



Electronic Submission Myths: How to Separate Fact from Fiction

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Objectives/Overview

- ◆ Describe the decision making process for implementation of electronic submissions
- ◆ Clarify agency requirements for electronic submissions
- ◆ Describe examples of best practices for eCTD implementation and regulatory operations
- ◆ Provide resources to educate company associates and decision makers

Setting the Scene

- ◆ Electronic submissions have been accepted at FDA for over 30 years
- ◆ Format has evolved from non-standardized organization of electronic files (no standard file format) to eNDA/eIND (PDF) to eCTD (XML)
- ◆ Significant eCTD activity in past 3 years
 - FDA
 - Globally

#1: Fact or Fiction?

- ◆ The eCTD format is still relatively new and paper format still represents the majority of submissions to FDA.



Myth Buster

◆ Fiction!

- eCTD format has been accepted at FDA for over 6 years
- 20% of submissions received by CDER are in eCTD format (February 2009)
- 70% of new submissions to OGD are in eCTD format (informal survey July 2009)
- Most **paper** submissions are amendments to approved NDAs, and previously filed INDs and NDAs

More Facts

- ◆ FDA requesting submissions in eCTD format
 - Pre-IND and Pre-NDA meetings
 - Recent experience
 - ◆ Sponsor planned on submitting in paper CTD format
 - ◆ Initiated preparation of documents based on paper requirements
 - ◆ Pre-IND meeting – FDA mentioned several times submitting in eCTD format
 - ◆ Post Pre-IND meeting – Sponsor decided to submit in eCTD format

Separating **Fact** from Fiction

- ◆ **Person A:** Is your organization currently using eCTD format?
- ◆ **Person B:** No, we're still trying to implement this new CTD format. Our regulatory group thinks we need to go electronic, but management isn't so sure. Is it required?
- ◆ **Person A:** Not yet, but effective January 1, 2008, the eCTD format is the required format for submissions to FDA.
- ◆ **Person B:** Oh, I didn't realize that. What are our options?
- ◆ **Person A:** Well, we have a software product available that can take care of preparing a compliant eCTD submission. Would you like to see a demonstration?

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- ◆ **Person B:** No, we're still trying to implement this new CTD format. Our regulatory group thinks we need to go electronic, but management isn't so sure. Is it required?
- ◆ **Person A:** Not yet, but effective January 1, 2008, the eCTD format is the required **ELECTRONIC** format for submissions to FDA.
- ◆ **Person B:** Oh, I didn't realize that. What are our options?
- ◆ **Person A:** Well, we have a software product available that can take care of preparing a compliant eCTD submission. Would you like to see a demonstration?

Separating **Fact** from Fiction

- ◆ Electronic submission terminology
 - Alphabet Soup
 - ◆ eCTD, SPL, XML, CDISC, SDTM, SEND, SAS, PDF, STF
 - Specifications
 - ◆ Document Type Definition (DTD)
 - ◆ Folder Names and Structure
 - ◆ File Names and Structure
 - ◆ Required File Formats

Separating **Fact** from Fiction

- Regulations
 - ◆ 21 CFR Part 11
 - ◆ CTD content determined by other CFR sections
 - Same CFR sections as traditional paper format
- ◆ Electronic submissions are simply applying technology to regulatory content



#2: Fact or Fiction?

- ◆ Adoption of the eCTD format is a financial decision and should be initiated by the finance group.



Myth Buster

◆ Fiction!

- eCTD adoption is a strategic business and regulatory decision
- **Adoption is** driven by need for:
 - ◆ **streamlined** interactions with global regulatory agencies
 - ◆ more efficient use of internal resources over product lifecycle
- Decision making process should be **initiated** by a program/project management and regulatory affairs collaboration team
 - ◆ Final decision will involve key business, product development and regulatory stakeholders

Is Electronic the Best Choice?

Overall Impact on Sponsor Organization



Evaluate existing document authoring processes

- If CTD implemented, 50% of transition is complete
- If CTD not implemented, starting point
 - ◆ Understanding CTD format is critical for transition to eCTD

Is Electronic the Best Choice?

Overall Impact on Sponsor Organization



Understand version control throughout document preparation process

- Simple or complex
- Discussion between document authors, Quality Assurance (QA), Regulatory Affairs (RA), and support staff

Is Electronic the Best Choice?

Overall Impact on Sponsor Organization



Understand version control throughout document preparation process

- Distinguish between major and minor versions
- Necessary revisions versus personal preferences
- Impacts overall project timeline by identifying availability of major versions for review

Is Electronic the Best Choice?

Overall Impact on Sponsor Organization



Evaluate document process flow and identify potential bottlenecks and process inefficiencies

- CTD format and version control standards add efficiencies
- Review and compilation activities are usually problem areas

Is Electronic the Best Choice?

Overall Impact on Sponsor Organization



Evaluate document process flow and identify potential bottlenecks and process inefficiencies

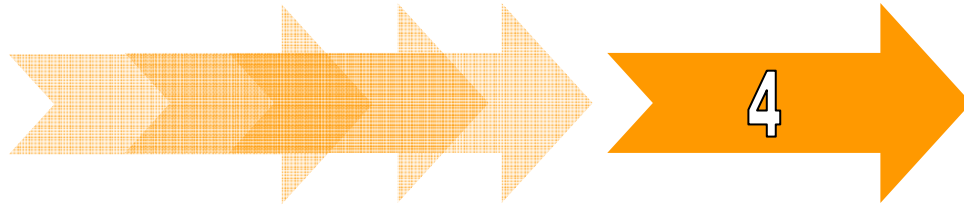
- If process is linear, determine if any activities can be parallel
- If process is already staggered or has parallel activities, evaluate value added by individual activities

Is Electronic the Best Choice?



- ◆ Evaluate regulatory submission pipeline
 - Type of submissions and typical lifecycle
 - Single or multiple regulatory agencies
 - All Projects
 - ◆ Time point for conversion

Is Electronic the Best Choice?



- Project-specific decision
 - ◆ Stage of development
 - ◆ Likelihood of reaching market
 - ◆ Partnership/Joint Venture
 - Partner request
 - ◆ Agency preference
 - Project manager request

Slide 19

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Move this later on in the presentation and group with other "Best Practices" material

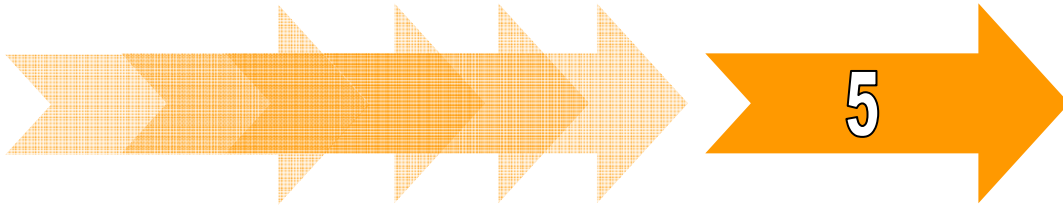
Greg O, 8/28/2009

GAR2

I believe that these are also important areas for an organization to evaluate trying to decide if electronic is the right way to go.

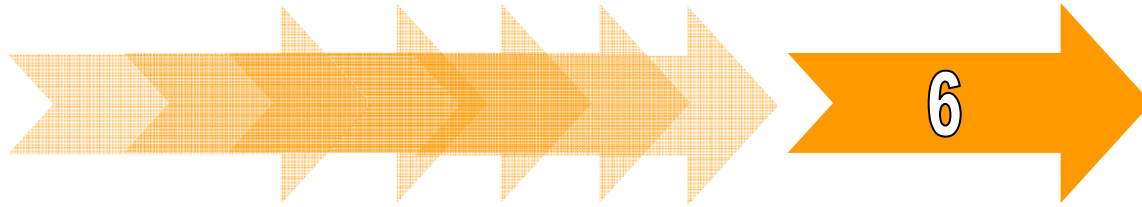
G. Ross, 8/30/2009

Is Electronic the Best Choice?



- ◆ Evaluate existing personnel and IT infrastructure
 - Experience
 - Aptitude/Attitude
 - Relationships between regulatory, document authors, and IT personnel
 - Network configuration

Is Electronic the Best Choice?

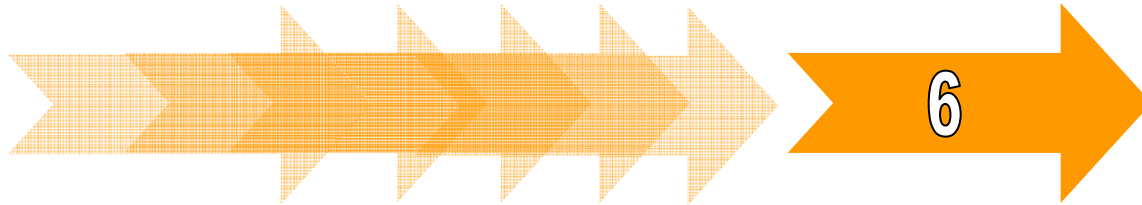


◆ In-house Solution

– Evaluate cost of:

- ◆ Software
- ◆ Hardware
- ◆ Validation (21CFR Part 11)
- ◆ Training
- ◆ Qualified personnel (existing or external)
- ◆ Ongoing maintenance costs

Is Electronic the Best Choice?



◆ Outsourcing Solution

- Partnership service model
- Seamless extension of internal processes
- Understand and support short and long-term goals of your organization
- Quality product at a reasonable price

#3: Fact or Fiction?

- ◆ Content of Labeling must be submitted electronically in Structured Product Labeling (SPL) format with an initial NDA, 505(b)(2), BLA or ANDA submission.



Myth Buster

◆ Fact!

- Docket 92S-0251, SPL is mandatory and is the only acceptable format for submission of content of labeling effective October 31, 2005
 - ◆ Original submissions, supplements, annual reports
 - ◆ PDF format acceptable during pre-approval labeling negotiations with reviewers
- Approved labels for Rx products posted on DailyMed website

Current FDA Requirements

- ◆ eCTD format is acceptable for:
 - NDA, 505(b)(2)
 - BLA
 - ANDA
 - IND
 - DMF

Current FDA Requirements

- ◆ eCTD format is not acceptable for:
 - 510(k)
 - ◆ CDRH has special software for preparing and submitting 510(k) application to Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)
 - Veterinary Products
 - ◆ Submit as single PDF with appropriate navigation
 - ODDR
 - ◆ Submit as single PDF with appropriate navigation

Current FDA Requirements

- ◆ Effective January 1, 2008, eCTD mandatory format for electronic submissions to FDA
- ◆ Current guidance documents posted on website
 - FDA eCTD Table of Contents and Headings Hierarchy
 - eCTD Backbone Files Specification for Module 1
 - ICH M2 eCTD Specification

Current FDA Requirements

◆ Specifications

- MS Word
- PDF v 1.4
- Module 4 datasets
 - ◆ Toxicology studies
 - ◆ Study Data Specifications v 1.3
 - ◆ <http://www.fda.gov/ForIndustry/DataStandards/CDISCDataStandards/default.htm>
 - ◆ SAS Xport Transport Files (.xpt)

Current FDA Requirements

◆ Specifications

– Module 5 datasets

- ◆ Study Data Specifications v 1.3
- ◆ <http://www.fda.gov/ForIndustry/DataStandards/CDISCDataStandards/default.htm>
- ◆ SAS Xport Transport Files (.xpt)

#4: Fact or Fiction?

- ◆ FDA forms 2656, 2657, and 2658 for labeler code request, drug establishment registration, drug listing, and drug listing for private label distributors are required to be submitted electronically in SPL format through the FDA Electronic Submissions Gateway effective June 1, 2009.



Myth Buster

◆ Fact!

- Docket 92S-0251 (July 10, 2008), CDER, CBER and CVM ready to accept drug establishment registration and drug listing in SPL format
- Final guidance document issued May 31, 2009 stating that FDA will no longer accept paper copies of drug establishment registration and drug listing information
- SPL files submitted through ESG

Current FDA Requirements

- ◆ Content of Labeling and Drug Listing
 - Duplicative submissions
 - ◆ Amendments to marketing application
 - ◆ Drug listing submitted through ESG
 - Both submissions are required and necessary at the current time
 - ◆ Drug listing submitted through ESG will be posted to DailyMed website
 - ◆ Future plans to eliminate submission to marketing application
 - System will allow reviewers access to FDA eList database

Current EU Requirements

- ◆ eCTD format is acceptable in specific countries for:
 - MAA
 - IMPD
 - ASMF
- ◆ EURS (European Review System for eCTDs)
 - European procedures shared eCTD processing and review system
 - Available to all Member States

Current EU Requirements

- ◆ NeeS format is acceptable for:
 - MAA
 - IMPD
 - ASMF
- ◆ Mandatory format for electronic submissions under the Centralised Procedure
 - Effective January 1, 2010

Current EU Requirements

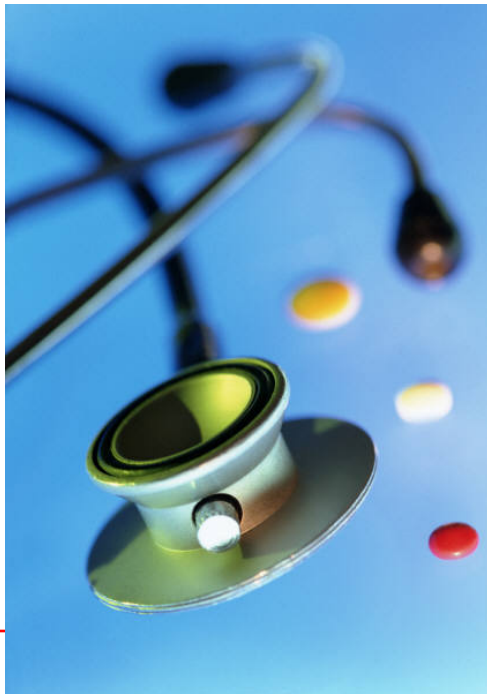
- ◆ Current guidance documents posted on various websites
 - Draft for Testing: Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions, v 1.0 (May 2009)
 - EU eCTD Module 1 Specifications, v 1.3
 - ◆ Mandatory guideline effective January 1, 2009
 - ◆ Primary difference from previous versions was addition of section 1.10 for Paediatric Requirements
 - ICH M2 eCTD Specification

Current EU Requirements

- EU eCTD Module 1 Specifications, v 1.4
 - ◆ Mandatory guideline effective January 1, 2010
 - Single Variation
 - Groupings
 - 3 Types of Groupings
 - Worksharing
 - 1 or more Type 1B or Type II variations affecting multiple marketing authorizations for the same Sponsor
 - Requires high-level submission number assigned by EMEA/regulatory agency/regulatory tracking system
 - ◆ Mandatory guideline effective July 1, 2010
 - All eCTD submissions and all procedures

#5: Fact or Fiction?

- ◆ There are significant benefits of preparing regulatory submissions in eCTD format for both the regulatory agency and the Sponsor.



Myth Buster

◆ Fact!

- Both Sponsors and Regulatory Agencies may recognize significant benefits from the eCTD format
 - ◆ Ease of storage and portability
 - ◆ Reduced use and costs associated with producing, reviewing and storing paper dossiers
 - ◆ Streamlined workflows
 - ◆ Enhanced information sharing between global regulatory agencies, especially EU

Sponsor Benefits

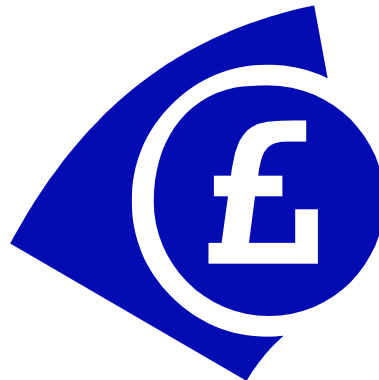
– Additional benefits to the Sponsor

- ◆ Increased use and value from electronic document management system deployments
- ◆ Reduced staffing levels in regulatory departments
- ◆ Simplified training of regulatory operations / submission resources
- ◆ Improved collaboration between teams of document authors, reviewers, publishers and external partners
- ◆ Efficient re-use of documents and submission components for projects involving applications to global regulatory agencies

Sponsor Benefits

– Additional benefits to the Sponsor

- ◆ Improved efficiency to respond to agency questions
- ◆ Support of more efficient and effective submission lifecycle management
- ◆ Enhanced information sharing during licensing, marketing and other business partnership transactions



eCTD Best Practices

- ◆ Ensure all associates are well-trained and understand the CTD requirements for content
- ◆ Ensure document authors understand minimum eCTD concepts, such as submission lifecycle management and operation attributes
- ◆ Develop internal standards for document authoring focused on electronic navigation
 - Document templates
 - Identify items for hyperlinks within text
 - ◆ @@, blue text, italicized text, etc.

eCTD Best Practices

- ◆ Develop process for interacting with vendors to provide eCTD-compliant deliverables
- ◆ Ensure Regulatory Affairs, Regulatory Operations, and IT personnel are well-trained and understand eCTD specifications and requirements
- ◆ Develop tracking tools to assist in managing details of eCTD activities
 - Project management
 - Scope of submission
 - Submission lifecycle management

eCTD Best Practices

- ◆ Develop internal standards for reviewing eCTD submissions focused on electronic navigation
 - % QC check of navigation aids (0 – 100)
 - ◆ Accuracy of destination
 - ◆ Completeness and accuracy of content
 - ◆ Appropriate level of navigation
- ◆ Develop internal standards for archiving eCTD submissions
 - Electronic media
 - FDA ESG



eCTD Best Practices

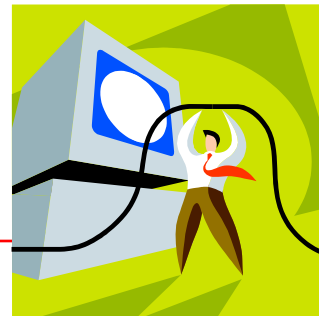
- ◆ Frequent communication between ALL project team members
 - Involve Regulatory Affairs/Regulatory Operations EARLY in preparation process
 - Regular project meetings
 - Roles and responsibilities
 - Milestone activities and deliverables

eCTD Best Practices

- ◆ Utilize all available resources, including industry groups, regulatory agencies, websites, etc.
- ◆ **ENGAGE** upper management
 - Management support is **CRITICAL** to successful eCTD implementation

Helpful Websites

- ◆ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>
- ◆ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm>
- ◆ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM085361>
- ◆ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm085324.htm>
- ◆ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>



Helpful Websites

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm#2a
- <http://esubmission.emea.europa.eu/index.htm>
- <http://estri.ich.org/>
- <http://www.edqm.eu/site/New-Applications-29.html>
- http://cbg.ddg24.tamtam.nl/CBG/en/human-medicines/regulatory-affairs/dossier_requirements/default.htm
- <http://www.hma.eu/225.html>
- <http://www.mhra.gov.uk/Publications/Newsletters/MAIL/CON2024282>

Wrap-Up

- ◆ Electronic submissions are **HERE** and **NOW** is the time to implement
- ◆ Capitalize on available information and resources
 - Industry groups
 - Regulatory agencies
 - Websites/Internet
- ◆ Fact vs. Fiction
 - Identify misinformation

Wrap-Up

- ◆ Organizational Decision
 - Existing processes for submission preparation
 - Regulatory submission pipeline
 - Personnel and IT Infrastructure
 - In-house vs. outsourcing
- ◆ Develop or revise processes and procedures to accommodate electronic requirements
 - Internal training programs
 - Regular review of procedures and training

Wrap-Up

- ◆ Communicate, Communicate, Communicate



Questions?

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