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**Navigating the eSub Landscape:**  
*Process Improvement for Implementing  
Electronic Submissions*

***November 9, 2005***

## Introductions

- **John Lawrie – VP, Process Solutions**
  - Background in process development, document management, and electronic publishing systems
  - 10 years of eSub experience
- **Tina Lewis – Senior Director, Process Consulting**
  - 18 years of industry experience
  - Background includes imaging, document management, and publishing systems as well as systems validation and process development

## Agenda

- Why should I want to submit electronically?
- What format should I submit?
- What impacts will eSubs have on our departments?
- How do I get started?



## Opportunities from eSubs

- 1) Give agencies what they want
- 2) Improve integration of cross-functional processes



## Give 'em What They Want

- Agencies currently support numerous submission formats
- FDA is 'asking' that companies submit electronic dossiers
- eCTD is a globally-defined submission standard

## eSub/eCTD Status by Region

### US:

- Since 2003 fully electronic eCTD accepted as both review & archive copy (wet ink signatures submitted in paper until electronic signatures are accepted)
- eCTD applies to IND, NDA, ANDA, BLA, DMF and related submissions
- Investigational application forms the building block of the marketing application – eCTD will allow for physical cross reference back to previously submitted documentation
- No need to resubmit on part of sponsor
- No need to re-review on part of agency
- Sponsors need to submit a pilot submission to eSub office before submitting
- eCTD Viewing System (EVS) tool upgraded with an “off the shelf” product [FDA Review]

## eSub/eCTD Status by Region

### EU:

- eCTDs cover supplements/variations of marketing applications only
  - eCTD currently accepted as ‘review aid’ along with a paper CTD submission via Centralised procedure, until ALL member states are e-Ready [Targeting 12/2006]
  - March 2005 - EU Heads of Agencies announced goal of 12/2009 for mandatory eCTD
- E-Only Countries
  - UK, Belgium, The Netherlands in 2005
  - Belgium and The Netherlands targeting 2007 for eCTD only

## eSub/eCTD Status by Region

### Canada:

- eCTD currently accepted along with a full paper-based CTD submission
- October 12, 2005 Notice: “Update: Transition to Acceptance of Drug Submissions in eCTD Form”
  - Health Canada is targeting Q2, 2006 for acceptance of ‘hybrid submissions’ (M1/M2 – paper & electronic; M3-M5 – electronic only)

## eSub/eCTD Status by Region

### Japan:

- eCTDs cover supplements/variations of marketing applications only
  - eCTD accepted as ‘review aid’ along with a paper CTD (6 received to date as “experimental”)
  - Web-based tutorial available to reviewers (in Japanese)
  - Final Guidance published May 2004
  - Module 1 Schema and Stylesheets
- Different interpretation of “lifecycle management” than other regions

## eCTD Status – FDA metrics

- eCTD submissions metrics as of 1 Sep 2005

Applications		Submissions
IND	26	141
NDA/BLA	45	556
ANDA	35	93
DMF	5	6
<b>Total</b>	<b>111</b>	<b>796</b>

## eCTD Status – EU metrics

- eCTD submissions metrics as of 31 May 2005

Applications		Comments
MRP	20	Not all true eCTDs
National	> 20	+ many sequences
Centralised	12	Over 40 variations EMEA expects to receive 10 more before end of 2005
<b>Total</b>	<b>&gt; 52</b>	<b>Most done in parallel with paper</b>

## Integrated Processes

- eSubs present opportunity to
  - Establish seamless flow of documents and data from contributing functional areas through Regulatory to the agencies
  - Automate activities (tools) and minimize rework (standards and processes) to decrease dossier compilation time
  - Improve quality of submission

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## eCTD vs. Hybrid

- What's the same?
  - Content defined by 21 CFR and ICH
  - Formats for documents still PDF
    - Text based PDF preferred
  - Formats for data still SAS xpt (v.5)
    - Datasets per 1999 Guidance or CDISC
  - Draft Label still submitted as MS Word
  - Document level publishing
    - Hyperlinks and bookmarks
- A Hybrid is approximately 80% of the way there...

## eCTD vs. Hybrid

- What's different in an eCTD?
  - Submission level publishing
    - No more Item/Module TOCs
    - No more Doc Info Fields
  - Navigation achieved via XML
  - Documents are much more “granular”
  - Many more files will be submitted
  - eCTD requires additional tools
    - Compiler, Validator, Viewer
  - Specifications are rigid – no flexibility
  - Once eCTD, always eCTD

## eCTD vs. Hybrid

- Considerations for selecting eCTD over Hybrid:
  - Experience / comfort with PDFs and datasets?
  - Adequate lead time for evaluation / selection / implementation of eCTD Compiler, Validator, and Viewer?
  - Adequate lead time to revise standards and processes?
  - Senior Management Committed?
- Risk increases exponentially with every “no”

## Agenda

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## Impact of eSubs

- Standards
- Processes
- Technology



## Agency Requirements

Regulatory Agency recommendations for electronic submission include:

- Files will be submitted in Portable Document Format (PDF)
- Text should be Times New Roman 12 point font
- Margins should be a minimum of 1”
- The Table of Contents should only contain 4 levels
- Hyperlinks and bookmarks should be added for navigation
- There should be a bookmark for each item in the TOC
- Hyperlinks should be provided for all cross-references
- Scanned documents should be avoided if at all possible
- Data will be submitted in SAS Transport files

## Regulatory Guidance Interpretation



OCTAGON RESEARCH SOLUTIONS, INC.  
GUIDANCE INTERPRETATION

### TABLE OF CONTENTS

1	OVERVIEW.....	5
1.1	Purpose.....	5
1.2	Scope.....	5
1.3	Extensible Markup Language (XML) Framework.....	7
1.4	Key Differences between an eCTD and a US Hybrid Submission Format.....	10
1.5	Key differences between Paper CTD and an eCTD for EMEA Submissions.....	11
1.6	EMEA Transition Period to eCTD.....	11
1.7	Procedure For Deviation From Interpretation.....	12
2	GENERAL REQUIREMENTS.....	13
2.1	General Document Requirements.....	13
2.2	General Submission Requirements.....	23

## Standards Impact

- Document authoring standards
  - Templates and style guide
  - Definition of “submission-ready”
- Cross-referencing standards
- All standards must be global to support multiple markets
  - Font styles and sizes
  - Common printable area to support both A4 & US Letter
- Data standards

## Process Impacts

- Document Processes
  - Authoring
  - QA/QC
  - Review and Approval
- Submission Processes
  - Compilation
  - QA/QC
  - Tracking

## Authoring Impact

- It's not just an electronic copy of a paper document
- Authors need to understand the fundamentals of MS Word and templates
  - Templates allow authors to focus on content and less on format
  - Training and support
- Well-formatted documents facilitate automation of downstream publishing activities
  - Creation of “good” PDFs
  - Extraction of heading styles for bookmarks
  - Conversion of cross-references to hyperlinks

## The “Good” and the “Bad” PDF

Good Clinical Study Report.pdf

Clinical Study Report <<Name of Sponsor>>

- 5. ETHICS
  - 5.1. Independent Ethics Committee (I
  - 5.2. Ethical Conduct of the Study
  - 5.3. Patient Information and Consent
- 6. INVESTIGATORS AND STUDY ADMIN
- 7. INTRODUCTION
- 8. STUDY OBJECTIVES
- 9. INVESTIGATIONAL PLAN
- 10. STUDY PATIENTS

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This looks like c-body text, but is it? The study protocol and protocol amendments c found in Appendix 16.1.1; IRB/IEC information can be found in Appendix 16.1.3.

This is c-body text

12 of 44 8.5 x 11 in

Bad Clinical Study Report.pdf

Clinical Study Report <<Name of Sponsor>>

- 5. ETHICS
  - This looks like c-body text, but
  - 5.2. Ethical Conduct of the Study
    - This study was performed in ac
  - 5.3. Patient Information and Consent
  - 6. INVESTIGATORS AND STUDY ADMIN

5. ETHICS

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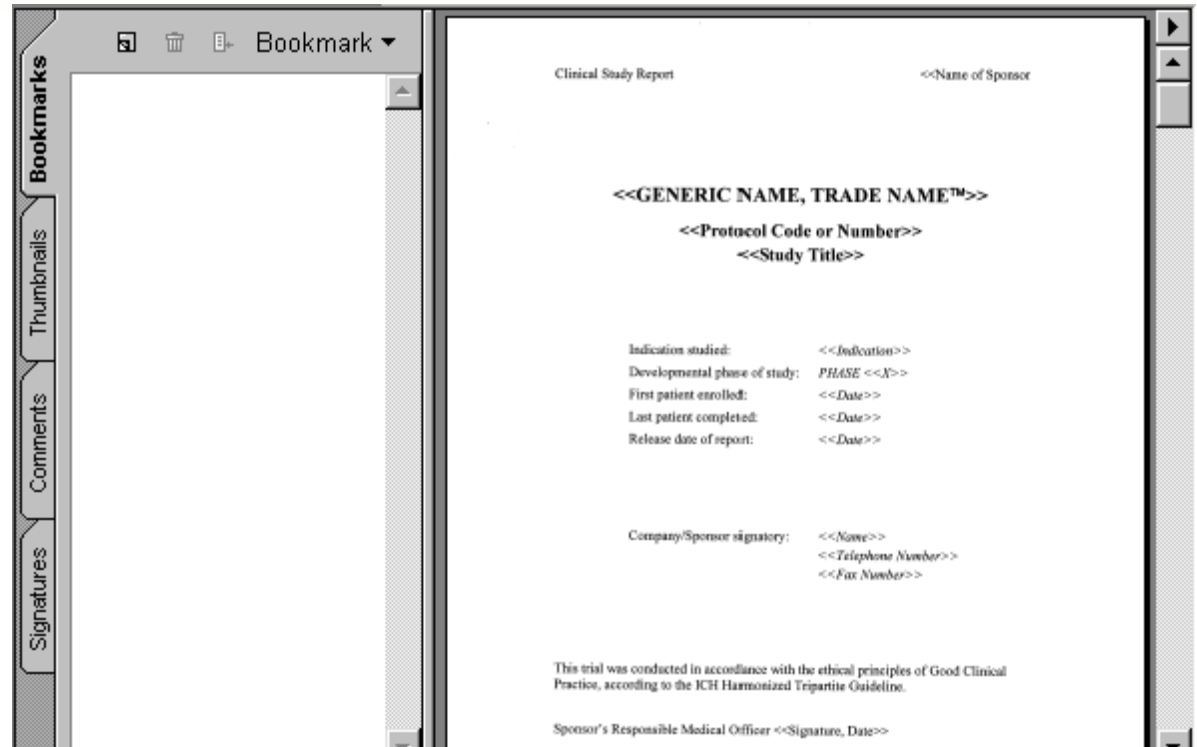
This is c-body text

12 of 66 8.5 x 11 in

## And the “Ugly” – Scanned PDF

The PDF image looks the same but...

- Text cannot be searched on
- Bookmarks must be manually typed or OCRed



The agency would prefer not to receive scanned images since they cannot copy and paste text from scanned files into their own review documents.

## Authoring Impacts

- CTD Document Granularity
  - New terminology
  - Templates should support ICH and FDA defined granularity
  - Flexibility in some areas:
    - Quality
      - 2.3 Quality Overall Summary
      - 3.2.P.2 Pharmaceutical Development
      - 3.2.A Appendices
      - 3.2.R Regional
    - Nonclinical
      - Single legacy report vs. multiple components

## Review & Approval Impacts

- Review and approval of small pieces means content will potentially be reviewed out of context
  - Most affected: Module 3 Quality & CSRs
- Possible new processes using:
  - EDMS virtual documents
  - Temporary concatenation of granular pieces (e.g. All 3.2.S components into one file)
  - Temporary XML backbone for navigation
- Review and approval of format as well as content
  - Content review
  - “eSub-ready” review

## Document Quality Impacts

- Quality Assurance/ Quality Control
  - Must begin at the planning stage in order to avoid unnecessary rework scenarios for content issues as well as format issues
  - Must clearly define roles and responsibilities
    - Must include subject matter experts
  - Must clearly define what checks occur when during the process
  - Must be an integral part of team training

## Submission Compilation Impacts

- No longer measuring stacks of paper to fit into binders!
- Submission Compilation Process
  - Start with structure
    - Most tools have a template to ensure consistency
  - Populate structure with content
  - Create cross-document hyperlinking, as necessary
  - Assign metadata for eCTD
  - Publish
    - For Hybrid, create item-level TOCs
    - For eCTD, build STFs and XML backbone

## Quality Impacts

- Validate (eCTD) and perform QA/QC of structure, metadata, and navigation
- For eCTD
  - Ensure correct use of operators
  - Ensure correct files identified in 'modified-file' attribute
  - Ensure consistent use of leaf titles – this is what the reviewer will see!
  - Ensure STFs include all study-related files
  - Ensure all files referenced in XML backbone

## Tracking Impacts

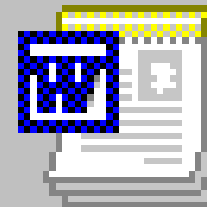
- Tracking submissions
  - Though the need existed previously, eCTD highlights the need to track submissions and their component pieces in order to properly apply operators to submission pieces
  - Append/Replace/Delete situations:
    - Need to find the document
    - Need to access the metadata associated with the document
  - Historical view of submission is key

## Technology Impacts

- Templates
- Electronic Document Management System (EDMS)
- Document Publishing
- Submission Publishing

## Templates

- CTD granularity
- Automated toolbar
  - Insert pre-formatted table
  - Insert symbol
  - Apply custom heading style
  - Insert table of contents
- Integration with EDMS



**MS Word  
Templates  
and Macros**

## Document Management System

- Minimum requirements
  - Security
  - Version control
- Options
  - Controlled network fileshare
  - Documentum-based system
  - Livelink-based system
  - Others

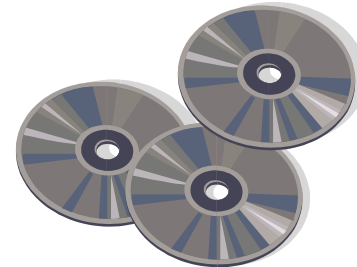
## Document Publishing

- PDF creation and manipulation
- Acrobat distiller
- Acrobat plug-ins



## Hybrid Submission Publishing

- Module TOCs
- Inter-document hyperlinks
- Document info fields
- Indexes



## eCTD Submission Publishing

- **Compiler** – application used to enter metadata and create the XML backbones
  - Can be standalone or integrated with EDMS
  - Submission publishing capability
- **Validator** – application used to validate the XML backbones and ensure that the eCTD submission will be viewable (and accepted) by the reviewing agency
  - Many compilers have a validator ‘built-in’
  - Use more than one – each validator is different!
  - Test and build tools into QC process

## eCTD Submission Publishing

- **Viewer** – application used to view a single instance or multiple instances (the ‘lifecycle’) of an eCTD dossier
  - FDA style sheet utility is limited
  - May be standalone or integrated with Compiler
- **Tool Considerations**
  - Identify who needs which tools
  - Link to EDMS for content
  - Link to EDMS to leverage metadata
  - View across submissions within an application
  - Update processes to incorporate new tools

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## Getting Started

- Take an inventory:
  - Regulatory Guidance Interpretation
    - eSub-ready definition
  - Authoring templates
    - CTD granularity
  - Document management system (or approach)
  - Author / Review / Approval processes
    - Documents and Data
    - QA & QC checklists

## Getting Started

- Take an inventory:
  - Document publishing tool
    - PDF creation
  - Submission publishing processes
    - QA & QC checklists
  - Submission publishing tools
    - eCTD – Compiler, Validator, Viewer
    - Approach for Lifecycle Management

## Getting Started

- Based on your inventory, develop a plan:
  - Assemble a cross-functional team
  - Address open issues with:
    - Document standards
    - Authoring processes
    - Document management technology
    - Document publishing technology
    - Submission publishing processes
    - Submission publishing technology
  - Incorporate both a communication plan and a training plan

## Thank You

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