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November 2010

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CDISC North American Interchange

Í am just back from the North American Interchange which was in Baltimore. I arrived on Monday evening as a number of team meetings were planned for Tuesday. So on Tuesday morning I attended the "Metadata Submission Guide" team meeting where I contributed considerably to the rewrite of the "define.xml" section in the draft guide. In the afternoon I then attended the "define.xml" team meeting, where we discussed the new features for the envisaged version 2.0 of the specification.

The conference then started on Wednesday morning with keynote presentations of Doug Fritsma (Office of the National Coordinator for Health Information Technology), Raymond Woosley (Critical Path Institute) and Theresa Mullin (FDA CDER). Mrs. Mullin spoke about the "CDER Data Standards Plan". The latter mentions for example that use of HL7 messages for submissions to the FDA may not be expected within the next few years: "Neither the HL7 standards, nor the agency, nor regulated industry are ready for such a transition".
Mrs. Mullin further mentioned that there is a very high variety in SAS XPT files they obtain as part of CDISC submissions. This does not wonder me, as these are usually the result of the inflexibility of the SAS Transport format, forcing sponsors to force square pegs in round holes (SUPPQUAL for non-standard variables, the RELREC disaster, the Comments domain ...). In my opinion, HL7-XML will not resolve this. At the contrary, it will make everything even more difficult.

After lunch, it was time for the "round table discussions". These were first established at the last European CDISC Interchange were they were a great success. I attended the "ODM – define.xml" round table discussion. The discussions there again showed that there is an urgent need for a "define.xml" implementation guide, wiki, or even training courses, as many people still seem to have trouble with the implementation of this standard.

In the afternoon, I gave my presentation on "Towards a fully machine-readable Protocol: from ODM-extension to Patient Study Calendar". The discussions with a number of people after the presentation strengthened me in my believe that this new ODM-based standard will be a key in interfacing between clinical research protocols and hospital planning systems, clinical trial registries, and submissions to the regulatory authorities.

I also attended the SHARE session later in the afternoon. SHARE is making good progress but is not so far yet that we can start developing a format to transport SHARE metadata and use it in applications. On the other hand, the ODM team is already thinking about how ODM can work with SHARE.

The social event in the evening was in the Maryland Science Center, close to the conference hotel. A few photographs can be found at the end of this newsletter.

Thursday morning was devoted to a multitude of topics: implementation of CDASH at Kendle, BRIDG, and the status of projects for integration with healthcare (CDISC Healthcare Link – Landen Bain). The second part of the morning was on "Standards and the Patient", and much more "high level": the millions of dollars for national projects floated over the screen.

The afternoon then was fully devoted to the topic of CDISC standards and the FDA.

The FDA at the CDISC Interchange

The first Thursday afternoon session consisted of a number of presentations by FDA representatives.

Vicky Seifert-Margolis is pretty new at the FDA "Office of the Commissioner" (OC). She has a background as a clinical science officer at a pharma company. As such we may hope there is a fresh wind at OC, finally having people there that understand the clinical process at pharma companies (and especially the IT involved). Until now, we had the impression that OC is slowly forcing the industry into (XML-based) standards that does not understand itself, just by believe-but-not-investigate that these standards are also suited for clinical research.

The second speaker was Amy Malla. She is the center lead for implementation of CDISC at CBER. One year ago she still had to report that CBER is not accepting SDTM submissions. Now she could report two SDTM submissions are being reviewed at CBER, a third being on the way. She could also report that there is an extensive training program in the use of CDISC standards currently being run at CBER.
Mrs. Malla positively surprised me with her knowledge of the CDISC standards, and her excellent analysis of the strengths and weaknesses of them. For example she stated that the sponsors need to know and understand their SDTM data, and not blindly rely on the CRO (or third party service provider) that the data is OK. She stated that the FDA will not communicate with the CRO or service company that created the SDTM datasets in case of problems, but only with the sponsor. I say this all as I observed that in most cases creation of the SDTM datasets is outsourced by sponsors to either the CRO or a specialized company. This is not bad, as long as the sponsor is strongly involved in the decisions that need to be made during the categorization steps that are necessary to come to SDTM datasets, I have however seen (too) many cases where the project is "thrown over the wall", with the idea "you do it, and we rely that you do it good". The owners of the result are however the sponsors, so it is essential that they known and understand their SDTM datasets when it comes to a submission to the FDA.
Mrs. Malla further made a strong emphasis on good communication between the sponsor and the FDA: "if your data is not 100% SDTM compliant that is OK, but at least you have to say us, and explain it to us".

The third speaker was Chuck Cooper (CDER). Mr. Cooper reported that they are now at least keeping track of which submissions are SDTM and which not. A year ago, he would not have to be able to give numbers, as CDER did not keep track of which submissions were SDTM and which were not. He also told us that CDER is developing a "CDER Standards Data Checklist" which will be shared with the industry, and even may be published as a kind of "CDER CDISC Implementation Guide". They will also analyze the last 100 CDISC submissions and report about the "most common errors".
I can only greet these initiatives. In the past, it was often not clear what the rules are that are being used at the FDA to accept or refuse an SDTM submission. The WebSDM rules were not public (they now are). OpenCDISC has certainly been a breakthrough here, and its rapid adoption by the FDA is a good sign that one can come to a common set of "playing rules" that is open (also for discussion) and machine-readable.

Steve Wilson (CDER) had his usual splendid talk, full of humor, and with many stories from his daily experiences with CDISC standards. His graphs showed that approximately 40% of the submissions use SDTM, the number being 20% for ADaM. The latter is astonishing, as the first really usable ADaM implementation guide is only one year old.
He also mentioned the FDA "Transparency Initiative" with the aim of making the review process much more transparent for the sponsors.

After coffee break there was a panel discussion. Additional FDA representatives were Ranjit Thomas and Jonathan Levine (OC). People could ask questions either directly or anonymous by giving the moderator (David Iberson-Hurst) a paper note during coffee break. This Q&A session again made clear that the FDA wants sponsors to communicate better (and especially earlier) with the FDA, and that the sponsor is responsible for the data they are submitting, not the CRO or service provider. So once again "sponsors need to know and understand their (SDTM) data".

One of the slides used by Steve Wilson (CDER)

German-speaking User Group Meeting

This was already the 9th user group meeting for the German-speaking user community, with the emphasys this time on CDASH.

Elke Sennewald (Kendle) started with a presentation about how Kendle implemented CDASH in its organization. As Kendle is a very large CRO, such an implementation is not without consequences for the whole organization and as such, not so easy to realize.
Elke also gave an excellent CDASH tutorial, going through the specification, and then treating a number of CDASH/SDTM domains and implementation scenarios.

Kurt Hellstern (Hands-on GmbH) then continued with a set of implementation examples, thereby (as usual) triggering a lot of discussions. This was surely the most useful part of the day.

My own short contribution was about the upcoming ODM implementation of the CDASH forms. My recent conversation with Rhonda Facile at the North American Interchange also learned me that the ODM implementation will be publised together with the Implementation Guide of CDASH v.1.1 in the near future.

All together, it was a very interesting user group meeting again, and we hope to see many of the german-speaking users again (and hopefully also a lot of new ones) at the next meeting in Munich in spring.

End-of-year discount action for our software products – 25% off

Our "end-of-year" discount action has started: if you order one of our software packages for working with CDISC standards (for an overview, see our website), before the end of the year, you get a 25% discount on the normal price.

You can find the normal prices either on the specific web page of each individual product, or obtain a quote from us.

All of our software products come with a 1-year free upgrade guarantee, and with full documentation and support.

A Schematron for ODM

We are currently developing a schematron for ODM 1.3/1.3.1. Schematron is a W3C standard for the description of "business" rules that cannot be enforced by XML-Schema. A very simple example for ODM is the rule that the "AsOfDateTime" must be earlier than the "CreationDateTime". The Schematron snippet for this rule is shown in the figure at the end of this newsletter.
Also much more complicated rules, such as the "reference-definition" rules can easily be expressed by Schematron.
A great advantage of Schematron is that when applied to an ODM instance file, and a rule violation is found, the schematron engine returns a detailed message (as developed by the Schematron author), including the exact location of where the violation was found in the file (as an XPath expression). As such, Schematron can easily be implemented in ODM viewers and designers, such as our "ODM Study Designer" (see our September issue).

We are steadily extending the Schematron for ODM. It will then be reviewed by the CDISC XML Tech team, and published on the CDISC website. This will make it much more easy for people wanting to develop validation software, as the rules then come in a machine-readable format, meaning that everyone uses the same rules, and different interpretations of the rules are excluded.

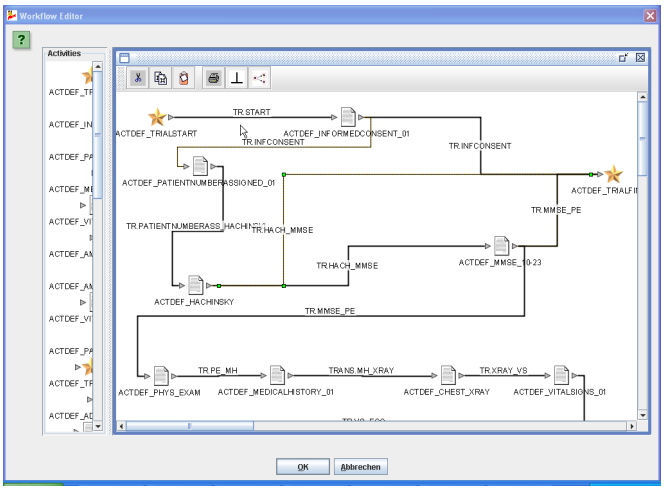
ODM-extension for the Study Design Model (SDM)

The SDM team is also now working hard on finalizing the specification and XML-Schema (also a Schematron is foreseen) for the "Study Design Model" extension of the ODM standard.

As already reported in our March newsletter, the extension will allow to add protocol information such as trial parameters, inclusion and exclusion criteria, information about arms, epochs, cells, segments, planned activities. Also workflows and timings between activities can be added.

Arms, epochs, cells, segments, activities

This new standard will mark a new milestone for CDISC ODM, as it will enable ODM to be used for looking for eligble subjects in hospital information systems, for setting up a patient calendar (as already demonstrated for the caBIG Patient Study Calendar), to set up workflows in hospital planning systems, and much much more.



The workflow of the LZZT trial

Our part in this project has been to test the model, generating software for working with it to see whether the model is really implementable. So we experimented with it in our "ODM Study Designer", and found that the model is indeed very well implementable.

This also means that immediately when the new standard is published, we will offer the ODM Study Designer with support for SDM.

The SDM team hopes to be able to publish the new standard for public review by the end of this year. So keep an eye on the CDISC website (and of course on our own website).

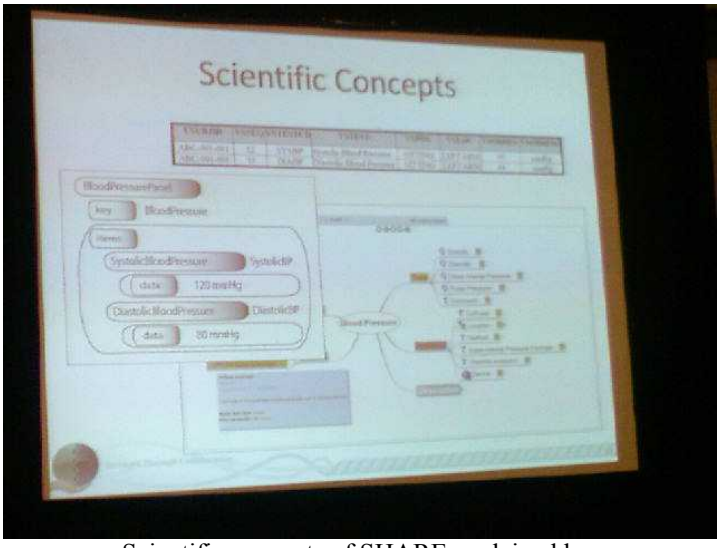
```
<sch:pattern name="ODM attribute AsOfDateTime usage">
  <sch:rule context="odm:ODM[@AsOfDateTime]">
    <sch:let name="ASOFDATETIME" value="@AsOfDateTime"/>
    <sch:let name="CREATIONDATETIME" value="@CreationDateTime"/>
    <sch:assert test="$ASOFDATETIME le $CREATIONDATETIME">
      It is an error to supply an AsOfDateTime that is later than the
        CreationDateTime. The value of AsOfDataTime found is '
      <sch:value-of select="$ASOFDATETIME"/>
      ', the value of CreationDateTime found is '
      <sch:value-of select="$CREATIONDATETIME"/>
      '
    </sch:assert>
  </sch:rule>
</sch:pattern>
```

Schematron Rule description that AsOfDateTime must be earlier than CreationDateTime

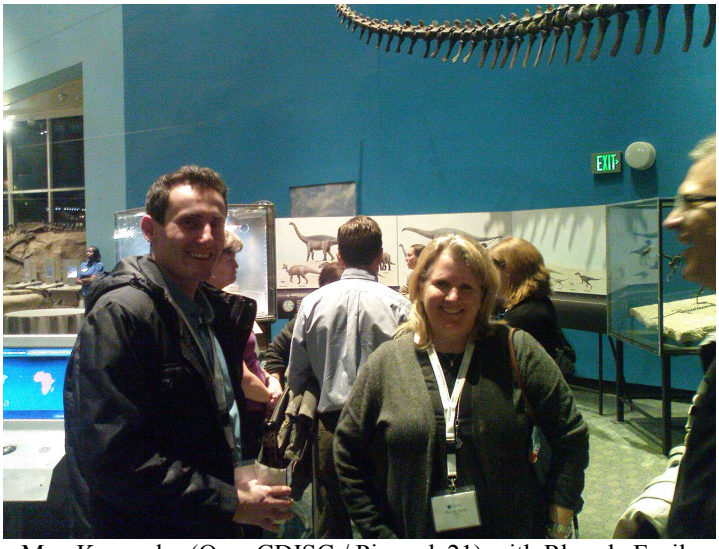
```
<sch:pattern name="FormRef element FormOID attribute">
  <sch:rule context="odm:FormRef">
    <!-- The FormRefs within a single StudyEventDef must not have duplicate
      FormOIDs -->
    <sch:let name="FORMOID" value="@FormOID"/>
    <sch:let name="STUDYEVENTOID" value="../@OID"/>
    <sch:let name="METADATAVERSIONOID" value="../../@OID"/>
    <sch:let name="STUDYOID" value="../../../@OID"/>
    <sch:assert test="not(preceding-sibling::*[@FormOID = $FORMOID])">
      Form with OID '
      <sch:value-of select="$FORMOID"/>
      ' is referenced more than once within the StudyEventDef with OID '
      <sch:value-of select="$STUDYEVENTOID"/>
      ' within the MetaDataVersion element with OID '
      <sch:value-of select="$METADATAVERSIONOID"/>
      ' within the Study with OID '
      <sch:value-of select="$STUDYOID"/>
      '.
    </sch:assert>
  </sch:rule>
</sch:pattern>
```

Schematron rule description that FormRef elements must not have duplicate FormOIDs within a single StudyEventDef

A few photographs from the North American Interchange in Baltimore

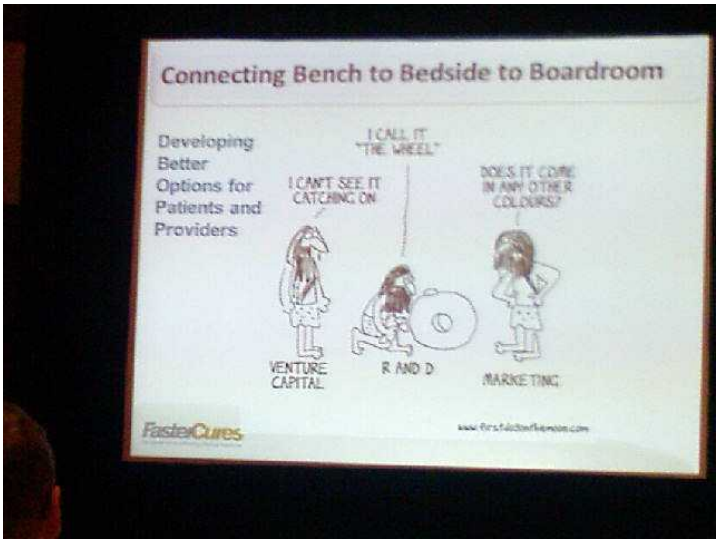


Scientific concepts of SHARE explained by David Iberson-Hurst (CDISC)



Max Kanevsky (OpenCDISC / Pinnacle21) with Rhonda Facile (CDISC) and David Borbas (Jazz Pharma)

A dinosaur at the Maryland Science Museum (we also have some in our industry ...)



Also humor has its place at the Interchange