

FDA's eCTD Mandate for 2017: Impact on PET Drug Manufacturers

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Disclosures

- Ted Hanebach is an employee of Mapi SRS
- Daniel Yokell is an employee of Massachusetts General Hospital
- Any products discussed in this presentation are for educational purposes only and do not constitute endorsements of products by the speakers

Agenda

- Introduction
 - Scope of new requirements
 - Clarification of nomenclature
 - Advantages and challenges of electronic Common Technical Document (eCTD)
- Guidance background and impact on the industry
- Options available for companies that need to comply with the guidance
 - In-house eCTD system
 - Software as a Service – SaaS (eCTD on the cloud)
 - Outsourcing of submission publishing and hosting
- Getting eCTD Ready - Tools

Introduction

- In the recently released guidance titled “Guidance on Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications”, the FDA stated that marketing authorization submissions (e.g. **NDA**, **BLA**, **ANDA**) must be submitted in the eCTD format beginning **May 15, 2017**. **IND** submissions must be submitted in eCTD format beginning **May 15, 2018**.
- These FDA requirements, although facilitating efficient submission review, create some significant operational and financial challenges for smaller companies, research institutes, hospitals, generic and API industries.
- While larger pharmaceutical companies with high submission volumes may have a compelling business case for implementing and maintaining an in house regulatory operations team and sophisticated publishing system, these costs are harder for small and medium-sized companies to justify.

Clarification of Nomenclature

- eCTD – electronic Common Technical Document
 - Global standard for filing investigational and marketing applications – scope of “Guidance on Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications”
- SPL – Structured Product Labeling, subset of HL7 RIM Model used for the following filings:
 - Establishment Registration
 - NDC Code Request
 - Product Listings and Content of Labeling
 - GDUFA Self-Identification
 - Lot distribution SPL
 - REMS SPL
- ESG - Electronic Submissions Gateway
 - Portal for transmission of eCTD, PV, and SPL submissions to the FDA

Submissions That are Exempted from the Guidance Requirements

- “Section 745A(a) allows FDA to establish exemptions from the electronic submission requirements. Accordingly, FDA has exempted all submissions regarding **noncommercial INDs** from the requirements under section 745A(a). For purposes of this guidance, the term noncommercial products refers to products that are not intended to be distributed commercially and includes **investigator-sponsored INDs** and **expanded access INDs** (e.g., emergency use INDs and treatment INDs).”

Impact of the Guidance

- The most, affected by the guidance are startup companies, research institutes, universities, smaller generic companies, API manufacturers. The impact on these organization includes:
 - Significant increase in operating costs
 - Potential for failing to have necessary systems by the time eCTDs are required, i.e., not being able to file and maintain submissions
 - Significant impact on internal business and regulatory processes
 - Migration form paper to electronic processes (conversion of legacy documents to eCTD-ready state)
 - Potential for Refusal to File (RTF), if the company files without building necessary expertise (refer to new FDA guidance on RTR for ANDAs*, and “Good Review Practice: Refuse to File”**)
 - Potential for 21 CFR Part 11 noncompliance

How can we get eCTD-Ready by 2017/2018?

- In-house eCTD system implementation
 - Using internal resources
 - Using internal and external resources (big-pharma option)
- SaaS/Cloud systems
 - Using internal resources
 - Using internal and external resources
- Full outsourcing, i.e., submission preparation and hosting is outsourced to the selected vendor

Deciding on the eCTD-Readiness Pathway - *Making the right decision is essential!!!*

- Decision on which option company should take, depends on multiple factors
 - Company size, type and stability
 - Big-, mid-, small-sized; Start-up vs well established company; Virtual company vs company conducting most of activities in-house; Number of partners and CROs involved; Need for eTMF, eDMS
 - Number of products company owns or is trying to commercialize
 - Number of open, or to be initiated submissions
 - Type of submissions - NDA, IND, ANDA, DMF?
 - Global Vs. Regional company reach
 - Business goals - Develop and license/sell Vs. Commercialize and hold
 - Existing departments and infrastructure, processes
 - Availability of templates, publishing processes and tools
 - Existing eCTD expertise, including specific FDA requirements for study data, study tagging files, etc.
 - Availability of government grants

Hospital Based PET Drug Manufacturer Prospective

- Our thought process at MGH:
 - Outsource eCTD filing to consulting firm
 - Conduct eCTD filing house
- Costs and Benefits of Each
 - Consulting firm – Who do other potential users in MGH/Partners Health Care System use?
 - In House – Cost and Requirements

What Would be Our Scope of Work?

- Two Approved ANDAs (FDG and NH_3)
 - Quarterly Safety Reporting for both
 - Annual Reports
 - Supplements as needed
- Estimated to be 8-10 filings per year
- New ANDA for NaF if CMS approves reimbursement

What Would We Need to do eCTD Filings?

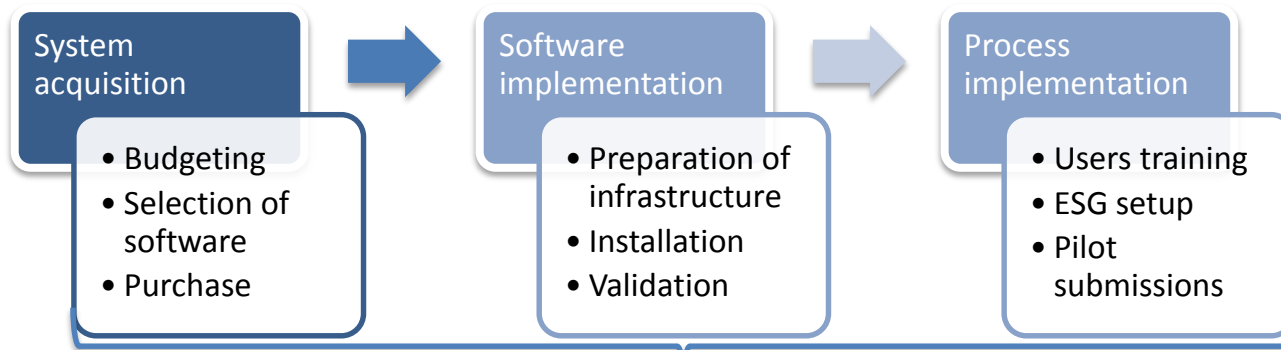
- Word Processing Software
 - Must be able to template the documents to meet FDA eCTD filing guidance for headers, footers and hyper linking
- PDF Publisher and Editor
 - FDA requires files submitted in PDF format, able to be Fast Web Viewed, etc
- eCTD publishing software to publish the filing
- XML software to edit/manage SPL labeling
- FDA Gateway Account
 - Digital Signature Certificate
 - Internet Explorer or Fire Fox with Java able to be limited to FDA supported version
- CDER Direct Account for SPL Labeling/GDUFA reporting, etc

Considerations for In-house eCTD system

- In-house systems provides the company with certain freedoms
 - Selection of the best, or the most appealing platform components available on the market
 - Configuration of software to express internal processes
 - Assignment of properly trained staff to maintain the critical components and processes
- In-house system allows utilization/sharing of existing software/and hardware
- Assures full control over system compliance, and confidentiality and security of the data
- Implementation of in-house system requires very careful (educated) and methodical approach to software/vendor selection, project planning, and implementation execution
- Software/vendor selection (you may need to involve third-party experts)
- Defining software business and functional requirements (including any compatibilities with existing software)
- Request for Proposal (RFP) and selection of vendors for consideration
- Short-list and in-house demo/presentation, reference checking, vendors knowledge verification, financial background checking, price negotiations
- Vendor selection!

Considerations for In-house eCTD system

- Timelines

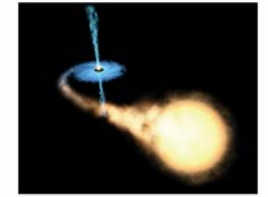


If properly approached, eCTD system implementation usually takes 6 to 10 months

Building eCTD expertise, preparation of SOPs, preparation of supportive systems/processes, TRAINING!

- Cost

- Software, hardware, additional infrastructure maintenance
- Additional IT/validation resources
- Regulatory Operations resources



In-house eCTD system Cost - Warnings

- *Note 1: Your project, if not carefully executed may become a financial black hole!*
- *Note 2: If the cost looks too good to be true – well, you get what you paid for*
- *Note 3: You can't save on 21CFR Part 11 compliance*
- *Note 4: Your IT manager may not be the best person to select your system – this is a team effort!*
- *Note 5: Your company CEO is not the best person for this task either. Let the management approve the budget, and stay away from the project*

SaaS/Cloud eCTD services

- Software as a Service (cloud) is an interesting option for companies that have no infrastructure able to support in-house eCTD implementation, the volume of submissions is too low to justify investment in the in-house system, or there is no plan for company expansion
- It is also a great option for companies that require immediate access to the system capable of eCTD compilation
- This option transfers responsibility of software updates, revalidations, eCTD-eDMS integrations, etc. to the vendor
- It gives companies an option for knowledge transfer from vendor's experts, and provides the company with a greater flexibility for "resources to cost" management
- It allows companies to outsource all publishing and compilation activities, while keeping QC and release activities within the company

SaaS/Cloud eCTD services

- In addition to what is expected from eCTD software vendor, we need to verify
 - Documentation for cloud qualification or attestation (e.g. Statement on Standards for Attestation Engagements 16) and eCTD software validation
 - Quality management policies
 - Data separation approach for multi-tenant systems
 - Documentation for processes (SOPs, training materials, manuals)
 - Support levels, logs for unexpected downtimes, maintenance schedules, backups, redundancies and other business continuity assurances, system performance, ...and referrals!
- Costing of SaaS services depend on
 - Required system components, e.g., eTMF, eDMS, eCTD, RIM, etc.
 - Vendors licensing pattern (per user vs per submission unit vs per project)
 - Additional resources required for the project

Full Outsourcing of Publishing and eCTD Hosting

- Outsourcing of submission publishing, compilation and hosting is a great option for small virtual companies, research institutes, universities, small generic companies, API manufacturers, companies that require eCTD and regulatory affairs/medical writing services, or companies that manage mature products
- It has most of benefits of SaaS options, including immediate access to highly trained resources and great project scalability, but it also provides the lowest cost of the project initiation and maintenance (no licensing), and no need for eCTD or technology expertise
- There is no need for internal technical or standards expertise
- Most of vendors can support the company with project involving other standards (SPL, CDISC, BIMO, etc)
- Vendors can support the company not only with ongoing eCTD hosting and filing, but can help in content migration from paper to electronic format

Full Outsourcing of Publishing and eCTD Hosting

- Such an arrangement, however, requires very close cooperation between the company and the vendor, as most of submission preparation and filing responsibilities are transferred to the vendor
- Selection of the vendor is crucial – look for:
 - Vendor's industry expertise
 - Capacity and financial stability
 - Vendors locations and support model
 - FDA expertise
 - Processes, SOPs, Quality systems, validation SOPs and records
 - Referrals,
 - PM expertise
 - **System security and 21CFR11 compliance!**
- Arrangement requires:
 - Well defined roles
 - Well defined Scope of services
 - FTE or per unit or time and materials?
- Potential Third-Party Audit!

Full Outsourcing of Publishing and eCTD Hosting

- Important aspects of collaboration:
 - Predefined roles:
 - Who does content review, QC, release
 - Who is responsible for hyperlinking QC
 - Who is responsible for QC and release eCTD aspects of the submission (file location, metadata, STF)
 - Common SOPs
 - Training
 - For bigger projects, a dedicated (full time) vendors PM is a key for the arrangement success
 - Communication channels
 - Predefined content transfer channels and workflows
 - Change management
 - Issue management plan

MGH – What We Did to Prepare for eCTD 2017

- After evaluating:
 - Cost of a eCTD publishing program and other eCTD supporting software
 - Cost of outsourcing
- We decide to try doing eCTD in-house
 - Went with a eCTD pay to publish sequence software model
 - Cost shared with another group within the health system license cost for Word eCTD templates and PDF plugin software
 - Setup FDA gateway and CDER direct Account
 - Needed dedicated Windows 7 PC – upgrade software as needed by FDA gateway (not controlled by hospital IT)

Thank You!
Questions please!

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Supporting Slides

Guidance background (PDUFA V/GDUFA I), and Scope

- *PDUFA V - Information Technology/Informatics Plan FY 2013 – FY 2017 (September 2014) - PDUFA V IT/Informatics Goals and Objectives: **Goal 2:** Electronic Regulatory Submissions - providing a consistent approach to the creation and review of regulatory submissions; **Objective 2.2:** Require submissions in a standardized format.*
- *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications - Guidance for Industry - May 2015*
 - Marketing authorization submissions (e.g. **NDA, BLA, ANDA**) must be submitted in the eCTD format beginning **May 15, 2017**.
 - **IND** submissions must be submitted in eCTD format beginning **May 15, 2018**.
 - FDA considers master files to be submissions to an NDA, ANDA, BLA, or IND, and therefore to fall within the scope of requirements set forth in section 745A(a). These include new drug master files (DMFs) (21 CFR 314.420), new biological product files (BPFs) (21 CFR 601.51), and any amendments to or annual reports on previously submitted DMFs or BPFs. This guidance also applies to submissions for drug/device combination products filed pursuant to section 505 of the FD&C Act or subsection (a) or (k) of section 351 of the PHS Act.”
- Beginning May 5, 2017, the ESG must be used for eCTD submission sizes of 10 GB or less for NDAs, BLAs, ANDAs and master files.
- Beginning May 5, 2018, the ESG must be used for eCTD submission sizes of 10 GB or less for commercial INDs.

Advantages and Challenges of eCTD

- **Main Advantages**
 - Provides predefined structural organization of data
 - Permits document and submission life-cycle
 - Helps in data accessibility, search and comparison
 - Supports organized information transfer through FDA's electronic submissions gateway
 - Supports utilization of other standards like SPL, SDTM
 - Improves communication on CRO-sponsor, sponsor-agency and agency-agency levels
 - Creates a process of very organized and controlled content preparation and submission compilation
- **Main Challenges**
 - eCTD causes a significant change in ways we create, manage, review and archive our documentation
 - Requires significant initial investments in software and infrastructure, training, and resources
 - Compliance (21 CFR Part 11, Annex 11)

In-house eCTD system Cost - Example

- E.g., average initial capital cost including basic hardware, installation, outsourced validation, licensing (assuming licensing for 5 users). No personnel cost taken into account.
 - eCTD system only
 - Infrastructure - \$18K
 - Supportive software - \$2K
 - Installation and validation - \$30K
 - Licensing - \$60K
 - **Total: \$110K**
 - **Range of quotes for the system as above: \$79K to 180K***
 - eCTD integrated with eDMS
 - Infrastructure - \$28K
 - Supportive software - \$21K
 - Installation and validation - \$50K
 - Licensing - \$115K (including additional 10 read only users)
 - **Total: \$214K**
 - **Range of quotes for the system as above**: \$130K to over \$400K**
- Annual maintenance cost
 - licensing – \$12.4K for eCTD system and \$23K for eCTD integrated with eDMS
 - Infrastructure updates, internal maintenance - ~\$10K
- **For a company with a significant volume of submissions, ongoing costs may be lower than SaaS or outsourcing options**

*based on 4 quotes,

**based on 3 quotes

	In-house	Cloud internal resources	Cloud internal/ external resources	Full outsourcing
Pros	<ul style="list-style-type: none"> • Full control of the content, processes, and infrastructure. • Independence from vendor's timelines • Ability to chose "the best of the crop" • Ability to customized configuration 	<ul style="list-style-type: none"> • Lower operational costs • Simplified system training • Company can decide on the system components, i.e., eTMF, eDMS, eCTD, RIM • Scalability and Minimal system setup /customization, minimal validation effort • Ease of access • Utilization of internal SOPs • Almost immediate system availability 	<ul style="list-style-type: none"> • plus • Opportunity for knowledge transfer • Availability of "as needed" extra resources 	<ul style="list-style-type: none"> • Low operational costs • No system implementation • Minimal system training • Help with conversion of legacy paper documentation to eCTD ready status at relatively low cost • Almost immediate system availability • Covers entire process from content creation to filing through the gateway (ESG)
Cons	<ul style="list-style-type: none"> • Very high cost of and long time of implementation • Responsibility for updates and maintenance • Requires resources with eCTD/DMS expertise • Temptation for minimalistic approach to the system (not 21 CFR 11 compliant) 	<ul style="list-style-type: none"> • Vendor selection process can be difficult – may require third-party input during the selection • Requires resources with eCTD expertise • No immediate access to external resources 	<ul style="list-style-type: none"> • As cloud with internal resources, plus • Danger of getting underqualified external resources • Complex PM and project governance • Complex document review and approval cycles • Cross-companies SOPs 	<ul style="list-style-type: none"> • Vendor selection process can be difficult – may require third-party input during the selection • No internal control over content flow • Dependency on external system
Typical user	Multinational companies. Some mid-sized and smaller companies	Medium sized companies	Medium and smaller sized companies Some big Pharma	Small and startup companies, research institutes, universities, big Pharma and some "next 20"

Getting eCTD Ready – FDA Help

- FDA support:
 - <http://www.accessdata.fda.gov/scripts/cder/training/eCTD/menu.htm>

The screenshot shows the FDA eCTD training menu page. At the top, the FDA logo is on the left, and the text "U.S. Food and Drug Administration" and "Protecting and Promoting Your Health" is in the center. To the right, there is a "Small Business Assistance" logo and the text "Center for Drug Evaluation and Research". Below this is a navigation bar with links: "Electronic Common Technical Document (eCTD): Overview and Submission", "GLOSSARY", "HELP", "FAQs", "RESOURCES", "FDA/DRUGS", and "CDERLearn". The main content area features ten blue buttons with white text and play icons, arranged in two rows. The first row contains: "Introduction / Overview", "Background on eCTD Standard", "Submitting in eCTD Format", and "Transmitting Electronic Submissions to CDER". The second row contains: "Submitting FDA Forms with Submissions", "Validating eCTD Submissions", "Submitting an eCTD Sample", "Requesting a Pre-Assigned Application Number", and "Summary". At the bottom right, there is a blue box with a document icon and the text "Currently submitting by paper? Select here.". At the bottom left, there is a "USER INSTRUCTIONS:" section with the text "Select any lesson to begin."

FDA U.S. Food and Drug Administration
Protecting and Promoting Your Health

Small Business Assistance
Center for Drug Evaluation and Research

Electronic Common Technical Document (eCTD): Overview and Submission GLOSSARY HELP FAQs RESOURCES FDA/DRUGS CDERLearn

Introduction / Overview

Background on eCTD Standard

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Requesting a Pre-Assigned Application Number

Summary

Currently submitting by paper? Select here.

USER INSTRUCTIONS:
Select any lesson to begin.

Getting eCTD Ready – Industry Help

- RAPS Advanced eCTD Submissions (Two-Day Workshop) - The Regulatory Convergence - Pre-conference workshops October 25, 26, 2015, Baltimore (<http://www.raps.org/2015/agenda/workshops/>)
- IRISS Forum (<https://www.iriss-forum.org/>)
- LinkedIn groups:
 - eCTD Submissions and eLabeling
 - eCTD Regulatory Submissions Network
- DIA EDM conferences
- Industry Book of Knowledge - Practical Considerations for eCTD Submissions: A CMC Perspective
- Industry Book of Knowledge Practical Considerations for eCTD Submissions: US IND Applications in eCTD format: A CMC Perspective
- Industry Book of Knowledge - Practical Considerations for eCTD Submissions: Quality Overall Summary (QOS) for Marketing Applications

CTD Format

- CTD format would be composed of 5 modules with CMC information contained in Modules 2 & 3:
 - **Module 1:** Administrative
 - **Module 2:** Summaries of CMC, Pre-Clinical and Human Experience modules
 - **Module 3:** Detailed CMC of API and finished pharmaceutical
 - **Module 4:** Pre-Clinical Experience and Pharmacology/Toxicology
 - **Module 5:** Previous Human Experience



Common Technical Document Format

- Common Technical Document format is an international standard format for regulatory submissions
 - Governed by international standard from ICH:
 - *THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY – M4Q(R1)*
 - Recommended for regulatory filings in EU, Japan and US



CTD Organization

- CTD documents are organized as follows:
 - 3.1 – Table of Contents
 - 3.2 – Body of Data
 - 3.2.S – Drug Substance Information (API)
 - 3.2.P – Drug Product Information (Finished Drug)
 - 3.2.A – Appendices (Facility Information)
 - 3.2.R – Regional Information (Batch records)
 - 3.3 - References



- FDA CTD M4 Guidance for Industry:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073257.pdf>

- ICH CTD Website

<http://www.ich.org/products/ctd.html>

- ICH CTD M4 R1 Guidance

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q_R1_.pdf

