Actions for FDA SEND:
What pathologists/toxicologists need to know

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Introduction

What is SEND? (Standard for Exchange of Nonclinical Data)

The Study Data Tabulation Model (SDTM), established by the Clinical Data Interchange Standards Consortium (CDISC) for US Food and Drug Administration (FDA) pharmaceutical submissions serves as the model for clinical study data. SEND is the implementation of SDTM for nonclinical studies and specifies the rules for standardizing nonclinical study data. SDTM is already used in over 60% of current clinical study applications. For studies starting on or after December 18, 2016, SDTM and SEND will be required for studies starting after that date that support NDAs, BLAs, and ANDAs. Studies supporting INDs will be required to conform to these standards one year later.

Both SEND and SDTM require the mapping of controlled terminology (CT), and dealing with pathological terms will be a huge challenge.

Recently, we submitted several SEND data sets to the FDA and were successful in getting the trial applications approved. Based on this experience, we obtained abundant information. We used the SEND data conversion device, TranSEND® (PDS Ltd.), to convert raw data or original electronic data and create an integrated SEND data sets that were compliant with the latest SEND Implementation Guide version 3.0 (SEND IG v 3.0). As a result, we identified a method for verifying consistency between the pre- and post-conversion data and the important points to note. In particular, the handling of pathological findings, including the usage of pathological terms, will be a common challenge for pathologists when creating SEND data.

Conversion of pathological terms for SEND

To create the SEND data set for a study, input (source) electronic pathological data was transferred directly to the SEND conversion tool, TranSEND®, using Ascentos® PathData version 11 (made by PDS) for immediate automatic conversions.

The pathological SEND data set was roughly divided into two domains (files):

- MA domain: Macroscopic findings (Necropsy observations)
- MI domain: Microscopic findings (Histopathology observations)

Modifiers for necropsy and histopathology findings (e.g., chronicity and distribution modifiers) were mapped to the SUPP- domains (SUPPMA, SUPPMI) automatically by TranSEND®.

Table 1 shows a sample of SEND output by TranSEND®. As shown here, the SEND data set contains the raw data for the sample findings (in --ORRES), as well as data mapped to supplemental (SUPP--) domains.

Creation of Study Data Reviewer's Guide (SDRG)

A Study Data Reviewer's Guide (SDRG) for SEND data submission is recommended as a roadmap, for FDA reviewers, in order to provide explanations of the datasets in addition to the define files outlining the data generated for studies.

Precautions in SEND conversion of pathological terms

What must be done by the sponsor before conversion:
1) Examine controlling policies for in-house pathological terms (Tables 2 & 3)
2) Construct findings in a consistent format for each anatomic site: finding, chronicity*, distribution*, laterality*, severity**
3) Ensure reliability of findings by peer review (Peer review before submission is highly recommended.)
4) Understand controlled terminology (findings stored in the latest CT)
5) Select appropriate tools (verify data accuracy to assure dataset completeness)
6) Select a browsing tool

* Optional based upon finding. ** severity includes "present" for non-graded findings such as cyst. Use the 5 severity grade scale, to eliminate mapping.

Precautions in conversion work:
1) Create data in agreement with the final report (no omissions, no contradictions – if there are differences, for example, due to rounding in numeric tables reported vs calculations from raw data, this can be brought forward in the SDRG
2) Assure appropriate variable data in each domain
3) Ensure appropriate mapping to CT
4) Create appropriate additional modifier domains
5) Allow for ample time to create a SEND dataset (Mapping work is not easy)

Precautions in checking a SEND data set:
1) Check appropriateness (QC) of CT mapping
2) Check accuracy of mapping throughout the different SEND domains (example – units in LB domain)
3) Confirm and adjust mapping with sponsor
4) Provide clear explanation for differences between Original results and SEND datasets (for example, severities) in the SDRG

Materials and Methods

Studies and tests using SEND data

Rat repeate dose GLP study

Tests: General conditions, weight, feed amount, hematology, blood biochemistry, necropsy, organ weights, histopathology

Data conversion method

Without changing the in-house system or glossaries, original data were extracted and converted to SEND data by the following two procedures:

① Excel database data were directly extracted from the in-house system and converted to SEND using TranSEND® via an adapter.
② Pathological data (MA and MI findings) were input into Ascentos® PathData version 11 (PDS) and directly converted, without processing, to SEND using TranSEND® (PDS) which is compliant with SEND Implementation Guide (SENDIG) v3.0.

QC was implemented using SEND Explorer® (PDS SEND viewer) to review all findings and calculate means & standard deviations from SEND data for comparison with those in the report.

Table 1 Microscopic (histopathologic) findings: Sample data

Raw data: **Kidney: Inflammation, chronic, pelvis, bilateral, slight**

MI: MI domain sample data

MIORRES	MISTRESC	MIRESCAT	MISPEC	MIANTREG	MILAT	MISEV
Inflammation, chronic, pelvis, bilateral, slight	Inflammation	NON-NEOPLASTIC	KIDNEY	PELVIS	BILATERAL	MILD

SUPPMI: MI additional modifier domain (SUPPMI sample data)

QNAM	QLABEL	QVAL
MIRESMOD	Result Modifiers	Chronic

Explanation of variables inside the domain

[MIORRES]: Result or findings as collected. Raw data (includes various modifiers as basic findings).
[MISTRESC]: Standardized result in character format. Basic findings excluding modifiers such as distribution, frequency, grade, etc.
[MIRESCAT]: Result category. Non-neoplastic.
[MISPEC]: Specimen material type. Observed organ / tissue.

[MILAT]: Specimen laterality within the subject. Unilateral/Bilateral.
[MIANTREG]: Anatomical region of specimen. (Further describes MISPEC)
[MISEV]: Severity Grade.
[QNAM]: Qualifier variable name. Abbreviated name of modifier.
[MIRESMOD]: Supplementary modifier.
[QLABEL]: Qualifier variable label. Official QNAM name.
[QVAL]: Data value. Modifier of basic findings.

Table 2   Expected cases ⇒ Grade names are inconsistent- using SEND defined CT eliminates the necessity of mapping!

Grade	Criterion used by Facility A	SEND CT	Criterion used by Facility B
1	Trace	MINIMAL	Minimal
2	Minimal	MILD	Slight
3	Mild	MODERATE	Moderate
4	Severe	MARKED	Marked
5		SEVERE	Massive

Example excerpt from SEND controlled terminology 2015-12-18
Source: http://evs.nci.nih.gov/ftp1/CDISC/SEND/

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	NCI Preferred Term
C90000		No	Severity	SEV	Severity	SEND terminology related to the degree of an occurrence of something undesirable.	CDISC SEND Severity Terminology
C25570	C90000		Severity	MINIMAL	Trace	The first (lowest) level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.	Minimum
C70666	C90000		Severity	MILD	Slight	The second level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.	Mild
C61376	C90000		Severity	MODERATE		The third level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.	Moderate
C48662	C90000		Severity	MARKED		The fourth level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.	Marked
C70667	C90000		Severity	SEVERE		The fifth (highest) level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.	Severe

Table 3

Organizations related to SEND controlled terminology

GESC (Global Editorial Steering Committee) — INHAND — go RENI — CDISC — FDA — SEND — NCI EVS
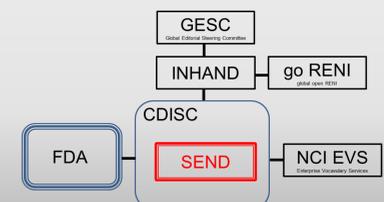
Summary   Roles of pathologists in SEND conversion:

- Need to ensure correct mapping of histopathological terms to SEND CT on a regular basis, and consider SEND requirements when creating findings.

- FDA recommends peer review before submission to ensure the reliability/quality of a percentage of histopathology findings.

- SEND is not only an IT issue. The pathologist should check if pathological terms are correctly evaluated after SEND conversion (Note: the original result ALWAYS appears in the SEND dataset).

- SEND will soon be a requirement. Pathologists need to focus effort on actively applying SEND in an optimal manner with the cooperation of SEND data managers. Modifying system settings or updating LIMS systems to utilize SEND standards is highly recommended.