

IRISS-Forum

eCTD Tool Interoperability Group

July 21, 2010

Attendees (20)

eTIG Update:

- Welcome to John Donohoe of the Australian Therapeutic Goods Administration (TGA)

Agency Updates and Specific Questions:

- EMA (not represented on the call)
- FDA (not represented on the call)
 - **Post-meeting email request and response:** Clarification of FDA's acceptance of the ICH valid-values v3.0 was requested after the meeting.
 - Ginny Hussong responded that "*FDA will begin accepting applications using Valid Values 3.0 as soon as we implement Global Submit Review and Validate 2010, which is targeted for October (but can change). We will post the document to our website at that time, but continue to support the existing version (2.2) for a period of time (now undetermined) to allow the tool vendors and industry to adopt the changes.*

Regarding lifecycle, if a submitter used data-tabulation-dataset and then submitted a later sequence using data-tabulation-dataset-legacy, the files will appear in two different folders. An exception to this would be if one file replaced the other. In that case, both files would appear in the folder associated with the file tag of the replacing file. This applies to all of the new tags."

- Health Canada (Vianney Caron)
 - In response to an industry concern that Health Canada will implement GS Validate 2010 and begin returning errors to sponsors immediately thereafter.
 - HC eCTD validation rules are published on our website, HC will not use a different set of validation rules until they are published on our website. An advance notice will be given to sponsor before adopting a revised set of validation rules. As indicated at the DIA conference in Washington last February application received still have numerous issues with regard to STF Health Canada accept STF although they are not mandatory. However, if STF are provided they have to meet ICH requirements. GS validate, GS review and Datafarm VUE are used in HC testing environment to help HC identify and resolve issues with submission, specially when containing STF. We have validation rules about STF. In some instance, although the submission pass validation, the submission is of a poor quality, therefore we need to improve our validation rules. HC is using only the Lorenz eValidator in it's production environment, all validation reports issue by HC are done using this software and the validation rules published on our website.

Post-meeting note: [Health Canada Confirms Exclusive Use of LORENZ Solutions in Production](#)

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- Swissmedic (not represented on the call)
- TGA (John Donohoe)
 - Since tenders closed for the supply of a review tool to support the eCTD requirements of TGA there have been a number of developments relevant to the TGA's requirements for this tool, so the procurement process was halted. They will put forth a new tender in the near future and do not expect to be accepting eCTDs during 2010.
 - Sponsors are encouraged to provide an electronic version of the paper submission to aid the review process while specifics of the electronic format are being developed.

Follow up to previous topic(s) (Lenore Palma)

- The Interoperability Group sponsored the first IRISS webinar on Tuesday, May 25th entitled "eCTD submission in the EU". Thank you to Hans van Bruggen from eCTD Consultancy for being our guest speaker. We had 68 connections from 35 companies to the webinar and a higher number of attendees as there were several groups on the line. Does anyone have comments or questions on that presentation?
- The FDA has provided the following response in regards to submissions which are not fully accepted by an agency ...
No advice or feedback is being provided from the FDA since they have not had or don't expect this scenario to occur. There are some files that are not allowed and should not be submitted by the FDA and sponsors should only submit allowed file types per specifications.
- An email was sent to EMA, FDA, HC and PMDA asking if they collect statistics on validation errors (e.g. specific errors, specific tools, etc.) and if so, what is done with the information. The following responses were received:
 - FDA (Ginny Hussong) – *"Because of the way our current validation reporting system works, we do not formally keep statistics on all eCTD errors received. However, we do keep monthly records on rejections, which frequently are related to a "high" error, but can be due to other errors such as broken media, or being sent to the wrong center. We use this information to contact sponsors in order to help deter future rejections. We also usually report and describe these errors to industry at various meetings hosted by DIA, GPHA or other organizations.*

In the near future, when we adopt GS Validate 2010, we will be keeping records on all validation errors, since the validation tool will utilize a database, which our current validation tool does not."

- PMDA (Taku Watanabe) – *"PMDA (Japanese regulator) is providing eCTD validation tool on its website by which applicants can check their instances before submitting to PDMA. PMDA also checks the instances on-site when applicants bring their eCTD in the form of DVD to PMDA office. The PMDA on-site validator checks some additional points in addition to the points the eCTD validation tool checks.*

So I think the validation errors that can be found in the process are:

- A. the errors that applicants detected in their site by the eCTD validation tool.*
- B. the errors that PMDA on-site validator detects when receiving eCTD DVD.*

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The applicants would correct the errors A. before submitting to PMDA, and therefore PMDA does not have them collected.

PMDA does have errors B. collected and some of them are posted on PMDA website, but it is available in Japanese only.

Also, PMDA receives questions with respect to how to build xml in specific case from applicants. Those include questions like “my tool creates xml in this way but is it acceptable for PMDA?” In some cases PMDA asks applicants to correct such xml manually. These might be informative for IRISS activity.

The errors and Q&A we experienced in past are referred when similar case occurs so that we can maintain the consistency to the utmost extent possible in our responses to applicants.”

ETICS III Status Update (Harv Martens)

- Phase I
 - 7 vendors and 4 agencies completed Phase 1.
 - 6 vendors who had enrolled did not complete Phase 1, although 1 indicated that they did not have a validation tool and will be participating in Phase 2.
 - Analysis by the regional teams is proceeding. Target date for completion of the analysis is end of August.
- Phase II
 - Separate telecons to prepare Phase 2 will begin shortly. There will most like be a “Phase 2B” in which vendors are asked to add a new sequence to an eCTD produced by another tool.

Best Practice Document (Barbara Jentges)

- Barbara is still looking for comments on the draft version that was sent out in May. The final version is planned for discussion at the August meeting.

Interoperability Scenarios of the Month (Group)

- When a dataset(s) changes ...
 - When a dataset(s) changes (replace) and the define does not, how should this be handled?
 - Should the define document be replaced even if nothing is changing in it or should it be replaced with an updated hyperlink?
 - **Post-meeting response to email from CDER eDATA:**
“When the sponsor’s submission is made, via the gateway or through delivery to the agency, a sequence number specified by the sponsor is used for change management and traceability. The submission (IND/NDA, etc) assigned number and the sequence number are tested to ensure the sequence number has not been previously used. If it has been used previously, a refusal to file occurs and the submission is rejected. Given the process of change management, the agency recommends that the dataset changes (replace) include only those datasets that have changed or any new datasets for the new sequence number provided. The define.xml and/or define.pdf in the directory with the datasets should “define” the

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datasets per the guidance and the location for the transport file(s) (.xpt(s)) should be linked in the file(s) in the same or relative directory. All “defines” (including index.xml and study specific xml and/or pdf) referencing the new or changed datasets should be updated and included in the submission. All datasets should be hyperlinked in the submission’s “defines”. For example, a hypothetical sequence number 0001 updating an AE dataset should include the updated m5 directory with the “defines” (corresponding hyperlinks) updated to the changes in the submission. The eCTD xml files provided by the sponsor in the submission control the life cycle management of objects in the submissions. Please reference “The eCTD Backbone File Specification for Study Tagging Files” for further guidance (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>). “

- When a dataset(s) changes (replace) and some of the define document aspects for those replaced datasets change, how should this be handled? For example, let’s say that there were originally 50 datasets and 2 are being replaced.
 - Should a new define be submitted with just the changed information on the 2 datasets (new? append?)?
 - Should a new define with the old and new information replace the old define, and everything be re-hyperlinked in the replacement define (i.e. the 2 new replaced datasets plus back to the 48 original unchanged datasets)?
 - Other options?
 - **Post-meeting response to email from CDER eDATA:**
“The comments above apply to these questions as well. Please only submit “changed” or “new” datasets in subsequent submission sequences.

The current reference is the Study Data Specifications, (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>) which provides most conducive data content definition and structure for the review team, although this may vary based on the submission and reviewing division (pg. 2).”

- Several sponsors agree that they would most likely (or have in the past) provide the new datasets and a new define.xxx for just those datasets. One sponsor stated that they had appended the new define.xxx to the previously submitted definition leaf.
- The Hyphens issue... (**Post-meeting details** provided by Dr Gerhard Neurauter, Extedo)
 - In EURSvalidator it’s our goal to follow the “common eCTD understanding” and to provide a single validation set for all EU regions – including Belgium. In the past, the Belgium checker did not allow any hyphens in the m2/m3 VAR part and therefore we reported a hyphen as violation of rule 0034 (0034_1). With this interpretation we ensured valid MRP/DCP submissions for all EU countries.

Since EURSvalidator 1.4.00 SP1 Build 03, hyphens are allowed in the VAR part of m2-m5 in EU-NEES and HR-NEES submissions. The 0034 violation is not reported (track number #16265). Please refer to our release notes for further details.

In case of eCTD (HR, CH and EU) this issue was identified and tracked with #17724. It is fixed in our internal version but – so far – not provided to public. It is included in our next release at the end of September 2010.

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The latest version of EURSvalidator is published 15th July 2010 (version number 1.4.SP2 Build 07). Information and the download can be found at <http://www.extedo.com/register-for-downloads.html>. On the webpage please select "EURSvalidator download". You are asked to add your contact data. Afterwards press "Send" to enter the download area. There you have access to the following files:



The validator includes the validation sets for
EU 1.2.1/1.3/1.4
CH 1.0/1.0.1/1.1
NEES 1.0 (EU)

One can download from the webpage (see above) HR 1.0 and HR-NEES 1.0 and add it to the EURSvalidator. On request (hotline@extedo.com or EURSvalidator@extedo.com) we are providing (free of charge) the FDA validation set too.

The Canadian validation set for EURSvalidator is under production and will be provided soon (beginning of 4th quarter of 2010).

Next eCTD Tool Interoperability Group teleconference:

18-Aug (7:30-9:00 am (US Eastern Daylight Time, UTC/GMT -4 hours))

Changes to the Interoperability Group (eTIG) will be announced at this meeting!