 AM	🔦 Find	
4.	Dispelling misconceptions that it will add preparation time.	Mon, Apr 12, 2010 9:44 AM	🔍 Find	
5.	Change thinking from a paper perspective into an electronic perspective	Mon, Apr 12, 2010 4:00 AM	🔍 Find	
5.	Sometimes the templates do funny things when they are not completed using the ISI add-on in Word. Using it in Citirix was slow so it was convenient to work on it outside of Citrix.	Sun, Apr 11, 2010 7:17 PM	🔦 Find.	
7.	(1) Lack of premature software used in my company (2) Lifecycle management instructions	Sat, Apr 10, 2010 1:49 PM	🔦 Find.	
	To make sense of the lifecycle management when submitting half way through the process or submitting without having a baseline Module 3	Sat, Apr 10, 2010 9:13 AM	🔦 Find.	
	As per as eCTD Submission is concerned the biggest challenge the within the shot period of tiem agencies keep changing the guidelines like EMEA released 1.2,1.3 and 1.4 and We were already submitted our submission through paper If we going to transmit the submission in electronic to main the product life cycle is very difficult.	Fri, Apr 9, 2010 10:18 AM	🔦 Find.	
).	Educating Regulatory Affairs in the importance of granularity and understanding the concept of lifecycle	Fhu, Apr 8, 2010 7:25 PM	🔍 Find.	
	Learning the differences between regional agency expectations.	Thu, Apr 8, 2010 5:47 PM	🔍 Find	
	Creating hyperlinks and lifecycle management	Thu, Apr 8, 2010 9:49 AM	🔍 Find	
	Get all documents submission ready. e.g. delivered in time, according the indusrty standards and requirements	Thu, Apr 8, 2010 7:41 AM	🔍 Find	
	Stonger validation criteria at submission	Fhu, Apr 8, 2010 7:15 AM	🔍 Find	
j.	global submissions and understanding requirements across regions.	Wed, Apr 7, 2010 6:05 PM	9	
i.	Import of existing eCTDs from a licensor in another system of the applicant for example (e.g. generics,)	Wed, Apr 7, 2010 1:27 AM	٩	
	Organization and planning	Tue, Apr 6, 2010 10:15 PM	٩,	
	streamlined process from authoring documents to publishing	Tue, Apr 6, 2010 1:04 PM	9	
	Submission ready documents	Tue, Apr 6, 2010 7:45 AM	9	
	Implementation of procedures for authoring submission ready documents to involved business units	Tue, Apr 6, 2010 1:12 AM	9	
	Helping the authors understand where documents belong in the CTD format - it's not intuitive.	Mon, Apr 5, 2010 5:52 PM	Q	
	Lifecycle activities for CMC and the management of post-approval changes and/or the cross reference of the CMC sections in between dossiers.	Mon, Apr 5, 2010 2:08 PM	Q	
	Hyperlinking and Bookmarking, especially across documents.	Mon, Apr 5, 2010 12:57 PM	. 🔍	
	comprehending and complying with electronic specifications; inexperience and lack of knowledge	Mon, Apr 5, 2010 12:26 PM	<u>م</u>	
	Bookmarking and linking legacy information and making it compliant.	Mon, Apr 5, 2010 10:45 AM		
	Late changes cannot be accomodated leading to submission of subpotimal data packages	Mon. Apr 5. 2010 9:14 AM	Q	
	The continuous amendments which sought to be implemented on a continuous basis	Mon. Apr 5: 2010 3:36 AM	Q	
	Document Quality (time required for remediation of missing pages sections bookmarks hyperlinks templates not used etc)	Fri. Apr 2, 2010 11:50 AM	Q	
•	Because of the time needed to publish, authors need to complete their work sconer. This shortening of timelines tends to receive resistance from authors and their management.	Fri, Apr 2, 2010 10:25 AM	Q	
•	Time required for the technical compilation shortens the timeline for document creation when submission targets are not adjusted to account for the additional work associated with electronic submissions.	Fri, Apr 2, 2010 10:03 AM	Q	
	Understanding the impact on life-cycle management of a dossier. Including the granularity	Fri, Apr 2, 2010 8:51 AM	Q	
	Lack of eCTD knowledge and understanding across the organization	Fri, Apr 2, 2010 7:18 AM	Q	
•	Shifting the organization's and other's way of thinking about a new submission process. Educating them and leading others through the terminology, benefits/value, and fears has been the bioaest challenge.	Fri, Apr 2, 2010 7:15 AM	Q	
	The biggest challenge seems to be an assumption that only submission publishers have to understand the concents of eCTD	Fri. Apr 2, 2010 6:16 AM	Q	
5.	The time spent in re-formatting word and/or pdf documents to be submission ready; the time spent to import each document one by on into the electronic system (e.g. Documentum) the time spent in reviewing/checking all documents one published.	e Fri, Apr 2, 2010 4:02 AM	Q	
	and an excerne eyotem (e.g. exotementarity, are ante open an externing/one using an obtainents once patrioned).		-	

11				-
	37.	Module 1 documentation. In EU you have to submit labeling, Application Forms, cover letters, proof of payments etc all centrally, where formally this was arranged at a local level.	Fri, Apr 2, 2010 2:42 AM	🔦 Find
	38.	Submission Ready Standards not followed -lack of knowledge of those responsible for preparing documents for eCTD submission, lack of knowledge of Reg Mgrs regarding eCTD submissions	Thu, Apr 1, 2010 4:48 PM	🔍 Find
			50 responses pe	r page 💌

9. Why do you feel that eCTDs increase/decrease application review time by regulatory agencies?

Bownload

			Response Count
		Hide replies	37
1.	I think it is about the same. Maybe for someone that loves paper it is more of a hassle but when you know how to handle eCTDs it should increase the review time as they can view the entire dossier more easily.	Wed, Apr 14, 2010 12:58 PM	🔍 Find
2.	The actual submission probably gets to the reviewer's desk quicker.	Mon, Apr 12, 2010 12:54 PM	🔍 Find
3.	XML is an issue. The technical aspects have still not been ironed out. Lifecycle management is a conundrum still. Just figuring these two things out takes much time and effort. Also the software vendors have not come up with the ultimate software yet - a package that does paper, CTD, and eCTD well. I tend to spend much more time thinking through the actual submission today than 10 years ago.	Mon, Apr 12, 2010 10:54 AM	🔍 Find
4.	n/a	Mon, Apr 12, 2010 9:44 AM	🔍 Find
5.	Easier to navigate and search trough electronic data and because of display of product's lifecycle	Mon, Apr 12, 2010 4:00 AM	🔍 Find
6.	NA - I never worked on paper submissions so I'm not sure if the review time has been affected.	Sun, Apr 11, 2010 7:17 PM	🔍 Find
7.	Twofolds, the submission is immediately electronically available to all reviewers within minutes from uploading in the ESG and (2) Using eCTD Viewer the lifecycle of the submission is available in minutes.	Sat, Apr 10, 2010 1:49 PM	🔍 Find
8.	The eCTD will eventually result in a reduction of the review time, but only in sofar as it makes easier for the reviewer to find the data, it still has to be read and analysed whether it is submitted in paper or elctronically	Sat, Apr 10, 2010 9:13 AM	🔦 Find
9.	The review process is very easy in eCTD submissions. So it decrease the time.	Fri, Apr 9, 2010 10:18 AM	🔍 Find
10.	I don't feel that they change the review time by regulatory agencies. I do feel that they're valuable to the sponsor in determining exactly what has been submitted and how it relates to everything else that has been submitted. Some companies were keeping "working copies" of submissions in an attempt to have a "current" view of their submission, however, different personnel could look at the historical files and have a different perspective regarding exactly what the "current" view was.	Thu, Apr 8, 2010 7:25 PM	🔍 Find
11.	They have access to all information with a click of a button. Most of the informaton they need is hyperlinked so they don't have to search for it. I know I can review an electronic application much faster than a paper application.	Thu, Apr 8, 2010 5:47 PM	🔍 Find
12.	The hyperlinks would be very usefull in accessing data withinn a module as well as between modules.	Thu, Apr 8, 2010 9:49 AM	🔍 Find
13.	It will should decrease the application review time after the first initial submission. After that the follow-up sequences should only contain the info that has been updated	Thu, Apr 8, 2010 7:41 AM	🔦 Find
14.	More convenient for processing, finding information, extracting parts to author the evaluation	Thu, Apr 8, 2010 7:15 AM	🔍 Find
15.	Decrease for the most part - but datasets pose a challenge for FDA reviewers.	Wed, Apr 7, 2010 6:05 PM	🔩 Find
16.	its easier to gain an overview of the whole submission and to navigate from one section to the other	Wed, Apr 7, 2010 1:27 AM	🔍 Find
17.	Do not now.	Tue, Apr 6, 2010 10:15 PM	🔍 Find
18.	i don't think there's any significant change on review time	Tue, Apr 6, 2010 1:04 PM	🔍 Find
19.	Agency staff's unfamiliarity with IT systems	Tue, Apr 6, 2010 7:45 AM	🔍 Find
20.	Fast access to all required information	Tue, Apr 6, 2010 1:12 AM	🔍 Find
21.	I have experience only with INDs and have not seen any change in review time.	Mon, Apr 5, 2010 5:52 PM	🔍 Find
22.	The minimal time savings appears to be in the activities related to the actual printing of copies and in shipment of compiled dossiers to the regulatory authorities.	Mon, Apr 5, 2010 2:08 PM	Sind
23.	The different views available using eCTDs and the 'quick-link' capabilites of hyperlinks appear to reduce Agency review time.	Mon, Apr 5, 2010 12:57 PM	Sind
24.	at this time unknown whether time is decreased or increased as IND submitted, not NDA, in eCTD format	Mon, Apr 5, 2010 12:26 PM	Sind
25.	I am not sure they increase / decrease actually review time, but being able to submit electronic submissions through the gateway allows the review access to submission related infomation almost instantly. This has helped when requested information has taken time to be gathered.	Mon, Apr 5, 2010 10:45 AM	🔍 Find
26.	While there is guidance available, there are still mnay different versions of eCTDs being submitted. Information is still not universally placed in the same section and different approaches to data are common, which in turn defeats the purpose of a universal submission platform as each reviewer has to learn how a company does an eCTD.	Mon, Apr 5, 2010 9:14 AM	🔍 Find
27.	The time is more or less th same for review. The submission time decreases for the applicant	Mon, Apr 5, 2010 3:36 AM	🔍 Find
28.	While e-CTD may facilitate FDA review (if reviewers are electronic saw) review times in my impression have not shorted due mainly to other factors such as impact of REMS initiative, limited and over worked resources at FDA, etc.	Fri, Apr 2, 2010 11:50 AM	🔍 Find
29.	In theory they should decrease review times, but so far I have not seen any real reductions. FDA, for example, still should meet their PDUFA target regardless of whether a submission is sent in electonically or not.	Fri, Apr 2, 2010 10:25 AM	Find
30.	The submitted information is more easily accessible to the reviewer; therefore, I think you are likely to receive some quick hit types of questions sooner than you might in the paper world.	Fri, Apr 2, 2010 10:03 AM	Sind
31.	no change	Fri, Apr 2, 2010 8:51 AM	Sind
32.	Not necessary to spend time printing, binding and shipping via truck. Submission is uploaded directly to a server and always available to the reviewer.	Fri, Apr 2, 2010 7:18 AM	G Find
33.	I don't think that the review time is decreased. The eCTD is just a move to a paperless system. The scientific content and data that have to be reviewed haven't changed and the FDA's PDUFA timeline requirements for review haven't changed just because the submission is electronic.	Fri, Apr 2, 2010 7:15 AM	Sind

34.	Because authorities only have to click on the dossier part they have to assess; they can find more easily one specific CTD section; they can search what they want by key word.	Fri, Apr 2, 2010 4:02 AM	🔍 Find
35.	Priority given to electronic review. Easiest way for evaluation.	Fri, Apr 2, 2010 3:56 AM	🔍 Find
36.	n.a.	Fri, Apr 2, 2010 2:42 AM	🔍 Find
37.	Document links and bookmarks make for quick navigation and structure of the applications are standardized making it easier and faster for reviewers to find exactly what they need with the click of a mouse instead of thumbion through volumes of paper to find a reference or	Thu, Apr 1, 2010 4:48 PM	🔍 Find

u. Ar	e you ramiliar with Regulated Product Submission (RPS) / II SO, What benefits do you feel this will bring over eCTD submissions		- Downios
			Respon: Count
		P Hide replies	
1.	no	Wed, Apr 14, 2010 12:58 PM	🔍 Find
2.	I'm familiar with it but I don't think the benefits will really be relevant to our company at the moment.	Mon, Apr 12, 2010 12:54 PM	🔍 Find
3.	Communication between agencies and companies will be one of the best benefits. If you consider the big picture, RPS is taking a structured model (eCTD) and making it more flexible. It does not however mitigate the technical aspects of electronic submissions.	Mon, Apr 12, 2010 10:54 AM	🔍 Find
4.	We are looking forward to the two-way communications it will provide.	Mon, Apr 12, 2010 9:44 AM	🔍 Find
5.	Yes, hopefully there is less information to be submitted and cross-referencing life cycle management will be solved.	Mon, Apr 12, 2010 4:00 AM	🔍 Find
6.	No	Sun, Apr 11, 2010 7:17 PM	🔍 Find
7.	The benefits of RPS will address lifecycle issues such linking between IND and NDA, thereby not having to submit documents submitted in the IND to the NDA years later. Will address lifecycle management issues.	Sat, Apr 10, 2010 1:49 PM	🔍 Find
8.	The main improvement I can see is the "two-way" communication between the agency and industry	Sat, Apr 10, 2010 9:13 AM	🔍 Find
9.	RPS Still in Developing stage still most the companies struggling to familiar with eCTD.	Fri, Apr 9, 2010 10:18 AM	🔍 Find
10.	I am familiar with RPS. There are 2 benefits that it affords: 1) 2-way communication with the Agency (currently looking at an eCTD is like only hearing one side of the conversation, 2) metadata lifecyle (so when metadata changes, e.g., manufacturer, it will display properly)	Thu, Apr 8, 2010 7:25 PM	🔍 Find
11.	Not familiar.	Thu, Apr 8, 2010 9:49 AM	🔍 Find
12.	The benefits will be that it is a 2-way communication between industry and agencies.	Thu, Apr 8, 2010 7:41 AM	🔍 Find
13.	Minimal knowledge - the benefits remain to be seen.	Wed, Apr 7, 2010 6:05 PM	🔍 Find
14.	know it, but have no experience/idea.	Wed, Apr 7, 2010 1:27 AM	🔍 Find
15.	Yes. Do not know.	Tue, Apr 6, 2010 10:15 PM	🔍 Find
16.	not much until all authoring process be incorporated to submission publishing process	Tue, Apr 6, 2010 1:04 PM	🔍 Find
17.	no	Tue, Apr 6, 2010 7:45 AM	🔍 Find
18.	I start to get familiar with the topic: I have the feeling that at least in a first phase it risks to bring more challenges than benefits to industry, especially industry submitting in Eu and US. It is actually the FDA which benefits most - at least this is the goal, to make procedures more efficient rensertively to have PDI IFA noals realised.	Tue, Apr 6, 2010 1:12 AM	🔦 Find

	more emicient, repsectively to have PUUFA goals realised.		
19.	I'm not familiar enough to have an opinion.	Mon, Apr 5, 2010 5:52 PM	🔍 Find
20.	Not familiar enough with this initiative to comment.	Mon, Apr 5, 2010 2:08 PM	🔍 Find
21.	Yes. RPS should allow updating of metadata over time, dissociate the file-folder path from the submission outline, and provide for more verstile applications and submissions.	Mon, Apr 5, 2010 12:57 PM	🔍 Find
22.	No	Mon, Apr 5, 2010 12:26 PM	🔍 Find
23.	Global acceptance is a key benefit if it is realized.	Mon, Apr 5, 2010 9:14 AM	🔍 Find
24.	No	Mon, Apr 5, 2010 3:36 AM	🔍 Find
25.	No	Fri, Apr 2, 2010 11:50 AM	🔍 Find
26.	I'm just beginning to learn about this technology. The main benefits I have heard about are the ability for two-way communication with health authorities, and some flexibility around metadata.	Fri, Apr 2, 2010 10:25 AM	🔍 Find
27.	While I do not foresee an improvement in the time required for compilation as a result of the RPS, having the ability to change metadata over lifecycle will be very helpful. I believe this will be implemented with RPS3.	Fri, Apr 2, 2010 10:03 AM	🔍 Find
28.	no	Fri, Apr 2, 2010 8:51 AM	🔍 Find
29.	RPS will facilitate communication between the reviewer and the sponsor.	Fri, Apr 2, 2010 7:18 AM	🔍 Find
30.	Yes. Based on my limited knowledge at this point, it most likely will be an advantage in that it will allow two way communication electronically between the FDA and a company and that it will reduce the redundancy of filing information more than once.	Fri, Apr 2, 2010 7:15 AM	🔍 Find
31.	Two-way communication between industry and agencies will be a subsstantial benefit of RPS, but challenges will remain if FDA, EMA, Japan, Australia, and other agencies don't adopt RPS as a global standard.	Fri, Apr 2, 2010 6:16 AM	🔍 Find
32.	No	Fri, Apr 2, 2010 4:02 AM	🔍 Find
33.	Not familiar	Fri, Apr 2, 2010 3:56 AM	🔍 Find
34.	Only working knowledge of RPS	Thu, Apr 1, 2010 4:48 PM	🔍 Find
		50 responses p	er page 💌
APPENDIX C – SAMPLE EMAIL REQUEST Informational Letter

3/29/2010

Dear Regulatory Professional:

I am a graduate student under the direction of Dr. Paul Brooks professor in the Department of Pharmacy, Regulatory Affairs Program at The University of Georgia. I invite you to participate in a research study entitled, "The History of Electronic Regulatory Submissions Technologies: A Focus on eCTD and its Challenges and Benefits". The purpose of this study is to collect electronic regulatory submission trends and to gather information on the benefits and challenges to the life sciences industry and regulatory agencies.

To participate in this study you must be a Regulatory Affairs professional with at least six months of experience, work in the biotech industry and make submissions to the FDA, EMA, Health Canada or Japan. You must also have participated or plans to participate in the review, approval, compilation or submittal of an electronic common technical document (eCTD) regulatory submissions to the FDA, EMEA, Health Canada or Japanand have a general understanding of eCTD requirements

Your participation will involve a short electronic survey of your opinions on the implementation of electronic common document (eCTD). This survey should only take about 10 minutes of you time. Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. Please note that Internet communications are insecure and there is a limit to the confidentiality that can be guaranteed due to the technology itself. However, the survey tool used does not store your personal information.

The results of the research study may be published, but your name will not be used. In fact, the published results will be presented in summary form only. Your identity will not be associated with your responses in any published format.

The findings from this project may assist those in the industry, who are responsible for submitting regulatory documents to the FDA, about the potential benefits and challenges of electronic regulatory submission. Consequently, this may contribute to enhancing the submission process and future electronic submissions initiatives; which in turn may contribute to increased efficiency in various submission compilation processes that you are currently involved in. There are no known risks or discomforts associated with this research.

If you have any questions about this research project, please feel free to call me at (404) 790-5764 or send an e-mail to chaross@uga.edu. Questions or concerns about your rights as a research participant should be directed to The Chairperson, University of Georgia Institutional Review Board, 612 Boyd GSRC, Athens, Georgia 30602-7411; telephone (706) 542-3199; email address irb@uga.edu.

By completing this questionnaire, you are agreeing to participate in the above described research project.

Thank you for your consideration! Please keep this letter for your records.

Sincerely, Charnelle Ross