CDISC SEND

Data Standardization and Exploration
Agenda

CDISC Standards and FDA Submission Requirements

SEND v3.0 and SEND v3.1 Overview

SEND Data Standardization Process

Standardised Data kick-start for Data Exploration
CDISC Standards

Standard for the Exchange of Nonclinical Data

- CDISC stands for Clinical Data Interchange Standard Consortium
  - supported by pharmaceutical companies, biotech companies, CROs / service providers, and technology providers

- CDISC has established WW industry standards to support
  - electronic acquisition
  - exchange
  - submission and archival
  - of clinical (SDTM / ADAM) and pre-clinical (SEND) trials data and metadata for medical and biopharmaceutical product development

- CDISC SEND is an implementation of the CDISC Standard Data Tabulation Model (SDTM) for non-clinical toxicology and safety pharmacology studies and is intended to:
  - provide an accurate standardized electronic representation of information included in study report
What is SEND?

Standard for Exchange of Nonclinical Data (SEND)

SEND Includes
- Study Design
- Individual animal details
- Dosing Informations
- Collected and derived individual results and observations

SEND Does Not Include
- Audit trails
- Analyses
  - No descriptive statistics
  - No incidence counts
  - No group comparative statistics
- Interpretations and conclusions

• SEND is built around the concept of observations collected about subjects included in a nonclinical study
• Test results, examinations, and observations are represented in a series of SEND domains through a list of variables
FDA Submission Requirements
Study Data for Submission to CDER and CBER

- FDA will no longer accept non-standardized and non-electronic submissions for studies started (Protocol Signature) after:
  - December 17 2016 for NDA's and BLA's
  - December 17 2017 for IND's.
- Data standards enable FDA to
  - Modernize and streamline the review process,
  - Enable more consistent use of analysis tools to better view drug data and highlight areas of concern.
- FDA accepts electronic submissions that provide study data using the standards, formats, and terminologies described in the FDA Data
Additional regulatory considerations:
- The SEND version required for your submission is determined by the **study start date** (protocol signature date)
- If you are including non-GLP studies in a regulatory submission, a **SEND package** is also required
- If you have legacy studies in your submission, an **abbreviated TS file** (Trial Summary file) is required for each one

What about PMDA and EMA?

EMA does not have formal plans to adopt CDISC standardized format

PMDA (Pharmaceuticals and Medical Devices Agency) will require drug makers to submit electronic data in CDISC standard format beginning 01 October 2016, with a 3.5 year transitional period
Agenda

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SEND Data Standardization Process

Standardised Data kick-start for Data Exploration
SEND 3.0 was the first version accepted by FDA for nonclinical submissions and was designed to support:
- General Toxicology
  - GLP / Non-GLP
  - Single-Dose / Repeat-Dose
- Carcinogenicity studies

SEND 3.1 (released by CDISC on June 27, 2016) expands on the previous version & supports the following study types:
- General Toxicology
  - GLP / Non-GLP
  - Single-Dose / Repeat-Dose
- Carcinogenicity studies
- Safety Pharmacology
  - Cardiovascular studies
  - Respiratory studies
SEND 3.1
What is changing

- SEND 3.1 improve the standard model for the collection of Cardiovascular and Respiratory endpoints
  - Test results previously collected in Vital Signs are now placed in Safety Pharmacology domains
- New variables were added to relevant domains to improve completeness on specific topics (e.g. unscheduled test results and nominal timepoint)

<table>
<thead>
<tr>
<th>Domain</th>
<th>SEND 3.0</th>
<th>SEND 3.1</th>
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</thead>
<tbody>
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<td>ECG Mean Heart Rate</td>
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<td>X</td>
</tr>
<tr>
<td>PR Interval</td>
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<td>QRS Duration</td>
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<td>RR Interval</td>
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<tr>
<td>Heart Rate</td>
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<tr>
<td>Respiratory Rate</td>
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<td>X</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
# SEND Data Model

**Where is your data?**

## Study Design
- Trial Elements
- Trial Sets
- Trial Arms
- Trial Summary

## Animal Details
- Demographics
- Subject Characteristics

## Animal Disposition
- Disposition

## In-Life observations
- Body Weight
- Body Weight Gain
- Clinical Observations
- Food and Water Consumption
- Laboratory Test Results
- Palpable Masses
- ECG Test Results
- Tumour Findings
- Exposure
- Vital Signs
- Cardiovascular Test Results
- Respiratory Test Results
- Pharmacokinetics Concentrations
- Pharmacokinetics Parameters

## Post mortem observations
- Macroscopic Findings
- Microscopic Findings
- Organ Measurements

## Unscheduled deaths Status and Causes
- Death Diagnosis

## Related Records
- Pool Definition
- Supplemental Qualifiers
- Comments
- Related Records
- Subject Elements
SEND Roadmap
Future Implementations

- DART (Developmental and Reproductive Toxicology)
  - extends the SEND standard into Reproductive Toxicology by supporting study data typically found in embryo-fetal development (EFD) toxicity studies (DART IG 1.1)
  - Fertility, Postnatal Development – Multi-generational will be covered in future releases

- Genetox
  - *In vivo* micronucleus
  - Comet test (*in vivo*) Single Cell Gel Electrophoresis assay
  - *In vitro* micronucleus
  - Ames tests (*in vitro*) Mutagenic bacterial test named for Bruce Ames

- Dermal / Ocular – add domains
  - Local irritation assessments (IA)
  - Allocation to Treatment (AT)

- Safety Pharmacology
  - Addition of CNS domain

- The timing of Standard FDA adoption is a process separate from standards development
SDTM Standard Model and SEND IG

SDTM 1.5 → SEND IG 3.1

General Observations Domains

Special Purpose Domains
- Demographics
- Comments
- Subject Elements

Interventions
- Exposure

Findings
- Body Weight
- Body Weight Gain
- Death Diagnosis
- Food and Water Consumption
- Macroscopic Findings
- Microscopic Findings
- Palpable Masses
- Pharmacokinetics Concentrations
- Pharmacokinetics Parameters
- Subject Characteristics
- Tumour Findings
- ECG Test Results
- Cardiovascular Test Results
- Respiratory Test Results

Events
- Disposition

Trial Domains
- Trial Elements
- Trial Sets
- Trial Arms
- Trial Summary

Relationships Domains
- Related Records
- Supplemental Qualifiers
- Pool Definition

PAGE 12

SDTM 1.5 Standard Model  SEND IG 3.1
Agenda

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SEND Data Standardization Process

Standardised Data kick-start for Data Exploration
### Evotec: SEND-ready Organisation

Data Standardisation Service for Nonclinical Studies and more

<table>
<thead>
<tr>
<th>SEND Data Standardisation Service Deliverables (SEND Package) for <strong>studies internally</strong> and <strong>externally</strong> executed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- SEND Standardised datasets in XPT format</td>
</tr>
<tr>
<td>- Define.XML files compliant with CDISC specifications</td>
</tr>
<tr>
<td>- Study Data Reviewer’s Guide (nSDRG)</td>
</tr>
<tr>
<td>- SEND dataset and define.xml validation reports generated by Pinnacle21 validator</td>
</tr>
</tbody>
</table>

- **3rd Party SEND Verification Service Deliverables:**
  - Discrepancies between SEND datasets and Study Report
  - Discrepancies between SEND datasets and FDA standards requirements
  - SEND dataset and define.xml validation reports generated by Pinnacle21 validator
  - Suggestion how to solve SEND conformance issues identified by Verification Service

- ~80 SEND Packages standardised: 100% Successful Submission
Why an internal solution?

- Keep SEND domain & related compliance requirements full knowledge
- Keep complete control of the standardisation process (no black box perception)
- Take advantage of a Flexible Solution to:
  - Promptly and independently adopt any new controlled terminology version
  - Promptly and independently adopt any new SEND standard version released
  - Capability to develop adapter (data-model focused) to:
    - integrate with any additional external legacy system
    - read raw data externally generated (format independent)
  - Capability to manage and adapt framework configuration in case of complex Study Design (time effective solution w/o 3rd Party dependency)
Evotec SEND Framework

Components of an e-Data Submission Package

- **Study Plan or Protocol**
  - Extract and Harmonize Naming Conventions & Terminologies

- **Study Reports**
  - Extract and, Relate and Annotate

- **Lab Data**
  - Extract from Multiple Data Sources, Relate across Data Sources, Normalize to Standardizes Representation, Harmonize to Controlled Terminologies

- **Data Definition File (Define.xml)**
  - E-Data Package for Submission to Regulatory Authority

- **Non Standard Files**

- **Study Data Reviewer Guide**

- **Study Results**

- **Related Records Comments**
Evotec SEND Framework

Architecture for Harmonisation and Aggregation of Data
SEND Package

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SEND Data Standardization Process

Standardised Data kick-start for Data Exploration
Standardised Data improve Data Exploration

- Single-Study-oriented: allow to generate individual or group summarisation with scientifically relevant visualisation to identify trends and patterns within a study
  - What were the most prevalent histopathology findings observed in the study?
  - Is there a changing trend between treatment and recovery period?

- Multi-Study-oriented: cross-study visualisations and comparison for analysis purposes
  - If there were observed trends in what other studies has this finding been observed?
What were the most prevalent histopathology findings observed in the study?

SEND Enlightening for Data Exploration

Severity Heatmap by Tissue and by Findings
Which is the time course pattern of following multiple endpoints: Body Weight, Food Consumption and Activated Partial Thromboplastin Time?
Questions and Answers
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