



# **Electronic Submissions (eCTD Format)**

**What, when, where, how,  
and why**

**ASQ Meeting  
21 March 2009, JCCC**

# About the Speakers

## **Kathy Oliva-Whalen, BS** **Regulatory Consulting**

- > 25 yrs experience in drug development and regulatory consulting
- US, Canadian, and EU regulatory submission experience
- Experience working with virtual and small to large pharma companies

### **Contact Information**

E-mail: [kathleen-whalen@sbcglobal.net](mailto:kathleen-whalen@sbcglobal.net)  
Phone: 816-728-7990

## **Laurie Leet, BS** **Regulatory Publishing**

- 15 yrs US, EU, and Canadian regulatory submission experience
- 12 yrs regulatory publishing experience
- Expertise implementing regulatory publishing at 3 service organizations
- Experience working with virtual and small to large pharma companies

### **Contact Information**

E-mail: [laurieleet@sbcglobal.net](mailto:laurieleet@sbcglobal.net)  
Phone: 913-709-7112



# Overview

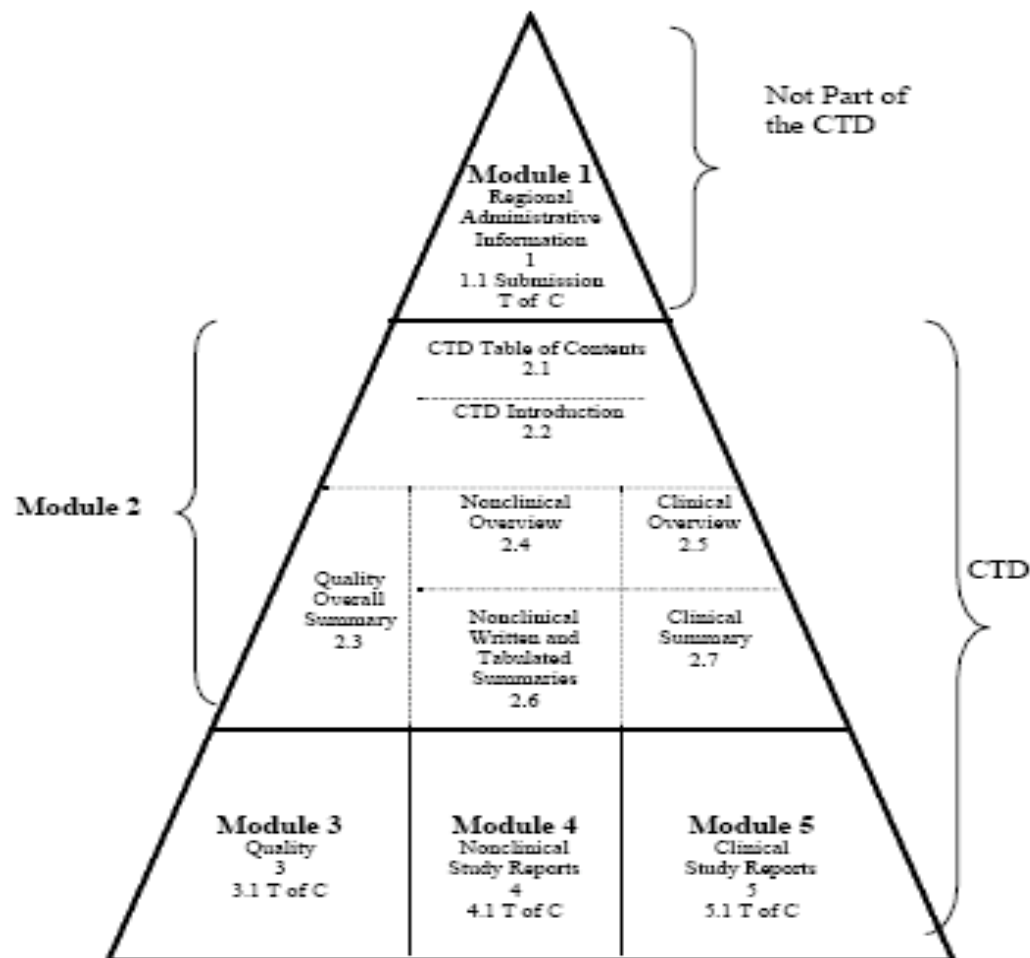


- CTD/eCTD description
- eCTD terminology and file structure
- Current regulatory environment
- Transitioning to eCTD
- eCTD best practices
- Submission document management and processing
- Legacy documents
- Submission media and delivery
- Submission lifecycle

# What is CTD?

- Common Technical Document
- Global format for regulatory submissions
- Consistent data organization
- Applies to NDAs, ANDAs, BLAs, MAAs, INDs, master files

# How is a CTD Organized?



# What is eCTD?

- Electronic Common Technical Document
- Method to electronically transfer product information and data
- Collection of electronic files organized according to guidelines defining file format, folder/file naming conventions, document specifications, etc.
- Designed with considerations that facilitate
  - creation
  - review
  - lifecycle management
  - archiving

# eCTD Terminology

- Granularity – individual documents within submission sections
- Lifecycle – the history of a product application
- XML backbone – structure used to navigate various submission sections
- Bookmark – navigation method in a PDF document = TOC
- Hyperlink – links within document text that take the reviewer to specified location either within that document or to another document within the submission

# eCTD File Structure

The image displays two screenshots of a file explorer window illustrating the eCTD file structure.

**Top Screenshot: Overall Folder Structure**

Name	Size	Type
m1		File Folder
m2		File Folder
m3		File Folder
m4		File Folder
m5		File Folder
util		File Folder
index	125 KB	XML Document
index-md5	1 KB	Text Document

**Bottom Screenshot: Contents of '26-nonclin-sum' Folder**

Name	Size	Type
introduction	27 KB	Adobe Acrobat Doc...
pharmacol-tabulated-summary	79 KB	Adobe Acrobat Doc...
pharmacol-written-summary	135 KB	Adobe Acrobat Doc...
pharmkin-tabulated-summary	80 KB	Adobe Acrobat Doc...
pharmkin-written-summary	120 KB	Adobe Acrobat Doc...
toxicology-written-summary	72 KB	Adobe Acrobat Doc...

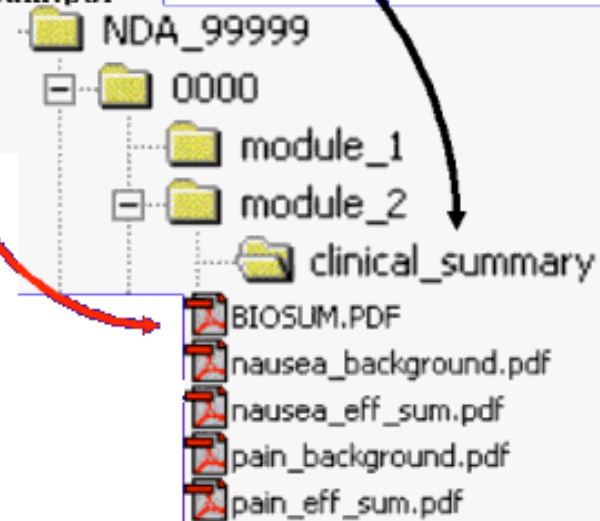
# Example of XML Backbone

## eCTD DTD version 3.2

- m1-administrative-information-and-prescribing-information
  - [us-regional](#) [new]
- m2-common-technical-document-summaries
  - m2-3-quality-overall-summary
    - m2-3-s-drug-substance [manufacturer: APTUIT] [substance: GoodPills]
      - [Drug Substance](#) [new]
    - m2-3-p-drug-product [manufacturer: Aptuit] [product name: Goodpills] [dosage form: tablet]
      - [Drug Product](#) [new]
    - m2-3-a-appendices
      - [Appendices](#) [new]
    - m2-3-r-regional-information
      - [Regional Information](#) [new]
  - m2-4-nonclinical-overview
    - [Nonclinical Overview](#) [new]
  - m2-5-clinical-overview
    - [Introductory Statement](#) [new]
  - m2-6-nonclinical-written-and-tabulated-d-summaries
    - m2-6-1-introduction
      - [Introduction](#) [new]
    - m2-6-2-pharmacology-written-summary
      - [Pharmacology Written Summary](#) [new]
    - m2-6-3-pharmacology-tabulated-d-summary
      - [Pharmacology Tabulated Summary](#) [new]
    - m2-6-4-pharmacokinetics-written-summary
      - [Pharmacokinetics Written Summary](#) [new]
    - m2-6-5-pharmacokinetics-tabulated-d-summary
      - [Pharmacokinetics Tabulated Summary](#) [new]

# XML Mapping to Folders

```
<m2-7-clinical-summary>  
<m2-7-1-summary-of-biopharmaceutics-and-associated-analytical-methods>  
<leaf operation="new"  
xlink:href="module_2/clinical_summary/Biosum.pdf"  
<title>HpBio Summary</title>  
</leaf>
```



# CTD vs. eCTD

## CTD (Paper)

- No specialized software
- Overall and module TOCs
- Printed documents, various formats
- Tabs for navigation
- More physical storage space
- More time to pack and ship
- Less efficient access and review
- Difficult to view entire submission lifecycle

## eCTD

- Specialized software
- XML backbone = TOC
- Electronic documents, PDF format
- Bookmarks/hyperlinks for navigation
- Less physical storage space
- Less time to pack and ship
- ESG available
- More efficient access and review
- Easy to view entire submission lifecycle

# Where is the industry going?

US

- eCTD for electronic submissions

EU

- Only eCTD (CP EMEA) by 1 Jan 2010

Canada

- eCTD format on CD/DVD + paper

**Global regulatory agencies are rapidly migrating towards electronic submissions!**



# eCTD Guidances



ICH

<http://estri.ich.org/eCTD/index.htm>

US

<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

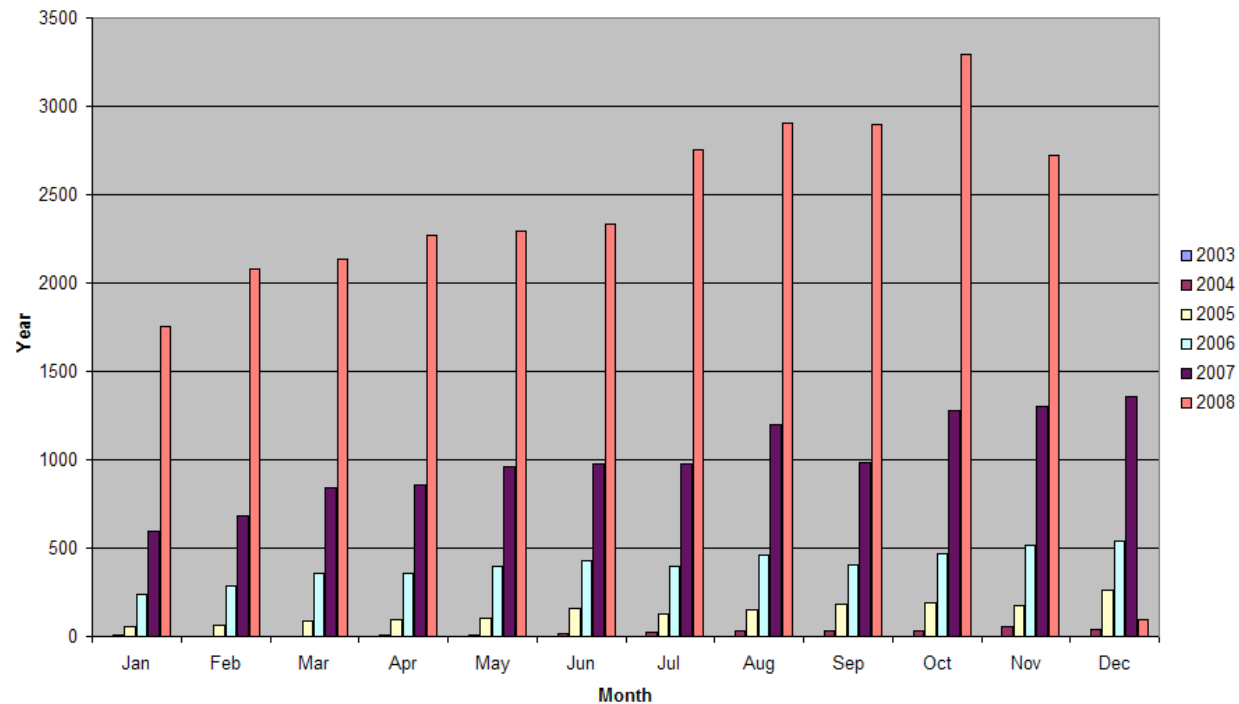
Canada

[http://www.hc-sc.gc.ca/dhp-mps/prodpharma/  
applic-demande/guide-ld/ctd/notice\\_avis\\_ctd-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/notice_avis_ctd-eng.php)

# Current Status of US eCTD Submissions

## eCTD Submissions

October 2003 - November 2008



FDA Office of the Chief Information Officer  
PDUFA IT Quarterly Briefing, 12 December  
2008

# Transitioning from Paper to eCTD

Basic principles for a successful transition include:

- Early planning and preparation
- Appreciation of regulatory science
- Understanding guidance documents
- Knowledge of CTD format/content and eCTD specifications
- Knowledge of the e-submission process
- Utilization of appropriate tools
- Consistent attention to detail
- Application of QC/QA principles

# Key Transition Factors

- eCTD specification = global electronic submission standard
- eCTD guidances further define regulatory authority expectations
- eCTD must be 21 CFR 11 compliant (US)
- FDA approval required to submit eCTDs

**21 CFR 11 compliance, process consistency, submission quality, and trained/knowledgeable publishing staff are absolutely critical**

# eCTD Best Practices

- Involve publishing early in the process
- Develop a regulatory submission map
- Prepare a written project plan
- Train authors on templates / formatting
- Insist on receiving documents on a rolling basis
- Include review cycles in timelines
- QC! QC! QC!



# Exchanging Submission Documents

- FTP site
- VPN
- SharePoint
- e-mail
- DMS
- File share
- Other



# File Formats for Electronic Documents

- PDF – should be text searchable; however some legacy documents may only be available in scanned form
- SASXPOR (XPT) – datasets
- ASCII text file – SAS program files
- XML – documents, data, document information files
- MSWord – draft labeling
- SPL – Structured Product Labeling



# Document Processing



- Compare file name with document contents
- PDF
  - Adobe 5, v1.4
  - Page orientation
  - Page size
- Word
  - Formatting
  - Page breaks
  - TOC and hyperlinks
- QC document bookmarks and hyperlinks



# Managing Submission Documents

- Log documents
- Track processing steps
- Control changes to “final” documents



# Pitfalls and Problems

- Software conflicts
- Printer drivers
- Software updates
- Graphics
- Fonts



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# Legacy Documents

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Legacy = paper or scanned electronic copies

Submit scanned copy

- Add bookmarks and hyperlinks

Convert to text searchable

- OCR
- Retype document



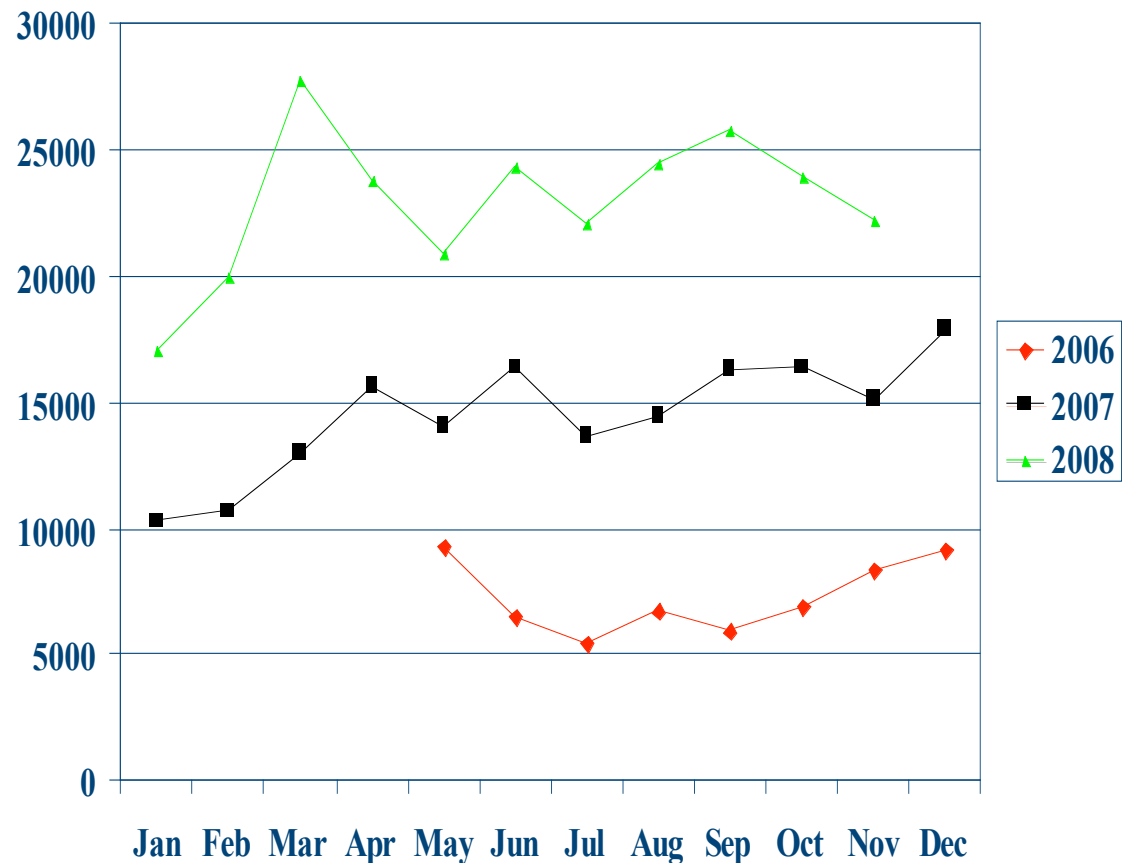
# Submission Media



- CD ROM
- DVD
- Digital Tape

# FDA Electronic Submission Gateway (ESG)

- Supports submissions up to 100GB - CBER, CDER, CDRH and CVM
- Speeds delivery to FDA reviewers
- Does not open or review submission



# Submission Lifecycle

Attribute that provides information about lifecycle

Operations = New, Append, Replace, Delete

- New – first time document is submitted
- Append – used for large documents
- Replace – replaces a document previously submitted
- Delete – removes a document previously submitted

Ability to view entire submission lifecycle

Can filter view by sequence, document, operation attribute

# Regulatory Reviewer View of an eCTD

The screenshot displays the Regulatory Reviewer View of an eCTD. The interface is divided into several sections:

- Life Cycle Tree (Left):** A hierarchical tree structure showing the document's organization. The selected item is "5.2. Tabular Listing of all Clinical Studies".
- Details Table (Top Right):** A table with columns: Reviewed, Title, Type, Status, Submitted In, File Extensi..., and Pa. The first row shows a file named "tabular listing of all clinical studies" with a status of "Current".
- Preview Window (Bottom Right):** Displays a preview of the selected document section, titled "Section 5.2 Table 1. Listing of All Studies".

The preview window shows a table with the following data:

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Sub (by Treat Group Options)
	between formulations		
<b>5.3.1.1 Healthy Subject PK and Initial Tolerability Study Reports</b>			
	Phase I, DB, 3 <sup>rd</sup> , partly open, randomized PC, 5-period ND, dose escalation in 2 PG Determine the safety	Healthy male subjects (Route : Oral solution; Dose regimen : Single dose - Cohort 1 : MVC 1mg, 10mg, 100mg, 900mg, all fasted	24 Cohort 1: Planned 12 Randomise/ Treated 12 Completed

[esub@cderr.fda.gov](mailto:esub@cderr.fda.gov)

Donovan Duggan, CDER, presentation, San Diego Tutorial



# Why eCTD?

- Facilitates efficient and rapid sharing of information
- Facilitates navigation through documents/submissions
- Increases efficiency of regulatory review
- Enables review of entire submission lifecycle with ease
- Enhances submission document storage/rapid retrieval
- Builds NDA/MAA submission DURING development
- Facilitates submission preparation across multiple countries
- Allows more efficient due diligence audits



# Closing Remarks

**The end is near for the traditional paper-based era of managing, reviewing, and submitting regulatory submissions**

Successful transition to eCTD provides competitive advantages:

- Cost savings
- Increased review efficiency
- Decreased risk of refusals to file
- Increased efficiency in preparing global submissions