

IRISS-Forum

eCTD Tool Interoperability Group

November 18, 2009

eTIG Update:

- The leadership team for eTIG has been expanded beyond U.S. and European vendor representation to include Mindy Sperling from sanofi-aventis representing the U.S. sponsors and Raj Maitra from Talecris representing BioPharm. There is a candidate just waiting to gain approval from his management to represent the European sponsors. This new leadership team will meet separately from these general membership eTIG teleconferences to strategize on the path forward for eTIG. The team will also oversee the sub teams as they are being formed to ensure that proper representation is being attained and the path being taken by the sub team supports the overall IRISS mission.

Agency Updates and Specific Questions:

- EMEA (Claire Holmes)
 - Q: Is the folder/filename listed in the EU M1 specification a requirement or is it just a recommendation? Version 1.4 of the specification states “*Fixed components are highly recommended.*” ICH Validation rules do not include criteria for this but some EU agencies are sending Invalid Reports on this topic claiming it is an ICH requirement.
 - Claire stated in an email response to Lenore Palma that there are 2 EU validation criteria (#34 & #35) that reference use of the file/folder naming convention. However, these criteria have severity codes B and C, rather than A, meaning that a lack of adherence to the file naming convention, if found, is presented as information to be passed on to the applicant if considered necessary by the regulator, but will not automatically lead to a validation failure.
 - The information on file/folder names is desired by many agencies in the EU as they do not use an eCTD review tool, or even the stylesheet, and instead rely on the folder and file names to navigate through the dossier. EMEA does not do this so of course the leaf titles and metadata are more important for us.
 - The agencies claiming that a submission is invalid if the file/folder naming convention is not met are wrong, and do not have the right to do this, as it is not an ICH requirement, nor even a category 'A' EU requirement, only highly recommended.
- FDA
 - Q: Sponsors have been receiving technical validation low level error reports recently. Has the agency become stricter on what they are looking for? For example, in the specification, it states that the language attribute (xml:lang) can be used in “Any table of contents element such as <m2-2-nonclinicaloverview>”. Most building tools include language at the leaf level. Sponsors are receiving reports with this listed as a low level error.
 - eTIG leadership is trying to schedule a follow-up meeting with the FDA to discuss the validation rules in general.
 - Q: Is it necessary to include the Medwatch report when submitting PSURs to the agency?
 - For post-marketing submissions, do not include the Medwatch form as part of the eCTD submission. For submissions going to CDER, these forms should be submitted via E2B or paper.
 - For submissions going to CBER, there was no definitive answer provided.

IRISS-Forum

eCTD Tool Interoperability Group

- Q: Questions submitted to esub@fda.hhs.gov are generally answered in 24-48 hours. Sometimes additional information needs to be gathered, involving other groups, and may take more time. It is OK to send a follow-up email to see what the progress of your question is.
- Health Canada – Not represented on the call
- Swissmedic (Stephan Järmann)
 - The following links were posted on 30-Oct-2009
 - [Swiss Module 1 Specification for eCTD](#)
 - [Swiss eCTD Validation Criteria](#)
 - [Questions and Answers of Swissmedic eCTD Implementation](#)
 - [Guidance for Industry on Providing Regulatory Information in eCTD Format](#)
 - There are 10 vendors working on implementation of the specification.
 - A free of charge validator tool is available only for applicants at this time.
 - The agency has developed a process to accept submissions that have been developed for other agencies.
 - They are continuing to review validation criteria until 2Q2010

Points to Consider Document Update (Terri Boothe-Genthe)

- No update provided

eCTD Tools Interoperability Study Update (Harv Martens)

- The sub-team is still getting organized
- It will be OK to use the ETICS acronym, but interoperability must be a key portion of the project, so this will more than likely mean a phased approach
- ETICS II general results presentations will be posted on the [ETICS](#) website soon

ICH M2 Meeting Update (Harv Martens)

- An updated ICH Q&A will be posted on the [ICH ESTR1 website](#) next week
- eCTD Next Major Version (NMV) Requirements v2 will also be posted next week
- Discussion regarding the acceptance of PDF versions higher than v1.4 will be discussed at the next ICH M2 meeting.

Follow up question to previous topic:

- Regarding IND submissions and the concept of combining many small granular documents into a comprehensive single document submitted under a higher element. eCTD was designed to be granular to aid in the life cycle of a drug. There are viewing tools available which allow the reviewer to go to the next document with just a single click. Should we put user-friendliness into the functionality of the viewing tools, thus making this a standard and allowing sponsors to keep the granularity? (Phyllis Thomas)
 - In general, FDA reviewers object to opening files containing one or two lines of text. They are not viewing the documents via their review tool, but rather using the tool simply to determine what document they need to open next and then viewing the document via Adobe Acrobat.

IRISS-Forum
eCTD Tool Interoperability Group

- A suggestion was made that the review tools be enhanced to allow for an easy way to navigate to the next document in the backbone. Several vendors commented that this would be difficult to do once life cycle on documents begins to happen.

STF Metadata Conflicts (Bernadette Billet) – see attachment

- A sub-team will be formed and will be asking the FDA for a teleconference and web meeting to discuss the inconsistencies of STF metadata.

Interoperability Scenarios of the Month (Group)

- A building tool allowed for replacement across sections, however a viewing tool was not able to interpret this cross-section replacement. The specification does not clearly state whether this can or cannot be done.
 - Generally, this type of action is not allowed by tools.
 - The only known exception is with the EU M1 Additional Data element.
 - This causes a problem for life cycle management and therefore is a good topic of discussion between the two topic groups.

How do we ...? (Group)

- Is the order of attributes important in the XML as far validation issues are concerned?
 - General answers from the group was that the attribute order is not important, but the element order in the XML must match the DTD order.

Next meeting

- The next meeting is scheduled for **December 16th @ 7:30am EST.**

1. Purpose

There are several places where information identifying a particular study report is provided in an eCTD index.xml and STF XML file. There appear to be varied/conflicting instructions and interpretations of how to populate this information. This document is intended to highlight the areas where the information is captured and identify unclear or conflicting areas of the specifications and validation criteria. The highlighting behind the element names is provided to aid in ease of differentiating the elements from one another.

2. Study Identifying Information

Information to uniquely identify a study report and its components is captured in the following locations:

1. The `<leaf><title>` in the index.xml that points to the STF XML file
2. The `<study-identifier><title>` in the stf XML file
3. The `<study-identifier><study-id>` in the stf XML file.
4. The `<doc-content xlink:href>` elements in the `<study-document>` element of the STF – one for each `<leaf>` comprising the study content pointing to the IDs of the appropriate `<leaf>` element. When viewed via IE, the stylesheet translates this to display the `<leaf><title>` values for each piece of `<doc-content>` element.
5. The optional `<doc-content><title>` element in the STF DTD that is not explicitly defined, nor used in any example in the specifications

3. Specifications/Validation Criteria

The STF 2.6 specification (superceded), indicated the value of the `<study-id>` (number 3 in Section 2 above) should be used for the value of the `<leaf><title>` pointing to the STF XML (number 1 in Section 2 above).

“For every submission to FDA that includes one or more files pertaining to a specific study, you should provide an STF. You should place the STF for the specific study in the module folder with the corresponding study files. You should place a leaf element in the Module 4 or 5 eCTD index.xml file for each STF...Use the study identifier (i.e., study-id described below) in the title of the leaf.” – STF v2.6 Specification, Page 4

This language was removed from the v2.6.1 specification, but not replaced with any specific instructions for the value of the `<leaf><title>` pointing to the STF XML file. However, the example XML portions in sections IV and V of the specification, show a brief value, similar to the value of the `<study-identifier><study-id>` appended with “Study Tagging File” or “STF”

```
<leaf
  checksum-type="MD5"
  version="STF version 2.2"
  xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272"
  operation="append"
```

```
xlink:href="m4/42-stud-rep/421-pharmacol/4211-prim-pd/stf-jm-12-345.xml"
modified-file="../0000/index.xml#m12345"
ID="m42111">
<title>jm-12-345 Study Tagging File</title>
</leaf>”
STF v2.6.1 Specification, Page 11
```

```
“<leaf
checksum-type="MD5"
version="stf version 2.2" xlink:type="simple"
checksum="421e55366d62fad0e9510f6aed005272"
operation="new"
xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
ID="idm42111-0002">
<title>Study No. JM-12-345 STF</title>
</leaf>
```

The study-identifier section of this STF contains the following information:

```
<study-identifier>
<title>Single dose oral toxicity study in the mouse and dog</title>
<study-id>jm-12-345</study-id>
<category name = "species" info-type = "ich">rat</category>
<category name = "species" info-type = "ich">dog</category>
<category name = "route-of-admin" info-type =
"ich">oral</category>
</study-identifier>”
STF Specification v2.6.1, Pages 11-12
```

The Specifications for eCTD Validation criteria v1.0 include a validation check (number 1952) the reports if the STF `<doc-content><title>` and `<leaf><title>` do not match. However, there is nowhere in the specification text or examples that explain or demonstrate the use of the `<doc-content><title>`. In practice, however, rather than this specific condition being reported, it appears that if there is a mis-match between the `<leaf><title>` pointing to the STF XML file and the `<study-identifier><title>` values, this error is reported. There here does not appear to be any documentation in the specification or validation criteria that indicates these values should match.

A table indicating which values are expected and whether or not there are dependencies could provide clarity around this issue. An example is provided below – it is not intended as a specific recommendation for how the values should relate, simply is derived from the current examples in the specification.

Study Tagging File Metadata Interpretations

Element Location	Element hierarchy/ description	Value description	Dependencies
Index.xml	<leaf><title> pointing to STF XML File	Unique study identifier, such as study number, followed by 'STF', ex: Study 123 STF	Same value as used for the <study-id> appended with 'STF'
STF XML	<study- identifier><title>	Full title of the study report	None.
STF XML	<study- identifier><study- id>	Internal code used by the sponsor to uniquely identify the study report	Used as the start of the value of the <leaf><title> that references this STF XML file
STF XML	<doc- content><title>	For each leaf pointing to content for the study, an <doc-content> element exists. The DTD allows for inclusion of a child <title> element, however, it is not used at this time.	None