Introduction to eStability

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Presentation Overview

- Stability Message Development
- Advantages of e-Stability for the FDA & industry
- Style-sheet
- e-Stability Message
- Validation of Messages
- Code Systems
- Getting started
- Current status of the message

Vision of Drug Stability Reporting

- Provide stability data in a standard electronic format
- Viewed in human readable format by regulatory agencies and industry
- Multiple transfer uses:
  - Company → Company
  - Testing Lab → Company
  - Company → Regulatory Agency

Stability Message Development

- **~1999** - Original concept for stability data in XML format developed by Naiqu Ya & Jon Clark for OGD
- **Jan 2001** - Development of HL7 Stability Standard started
- **Sept 2005** - Stability Standard is ANSI approved & 1st public draft of IG
- **May 2006** - Published FR notice (Docket No. 2006N-0181 (Product Stability; Data: Notice of Pilot))
- **May 2008** - Product Stability Data Pilot Project Completion Announcement
- **January 2009** - Stability Standard (R2) as Draft Standard for Trial Use (DSTU) and Implementation Guide Pass ballot
- **May 2010** - Stability Standard (R2) approved as HL7 standard
- **May 2011 –** Included in normative edition of HL7 messages

Advantages of e-Stability for the FDA

- Improves stability data exchange
  - Companies and reviewers can precisely reference what was submitted
- Reduce review times with the aid of data viewer
  - No need to re-enter data for trending
- Data is validated before it is received
- Facilitates development of software to graph stability trends and view tabular data
- Reviewers can view any subset of the data without contacting the company for an additional graph or table

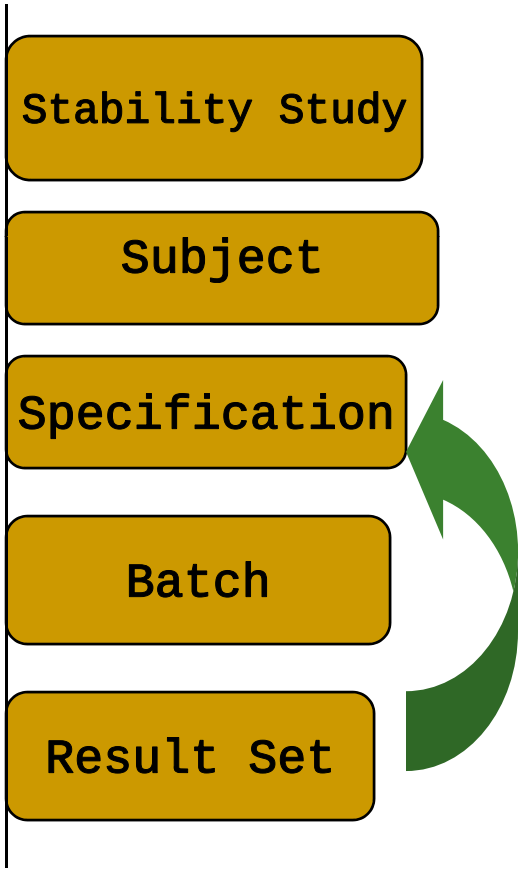
Advantages of e-Stability for Industry

- Increase efficiency of submissions
  - reduce number of tables & graphs in the CMC section
  - reviewer will be able to view them easily in their tool
- Improve stability data exchange between contract testing labs and companies
- Message does not change the study plan or data capture
- Facilitates the exchange of stability data between different LIMS and OOT analysis packages
- All LIMS vendors to produce a uniform stability report

e-Stability Characteristics

- Part of a larger framework – contents must belong to the HL7 namespace
- Extreme Extensibility
- Aggregation of complex types
- Sparsely populated types

e-Stability Message Structure



Name of study and sponsor

Particulars of the material being studied

How the study is conducted

Particulars of the lot that was tested

Results from testing done in accordance with the specification

XML – the Common Language

- Common to both Ya-Clark and HL7
- Only general understanding required
- XML is only a syntax
- An XML "document" is the message in its entirety
- A document is composed of elements and attributes separated by tags

Drug Stability Reporting

<component>
<testDefinition>
<id root="2.16.840.1.19927.1.12345.202.30.339"/>
<code code="physical" displayName="Permeation"/>
<text/>
<methodCode code="Compendial" displayName="USP <671> Containers Performance Testing"/>
<referenceRange>
<acceptanceCriterion>
<text>NA</text>
<value xsi:type="ST" nullFlavor="NA"/>
<interpretationCode displayName="Passed"/>
</acceptanceCriterion>
</referenceRange>
<component>
<testDefinition>
<id root="2.16.840.1.19927.1.12345.202.30.340"/>
<code code="physical" displayName="Water Weight Loss"/>
<text/>
<methodCode code="Compendial" displayName="USP <671> Containers Performance Testing"/>
<referenceRange>
<acceptanceCriterion>
<text>NMT 1 to 2.5% (W/W)</text>
<value xsi:type="PQ" value="2.5" unit="%"/>
<interpretationCode displayName="NMT"/>
</acceptanceCriterion>
</referenceRange>
</testDefinition>
</component>
<component>
<testDefinition>
<id root="2.16.840.1.19927.1.12345.202.30.341"/>
<code code="physical" displayName="Light Transmission"/>
<text/>
<methodCode code="Compendial" displayName="USP <671> Containers Performance Testing"/>
<referenceRange>
<acceptanceCriterion>
<text>290 nm to 450 nm</text>
<value xsi:type="PQ" value="290" unit="nm"/>
<interpretationCode displayName="NLT"/>
</acceptanceCriterion>
</referenceRange>
<referenceRange>
<acceptanceCriterion>
<text>290 nm to 450 nm</text>
<value xsi:type="PQ" value="450" unit="nm"/>
<interpretationCode displayName="NMT"/>
</acceptanceCriterion>
</referenceRange>
</testDefinition>
</component>
</testDefinition>
</component>

- Stability data in a standard electronic format
- Viewed in human readable format

Specification			
Test	**Acceptance Criteria**	**Analytical Procedure**	**Component Tests**
Sterility (biological)	Passed	USP <71> Sterility (Compendial)	
Appearance (physical)	Pink round, film-coated tablet scored 99 0T9 one side and plain on the other	NH401 General appearance method (Proprietary)	
Microbial Limits (biological)		USP <61> Microbial Limits (compendial)	P. aeruginosa S. aureus Salmonella
Container Integrity (physical)	Passed	NH401 General appearance method (Proprietary)	Closure Appearance Container Appearance
Total Viable Aerobic Count (biological)	< 100 CFU/g	2.6.12 Ph. Eur. Total Viable Aerobic count (Compendial)	
Assay (chemical)	90.0% - 110.0% of labeled claim 90.0% - 110.0% of labeled claim	NH432 Assay (Proprietary)	
pH Measurement Average (chemical)	3.3 to 4.5 3.3 to 4.5	USP <791> pH Measurement (Compendial)	pH Measurement
Dissolution Average (physical)	1 hr: Average (n=6) is 26%-34%; 4 hr: Average is 56%-73%; 12 hr: Average is NLT 72%	NH772 Dissolution Profile (Proprietary)	
Dissolution (physical)	1 hr: Each tablet is 20%-40%; 4 hr: Each tablet is 50%-75%; 12 hr: Each tablet is NLT 85%	NH772 Dissolution Profile (Proprietary)	Dissolution Hour
Impurity - Elemental (chemical)		NH740 Elemental Impurity Estimation (Proprietary)	Nickel Chromium Palladium
Permeation (physical)	NA	USP <671> Containers Performance Testing (Compendial)	Water Weight Loss Light Transmission
Total Count of Failures (chemical)	NMT 1 (n = 12)	NH432 Extractables (Proprietary)	Individual Alkali Oxide Extractables

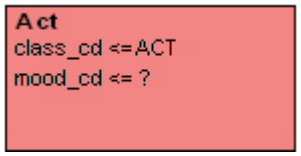
Infrastructure

- The schema defines legal element names, their attributes and how they nest
- XML messages can be validated against the schema before it is sent
- The e-Stability standard compels syntactically acceptable data

Implementation Guide Structure

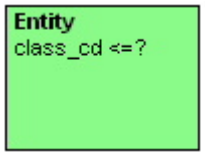
- Introduction that presents the model of the message and broad concepts
- Detailed Description of the elements
- Appendix of codes
- Example message with annotations

UML - The Modeling Language in HL7



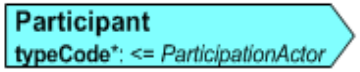
Act

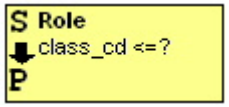
Act_Relationship



Entity

Participation

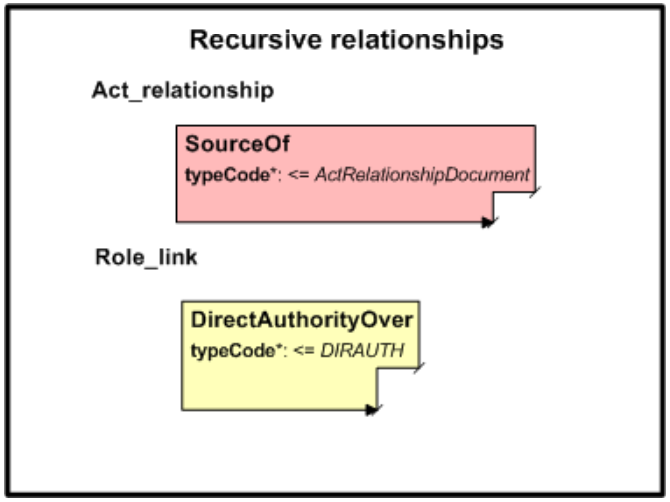


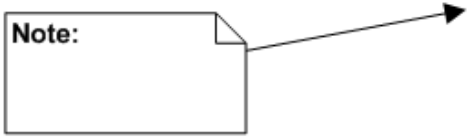


Role

Role_Link

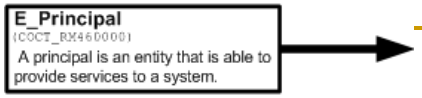
Choice construct for Acts, Roles or Entities





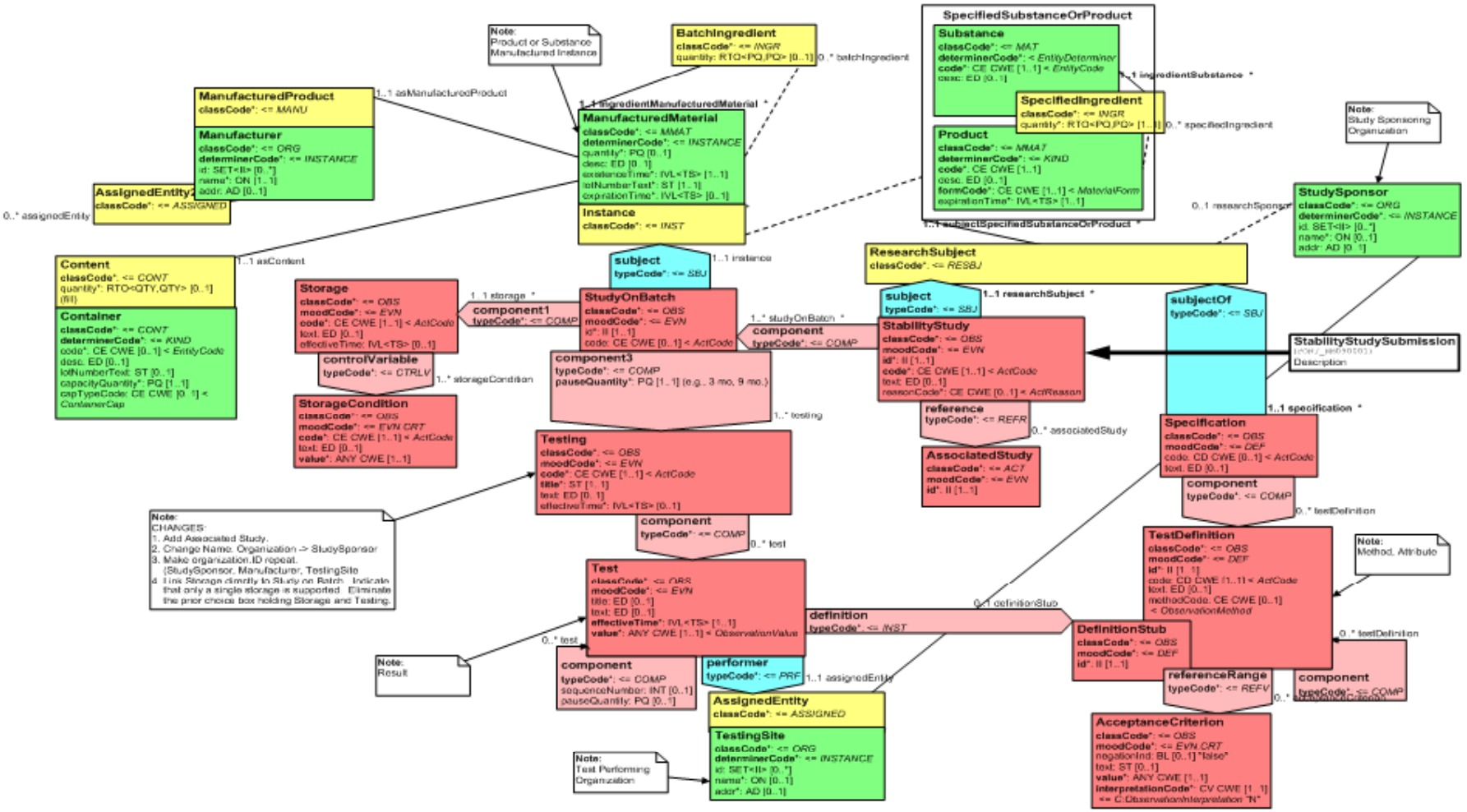
Note

Entry Point

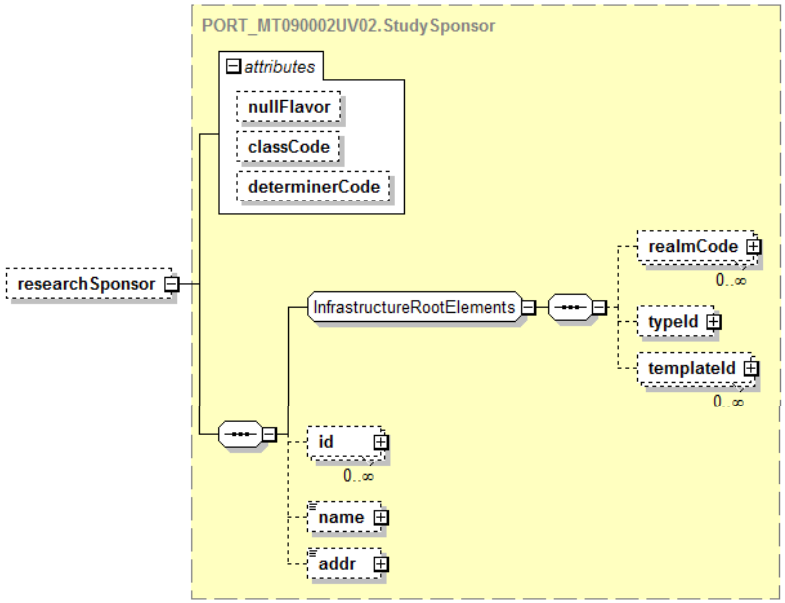


- http://www.hl7.org/v3ballot/html/help/v3guide/v3guide.htm

e-Stability Schema Modeled in UML



Element Details - Example



Sample Code

```
<researchSponsor>
   <id root="D123456789" assigningAuthorityName="Dun and Bradstreet D-U-N-S Number"/>
   <id root="2.3.6.1.4.1.24263" assigningAuthorityName="Internet Assigned Numbers Autority"/>
   <id root="F1234567890" assigningAuthorityName="FDA FEI OID"/>
   <name>up to data professional service GmbH</name>
   <addr>
        <country>Germany</country>
        <city>Wörrstadt</city>
        <postalCode>55286</postalCode>
        <streetAddressLine>Am Pfädchen 4</streetAddressLine>
   </addr>
</researchSponsor>
```

StudySponsor
/stabilityStudy/subject/researchSubject/researchSponsor

Description:

The research sponsor for the study.

Simple Children:

Name	Type	Description	H	F
id	II	A set of identifiers used to uniquely identify the study sponsor. Use the DUNS number as the primary identifier. Other examples can be FEI number or a global unique identifier for the sponsoring organization assigned by IANA. For DUNS number, remove hyphens if present and prefix with "D" and if an FEI number prefix with an "F". Note: The assigningAuthorityName for a DUNS number is "Dun and Bradstreet D-U-N-S Number" and for a FEI number is "FDA FEI OID". A DUNS number and FEI number example are shown here. The assigning authority name is mandatory for all OIDs for organizations. Always list the DUNs number first if listing multiple numbers. It is the submitter's responsibility to ensure that the DUNS number id along with the firm's postal code (if any) and country match the DUNS number, postal code and country in the Dun and Bradstreet database. <id root="D123456789" assigningAuthorityName="Dun and Bradstreet D-U-N-S Number"/> <id root="F1234567890" assigningAuthorityName="FDA FEI OID"/>. **Attributes** Root — Identifier — M M Extension — N N assigningAuthorityName — N M displayable — N N This identifier should be the same for one organization within all submissions of one company. .The provided identifiers should be chosen in a way, that if a company has more than one location (e.g., with different addresses), the identifier is specific for this location (same address – same number).	O	M
name	ON	Name of the organization sponsoring the study.	R	M
addr	AD	Address of the organization.	O	M

IG - Identify Mandatory Data

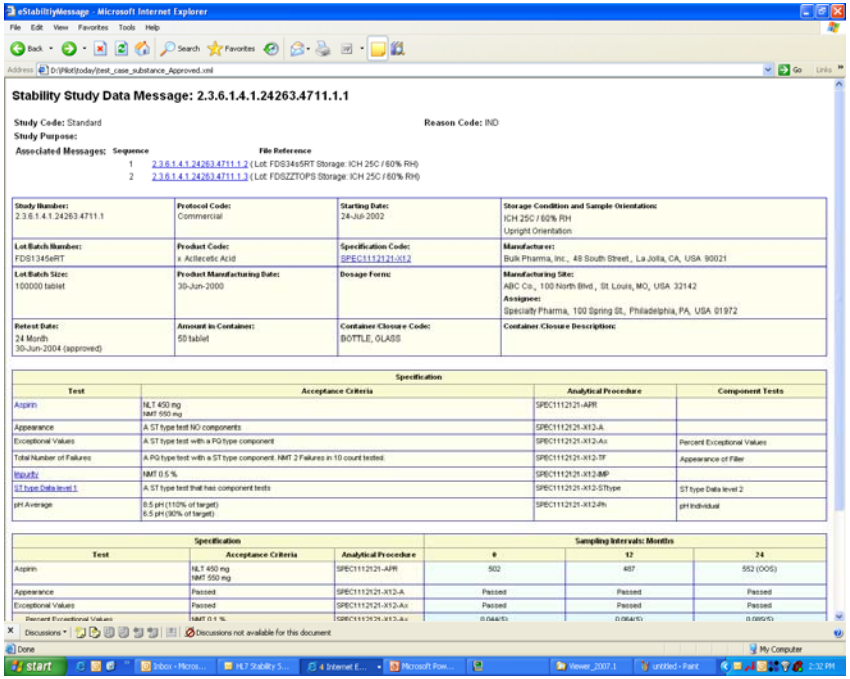
- Scan IG for M in the F column
- Note where your organization stores the information
- Identify gaps
- Missing test dates or testing sites = RTF

How Deep?

- Software developer working with eStability requires an understanding of the modeling language
- Stability managers do not go that deep
- Go as deep into the eStability model and message as far as you are technically capable
- Hire capable people to go deeper
- Look to IT and Regulatory Operations groups for support

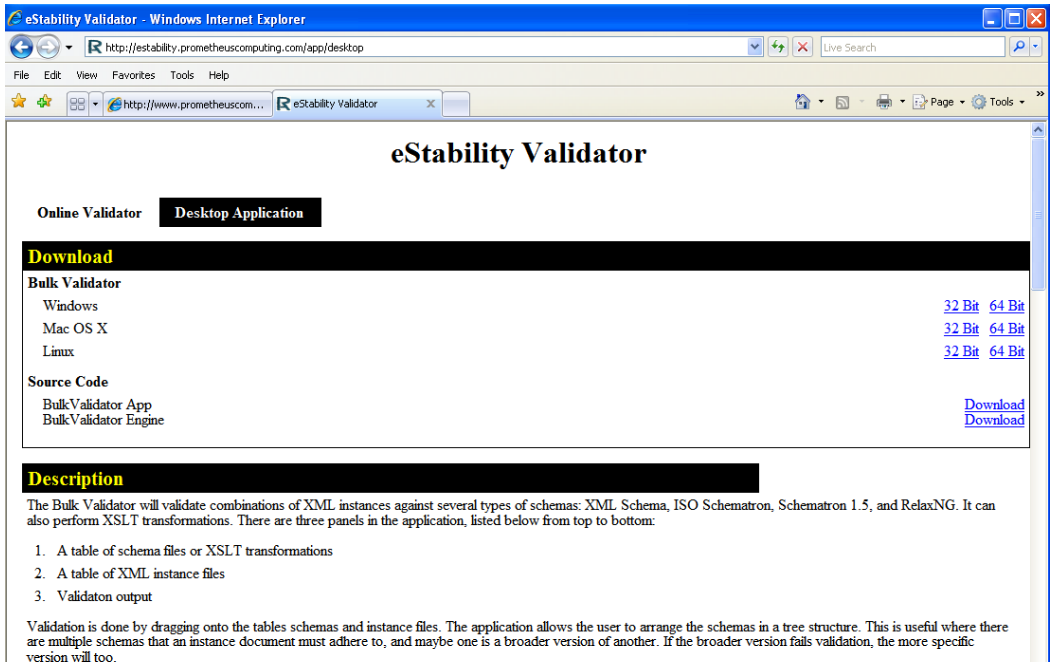
Style-sheet

- FDA funded development of style sheet
- Return of Ya – Clark view of stability
- http://www.accessdata.fda.gov/stabilitydata/stylesheet/eStability.xsl
- Demo style sheet



Valid Messages

- FDA funded development of a Schematron for eStability
- Validate you messages at http://estability.prometheuscomputing.com/app/desktop



Code Systems

- NCI maintains stability code lists
- Code lists are specific to Stability
  - http://evs.nci.nih.gov/ftp1/FDA/Stability
- Updated by NCI on monthly basis
- Request codes if desired term in not found

Preparedness for e-Stability

- All companies will face unique circumstances
- Division of work by function and distribution of responsibilities
- Timelines and sense of urgency will vary
- Until it is mandated, it does not grab attention
- Drivers – Regulatory, stability data experts, IT?
- Implementation
  - Short term – indentify gaps
  - Long term - indentify solution

Seven Steps

1. Identify key stakeholders
   - Regulatory Affair
   - Regulatory Operations
   - Stability Study managers
2. Create a steering committee
3. Identifying Data Sources
   - LIMS
   - Specifications
   - DUNS numbers - Testing sites, even foreign sites will need a DUNS number

Seven Steps – Continued

4. Choose Identifiers - OIDs or GUIDs
5. Identify the best method to create the messages
   - Extension to eCTD tools
   - Stand alone product
   - Extension to LIMS
   - Outsourced conversion by service providers
   - Deciding factors include:
     - Expected costs and budget process
     - Timelines
     - Volume of messages submitted annually
     - In-house XML expertise

Seven Steps

6. Decide levels in the test definitions

7. Develop Standards awareness

Current Status

- FDA Data Standards Pages – always check for updates
- Completed Infrastructure
  - Style sheet
  - Implementation Guide
  - Schematron
  - NCI Codes
  - Validation Guide
- October 2011 PhRMA, CDER and OPS meeting
  - Concerns
    - Cost (getting information to XML)
    - Getting vendors on board without message mandate
    - usability of the standard by the rest of the world
  - Data presentation in style sheet well received
  - Next step - CFR Q&A for eStability for comment