Standardized Data Sample: Key to Improving the Submission Strategy

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Agenda

• What is standardized data sample (sample submission)?
• Sample submission process
• Why sample submission?
• Sponsor’s practical experience on sample submission
• Conclusion
Engagement with Regulatory – Key to Submission Success

- Pre-NDA/BLA briefing document
- Attendance at Pre-NDA/BLA FDA meetings
- Type C meetings
- Study Data Standardization Plan
- Leverage eData mailbox at FDA
- Data Standards integrated into Regulatory filing team for submissions
- Sample Submission
What are Sample Submissions?

• From FDA’s SDTCG V4.1:
  o Two types of sample submissions*
    ▪ eCTD Sample Submission
    ▪ Standardized Data Sample
  o Sample submissions are tests only and not considered official submissions*
  o Sample submissions are not reviewed by FDA reviewers at any time*

• Sample submissions are optional

• The validation of sample submissions does not involve scientific review of the content**

• Only intended to address conformance to FDA supported electronic submission and data standards**

• Only applicable to CDER submissions. For CBER test submissions, sponsors should check with respective review division

**https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
Requesting Sample Application Number*

- Refer to FDA’s sample submission validation process page for latest information*
- Send email to: ESUB-Testing@fda.hhs.gov
- Include in the email:
  - Contact’s Name, Company Name, Mailing Address, Phone Number, Email Address
  - NDA, IND, BLA, or ANDA number
  - Planned Date of Official Submission
  - Description of test requested, including application type (e.g., CDISC/SDTM, CDISC/ADaM or CDISC/SEND dataset)
- The information in the email request for sample application number should also be provided in the cover letter of your sample submission.

*https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
Submitting Sample Submission*

- Refer to FDA’s sample submission validation process page for latest information*
- Limit sample submission to one of each data standard (i.e. SEND, SDTM, or ADaM)*
- Follow latest FDA guidance & specifications, and consult FDA’s Study Data Standards Resources web page for information on currently accepted data standards and related resources*
- Should be submitted according to the instructions provided with sample application number. Do NOT submit via the Electronic Submissions Gateway*. 

*https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
After Sample Submission Feedback

• Sponsor should review FDA’s comments and correct all issues identified before making an actual submission*
• If there is an explanation for a data issue, it should be documented in the data reviewer’s guide*
• Do not resubmit any sample information as it will NOT be further evaluated*

*https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm
Why Sample Submissions?

• Opportunity to understand FDA’s current thinking on data standards and submission requirements
• Influence improvements to internal data standardization and submission strategy
• Enhances collaboration and dialogue with internal regulatory team
• Submission dry run opportunity for sponsors
• Pressure test evolving operating models (if any)
How Sample Submission Process May Look Like for a Sponsor

1. **Biometrics**
   - Identify a need for a sample submission for a given drug compound

2. **Biometrics**
   - Identify a study and associated eSUB components

3. **Biometrics & Regulatory (Affairs & Operation)**
   - Collaborate to establish a plan and timelines

4. **Regulatory (Affairs & Operation)**
   - Request sample application number

5. **Biometrics**
   - Prepare eSUB deliverable for sample submission

6. **Biometrics & Regulatory (Affairs & Operation)**
   - Execute on the action plan. Implement lessons learnt.

7. **Biometrics & Regulatory (Affairs & Operation)**
   - Meeting to discuss feedback and develop plan of action

8. **FDA**
   - Process sample submission and provide feedback to sponsor

9. **Regulatory Operations**
   - Deliver sample submission to FDA

10. **Regulatory Affairs & Biometrics**
    - Prepare cover letter
# Sponsor’s Sample Submissions

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Type of Actual Submission</th>
<th>Sample Submission Timing</th>
<th>Actual Submission Timing</th>
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<tr>
<td>Hemophilia A*</td>
<td>BLA to CBER</td>
<td>2012</td>
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<td>Hemophilia B*</td>
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<td>Multiple Sclerosis (MOAB)</td>
<td>BLA to CDER</td>
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<td>Multiple Sclerosis (another MOAB)</td>
<td>BLA to CDER</td>
<td>Q2 2014</td>
<td>Q1 2015</td>
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<tr>
<td>Spinal Muscular Atrophy (Small Molecule)</td>
<td>NDA to CDER</td>
<td>Q2 2016</td>
<td>Q3 2016</td>
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*Hemophilia business unit is no longer with Biogen. It is currently operated as a separate company called Bioverativ, a Sanofi company.
CBER Sample Submission – Response from CBER (Excerpts)

• The submitted Define.xml was invalid
• The validation errors identified were not explained or were not adequately addressed
• Please resubmit a corrected define.xml in order to complete the sample submission (DEMO)
• If these issues persist in the regulatory submission, it could result in “Refuse to File”
Sponsor Action

• Resolved Define.xml errors
• Enhanced quality of reviewer’s guide (i.e. rationale for unresolved errors/warnings)
• Resubmitted the sample submission
• Substantiated need for better software for define.xml
• Substantiated need for Sponsor’s CRF update (related non-extensible codelist issue)
Multiple Sclerosis Sample Submission (MOAB) - Response from CDER (Excerpts)

• Reviewer’s guide should be study-specific (versus one guide for multiple studies)
• Reviewer’s guide should be placed in the same folder as datasets
• Validation issues should be explained, not just described
• Some warnings can and should be fixed
• Data should be mapped to existing controlled terms if equivalent (e.g. “INCLUSION CRITERIA” in the data is equivalent to “INCLUSION”)
Sponsor Action

- For actual filing, one reviewer’s guide per study was created and was placed in respective datasets folder.
- Datasets were updated to remap data to existing controlled terminologies where possible.
- Validation issue rationale language was updated where needed to provide rationale for an issue (versus describing the issue).
Multiple Sclerosis Sample Submission (another MOAB) - Response from CDER

- Most recent version of data validation software is used
- Variables (e.g. EPOCH) requested by FDA in CDER Common Issues Document should be included in the dataset
Sponsor Action

• For actual filing, data for all studies was validated using the latest version of data validation software (i.e. Pinnacle21 latest version)

• A decision was made to always use the latest version of data validation software as a best practice
SMA Sample Submission (Small Molecule) - What we Submitted?

• Cover letter describing:
  o Which studies are being submitted
  o Data format
  o Which eSUB components are being submitted
  o Plan for actual NDA filing

• Datasets and associated eSUB components for three studies
SMA Sample Submission (Spinraza) - Response from CDER

• Email response with a note “...we only validate one study for each type of data.”

• Two attachments with the email:
  o Data validation report
  o Summary of evaluation findings
    § Type of validation software used and its version and configurations
    § Summary of findings
Excerpts from Summary of Evaluation Findings

• Few instances of confusing and potentially invalid computational method in define.xml
• Missing codelist or external dictionaries where they are expected
• Inconsistency in MedDRA version between define.xml and SDRG
• Codelists are merged across many variables. Codelist is expected to be variable specific (e.g. NY consists of 2 terms (Y,N) but valid values for DTHFL is Y or null)
• All datasets should be properly file tagged to avoid being placed in the “unassigned”
• Other feedback based on Pinnacle 21 validation report
SMA Sample Submission - Sponsor Action

- Prepared and sent a response letter to FDA

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- Issues identified were either fixed or explained in the actual filing
Conclusion

• Sample submission has been a key to improving submission strategy at Sponsor:
  o eCTD best practices
  o Software development (internal Define.xml tool to enhance quality)
  o Best practice of using latest versions of validation software
  o Improving quality of rationale language for validation errors/warnings
  o Helped better manage internal disagreements and senior management support
  o Helped pressure-test evolving operating model

• Carefully evaluate need for sample submission in your organization
  o Consider various factors such as size of the group, operating model, decision making framework, resources, management support etc.
Questions or Feedback

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