Ensuring Consistent and Supported Standards Across Data and Metadata in a Large Regulatory Filing is Tricky Business

Lisa Brooks, Independent Consultant
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Disclaimer:
I am not a Regulatory Professional, I only play one on TV. Although I am often asked about planning data submissions, I am no regulatory expert. This presentation is based solely on my own experience. Data submission decisions are very complicated and require written FDA agreement.
Preparing Clinical Data for a Large Regulatory Filing

- Set the Stage
- Act I
- Intermission
- Act II
- Curtain Call
- Post Production Meeting
Gap Analysis - What do we got?

• How many studies are pivotal, phase I-III, bridging, QT, included in pooled analysis, or needed for special reports? Reviewers are likely to spend time on the most interesting 5 studies plus the ISE/ISS. These are often considered important studies.

• Do we have all versions of the protocol, ICF, CRF, data specs, imported data files (randomization, pv, pk, lab), analysis programs, TLFs, hard code explanations, study reports, and CSRs?

• What is the status of studies? Can we assess and impact compliance? When did the study start?

• What version of data standards were used and are they supported by FDA: SEND, SDTM, ADaM, CT, MedDRA, WHODD, LOINC, SNOMED, XML?
Is the Standard Supported? Check the Data Standards Catalog

**SUPPORTED**: “For the purposes of this catalog, “supported” means the receiving FDA Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified standard.”

**DATE SUPPORT ENDS**: “Sponsors cannot use the standard or terminology after this date. Generally, a waiver process may be available. Sponsors and applicants should consult with their review division. An empty field in this column means that a support end date has not been established.”

<table>
<thead>
<tr>
<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Standards Development Organization (SDO)</th>
<th>Supported Version</th>
<th>Supported Implementation Guide Version</th>
<th>FDA Center(s)</th>
<th>Date Support Begins (MM/DD/YYYY)</th>
<th>Date Support Ends (MM/DD/YYYY)</th>
<th>Date Requirement Begins (MM/DD/YYYY)</th>
<th>Date Requirement Ends</th>
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<tbody>
<tr>
<td>Study Data Tabulation Model (SDTM)</td>
<td>XPT</td>
<td>Clinical Data Interchange Standards Consortium (CDISC)</td>
<td>1.1</td>
<td>3.1.1</td>
<td>CDER, CBER</td>
<td>Ongoing</td>
<td>01/28/2015</td>
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As of March 2019 the following will not be supported for NDAs:

<table>
<thead>
<tr>
<th>Data Exchange Standard</th>
<th>Exchange Format</th>
<th>Version</th>
<th>Implementation Guide Version</th>
<th>Date Support Ends for NDA</th>
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<td>1.0</td>
<td>03/15/2019</td>
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<td>XPT</td>
<td>1.2</td>
<td>3.0</td>
<td>03/15/2019</td>
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<td>Define</td>
<td>XML</td>
<td>1.0</td>
<td>N/A</td>
<td>03/15/2018</td>
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</table>

<table>
<thead>
<tr>
<th>Terminology Standard</th>
<th>Version(s)</th>
<th>Date Support Ends for NDA</th>
<th>Supported Version</th>
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<tbody>
<tr>
<td>Medical Dictionary for Regulatory Activities (MedDRA)</td>
<td>8 or earlier</td>
<td>03/15/2019</td>
<td>Anything after Version 8 to the Current Version</td>
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<td>WHO Drug Dictionary</td>
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<td>03/15/2019</td>
<td>Supported standard is WHODrug Global Current Version-B3 Format</td>
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Building a Data Submission Strategy Study by Study – A Simplified Decision Tree

Study Start Date is defined as the informed consent date of the first enrolled subject.
Legacy Data Package

Set the Stage

*eDT = Electronic Data Transfer (e.g. central lab data, ECG vendor data, PK data, etc.)
Legacy Data Package

• Only for studies that started before December 17, 2016
• Studies are not particularly important (for example, early ClinPharm studies under another indication)
• Will need to be made into submission ready data*

*Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs (see references) under the section “Item 11: Case Report Tabulations (CRTs).”
Legacy Data Conversion Package

Set the Stage

Traceability Data Flow

Folder Structure and Contents

[study]
- analysis
  - adam
    - datasets
    - programs
  - legacy
    - datasets
    - programs
    - tabulations
  - sdtm
  - legacy

**analysis-adam-datasets folder:**
1. ADaM data
2. define.xml
3. adrg.pdf (with LDCP, if needed)

**analysis-adam-programs folder:**
1. SAS® programs for ADaM

**tabulations-sdtm folder:**
1. SDTM and TDM
2. define.xml
3. acrf.pdf (annotated for SDTM data)
4. csdrg.pdf (with LDCP, if needed)

Note: legacy folders are the same as Legacy Data Package
Legacy Data Conversion Package

Why convert to CDISC?

• A sponsor wants to submit electronic data in CDISC format, the study started on or before December 17, 2016, the study is important, the CDISC data may be needed for a pooled analysis or special report, and/or the data used to generate the CSR appendices was not in CDISC format.

• The study started after December 17, 2016, CDISC study standards are required, and the data used to generate the CSR appendices was not in CDISC compliant format. In this case both SDTM and ADaM compliant data are required for submission.

• The FDA may request that data be submitted in CDISC format even if it is not required.
CDISC Data Package

Traceability Data Flow

Set the Stage

Folder Structure and Contents

**analysis-adam-datasets folder:**
1. ADaM data
2. define.xml
3. adrg.pdf

**analysis-adam-programs folder:**
1. SAS® programs for ADaM derivation
2. SAS programs for analysis TLFs

**tabulations-sdtm folder:**
1. SDTM and TDM
2. define.xml
3. acrf.pdf (annotated for SDTM data)
4. csdrg.
CDISC Data Package

- The CDISC data package is submitted for studies with CSR appendix TLFs generated from ADaM data which were generated from SDTM data.
- If the study started after December 17, 2016, data in CDISC format is required for an NDA submission.
- Study Start Date is defined as the informed consent date of the first enrolled subject.
- CDISC data that was prepared in the past, may not be up to existing standards and could require remediation.
• Compare your Gap Analysis to your SDSP and update accordingly.
• If you don’t have an SDSP, now is the time to make one!
• Try to get stakeholders to consider data pooling as early as possible.
• Sponsor stakeholders review and buy-in to SDSP and overall data strategy.
• The SDSP should be the authoritative document for standards versions.

Study Data Standardization Plan
<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Brief Title</th>
<th>Study Design</th>
<th>Study Status</th>
<th>Study Start Date</th>
<th>Exchange Standards</th>
<th>Terminology Standards</th>
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<tr>
<td>DRG-102</td>
<td>The Protocol Title in a Brief Way for Study DRG-102</td>
<td>SINGLE DOSE, RANDOMIZED, OPEN LABEL, PLACEBO CONTROL, PHARMACOKINETIC, SAFETY, TOLERABILITY</td>
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<td>2014-11-13</td>
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<td>MedDRA (Adverse Events/Medical History) 17.0</td>
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<td>2015-03-14</td>
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<td>CDISC ADAM Terminology 2014-07-22</td>
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<td>CDISC SDTM Terminology 2014-06-27</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td>SDTM v1.3/SDTM IG 3.1.3</td>
<td>MedDRA (Adverse Events) 17.0</td>
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<tr>
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<td>Study Identifier</td>
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<td>Study Design</td>
<td>Study Status</td>
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<td>Exchange Standards</td>
<td>Terminology Standards</td>
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<td>DRG-104</td>
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<td>2017-12-12</td>
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<td>CDISC ADAM Terminology 2017-09-29&lt;br&gt;CDISC SDTM Terminology 2017-09-29&lt;br&gt;MedDRA (Adverse Events) 20.1&lt;br&gt;WHO-DD (Medications) 2017-Q1</td>
</tr>
</tbody>
</table>
ACT I

Run the Plan by FDA

- Include SDSP in End of Phase 2 or Pre-NDA briefing documents

- Ask FDA in writing if they agree with the SDSP with the intention of obtaining a formal written response
ACT I

Request FDA Waivers

• Submission Data Exchange Standards
  (SEND v3.0, SDTM v3.1.2 and earlier, ADaM v1.0, and Define v1.0)

• Submission Terminology Standards
  (MedDRA v8.0 and earlier, WHODD not Global Current Version-B3 Format)

• See FDA Website “Guidelines for Requesting Waiver to Current Supported Study Data Standard Version” (hyperlink at the end of presentation)
Submit Sample Submission to FDA

- See FDA Website “Submit an eCTD or Standardized Data Sample to the FDA” (hyperlink at the end of presentation)
- Request a Sample Application #
- Select a study:
  - Important, but not pivotal
  - CDISC study (SDTM & ADaM)
- Prepare sample submission – SDTM, ADaM, and metadata prepared in the past may require remediation to bring to compliance with new guidance. Run latest version of validator to determine if any issues can be corrected while maintaining data traceability. Update reviewer guides with explanations for issues that cannot be fixed without disrupting traceability.
- Work with regulatory to send sample submission to FDA.
Address Sample Submission Findings

- You may not agree with all the findings.
- The Division Reviewer that will review the NDA, will not be the same person who looked at the sample submission and will likely not be aware of the findings.
- Address what findings you can.
- Do not re-submit an updated sample. Apply resolutions to actual submission.
ACT I

ACT II

Create a Submission Readiness Checklist

Are data packages compliant and informative?

Check things not covered by validation software!

Is the checklist comprehensive?

Is the data package readable?

Includes lessons learned from sample submission?

Are standards consistent across data and metadata (SDSP, ts.xpt, Reviewer Guides, and Defines)?

Are my checks backed up by regulatory or sponsor requirements?

Is this checklist up to date?

Does it cover any recent changes to the TCG?

<table>
<thead>
<tr>
<th>Data Pkg</th>
<th>Types of Checks to Include (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADaM data</td>
<td>• Meets Technical Rejection Criteria (contains an ADSL)</td>
</tr>
<tr>
<td></td>
<td>• Dataset size (datasets are less than 5 gigabyte or split)</td>
</tr>
<tr>
<td>aedr.pdf</td>
<td>• Complete and well written (all sections match the PHUSE template)</td>
</tr>
<tr>
<td></td>
<td>• Legacy Data Conversion Plan &amp; Report Appendix is included as needed</td>
</tr>
<tr>
<td>ADaM define.xml</td>
<td>• Meets Technical Rejection Criteria (define.xml is in a supported version)</td>
</tr>
<tr>
<td></td>
<td>• Parameter Value Level Metadata includes all possible values</td>
</tr>
<tr>
<td></td>
<td>• Computational algorithms use English language and not SAS lingo</td>
</tr>
<tr>
<td>SAS programs</td>
<td>• Filename meets requirement in TCG</td>
</tr>
<tr>
<td>for ADAM and</td>
<td>• Programs are appropriate, no excessive comments, no heavy macro use</td>
</tr>
<tr>
<td>analysis TLFs</td>
<td>• All programs are present</td>
</tr>
<tr>
<td>SDTM and</td>
<td>• Meets Technical Rejection Criteria (contains ts.xpt)</td>
</tr>
<tr>
<td>TDM Data</td>
<td>• TDM matches protocol and dm.xpt</td>
</tr>
<tr>
<td></td>
<td>• ts.xpt has all versions of inclusion/exclusion criteria from the protocol</td>
</tr>
<tr>
<td>acrf.pdf</td>
<td>• All fields are fully annotated</td>
</tr>
<tr>
<td></td>
<td>• All annotated variables are documented in define.xml</td>
</tr>
<tr>
<td></td>
<td>• Duplicate pages are marked “For annotations see CRF page X”</td>
</tr>
<tr>
<td>csdrrg.pdf</td>
<td>• Complete and well written (all sections match the PHUSE template)</td>
</tr>
<tr>
<td></td>
<td>• Inclusion/Exclusion Appendix includes original and amended criteria</td>
</tr>
<tr>
<td></td>
<td>• Legacy Data Conversion Plan &amp; Report Appendix is included as needed</td>
</tr>
<tr>
<td>SDTM define.xml</td>
<td>• Meets Technical Rejection Criteria (define.xml is in a supported version)</td>
</tr>
<tr>
<td></td>
<td>• Standards are supported (SDTM version is supported)</td>
</tr>
<tr>
<td></td>
<td>• Global variables match the study protocol</td>
</tr>
</tbody>
</table>
Intermission

Reassess Strategy

- Based on FDA feedback on Sample Submission and SDSP
- Based on lessons learned from preparing sample submission study
Check-in with Study Team

- Are the studies you plan to convert still important?
- Has there been a decision to add any studies to pooled analysis?
- Amend Submission Readiness Checklist based on sample submission and updates to guidance.
SDSP

- Update SDSP based on:
  - Changes to strategy
  - FDA feedback on waiver
  - Update section on FDA Data Standards
  - Discussions based on waiver request response and other communications
  - FDA response to briefing document question
- Provide the SDSP to the programmers to ensure that documented standards are implemented.
Prepare and Review Deliverables

- Ensure resources are readily available to prepare and evaluate submission deliverables based on checklist and confirming primary endpoints.

Populate eCTD

- Have a CDISC Subject Matter Expert work directly with Regulatory Publishing to ensure the files uploaded to software are the correct files prepared for the submission.
Take a bow because you have just masterminded a Study Data Submission for a filing and that is pretty cool.
But wait! It isn’t over yet, next comes…

- FDA Information Requests
- Ad Hoc Analysis
- Approval
THANK YOU!

Lisa Brooks, Independent Consultant
Lisa@IrisStatComp.com
REFERENCES


• U.S. Department of Health and Human Services, Food and Drug Administration. “Submit an eCTD or Standardized Data Sample to the FDA” FDA Website, December 2017. https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm174459.htm


• cSDRG Project Teams, PhUSE Optimizing the Use of Data Standards Working Group. “cSDRG Packages” PhUSE website, November 2018. https://www.phuse.eu/css-deliverables

• ADRG Project Teams, PhUSE Optimizing the Use of Data Standards Working Group. “ADRG Packages” PhUSE website, October 2014 and January 2015. https://www.phuse.eu/css-deliverables