eCTD in Other Jurisdictions: US Update

Joseph A. Cipollina

Bristol-Myers Squibb Company

PhRMA Electronic Regulatory Submissions (ERS) Working Group

Overview

- U.S. FDA Implementation
- Submission Management Needs
- Submission Management Solutions
- eCTD Shortcomings
- Moving Forward

U.S. FDA Implementation

U.S. FDA is…

- moving toward a paperless submission environment (prefers electronic over paper)
- accepting all submission types (IND, NDA, ANDA, BLA, DMF and related submissions) in eCTD format
- accepting NDA and BLA applications in either eCTD or eNDA format
- accepting CTD documents in eNDA submissions
- not requiring paper review copies for eCTD submissions

U.S. FDA Implementation

eCTD Test Program

- Submit sample eCTD submission for testing
- Evaluate compliance with Guidances; validation against DTDs
  - 22 sponsors have enrolled
  - 12 sponsors have submitted test submissions

U.S. FDA Implementation

eCTD Submissions

- Four Marketing Applications (one NDA, three sNDA) have been submitted
- 30+ eCTD submissions
- Two additional marketing applications targeted for 3Q04

U.S. FDA Implementation

eCTD Review Tool

- eCTD Viewer System (EVS)
  - In production at FDA
  - Released to the public on 02-Mar-2004
  - EVS processor performs rigid validation of backbone against DTD
  - Reviewer Training (just-in-time basis)
  - Limited experience

U.S. FDA Implementation

EVS Further Development

- Collect additional reviewer requirements
  - Views and queries across submissions
- Collect additional Agency requirements
  - Cross-application needs
  - Utilization of Module 1 information (display vs. analysis)

U.S. FDA Implementation

Other Development Efforts

- Secure electronic transmission of eCTD submissions
  - Secure email (submissions up to 50MB)
  - FDA Gateway
- XML Documents
  - Structured Product Labeling (SPL)
- Electronic Standards
  - HL7, CDISC

Submission Management Needs

- Current eNDA submissions (PDF tables of contents based) are standalone submissions
  - No hyperlinks to other submissions
  - Relationships between submissions and relationships between the contents of submissions have to be manually tracked

Submission Management Needs

In addition to Summary Documents and Study Reports, the content of U.S. marketing applications also includes patient Case Report Forms (CRFs) and Case Report Tabulations (CRTs)

- Data tabulations datasets
- Data listing datasets
- Subject profiles
- Analysis datasets
- Programs

Submission Management Needs

- U.S. FDA reviews documentation at the investigational application level (IND) and in most cases, much of this information is resubmitted for review with the marketing application (NDA)

Submission Management Needs

- U.S. FDA marketing application review process requires management and review of multiple submissions for each application
  - The ten most active eNDAs ranged from 76-200 electronic submissions
    - Six had 111-139 submissions
    - One had 85
    - One had 202

Submission Management Solutions

- eCTD provides the mechanism to collate and present information across submissions
  - Readily generate cumulative views of the dossier over time
  - Increased ability to collate\sort information (XML based) at the more granular CTD level
- eCTD provides the mechanism to relate specific documents and files across submissions

Submission Management Solutions

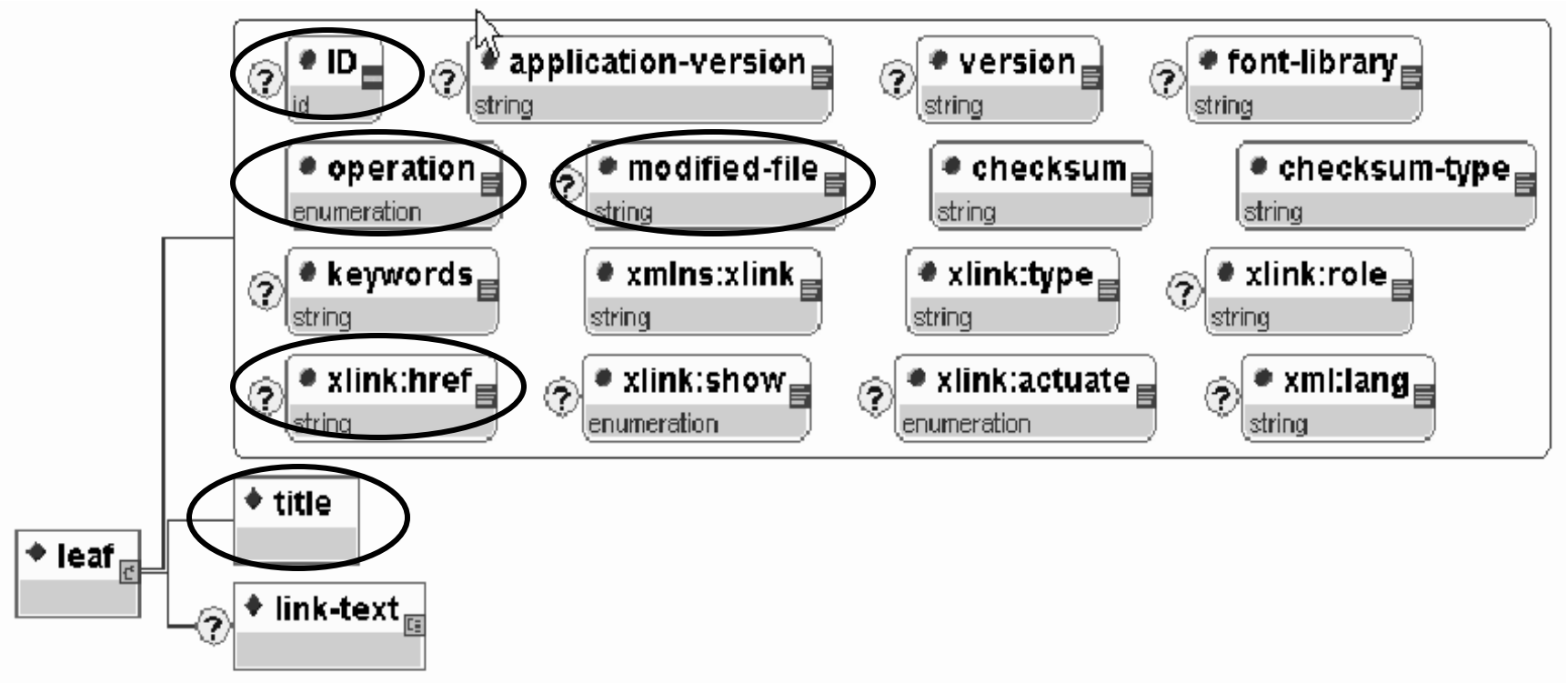
The eCTD changes the focus of regulatory information exchange from the submission of documents to the submission of structured information!

- "Global" messaging standard
  - CTD Elements
  - Leaf Attributes
- Standards for defining document\data\file relationships across submissions

eCTD Shortcomings

- Essentially all information about the file is relayed to reviewer by the Title field of the leaf
- No mechanism for organizing cumulative views of documents (e.g., by species)
- No mechanism for grouping related files across CTD sections or in cumulative views
- No standardization of metadata\properties
- No concept of a logical document

eCTD Messaging Standards
Leaf Attributes



eCTD Shortcomings

The Common Technical Document - Safety

General Presentation Issues

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

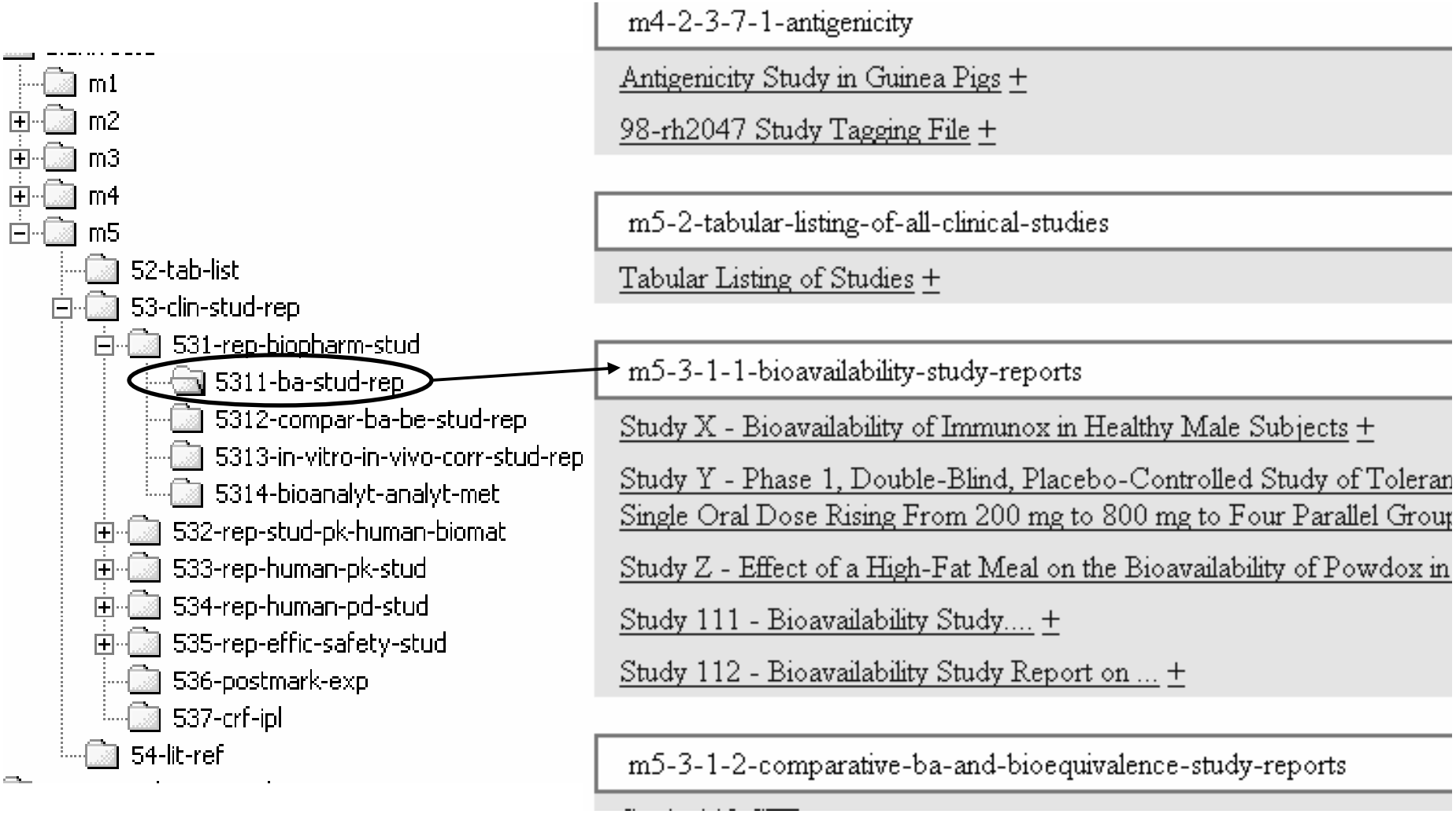
m4-2-3-2-repeat-dose-toxicity

- One-Week Oral Toxicity Study in Mice +
- One-Month Oral Toxicity Study in Mice +
- One-Week IV Toxicity Study in Mice +
- One-Week Oral Toxicity Study in Rats +
- Two-Week Oral Exploratory Toxicity Study in Rats +
- One-Week IV Toxicity Study in Rats +

m4-2-3-3-1-in-vitro

- Cytogenetics Study in Primary Human Lymphocytes +

eCTD Shortcomings



eCTD Shortcomings

Moving Forward

Short Term Solution

- Study Tagging File DTD
  - XML file representing the logical document (e.g., clinical study report)
    - Document-specific attributes (e.g., study number, study title, species, RoA) that apply to all component files
    - File-specific tags to define content of component files (based on ICH E3 granularity)

Moving Forward

- Long Term Solution being developed by ICH M2 Expert Working Group (EWG)
- To be discussed at ICH Meeting this week (June 6)

THANK YOU!

joseph.cipollina@bms.com