SEND

Standard for the Exchange of Nonclinical Data

Basel, Switzerland 2014 SDE

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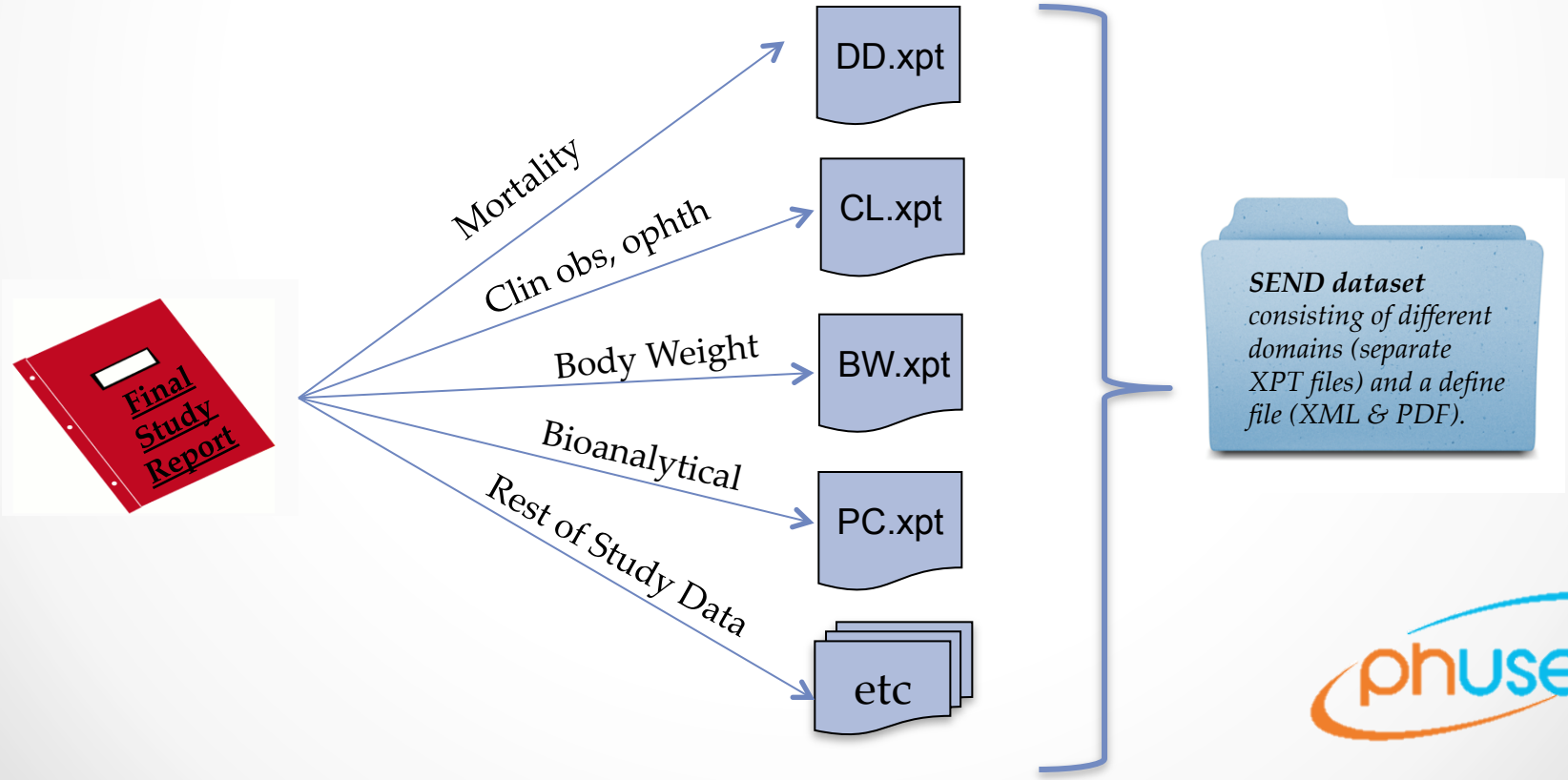
What is SEND?

- In development >10 years by CDISC along with FDA
- 2012: FDA granted authority to establish & require a standard electronic format for INDs, NDAs, ANDAs, BLAs
- SEND is the same electronic standard used by Clinical for FDA submissions

What is SEND?

- SEND is a giant mapping exercise: different sections of a toxicology report get mapped to corresponding domains within SEND



What is Send?

- All original findings **must be** recorded in SEND; some are mapped to controlled terminology
- Portion of populated **Microscopic Domain** from SENDIG 3.0:

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MIGRPID	MISPID	MISTESTCD	MITEST	MIORRES	MISTRESC
1	123	MI	123-01	1			MIEXAM	Microscopic Examination	Amyloidosis	Amyloidosis
2	123	MI	123-01	2			MIEXAM	Microscopic Examination	Inflammation, acute	Inflammation, acute
3	123	MI	123-01	3			MIEXAM	Microscopic Examination	Degeneration/regeneration epithelial	Degeneration/regeneration epithelial
4	123	MI	123-01	4			MIEXAM	Microscopic Examination		
5	123	MI	123-01	5			MIEXAM	Microscopic Examination	Normal	NORMAL
6	123	MI	123-02	6			MIEXAM	Microscopic Examination	Inflammation	Inflammation
7	123	MI	123-03	7			MIEXAM	Microscopic Examination	Hyperplasia, endometrial cystic	Hyperplasia
8	123	MI	123-03	8		MASS 1	MIEXAM	Microscopic Examination	Adenoma: tubulostromal (benign neoplasm)	ADENOMA, TUBULOSTROMAL, BENIGN

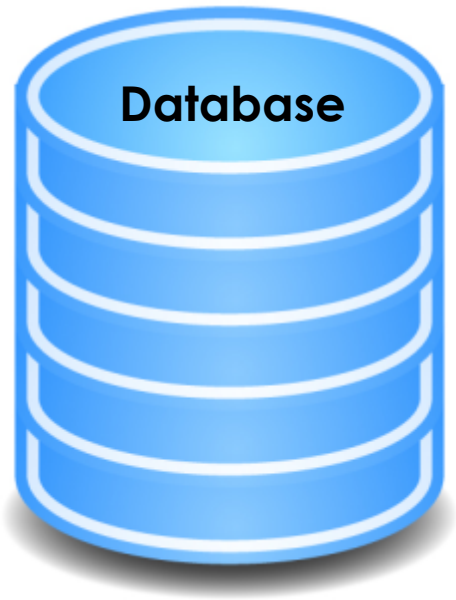
- **Blue arrows** point to columns with controlled terminology
- **Red arrow** points to column with findings as recorded by pathologist
- **Green arrow** points to column with some findings as recorded by pathologist (lowercase) and other findings (neoplasms) mapped to controlled terminology (uppercase).

Timing for SEND Implementation

- "Trigger" for SEND implementation is finalization of guidances:
  - For NDAs, ANDAs, BLAs: studies starting no sooner than 24 months after issuance of final guidances
  - For INDs: studies starting no sooner than 36 months after issuance of final guidances
  - 3 draft FDA guidances issued in Feb 2014; comment period closed May 7
  - Implementation expected to begin 4 Q 2016 (start of US fiscal year 2017), assuming guidances are finalized 4 Q 2014
  - Guidances become binding at time of implementation
  - FDA's **preferred submission format at this time**: SEND

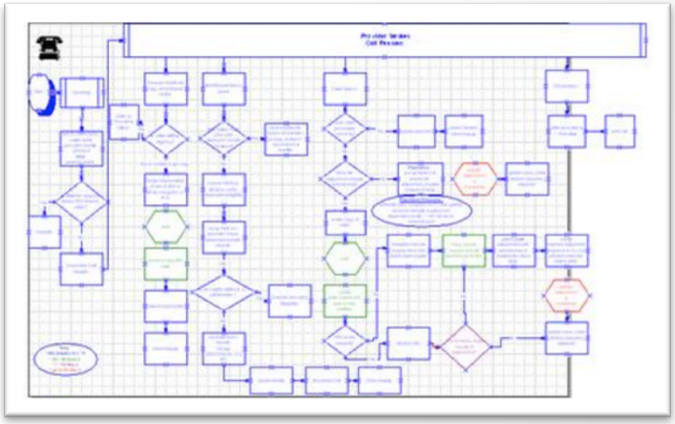
Why is SEND Being Developed?

- SEND will benefit FDA:
  - Faster submission review – *already demonstrated*
  - SEND datasets used to analyze submissions – *already being done*
  - SEND-based data warehouses – *already being done*
- FDA wants rapid access to large amounts of data to better understand nonclinical predictability
- SEND can benefit Sponsor for the same reasons



SEND Readiness

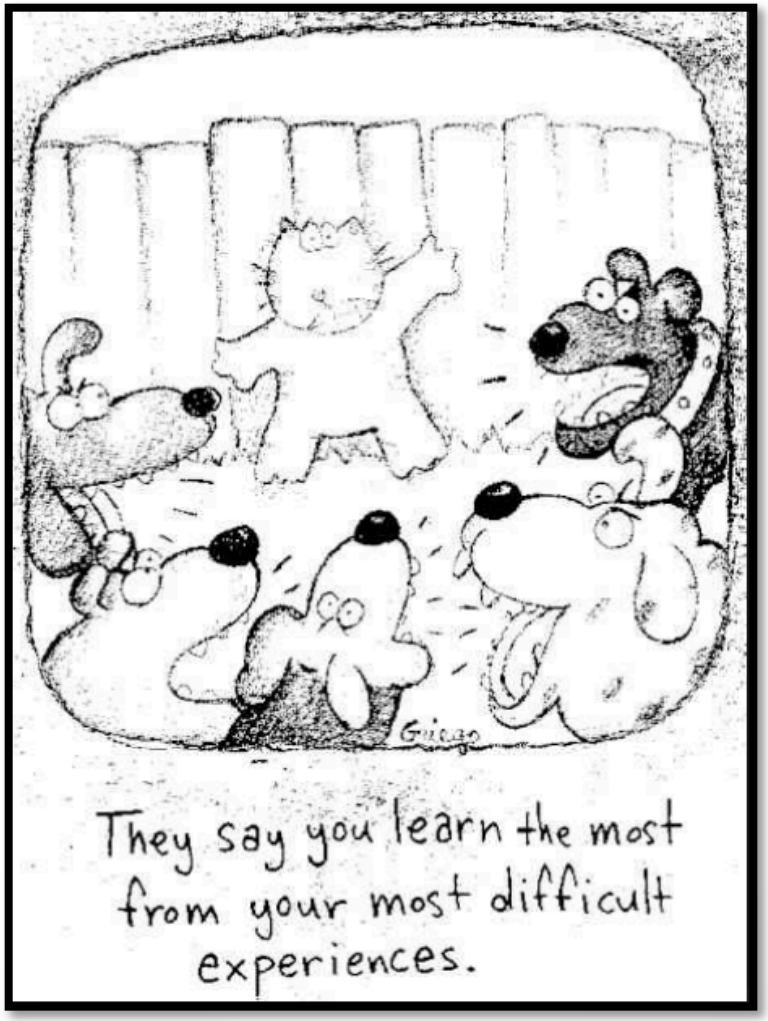
- SEND readiness is a process!
  - Formation of interdisciplinary SEND team
  - Workflow definition
    - LIMS to SEND
    - Integration of different LIMS extracts
    - Strategy for working with CROs
    - QA & validation against SEND model
      - Metadata Harmonization across vendors and LIMS
  - Resources
  - Timelines
  - Budget
  - Study protocol compatibility for SEND mapping
  - Controlled terminology mapping
    - *"I thought this was an IT problem – boy, was I wrong"*



SEND Readiness - Continued

- FDA SEND Pilot Projects - Best Way to Assess SEND readiness
- FDA will accept SEND datasets to validate against SEND model using their validation tools
  - OpenCDISC Validator
  - NIMS
- If FDA finds validation errors:
  - FDA will send Sponsor a validation report with specific deficiencies
  - Sponsor corrects deficiencies and resubmits SEND datasets to FDA
- The first few submissions will likely result in errors requiring correction

Value of FDA SEND Pilot Cannot be Underestimated!



Sponsor's Role in SEND

- If using a CRO or SEND Vendor, work together!
  - Need to understand partner's SEND process:
    - Validation of SEND software
    - Domains & variables to be included
    - QC of datasets
    - Controlled terminology

- **Data Standardization Plan:**
  - "…sponsors should include a plan (eg, in the IND) describing the submission of standardized study data to FDA…For INDs, the Standardization Plan should be located in the general investigational plan"[1]

[1] FDA, CDER, CBER: Draft Study Data Technical Conformance Guide, February 2014

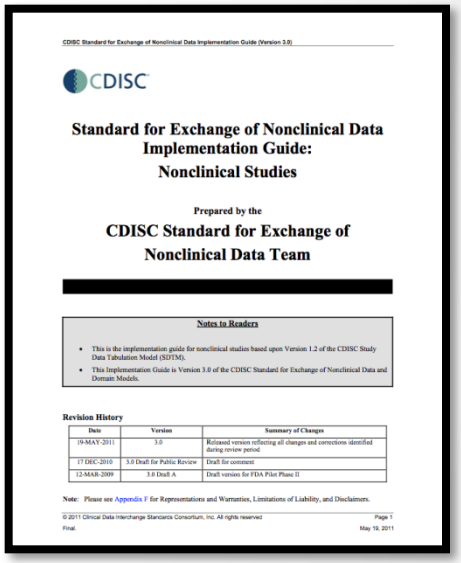
Validation of SEND Datasets Against SEND Model

- Validation tools used for SEND by FDA:
  - OpenCDISC
  - NIMS

- FDA validation rules are available on FDA website
  - http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
- OpenCDISC
  - http://www.opencdisc.org
  - Open source
  - Extensible
  - Includes FDA validation rules

SEND Implementation Guide Versioning

- Current SENDIG: v3.0
  - Based on SDTM (Study Data Tabulation Model) 1.2
  - Includes single & repeat-dose tox, carcinogenicity
- Next SENDIG: 3.1
  - Based on SDTM 1.4
  - New features:
    - Cardiovascular & respiratory safety pharmacology
    - New variables for microscopic domain
    - Ability to create custom domains
    - Expected release by CDISC end of 2014; timing for FDA acceptance of SENDIG 3.1 datasets to be determined
- DART SEND (Developmental & Reproductive Toxicology)
  - A separate SENDIG
  - Model is mature, but timeline for issuance not established



CDISC Standard for Exchange of Nonclinical Data Implementation Guide (Version 3.0)

CDISC

Standard for Exchange of Nonclinical Data Implementation Guide: Nonclinical Studies

Prepared by the

CDISC Standard for Exchange of Nonclinical Data Team

Notes to Readers

- This is the implementation guide for nonclinical studies based upon Version 1.2 of the CDISC Study Data Tabulation Model (SDTM).
- This Implementation Guide is Version 3.0 of the CDISC Standard for Exchange of Nonclinical Data and Domain Models.

Revision History

Date	Version	Summary of Changes
19-MAY-2011	3.0	Released version reflecting all changes and corrections identified during review period.
17 DEC-2010	3.0 Draft for Public Review	Draft for comment
12-MAR-2009	3.0 Draft A	Draft version for FDA Pilot Phase II

Note: Please see Appendix F for Representations and Warranties, Limitations of Liability, and Disclaimers.

Final.

May 19, 2011

Controlled Terminology (CT) Versioning

- CDISC is responsible for CT
- CT may be revised as often as 4x/year
- Current version (18) released 27 Jun 2014
- Draft CT (version 19) out for review; changes include:
  - Addition of CT code lists for new MI variables: chronicity & distribution
  - Will be issued at the same time as SENDIG 3.1
  - Addition of CT code list for non-neoplastic lesions (INHAND)
- CT in different file formats can be found at: CDISC.org

SEND Challenges

- Toxicology Studies generally conducted over multiple CROs, LIMS:
  - In-life
  - microscopic
  - Bioanalytical
  - PK
- Harmonization of metadata from different CROs, LIMS
- Relationships between different domains (RELREC)
- Controlled terminology mapping and updating
- Validation against SEND model
- Trials Domains – more than one correct way to map

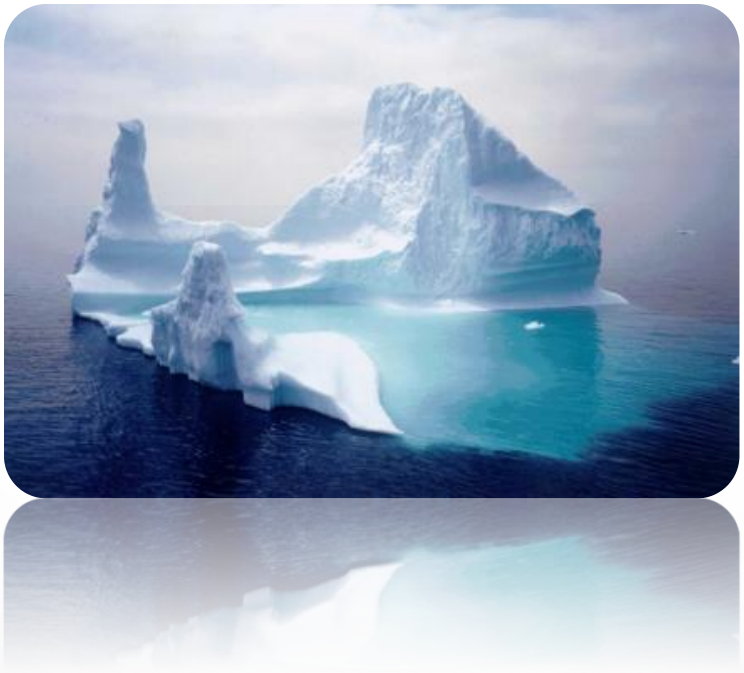
Join a SEND Working Group!

- PhUSE: Pharmaceutical Users Software Exchange
  - http://www.phusewiki.org
- CDISC: Clinical Data Interchange Standards Consortium
  - http://www.cdisc.org/
- Both groups are active in Europe and Japan
- Both sites contain a lot of very useful SEND information and updates

This is just the tip of the SEND info iceberg!

Additional Information:

- FDA electronic standards website:
  http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm



Sanitized Datasets

- Sanitized Datasets
  - https://sendexplorer.azurewebsites.net/
  - http://senddataset.org/