

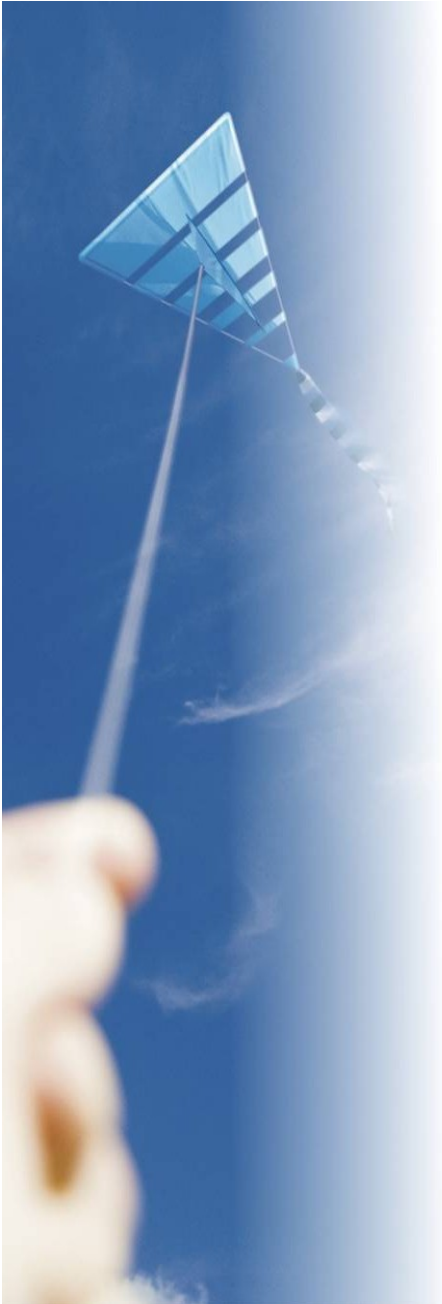


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Introduction to Document Authoring Best Practices for eCTD Submissions

25 March 2010

Sybille L. Sauter, Ph.D., R.A.C.
Senior Regulatory Scientist
Cato Research, Ltd.
ssauter@cato.com

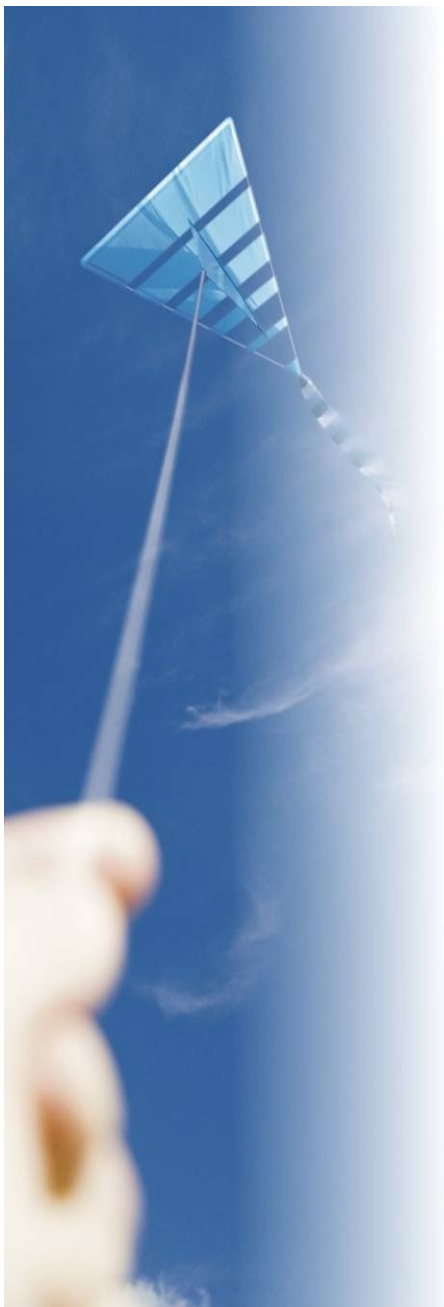


Learning Objectives

- To recognize and avoid common problems during the transition from paper-based to eCTD regulatory submissions (e.g., INDs, NDAs)
- To minimize the impact of medical authoring on the electronic submission process and promote more efficient submission compilation through best authoring practices

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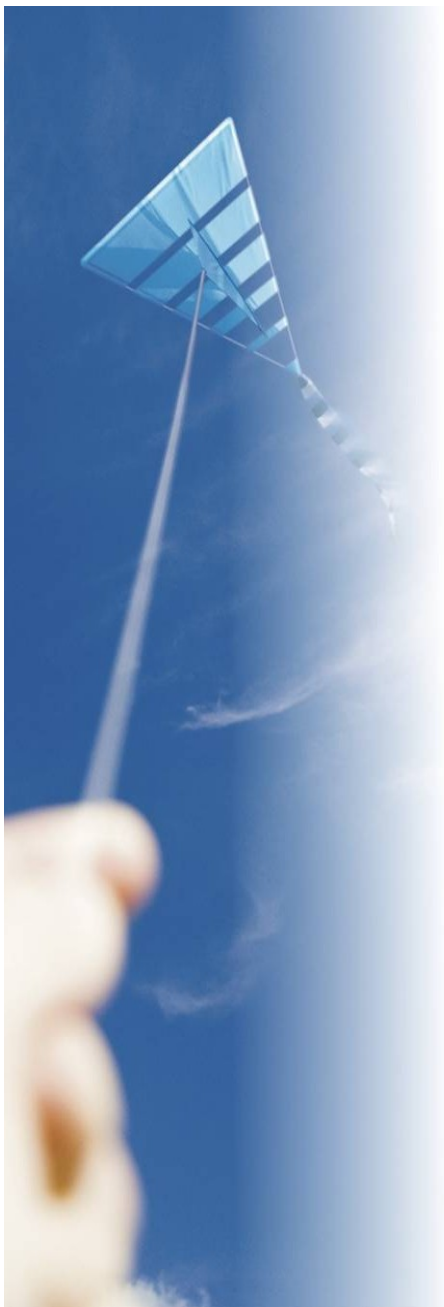


Agenda

- Background on eCTD
- How to get started?
- Best authoring practices for eCTD documents
- Summary
- Questions

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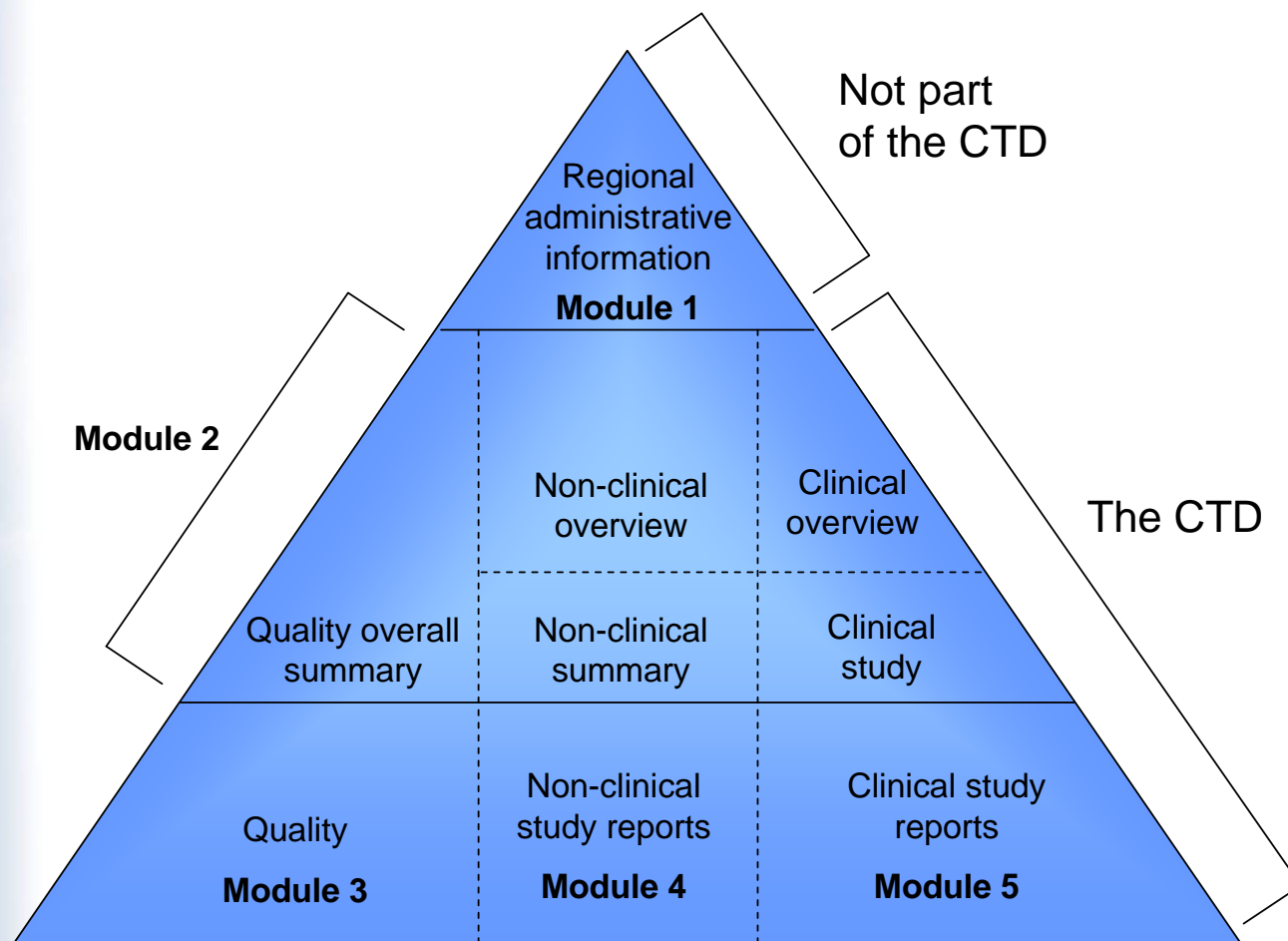


Background

- **eCTD** (electronic common technical document) developed over several years by the ICH Multidisciplinary Group 2 Expert Working Group
- Implemented in 2005
- Applies to **IND, NDA, ANDA, BLA, DMF** and associated submissions
- United States
 - 01 Jan '08: electronic submissions must be eCTD
 - eCTD not mandatory but industry standard
- Europe
 - 01 Jan '10: all electronic submissions must be in eCTD format (centralized procedure, EMEA)

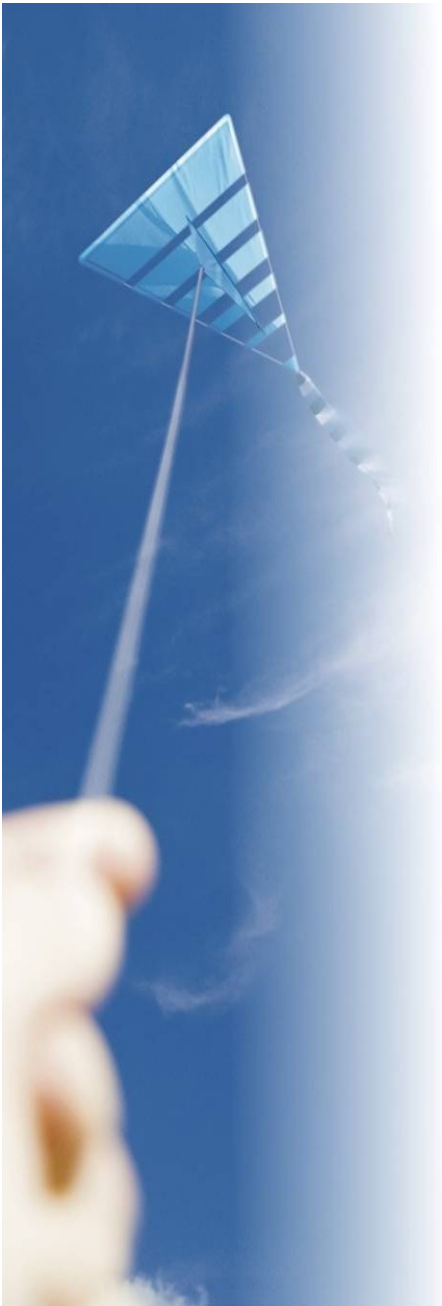
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The CTD Pyramid

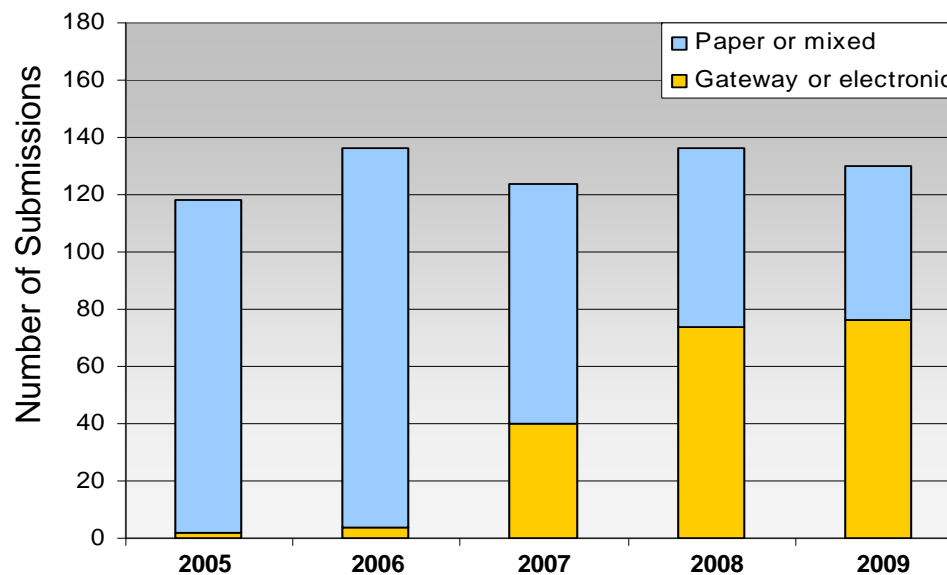


CTD: common technical document

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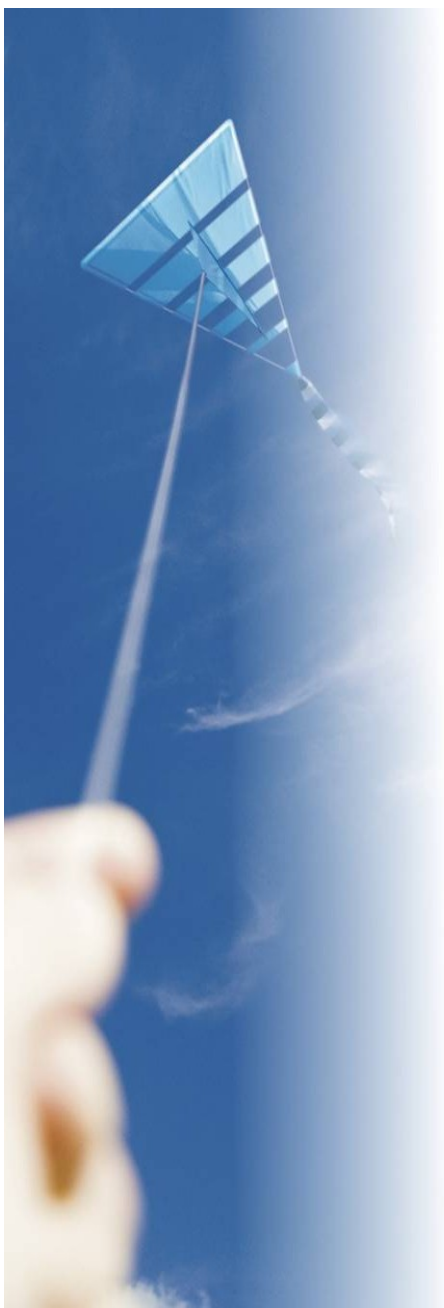


How Are We Doing? - an FDA Perspective



- 56.2% of original NDAs (70% NDA amendments) in fully electronic format
- Only 12.5% of original INDs (29.7% amendments) in fully electronic format

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Kick-Off for eCTD Document Authoring

- Include key stakeholders to obtain agreement on:
 - Critical milestones, objectives, and submission timeline
 - Resource allocation and responsibilities
- Specifically, support medical authors with:
 - Upfront agreement on placement of submission documents within eCTD
 - Application content, format, and layout
 - Style guide and document templates

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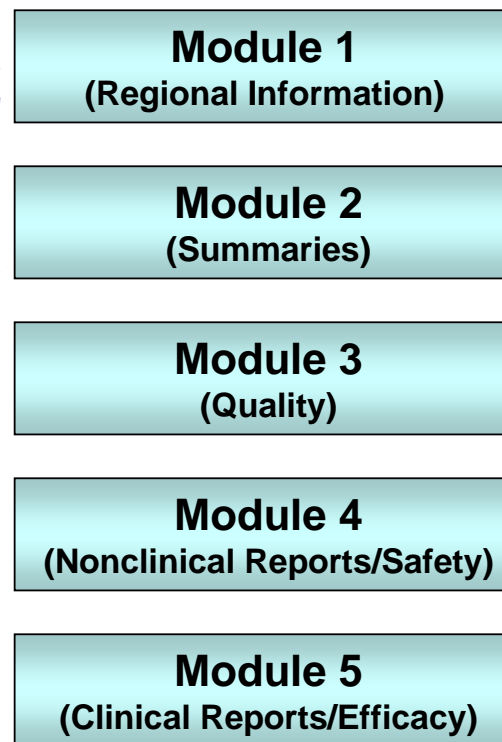
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Traditional IND to CTD format

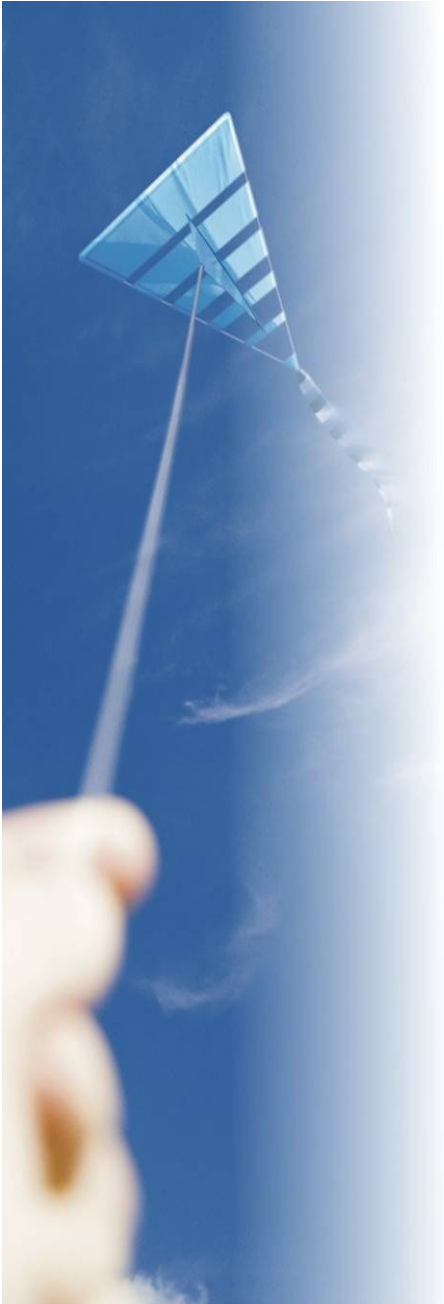
Traditional IND (US) Format

1. Form FDA 1571
2. Table of Contents*
3. Introductory Statement
4. General Investigational Plan
5. Investigator's Brochure
6. Clinical Study Protocol
7. Chemistry, Manufacturing, and Controls Data
8. Pharmacology/Toxicology Data
9. Previous Human Experience
10. Additional Information
 - a. pre-IND correspondence
 - b. Literature References
 - c. Investigational Drug Labeling

CTD Format



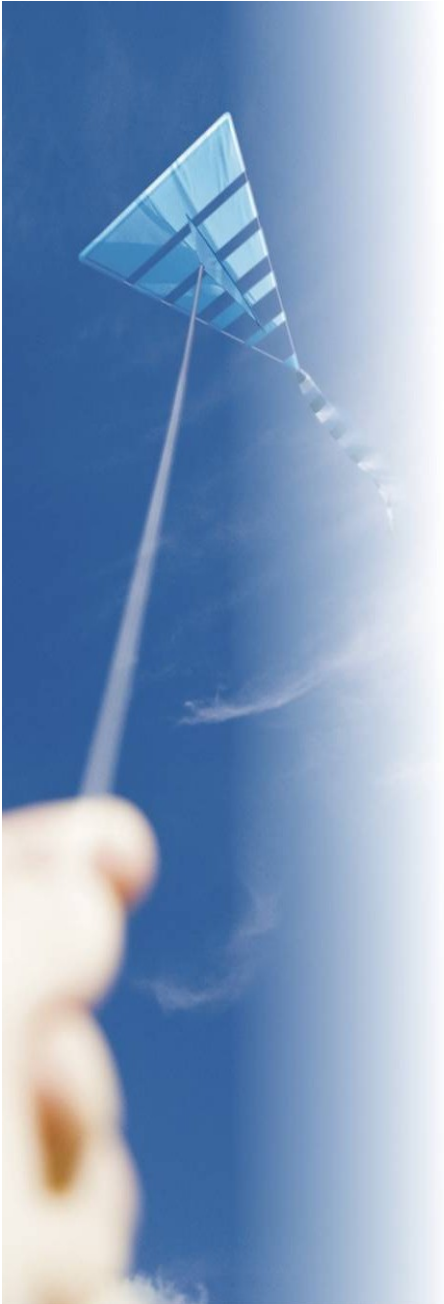
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Best Authoring Practices for eCTD Documents

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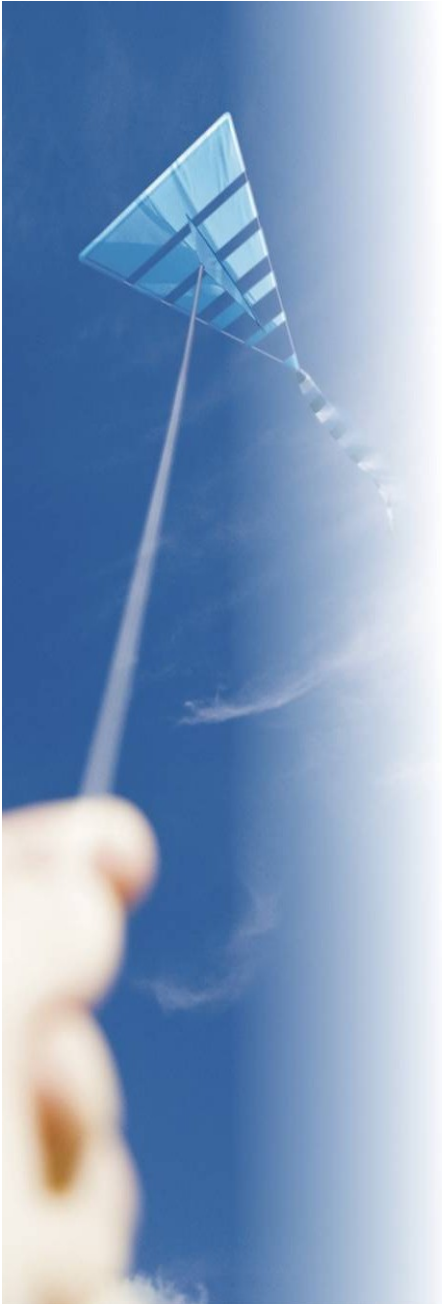


And Your Main Goal Is...

- Effective communication!
- Clarity improves reviewability!

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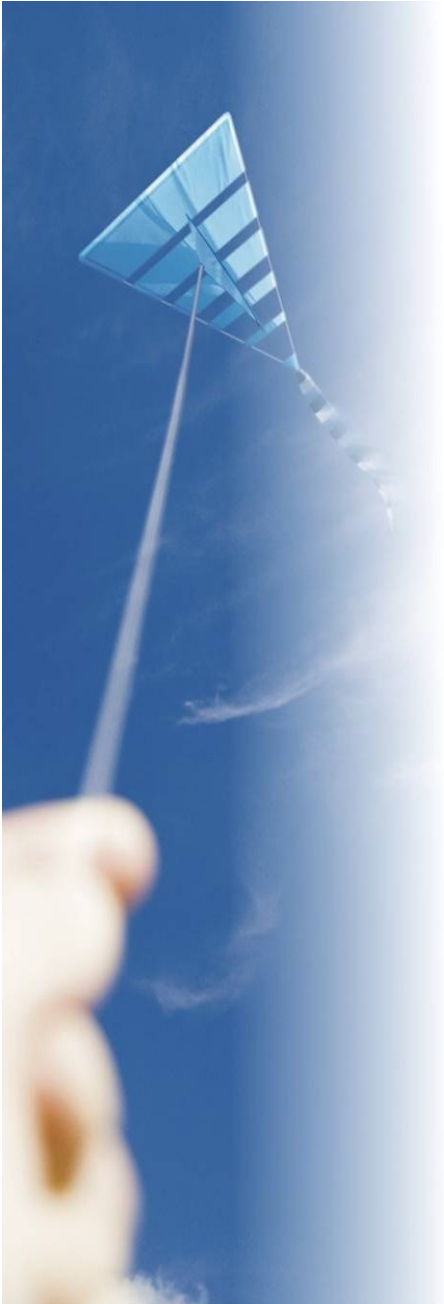


Best Authoring Practices

- Adhere to CTD hierarchy
- Use appropriate level of granularity
- Generate comprehensive study tagging files
- Make clear references to study reports
- Use smart hyperlinking practices
- Use meaningful file names
- Consider application from reviewer's standpoint

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CTD Hierarchy

- Electronic submissions require adherence to CTD hierarchy
- Placement of documents lower than the CTD headings is discouraged
- Map submission document to a CTD section early in the planning process

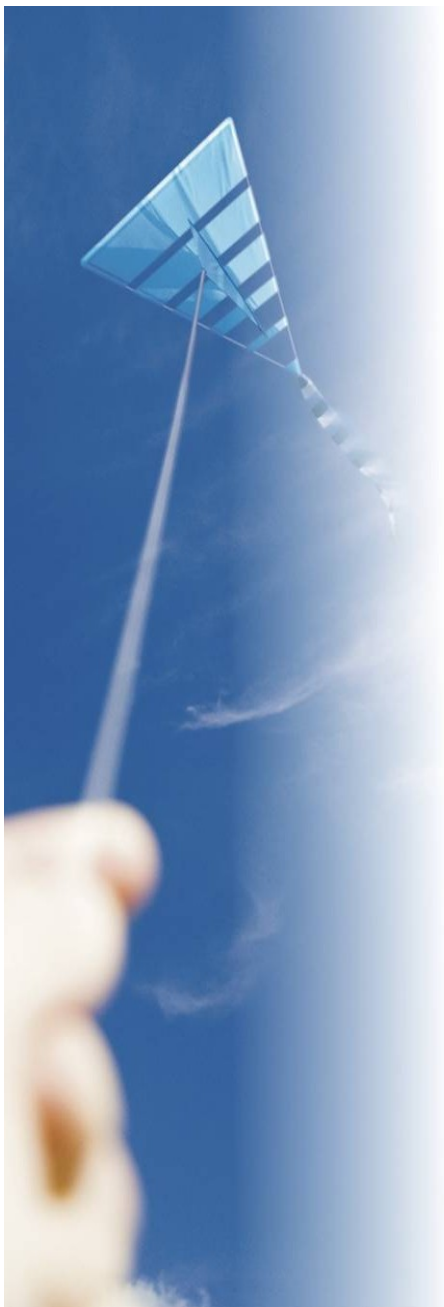
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CTD Mapping Strategies: Granularity

- In contrast to standard paper format, for the eCTD format the entire document changes
 - Consider using high degree of granularity from the beginning to plan for changes/updates/additions to documents
 - Most significant for Module 3 CMC/Quality
 - Maintain highest level of granularity for Module 3, e.g. 3.2.S.X.X, 3.2.P.X.X.
 - Increased granularity allows for frequent updates and revisions which are common

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CTD Mapping Strategies: Study Tagging Files

- Assign nonclinical and clinical study reports to appropriate 4th level CTD section
 - All repeated dose toxicology studies assigned to 4.2.3.2 by species
 - Further numerical ordering (i.e., 4.2.3.2.1) within section 4.2.3.2. not recognized in the XML backbone but useful tool for project management
 - Study tagging files contain required information to sort the studies appropriately

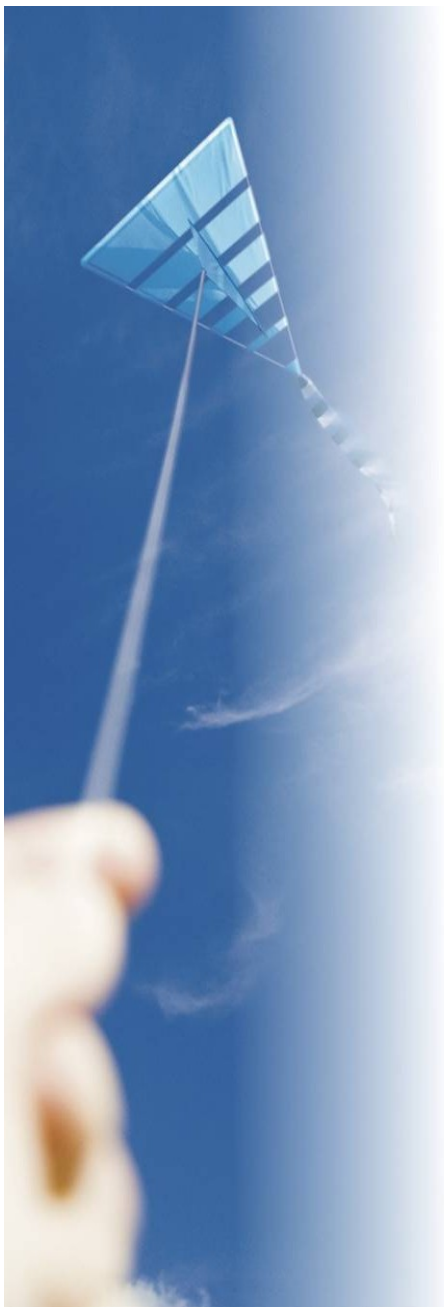
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File Specification for Study Tagging Files

The eCTD Backbone Files Specification for Study Tagging Files -- 2005						
	Section 4.2.3.1		Section 4.2.3.2		Section 4.2.3.4.1	
3	species	mouse	species	mouse	species	mouse
4		rat		rat		rat
5		hamster		hamster		hamster
6		other-rodent		other-rodent		other-rodent
7		rabbit		rabbit		rabbit
8		dog		dog		dog
9		non-human-primate		non-human-primate		non-human-primate
10		other-non-rodent-mammal		other-non-rodent-mammal		other-non-rodent-mammal
11		non-mammals		non-mammals		non-mammals
12						
13	route-of-admin	oral	route-of-admin	oral		
14		intravenous		intravenous		
15		intramuscular		intramuscular		
16		intraperitoneal		intraperitoneal		
17		subcutaneous		subcutaneous		
18		inhalation		inhalation		
19		topical		topical		
20		other*		other*		
21		*(consult regional authorities)		*(consult regional authorities)		
22						
23			duration	short		
24				medium		
25				long		

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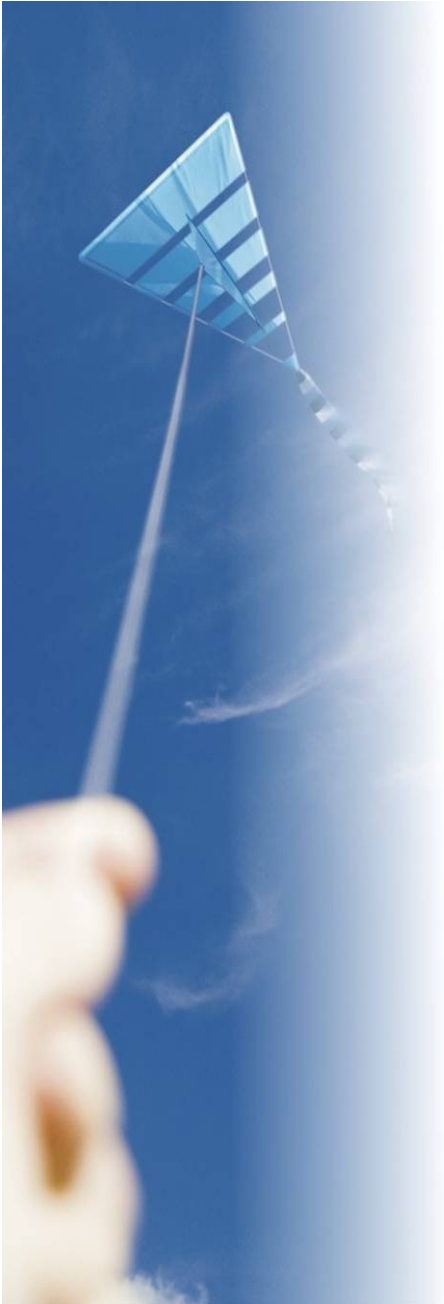


CTD Mapping Strategies: Report Placement

- Sometimes reports could go in more than one CTD section
 - Example: Bioanalytical report for metabolite ID in dog, mouse, and human plasma
 - 4.2.2.1 Analytical Methods and Validation Reports
- OR**
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

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Referencing Study Reports (I)

- A common mistake is to refer to nonclinical or clinical studies by CTD section only rather than by study number/name
- FDA reviewers typically focus on study number, not CTD section

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Referencing Study Reports (II)

- **Unclear**

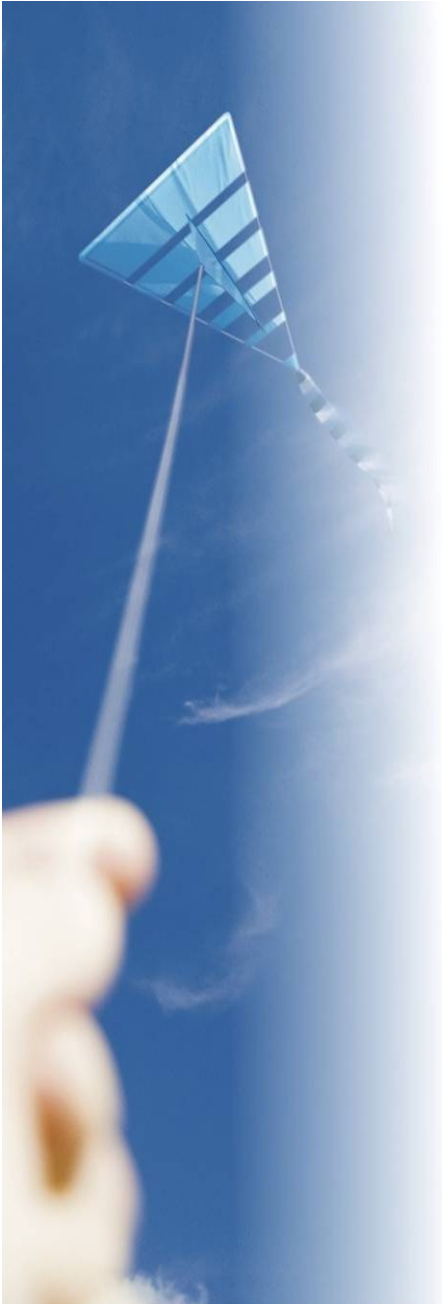
In vitro studies showed that CureAll does not inhibit CYP450 ([Section 4.2.2.4.1](#)). Further *in vitro* studies showed that CureAll appears to be a substrate for CYP226, with a $t_{1/2}$ of 36 min ([Section 4.2.2.4.2](#) and [4.2.2.4.3](#)).

- **Better**

As shown by [Study ABC-001](#), CureAll does not inhibit CYP450. Further *in vitro* studies showed that CureAll appears to be substrates for CYP226, with a $t_{1/2}$ of 36 min ([Study OPQ-002](#) and [Study XYZ-003](#)).

- **Or**

As shown by [Study ABC-001](#) ([Section 4.2.2.4](#)), CureAll does not inhibit CYP450. Further *in vitro* studies showed that CureAll appears to be substrates for CYP226, with a $t_{1/2}$ of 36 min ([Study OPQ-002](#) and [Study XYZ-003](#) in [Section 4.2.2.4](#)).



Smart Hyperlinking Practices (I)

- What do you [hyperlink](#)?
 - References to tables, figures, sections, study reports, appendices, etc. that are NOT on the same page
 - Avoid repeated hyperlinking to the same location within one page
 - Internal/external hyperlinks

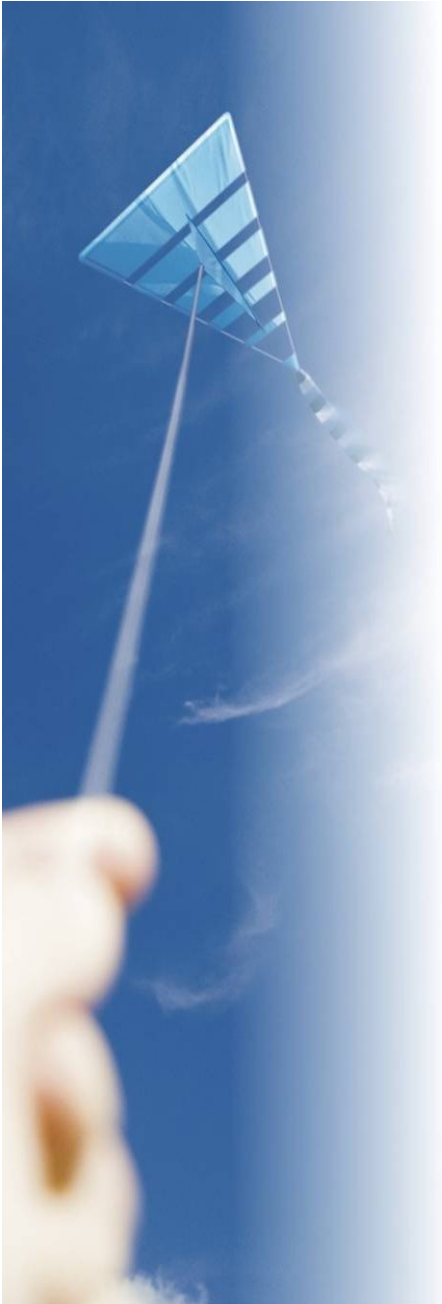
Examples of Helpful Hyperlinking

- **Embed links to narratives within the body of text**
 - “Narratives for subjects who died during the first 48 weeks are presented in the [48-Week CSR, Section 14.3_3.](#)”
- **Organize narratives by death, premature D/C, SAE etc.**
 - Deaths-Subject Numbers
[7033](#), [7244](#), [7336](#)
 - Hepatitis-Subject Numbers
[7055](#), [7574](#)

- **Provide source of summary information**

Number of Patients n(%)		
Completed	214 (93.9%)	202 (86.7%)
Discontinued	14 (6.1%)	31 (13.3%)
Discontinuation due to:		
Adverse Event	6 (2.6%)	20 (8.6%)
Protocol Violatio	3 (1.3%)	2 (0.9%)

Source: [Table 14.1-2](#)

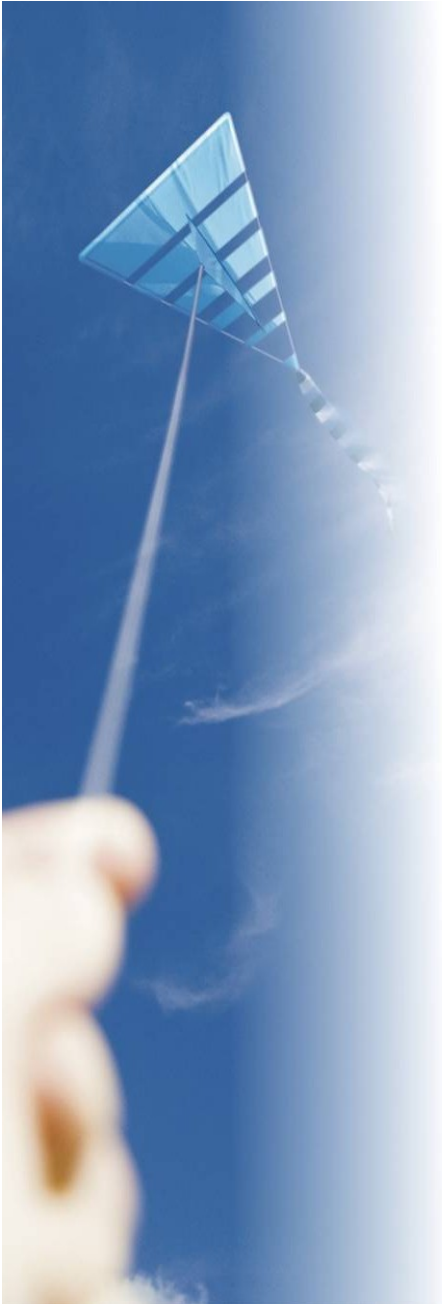


Smart Hyperlinking Practices (II)

- **Unclear:**
[Tables 1-3](#) indicate the significant SAEs reported for each clinical study
- **Clear:**
All significant SAEs reported for each clinical study are indicated in [Table 1](#), [Table 2](#), and [Table 3](#)

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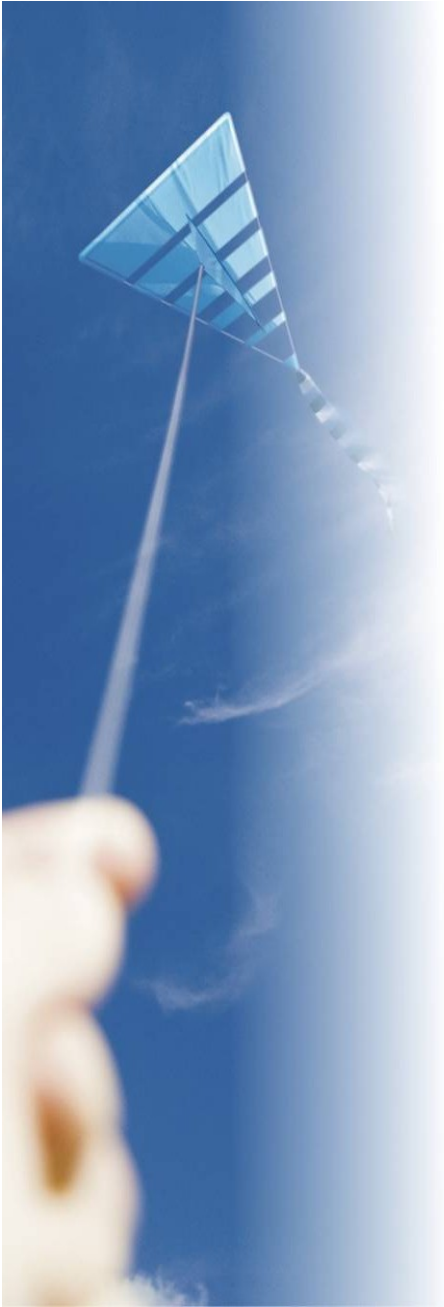


Smart Hyperlinking Practices (III)

- List of Investigators
 - Submit individual files by investigator rather than one main hyperlinked list
 - The main list is quickly outdated as new investigators are added to the study
 - Avoid constant need to replace this document and a help generate a cleaner profile

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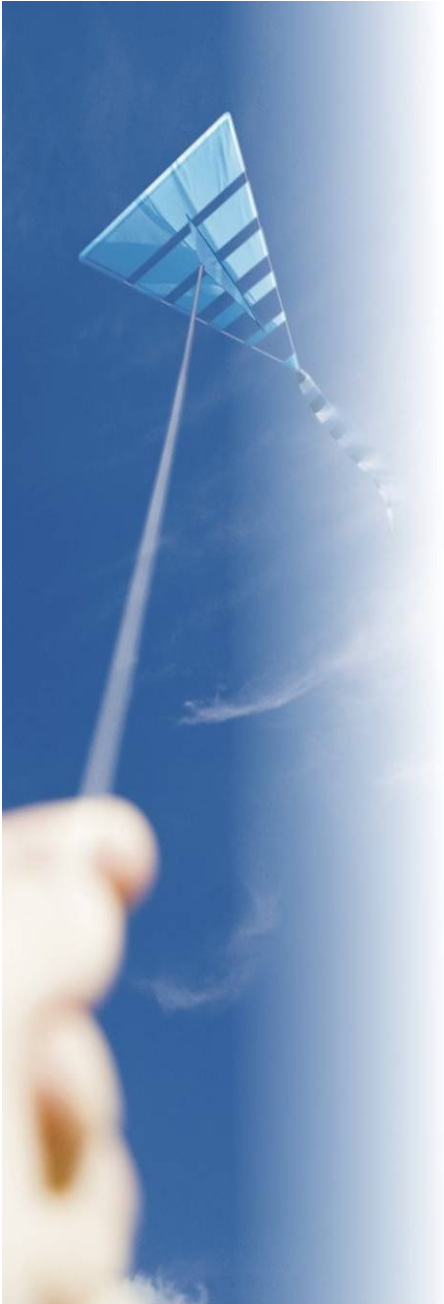


Size of Study Reports

- Avoid files larger than 100 Mbytes
 - Main body of CSR in one document (Sections 1-13)
 - Sections 14-16 separate documents
 - Section 16 Appendices: multiple documents

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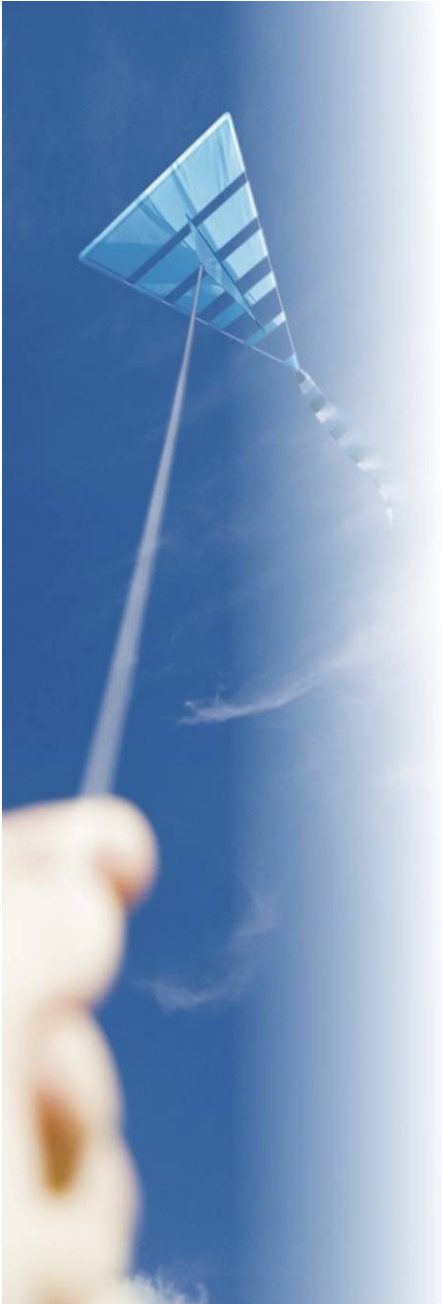


Clinical Study Reports

- Where to place clinical study reports if one trial contains controlled and uncontrolled studies?
 - Generate 1 CSR and place under heading of controlled studies

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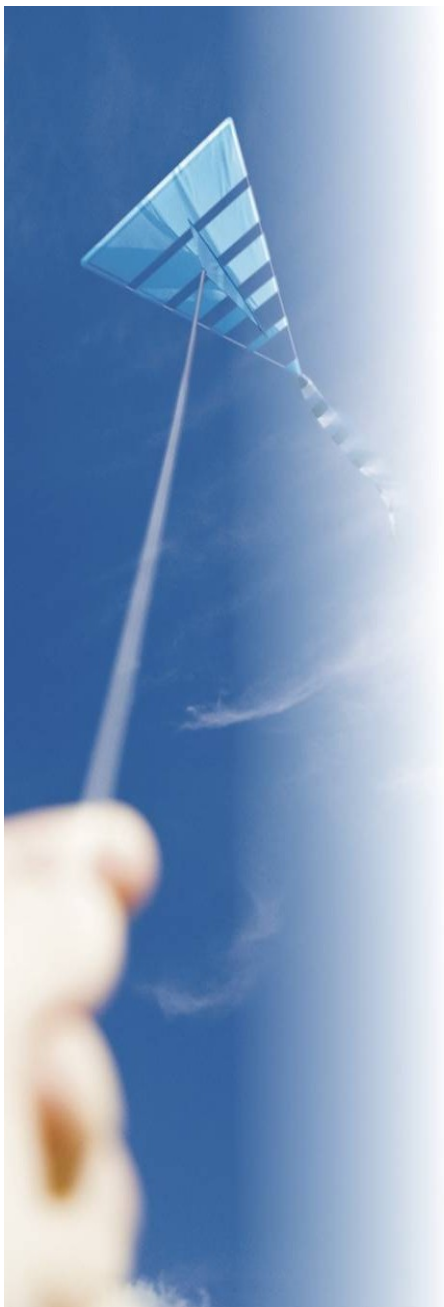


Consistent Naming Conventions

- Examples found for references to cover letters within one application:
 - Cover Letter
 - Cover Letter – December 12, 2008
 - CL
 - 1.2 Cover Letters
 - Cover Letter 8/15/2009
- Keep consistent names for documents

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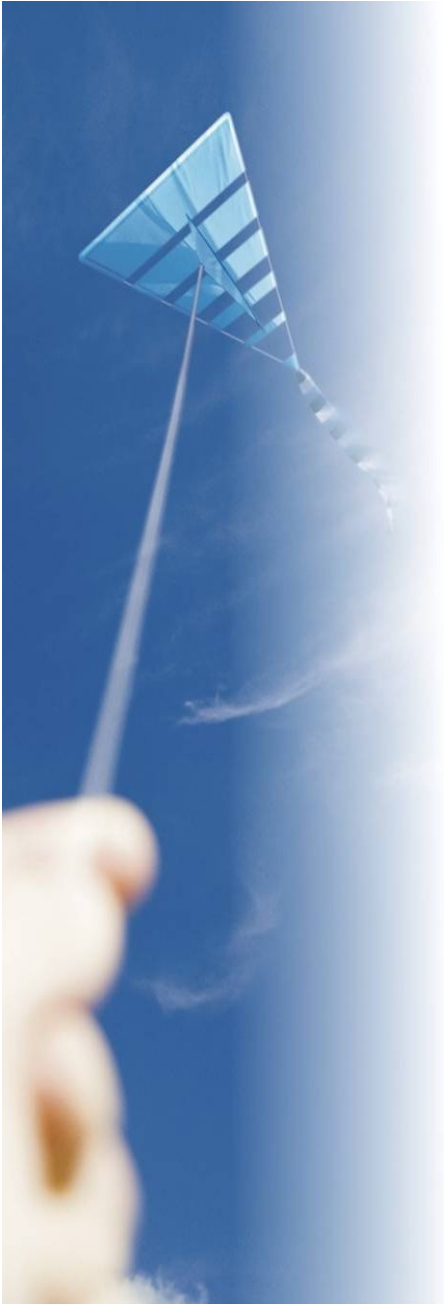


Lifecycle Management

- Dossiers develop over time
- Electronic CTD submissions have “new”, “replace”, “append”, “delete”
 - Keep these options in mind as you plan amendments to maintain current view
 - Use “append” function only once

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Multiple Lifecycle Changes

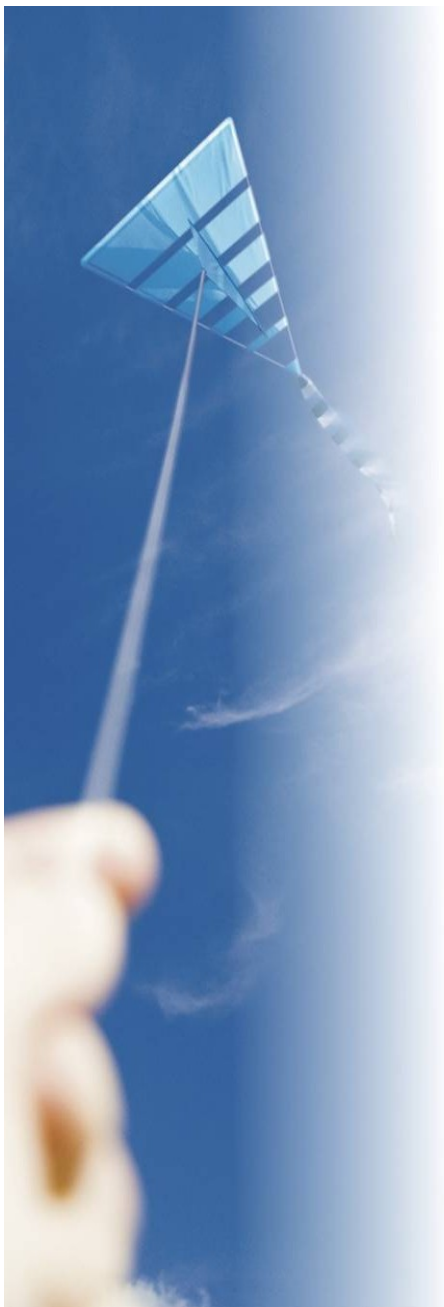
- Example:

 Current	0003 (Original)
---	-----------------

 Append	0006 (Amendment)
--	------------------

 Replaced	0003 (Original)
 Current	0013 (Amendment)

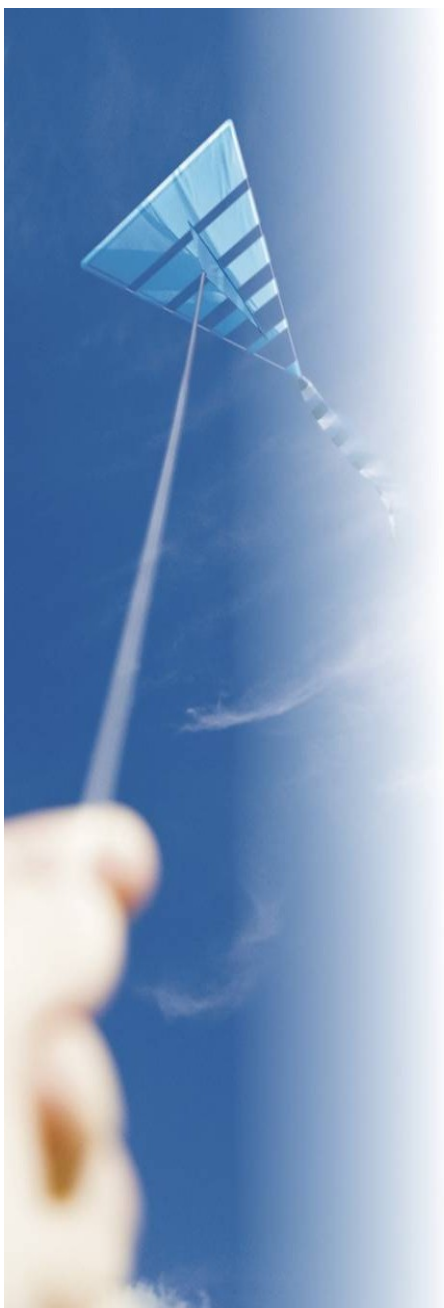
 Withdrawn	0006 (Amendment)
---	------------------



QC and Project Management of eCTD documents

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Quality Control Procedures

- In traditional paper format, QC consists of verifying pages and tabs printed correctly in all volumes
- In eCTD format, QC includes check of
 - All hyperlinks and bookmarks
 - Lifecycle functions (new, append, delete, replace)
 - Validation of XML backbone against DTD
 - Validation of checksums

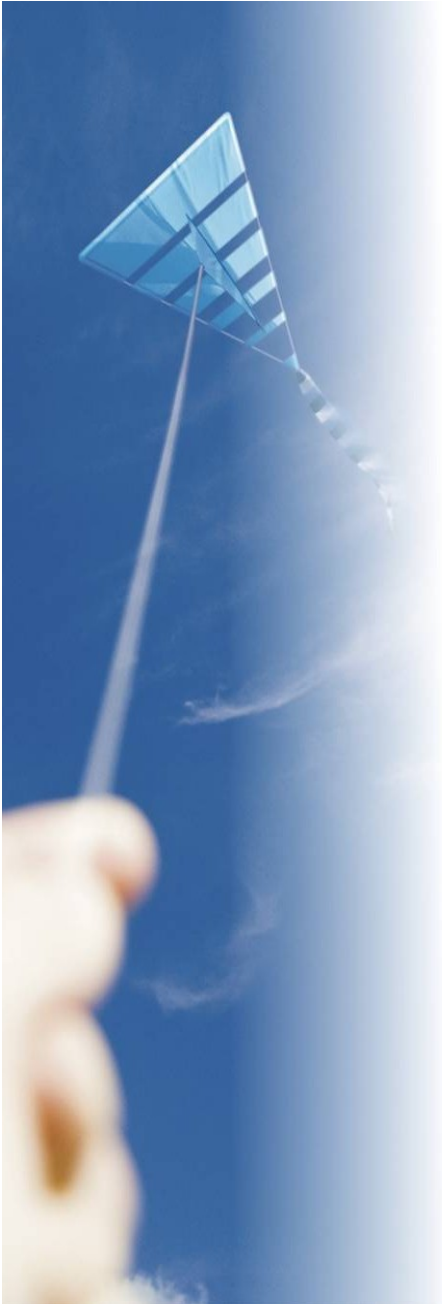
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Integrated Table of Contents

eCTD Section	SECTION NUMBER	SECTION TITLE	NOTES	Final Received	To Formatting	Return from Format	Sent for Hyperlink/Bookmarking To Subs	Internal links and bookmarks done	External hyperlinks done	Sent for QC	QC Complete
Heading Node	2.3.P.2	Pharmaceutical development									
Doc Node	2.3.P.2.1	Clinical and Commercial Formulation Development		√	√	√	√	√	√	√	√
Doc Node	2.3.P.2.2	Manufacturing Process Development		√	√	√	√	√	√	√	√
Heading Node	2.3.P.3	Manufacture									
Doc Node	2.3.P.3.1	Information on Manufacturer		√	√	√	√	√	√	√	
Doc Node	2.3.P.3.2	Manufacturing Process and Controls		√	√	√	√	√	√		
Doc Node	2.3.P.3.3	Flow Diagram		√	√	√	√	√	√		
Doc Node	2.3.P.3.4	Process Validation		√	√	√	√				
Doc Node	2.3.P.4	Control of excipients		√	√	√	√				
Heading Node	2.3.P.5	Control of drug product									
Doc Node	2.3.P.5.1	Specifications		√	√	√	√	√	√		
Doc Node	2.3.P.5.2	Analytical Procedures and Validation		√	√	√	√	√	√		
Doc Node	2.3.P.5.3	Batch Analyses		√	√	√	√	√	√		
Doc Node	2.3.P.5.4	Characterisation of Impurities		√	√	√	√	√	√		
Heading Node	2.3.P.5.5	Justification of Specifications									
Doc Node	2.3.P.5.5.1	Identity Tests		√	√	√	√				
Doc Node	2.3.P.5.5.2	Purity Tests		√	√	√	√				
Doc Node	2.3.P.5.5.3	Potency Tests		√	√	√	√				
Doc Node	2.3.P.5.5.4	General Tests		√	√	√	√				
Doc Node	2.3.P.6	Reference standards or materials		√	√	√	√	√	√	√	
Doc Node	2.3.P.7	Container closure system		√	√	√	√	√	√	√	

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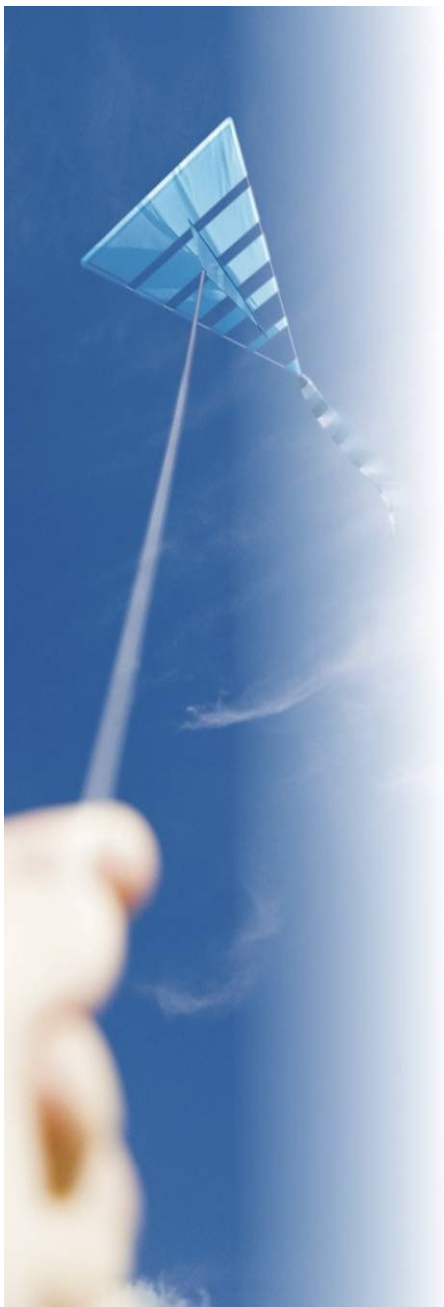


Project Execution

- Revisit the project plan often to confirm project is on track
 - During early phases of project, monthly team meetings sufficient
 - During critical path periods, weekly or daily meetings were required

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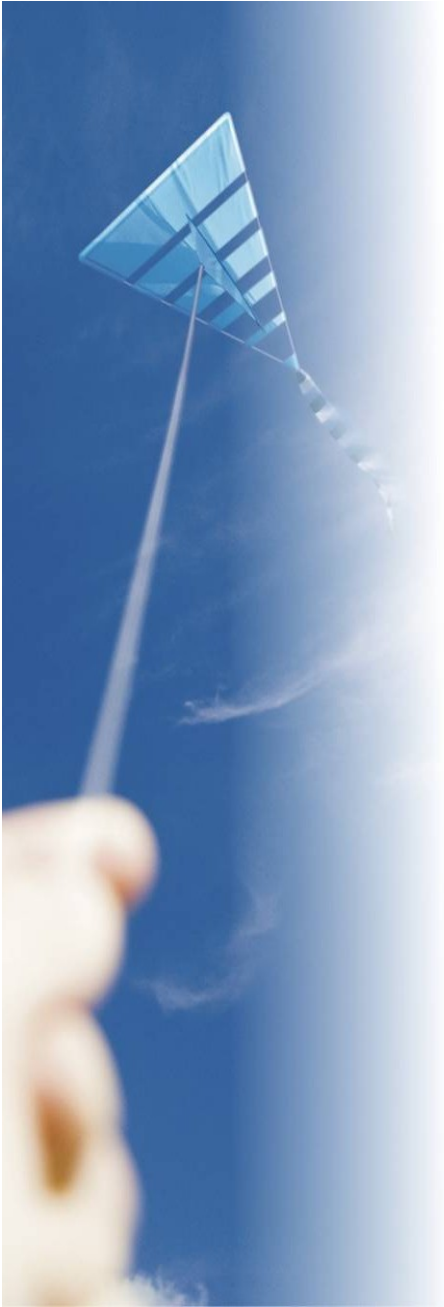
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Lessons Learned for eCTD Authoring

- Have a style guide for consistency
 - set standards in the beginning
- Chose meaningful file names
- Study reports: place similar studies together
- Communicate clearly to reviewers where the studies can be found
- Chose an appropriate level of granularity
- Apply helpful hyperlinks
- Consider future life cycle management

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Questions and Answers

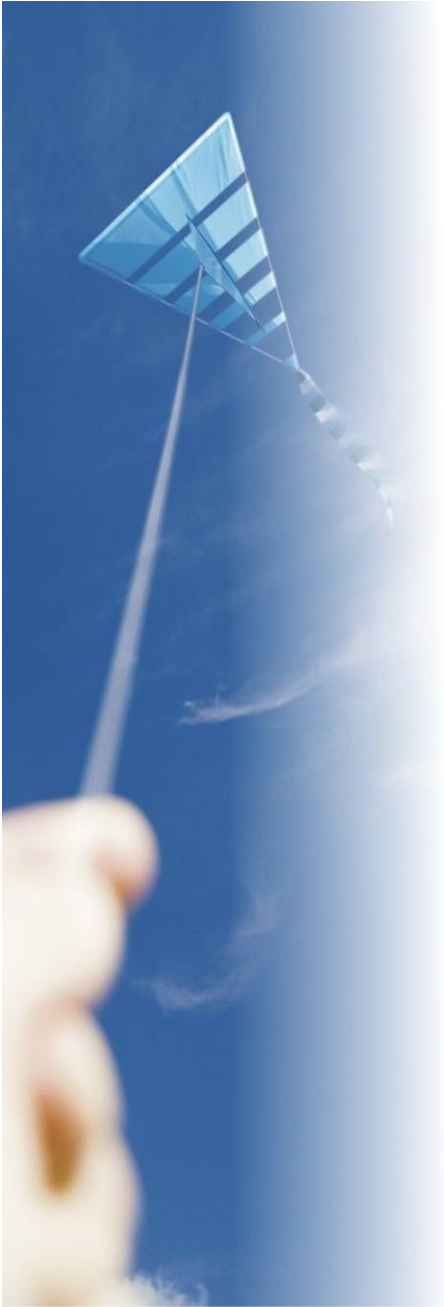
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Senior Scientist, Regulatory Affairs
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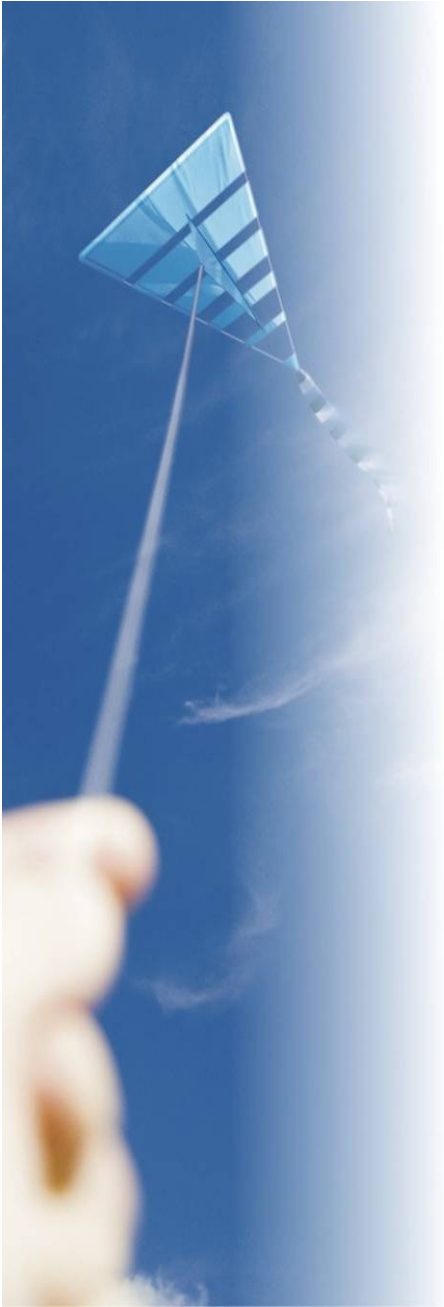
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Contact

Christine Warrington
Global Sales and Marketing
Cato Research
cwarring@cato.com
919-368-5995

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