Standardized Data Sample: Key to Improving the Submission Strategy

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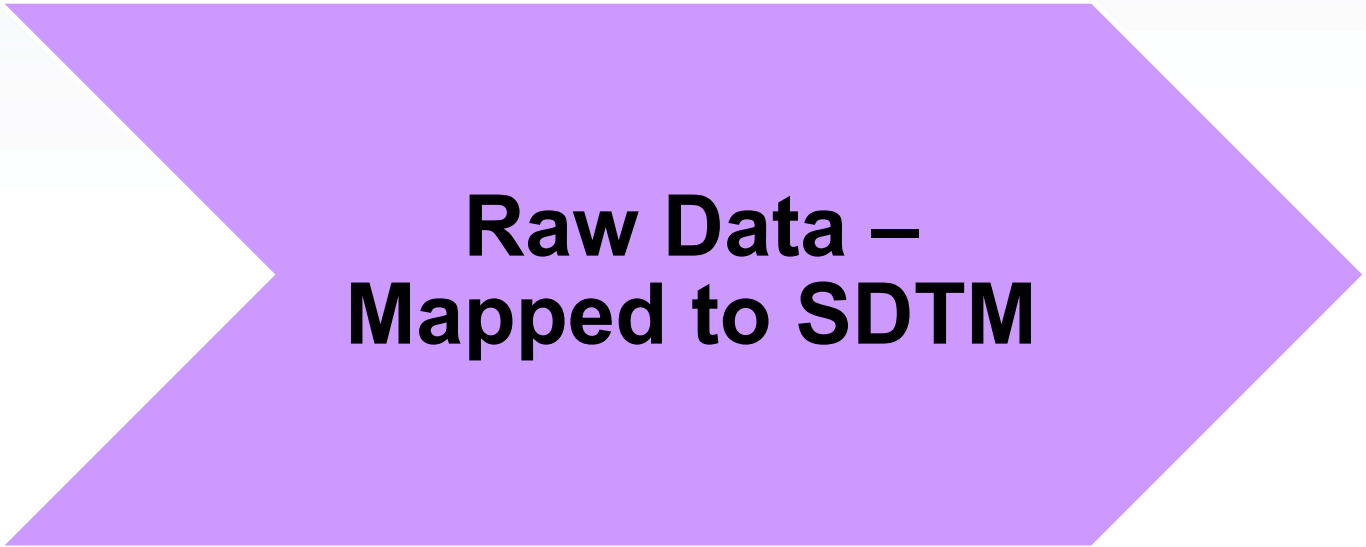
Agenda

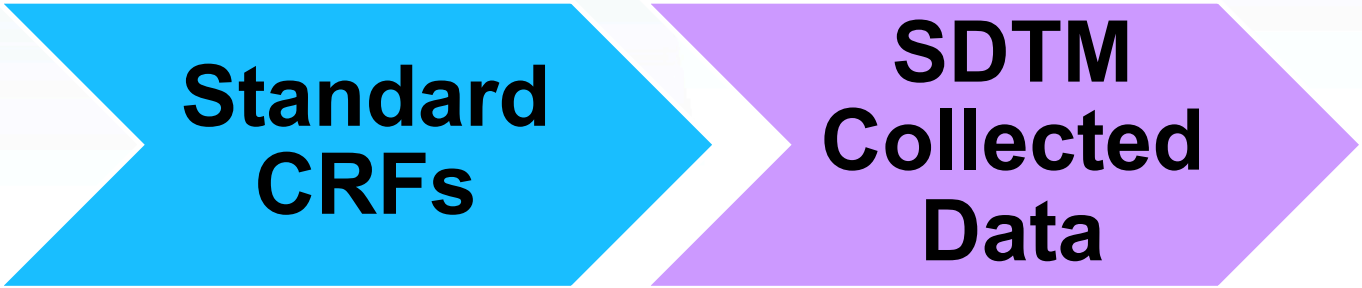
- Evolution of Biogen data standards
- What is standardized data sample (sample submission)?
- Why sample submission?
- Sample submission process
- Biogen's practical experience on sample submission
- Conclusion

Data Standards at Biogen - 2004



Release of SDTM 3.1

Data Standards at Biogen - 2007



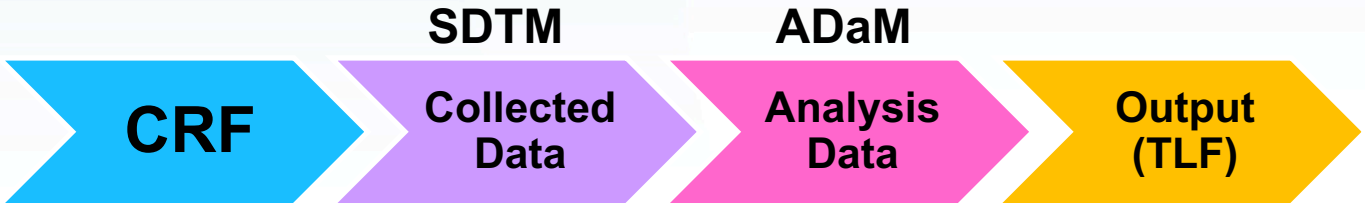
Standard Global CRFs

TA specific CRF standards

- **MS**
- **Immunology**
- **Oncology**

SDTM v3.1.1

Data Standards at Biogen - 2010



Standard Global CRFs

TA specific CRF standards

SDTM Specifications

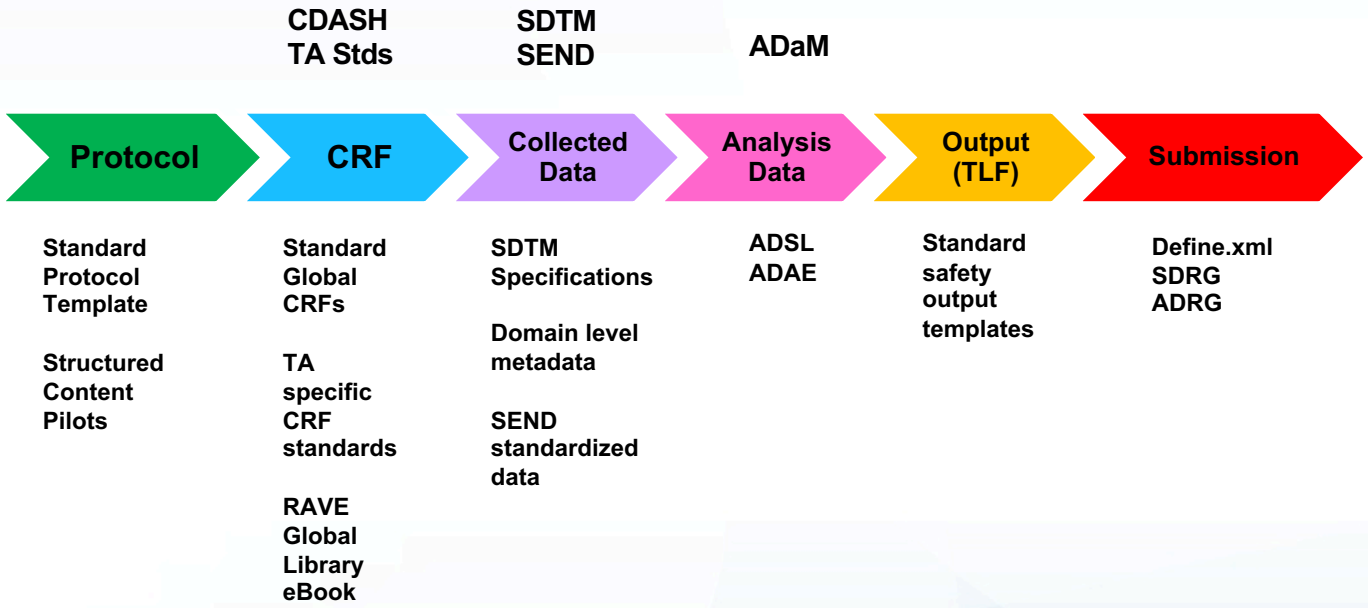
Conversion to SDTM v3.1.2

ADSL General Rules

Standard safety output templates

*1st Biogen "CDISC" submission in 2011

Data Standards at Biogen - 2014



Data Standards at Biogen – Current State

Controlled Terminology Standards

Protocol	CRF	Collected Data	Analysis Data	Output (TLF)	Submission	Data Sharing
Standard Protocol Template Structured Content Pilots	Standard Global CRFs TA specific CRF standards 3rd Party data standards RAVE Global Library eBook	Biogen SDTM IG work package: -SDTM Specifications -Domain level metadata -User guides -Training -Examples -Validation Guide -Issues log SEND standardized data	Biogen ADaM standard datasets -ADSL -ADAE -ADLB -Examples library	Standard safety output templates Technology to automate creation of STAN shells and outputs	Standard templates User guides Examples	Standard De-Identification Macros Based on SDTM data structures

Standards Automation Program launched

5 successful CDISC-compliant submissions since 2011

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:
  - Two types of sample submissions*
    - eCTD Sample Submission
    - Standardized Data Sample
  - Sample submissions are tests only and not considered official submissions*
  - 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/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
**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.

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*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*.

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

After Sample Submission Feedback

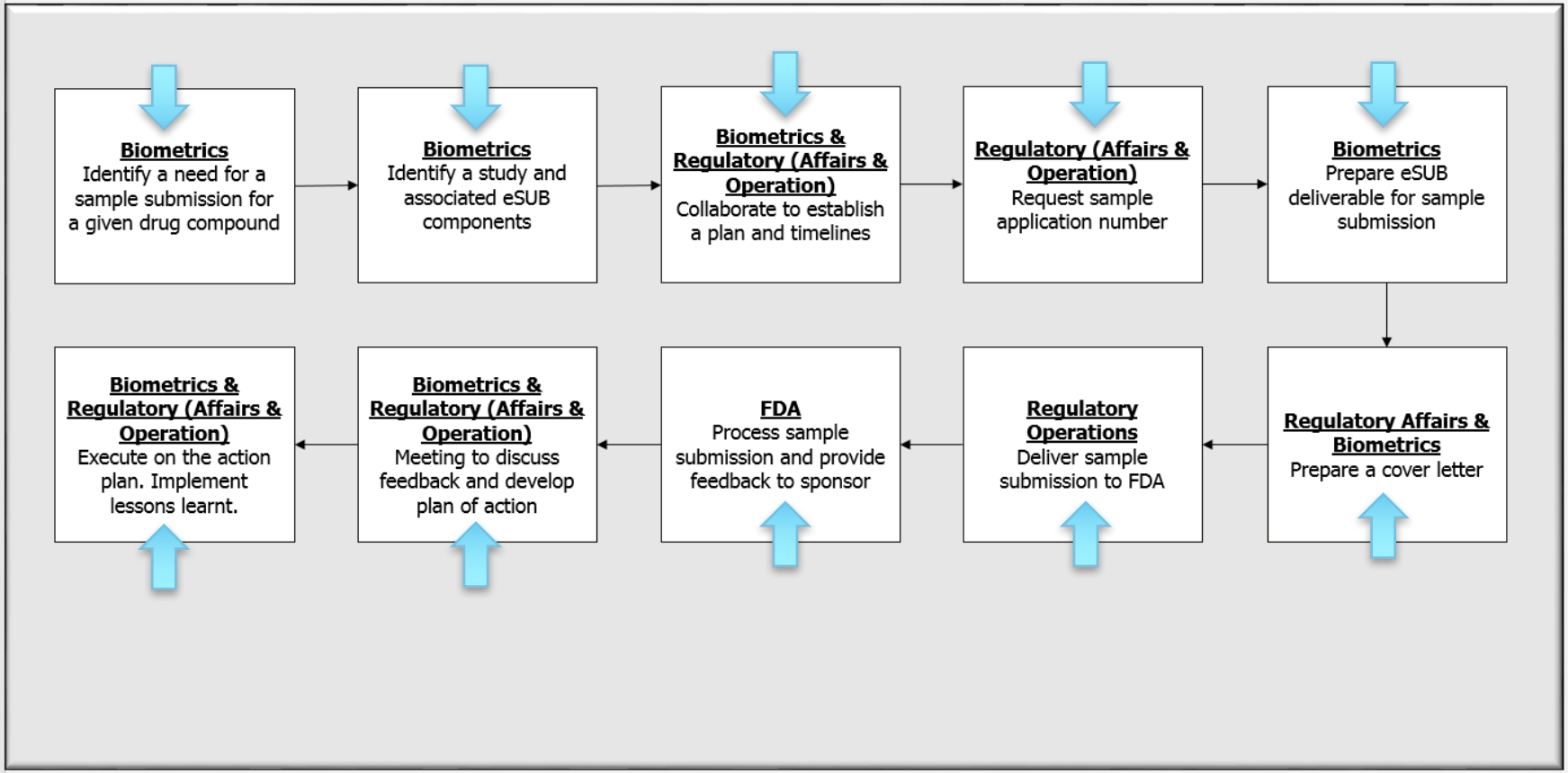
- Sponsor should review FDA's comments and correct all issues identified before making an actual submission*
- If there is an explanation for a data issue, it should be documented in the data reviewer's guide*
- Do not resubmit any sample information as it will NOT be further evaluated*

*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



Biogen's Sample Submissions

Therapeutic Area	Type of Actual Submission	Sample Submission Timing	Actual Submission Timing
Hemophilia A*	BLA to CBER	2012	2013
Hemophilia B*	BLA to CBER	2012	2013
Multiple Sclerosis (MOAB)	BLA to CDER	2012	2013
Multiple Sclerosis (another MOAB)	BLA to CDER	Q2 2014	Q1 2015
Spinal Muscular Atrophy (Small Molecule)	NDA to CDER	Q2 2016	Q3 2016

*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”

Biogen 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 Biogen'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")

Biogen 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

Biogen 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:
  - Which studies are being submitted
  - Data format
  - Which eSUB components are being submitted
  - 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:
  - Data validation report
  - Summary of evaluation findings
    - Type of validation software used and its version and configurations
    - Summary of findings

SMA Sample Submission - Response from CDER
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 (Spinraza) - Biogen Action

- Prepared and sent a response letter to FDA

DATA ISSUES

Agency Feedback	Sponsor Action

DEFINE.XML

Agency Feedback	Sponsor Action

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

Conclusion

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