

# ***IRISS-Forum***

## **eCTD Tool Interoperability Group**

**April 15, 2009 - 7:30am EDT**

### **Attendees (28)**

Bernadette Billet, Terri Booth-Genthe, Kelli Case, Ian Child, Kathy Clark, Joel Finkle, Andreas Franken, Ted Hanebach, Leah Kleylein, Shy Kumar, Jennifer LaFleur, Alex Lawrence, Raj Maitra, Harv Martens, Deanna Murden, Lenore Palma, Don Palmer, Pee Tanja, Lillian Reilly, Leigh Sandwell, Norman Schmuft, Alain Seront, John-Paul Smith, Mindy Sperling, Phyllis Thomas, Ginny Ventura, Kevin Wing, Peggy Zorn

### **Questions to FDA**

- What is the FDA's preferred physical location for CRF files within the folder/file hierarchy? Some tools place the files in 5.3.7 and some in 5.3.x with the other study components.
  - *Ginny Ventura from FDA stated that CRF files should be located with the study files. FDA does not use 5.3.7. CRFs are sometimes located in 5.3.7, and it won't cause validation issue, but the preferred location would be following the E3 granularity and having it under the study it pertains to. It has not been an item of discussion at FDA recently.*
  - *Ginny offered to bring it up and discuss at a future meeting. CRFs have not been a topic of recent discussion. FDA is mainly concerned with being able to locate them in the backbone within their viewer. Ginny is not aware of CBERs request for leaf in both locations, physical file in 5.3.7, so she could not comment on that. ETICS results led vendors to believe that CRFs should be located with the other study documents and not physically located in m5/m53-clin-stud-rep/m537-crf-ipl in US submissions.*
  - The FDA is also concerned with the foldering for SPL and sponsors should follow the specifications and published guidance regarding folders. However, they are not validating this except in the case of datasets and SPL. Folders do matter.
  - *Canada's validation criteria indicates that the CRFs should be located in m537-crf-ipl/study-1.*
- Withdrawn eCTD Specifications / Guidance
  - Was the "eCTD Backbone File Specification for Modules 2 through 5 version 1.1" withdrawn?
    - *Ginny Ventura answered: The FDA "eCTD Backbone File Specification for Modules 2 through 5 version 1.1" was withdrawn and replaced by the ICH eCTD Version 3.2.2 specification.*
  - Was the "FDA Implementation of Study Tagging File Specification 2.6.1" withdrawn?
    - *For STFs, version 2.6.1 is the correct one, which is dated June 2008.*
  - Were any other specifications / guidance withdrawn?
    - *Ginny confirmed that the website will be updated in the next couple of weeks. There are going to be a lot of changes to the website over the*

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*next few weeks and hopefully it will be clear which specification or guidance is current.*

- *Concerning how the website looks, there will be a onetime change that will be creating new pages and removing existing pages. Shortly after that, the FDA will post some new eCTD validation criteria.*
- *This update will not include updates to the forms. Ginny's group doesn't have direct control over the forms, there many other groups within the FDA that control the forms. The FDA formed a task group to re-organize the publishing of forms.*

#### **Best Practice Document Update**

- **Bookmark discussion**
  - *Terri Booth-Genthe presented some examples of bookmarking. It was decided that the best practice document would be called a "**Points to Consider**" document. Reasoning is that people should not make assumptions that if they follow ideas from best practice to the letter that they will not encounter problems in future. Cannot apply absolute rule to how bookmarks and links are managed. Need to understand how the author was referring to information before deciding whether to go to a cover page, an introductory page, the page with just the data, etc. Tables with no list of tables may have an explanatory cover page so that the creation of a "Tables" bookmark to hold the specific Table 1, Table 2 bookmarks makes sense. However, there should definitely not be any bookmarks or links with an action of "None". Terri will do first draft of document.*

#### **Update on Preparation of Change Request for Q&A #55 - PDF Document Properties (Security tab)**

- *The issue at hand is published literature that has security on it. Many companies are wasting time scanning and OCRing these PDFs.*
- *Original intention of no security rule was to avoid PDFs that couldn't be opened, or that needed passwords. Most published literature PDF security is around whether content can be copied and pasted, or whether it can be printed.*
- *Perhaps ICH M2 should consider the "no security" rule for PDFs and make an exception for literature references sections in eCTD. (possible Change Request?).*

#### **PDF 1.4 issue**

- *The PDF version issue will be discussed in June at ICH. All regulators and ETICS vendors have been asked for their input on this issue.*

#### **Update on Change Request for making "title" a required attribute regardless of operation attribute**

- *Shy has written the Change Request which includes explicit examples of how it should be implemented and validated*

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- Harv will make one change, sent to Lenore and she will circulate it

#### **Viewer Inconsistencies**

- Vendors: What criteria does your tool use to display leafs in the sequence view? In the current view?
- Sponsors: Do you spend time agonizing over the order of leafs in the backbone?
  - *Part of this is related to title of deleted leafs: When opening in the viewer, and looking at a current or cumulative view, you will see different things in different viewers. This is a follow-on to the ETICS project. If you've seen Joe Cipollina's ETICS presentation from the DIA EDM meeting, you know that different tools interpret lifecycle operations in a different manner.*
  - *2 people in the group mentioned that deleted leafs show up in current view in the tools they are using. 1 person is also seeing a couple products that have trouble when a new node is added, like a new dosage form, it doesn't show up in the current view if it wasn't in the 0000 sequence. Shy says this should be considered a bug for those products.*
  - *Would be good if the group could get together and have a meeting of the minds on how viewers display complex lifecycle situations (e.g., appended and replaced, replaced again).*
  - *Deanna brought up situation: original formulation was oral formulation. Company developed new formulation. What is the proper lifecycle of a new form of dosage form? Is it right to do a replace on that existing formulation when the existing formulation is still out there on the market? Replacing it will remove it from the current view, when it's still valid. Currently people are handling by having 2 separate documents.*
  - *Another concern right now is the hot fix from Global Submit that will place leaf titles in alphabetical order. This could be a real problem for Module 3. People will sometimes prefix their names (01, 02, 03, etc.), some sponsors put the 32s21 in front of leaf title, but many health authorities don't like this (ex. HC). Jason Rock said tool preserved the order in which it was presented, but Norman hasn't seen evidence of that yet. This originally all came out of a discussion at EDM in February where there was a discussion about CRFs, and how they were presented in a submission to FDA in a seemingly random order. FDA wanted to sort them.*
  - *Harv stated there are 2 issues here: First, a building tool should handle order of leafs in a specified way, and if the preference is "you choose the order", then that should be clear. Secondly, a viewing tool should retain that order.*
  - *Kevin Wing mentioned that he had submitted a change request to ICH M2 in the past regarding the re-ordering of 3.2.P elements in a more logical manner. M2 considered it to be a viewing tool issue and rejected it because they did not want to devote resources to modifying the stylesheet. (see attachment)*
  - *Mindy Sperling provided post-meeting comments based on feedback from her company's functional areas.*

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- *CMC opposes alphabetical sorting, while Clinical and Regulatory have requested that clinical content be sorted in a logical order in the Current/Cumulative views, especially at the study level.*
  - *For years, we have ordered our DS/DP methods according to how they are listed in the specifications. In the old days, the FDA asked to do this so that they could easily bounce back and forth between the spec and methods. This is certainly not in alphabetical order.*
  - *We have also heard that this creates a problem when one has a complicated P.2 section in a Quality by Design submission. Rather than listing reports in the order in which you may want the reviewer to work through the submission, they now are in an undefined order....and certainly not looking like what you see in your viewer.*
  - *Similar problems in P.7 Container Closure and the stability section would exist. Several documents can be associated with one container closure system. If there is more than one container closure system to describe, clustering the documents pertaining to each container closure together would aid in the review. There has been a request to have repeating P.7 sections like we have for P.4. The same could be true for Stability sections.*
  - *What may result is a prefix system in the eCTD titles to help keep files in the proper order which goes against the concept of having the important title content information for the reviewer at the beginning.*
- *In NDAs there may be numerous submissions for a specific clinical study, including 100s-1000s of case report forms, datasets, etc.*
- *But the real business need is in INDs, where there are many updates to a STF including protocol amendments, new investigator documents, and then the final study report. It would be helpful for Current/Cumulative views to sort all study-related documents in order per STF hierarchy and then alphabetically*

**Interoperability topics**

- Please forward any suggestions for topics to discuss to Lenore

**Next meeting**

- The meetings in 2009 will be held on the 3rd Wednesday of each month ... the next meeting is scheduled for **May 20th @ 7:30am EDT.**