SDTM and SEND – An Integrated View and Approach

PhUSE Connect 2018

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Overview

- Nonclinical and Clinical Development Phase
- Regulatory Agency Needs
- Deliverables to Regulatory Agencies
- Similarities & Differences
  - Process and Tools
  - Controlled Terminology
  - Domains Structure
  - Trial Design
  - Validation Checks
  - Submitted Documents
Drug Development Process

- Nonclinical: Investigational New Drug (IND) Application
- Phase I
- Phase II
- Phase III
- Post Marketing: New Drug Application (NDA)/Biologics License Application (BLA)

SENDIG, CDASHIG, SDTMIG, ADaMIG
Regulatory Agency: US Food and Drug Administration (FDA)

Roadmap for Standardized data

1992
- US Congress passed Prescription Drug User Fee Act (PDUFA)

1997
- Renewal of PDUFA

2002
- SDTM v1.0 Released

2003
- SDTM in Study Data Specs 1.0
- SDTM Pilot with FDA

2004
- SDTM in Study Data Specs 1.0

2005
- Define-XML in Study Data Specs 1.1

2007
- Renewal of PDUFA

2008
- SDTM in Study Data Specs 1.2

2009
- SDTM in Study Data Specs 1.3

2010
- SDTM in Study Data Specs 1.4

2011
- SDTM in Study Data Specs 1.5

2012
- Renewal of PDUFA
- FDASIA Act that requires submission of standardized data
- PDUFA V – need for CDISC Standards
- Draft Guidance on electronic format

2017
- FDARA – new legislation
- PDUFA VI

2018
- CBER-CDER FDA Data Strategy (2018-2022)
Regulatory Agency - Pharmaceuticals and Medical Devices Agency (PMDA):

Roadmap for Standardized data

2001
- Ministry of Health, Labor and Welfare (MHLW) Rationalization Plan by Japanese Cabinet

2002
- Enacted Pharmaceuticals and Medical Devices Agency Law

2004
- PMDA established to enhance review system

2014
- Basic Principles on Electronic Submission of Study Data for New Drug Applications

2015
- Notification on Practical Operations of Electronic Study Data Submissions
- Technical Conformance Guide
- Data Standards Catalog
SDTM and SEND Data Standards

Study Data Tabulation Model (SDTM)

- SDTM Implementation Guide (SDTMIG)
- SEND Implementation Guide (SENDIG)

Electronic Common Technical Document (eCTD)

- Module 4 (Nonclinical)
- Module 5 (Clinical)

Format and structure aids reviewers to discover common trends
## Deliverables to Regulatory Agencies

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<th><strong>FDA</strong>*</th>
<th><strong>PMDA</strong>**</th>
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<td>• SDTM Datasets v3.1.2, v3.1.3, v3.2</td>
<td>• SDTM Datasets v3.2</td>
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<td>• Define XML 2.0</td>
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<td>• aCRF.pdf</td>
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<tr>
<td>• Study Data Reviewer’s Guide (cSDRG)</td>
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<td>• ADaM Datasets v1.0, v1.1</td>
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<td>• Define XML 2.0</td>
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<td>• Study Data Reviewer’s Guide (nSDRG)</td>
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### Study Data Standardization Plan (SDSP):

- Assists FDA in identifying potential data standardization issues
- FDA Study Data Technical Conformance guide describes SDSP needs
- PhUSE has developed the SDSP Template
- Describes both clinical and nonclinical studies within a program
- Sponsors may initiate discussions at pre-IND meeting
- FDA CBER expects SDSP Appendix no later than end-of-Ph2 meeting

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* Based on current versions of:
  - FDA Data Standards Catalog v5.0
  - FDA Study Data Technical Conformance Guide v4.1 March 2018

**Based on current versions of:
  - PMDA Data Standards Catalog v March 2017
SDTM and IG Development (Clinical)

SDTM v1.4
- SDTMIG v3.2
- SDTMIG - AP
- SDTMIG - MD

SDTM v1.5
- SDTMIG - PGx

New special purpose domains + New Variables added to SDTMIG-MD

Therapeutic Area User Guides Releases (Provisional)

Each user guide states the different implementation guides and identifies new domains, variables needed for that particular Therapeutic Area

Timeline

2013

Present

SDTM1.5 has new variables needed due to SEND 3.1
SDTM and IG Development (Nonclinical)

Timeline

2011

SDTM v1.4
SEND v3.0

SDTM v1.5
SEND v3.1

SDTM v1.6
SEND-DART v1.1

Supports embryo-fetal developmental (EFD) toxicity studies

Present
Similarities and Differences

“Share our similarities and celebrate our differences” – M. Scott Peck
Process and Tools used for SDTM deliverables (Clinical)

**Study Design Initiation**
- Ensure Study Protocol contains SDTM Terminology
- The Statement of Work with CRO includes SDTM and ADaM deliverables

**Contract Research Organization**
- Conducts the study including collecting data, cleaning, reconciling
- Creates SDTM and ADaM deliverables

**Sponsor Company**
- Oversees the study and CRO
- Review and accept the SDTM and ADaM Datasets and Study Data Reviewer’s Guide and Analysis Data Reviewer’s Guide

ROLES AND RESPONSIBILITIES OF CLINICAL RESEARCH
**Process and Tools used for SEND deliverables (Nonclinical)**

### Study Design Initiation
- Ensure Study Protocol contains appropriate study endpoints, SEND Terminology
- The Statement of Work includes SEND deliverables

### Contract Research Organization
- Performs the Study and provide deliverables
- Provide Study Report
- Partial SEND Dataset package

### SEND Vendor
- Assess, verify and convert study information into SEND-Compliant Dataset Package
- Provide submission ready SEND Datasets and Study Data Reviewer’s Guide

### Sponsor Company
- Review and accept the SEND Datasets and Study Data Reviewer’s Guide

**Roles and Responsibilities of Nonclinical Research**
Using common CT helps compare and visualize the data across clinical and nonclinical

- Comparing SDTM CT v2018-03-30 and SEND CT v2018-03-30
  - 34 codelists are common between SDTM V3.2 and SEND 3.1
  - 18 codelists have similar codelist names but the code terms are specific to each standard

For Nonclinical studies, there are other organizations such as International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) – composed of toxicological pathology societies across the world developing terminologies by providing a standardized nomenclature for the findings
## Comparing SDTMIG 3.2 and SEND 3.1 Models

### SDTM Domains (only)

- **Interventions General Observation Class**
  - Concomitant Medications (CM)
  - Exposure as Collected (EC)
  - Procedures (PR)
  - Substance Use (SU)

- **Events General Observation Class**
  - Adverse Events (AE)
  - Medical History (MH)
  - Protocol Deviations (DV)
  - Clinical Events (CE)

- **Findings General Observation Class**
  - Drug Accountability (DA)
  - Immunogenicity (IS)
  - Immunogenicity Specimen Assessments (IS)
  - Microbiology (MB)
  - Susceptibility Test (MS)
  - Questionnaires (QS)
  - Physical Examination (PE)
  - Subject Status (SS)

- **Findings About**
  - Findings About (FA)

- **Trial Design Domains**
  - Trial Inclusion/Exclusion Criteria (TI)
  - Trial Disease Assessment (TD)
  - Trial Visits (TV)

### Common Domains

- **Special Purpose Domains**
  - Comments (CO)
  - Demographics (DM)
  - Subject Elements (SE)

- **Interventions General Observation Class**
  - Exposure (EX)

- **Events General Observation Class**
  - Disposition (DS)

- **Findings General Observation Class**
  - Death Details (DD)
  - Laboratory Test Results (LB)
  - Microscopic Findings (MI)
  - Pharmacokinetic Parameters (PP)
  - Vital Signs (VS)

- **SEND Domains (only)**

  - **Findings General Observation Class**
    - Body Weight (BW)
    - Body Weight Gain (BG)
    - Clinical Observations (CL)
    - Food and Water Consumption (FW)
    - Macroscopic Findings (MA)
    - Organ Measurements (OM)
    - Palpable Masses (PM)
    - Tumor Findings (TF)
    - Cardiovascular Test Results (CV)
    - Respiratory Test Results (RE)

  - **Trial Design Domains**
    - Trial Sets (TX)

  - **Relationship Datasets**
    - Pool Definition (POOLDEF)

* DART 1.0 domains not included
Trial Design

FDA Study Data Technical Conformance guide V5.0 states

“The Trial Summary (TS) dataset will be used to determine the time of study start. The requirement to submit using a particular study data standard is dependent on its support by FDA as listed in the Catalog at the time of study start. TSPARMCD = SSTDTC will allow the determination of the study start date and should be included in all SDTM submissions. Sponsors submitting legacy data (See section 8.3.2) should provide a TS dataset (ts.xpt) which includes the study start date in the form of SSTDTC (TSPARMCD = SSTDTC) and TSVAL= ‘yyyy-mm-dd’”

- Clinical studies use
  - All Trial Design datasets except Trial Sets (TX)
- Nonclinical studies use
  - Trial Arms (TA), Trial Sets (TX), Trial Elements (TE) and Trial Summary (TS)
- FDA has announced the addition of Technical Rejection Criteria to the existing eCTD validation criteria to ensure study data conformance validation. One of the checks is “Trial Summary (TS) dataset must be presented for each study in Module 4 or 5.”

For more information on FDA Technical Rejection Criteria:
Validation Checks

- Checks the conformance to CDISC Model
- Validator Tools available check compliance or conformance to CDISC Standards (SDTMIG, SEND, ADaM, Define-XML)
- Validation report generated produces the results of validation. These findings should be explained in the Study Data Reviewers Guide.
  - **FDA suggests cSDRG for clinical and nSDRG for nonclinical**
Best Practices

• Keep track of the
  - commonly released agency documents
  - understand what constitutes a requirement versus a guidance
  - released CDISC Implementation Guides (IGs) and related documents

• At Shire, we established a Data Standards Governance Model
  - provides a cross-functional forum for discussing specific needs and solutions
  - helps to propagate throughout the organization some of the challenges discussed in industry forums (e.g. PhUSE, CDISC)

• Volunteer in CDISC and/or PhUSE groups to learn and collaborate on how to handle such changes.
• Understand external CRO partner and vendor capability
  − how they affect the submission-ready package creation
  − ensure proper oversight capabilities to ensure quality and timing of the deliverables
• Industry Resources available
  − collaborate with groups or SMEs who support delivery of standardized data on clinical and nonclinical studies to understand the intricacies of the model and implementations
  − attend courses/webinars to develop topic-specific skills and learn about the changes
Conclusion

• Understand the **agency requirements** for data standards, changing landscape of CDISC, and internal company needs

• As SEND is fairly new requirement to the industry. Organizations have to create new processes to support this requirement.
  – Helpful to **collaborate** with clinical teams as they are submitting standardized study data (SDTM) since 2004
  – Understand **deliverables** and oversee the vendors

• Sponsor organizations have to build processes that are **lean and adaptable** to this changing landscape which can support global standardized study data submissions.

• Consistent use of format and standard within the nonclinical and clinical modules supports regulatory agencies review times. Having a **robust Data Standards Governance** process, supports overall standards development and helps to ensure quality data submissions.