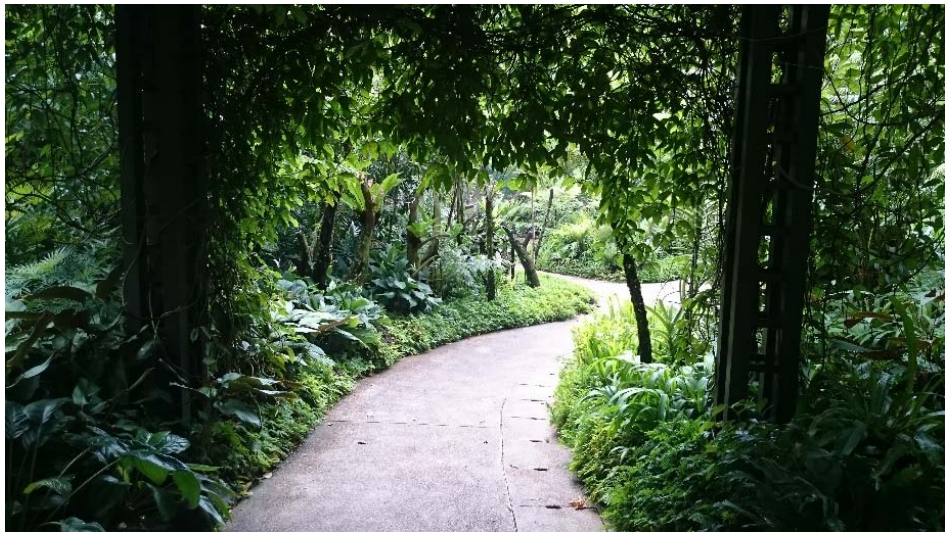
DATA STANDARDS DECISIONS

Insight → Interpretation → Implementation



SEND Introduction

– 2018 CDISC User Group Meeting

Gitte Frausing
Principal Consultant
Data Standards Decisions

My background

- Principal industry consultant in CDISC standards with focus in the nonclinical area
- Authorized CDISC SEND instructor, SEND core team member and workstream lead since 2007
- PhUSE working group member and co-lead since 2012
- Pharmaceutical industry background (Toxicology & Regulatory Affairs)

DATA STANDARDS DECISIONS

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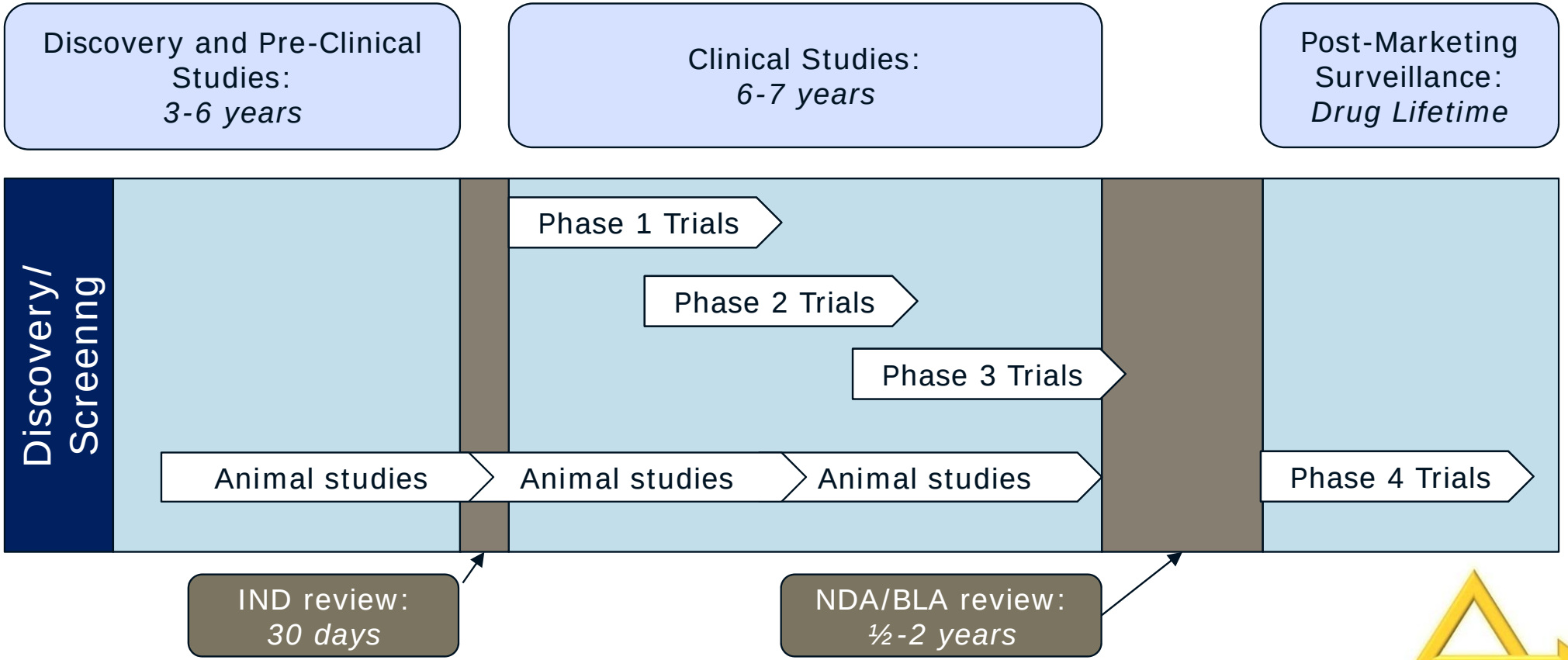
DATA STANDARDS DECISIONS

Drug Development Process



[Modified from 1]

DATA STANDARDS DECISIONS

Overview of study types (clinical and nonclinical)

Nonclinical Study Types

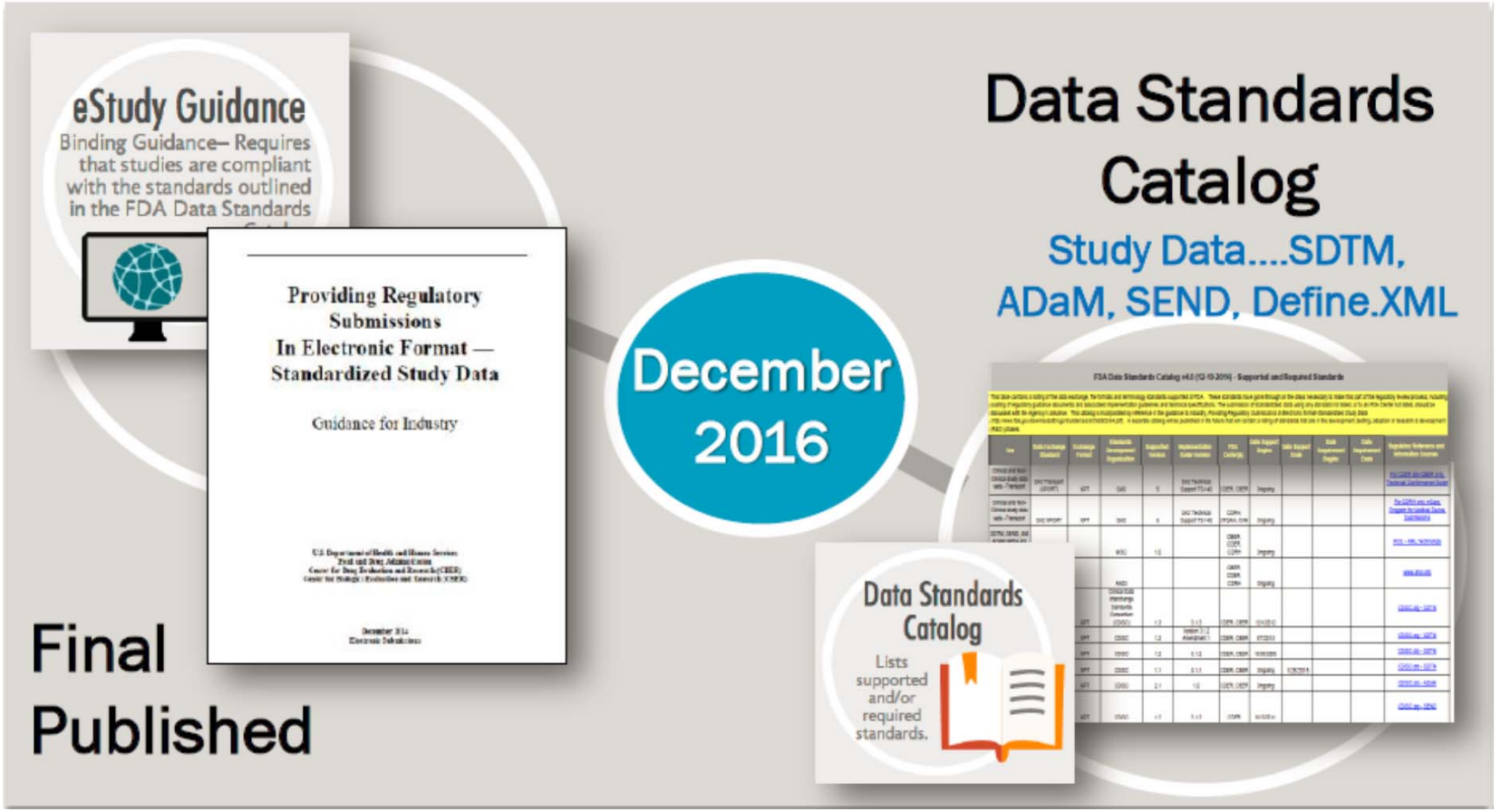
- General Toxicology (2 species, same endpoints – different methodology)
- Safety Pharmacology (Safety on single body systems, “efficacy-like”)
- ADME studies (PK same as clinical, but also many other nonclinical endpoints)
- Reproductive Toxicology (only nonclinical endpoints)
- Carcinogenicity (only nonclinical endpoints)
- Several other study types may come in play, dependent on compound/indication/route

Clinical Trial

- Phase 1 (Often standard safety endpoints, “General Toxicology-like”)
- Phase 2 (“POC” studies, indication specific, often efficacy endpoints included)
- Phase 3 (very indication specific, primary objective: efficacy measures)
- Phase 4 (Safety measurements on one or more disease parameters)

DATA STANDARDS DECISIONS

What study data standards are required



DATA STANDARDS DECISIONS

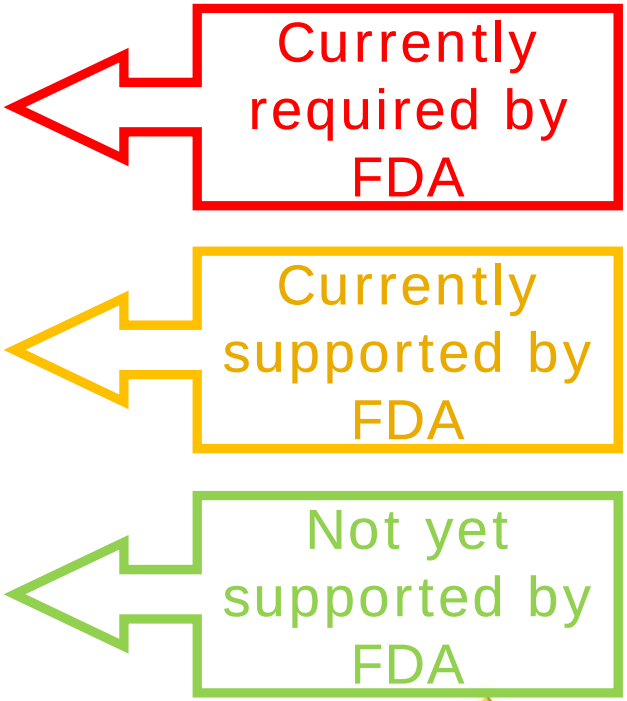
FDA Data Standards Catalog v4.7 (09-01-2017) - Supported and Required Standards

This table contains a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of regulatory guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*.

Use	Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
Clinical study datasets	SDTM	XPT	CDISC	1,3	3.1.3	CDER, CBER	12-01-2012		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,2	Version 3.1.2 Amendment 1	CDER, CBER	08-07-2013	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,2	3.1.2	CDER, CBER	30-10-2009	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - SDTM
Clinical study datasets	SDTM	XPT	CDISC	1,1	3.1.1	CDER, CBER	Ongoing	01-28-2015			CDISC.org - SDTM
Clinical study datasets	Analysis Data Model (ADaM)	XPT	CDISC	2,1	1,0	CDER, CBER	Ongoing		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - ADaM
Animal study datasets	Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1,2	3,0	CDER	06-13-2011	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	CDISC.org - SEND
Animal study datasets	SEND	XPT	CDISC	1,5	3,1	CDER	08-21-2017		3/15/2019 [1] 3/15/2020 [2]		CDISC.org - SEND
Study data definition	Define	XML	CDISC	1,0	N/A	CDER, CBER, CDRH	Ongoing	03-15-2018	12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML
Study data definition	Define	XML	CDISC	2,0	N/A	CDER, CBER, CDRH	08-07-2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML

Studies in scope for SEND

- SENDIG v. 3.0
  - Single dose, repeat dose and carcinogenicity studies
- SENDIG v. 3.1
  - As above plus cardiovascular and respiratory safety pharmacology
- SENDIG-DART v. 1.1
  - Early embryo-fetal developmental toxicity studies



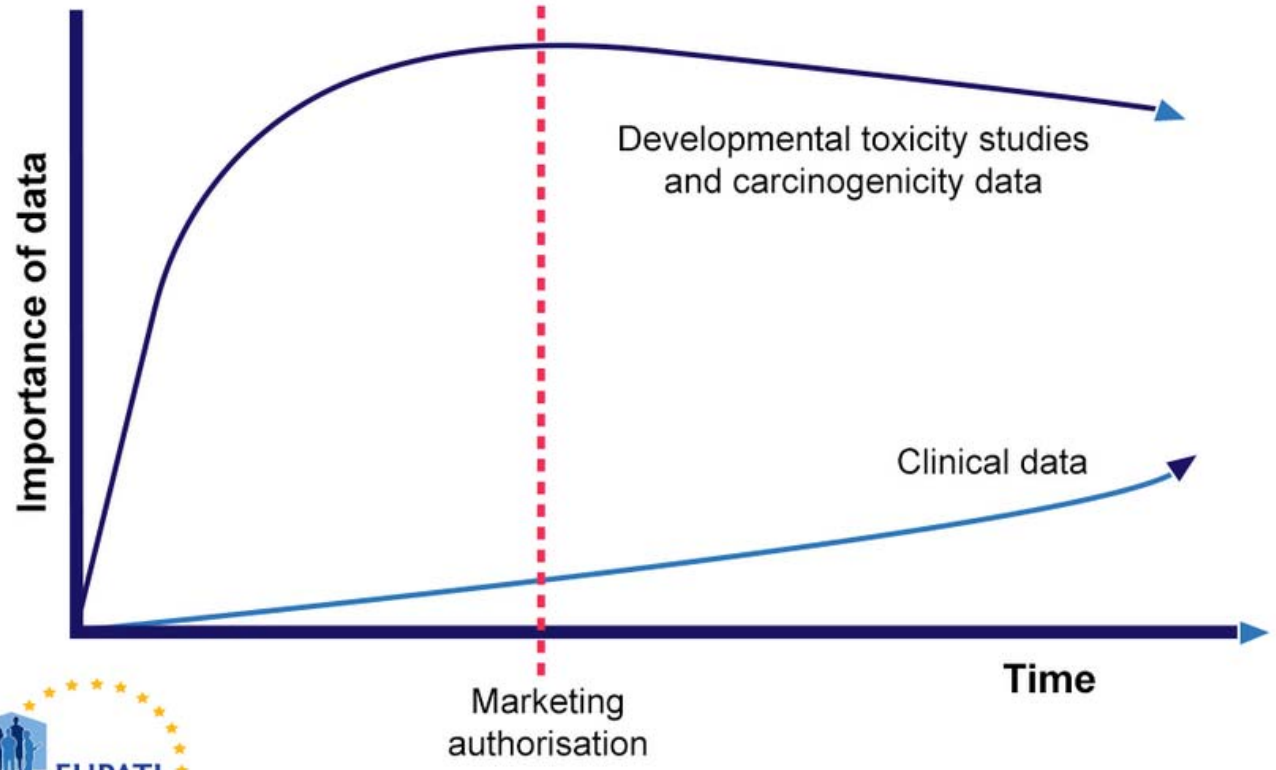
DATA STANDARDS DECISIONS

Nonclinical data in submissions

- Nonclinical data critical in a submission package
  - Primary data in an IND
    - Target organs to be monitored
    - Safety biomarkers for clinical trials
    - Setting of FHD
  - Pivotal data in an NDA
    - Reproductive effects
    - Carcinogenic effects

DATA STANDARDS DECISIONS

Importance of developmental toxicity and carcinogenicity data vs. clinical data



EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Adapted from Nieto-Guiterrez, M. (2011) *Non-clinical assessment requirements.* London: European Medicines Agency.

[3]

DATA STANDARDS DECISIONS

Content

DATA STANDARDS DECISIONS

Study conduct: Nonclinical

- Good Laboratory Practice (GLP)
- Study responsibility resides at Test Facility

Test Facility

- Protocol writing
- Animal management,
- Data collection
- Study reporting

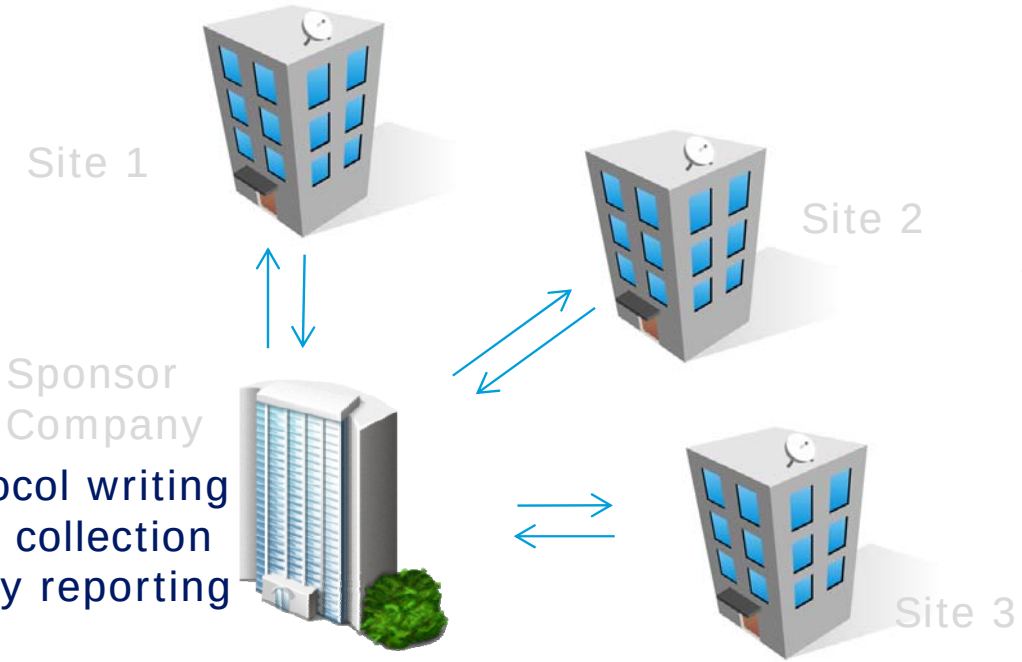
Sponsor Company

- Study outline
- Protocol review
- Report review

DATA STANDARDS DECISIONS

Study conduct: Clinical

- Good Clinical Practice (GCP)
- Study responsibility resides at the Sponsor



Sponsor Company
- Protocol writing
- Data collection
- Study reporting

Sites
- Data collection

DATA STANDARDS DECISIONS

Differences between Clinical and Nonclinical on a dataset level

Nonclinical studies

- Pool concept: One result belonging to multiple subjects
- Post-mortem data
- “Everything is a finding”, only one SEND events domain
- Industry terminology standards are rare

Clinical Trials

- Trial and subject visits
- Informed consent
- Subject baseline values
- A lot of coding to external dictionaries

DATA STANDARDS DECISIONS

Data: Collection

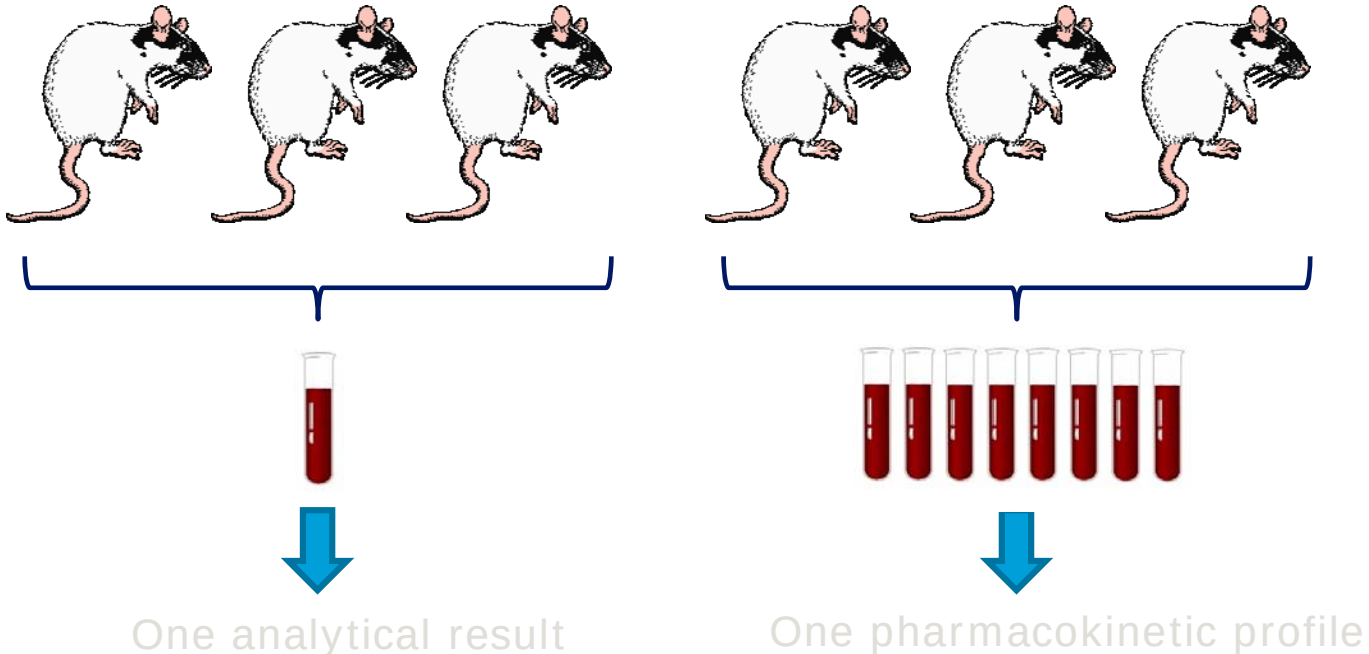
- Subject-based or pool-based
- USUBJID and POOLID mutually exclusive
- Pool-based data collection
  - One collected result that cannot be attributed to only one subject

Cage-based observations

- Food and Water consumption
- Clinical Observation
- Cage-based dosing
  - Food dosing
  - Whole cage inhalation

Data: Collection - Pools

- Pool-based data in LB, PC and PP



Data: Collection - POOLDEF

- A pool must have at least one subject
- A POOLID must be unique for a given set of subjects
- A given set of subjects may have multiple POOLIDs

- Operationally, pools can be defined each day or at the start of a collection interval

Variable Name	Variable Label	Type	Controlled Terms, Codelist, or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
POOLID	Pool Identifier	Char		Identifier	Identifier used for pooling subjects to assign a single finding to multiple subjects.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify across all studies for all applications or submissions involving the product.	Req

Data: Collection – Post-mortem data

- Non-clinical studies contain a great deal of post-mortem data
  - OM – Organ Measurements
  - MA – Macroscopic Observations
  - MI – Microscopic Observations
  - TF – Tumor Findings

- Specimen-dependant domains, similar to LB
  - --DTC is Date/Time of specimen collection, not Date/Time of sample analysis
  - For post-mortem data, --DTC will always equal DSSTDTC

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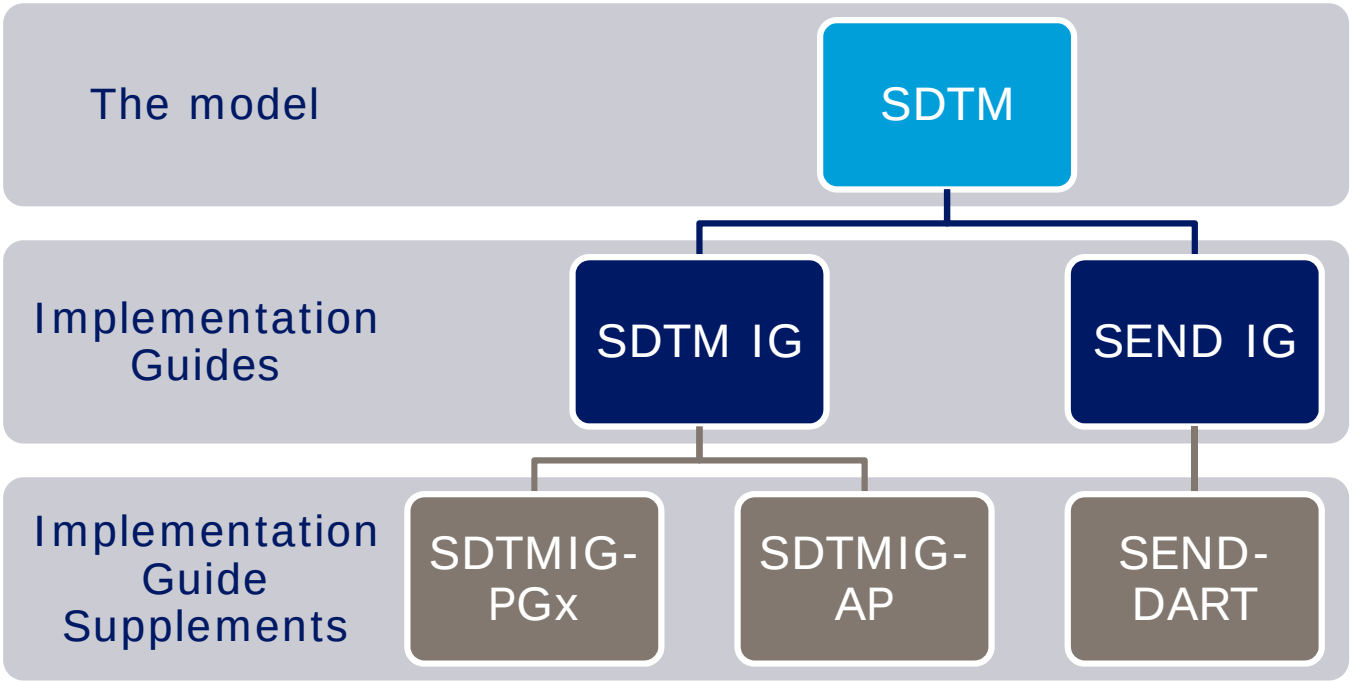
DATA STANDARDS DECISIONS

SEND and SDTM



DATA STANDARDS DECISIONS

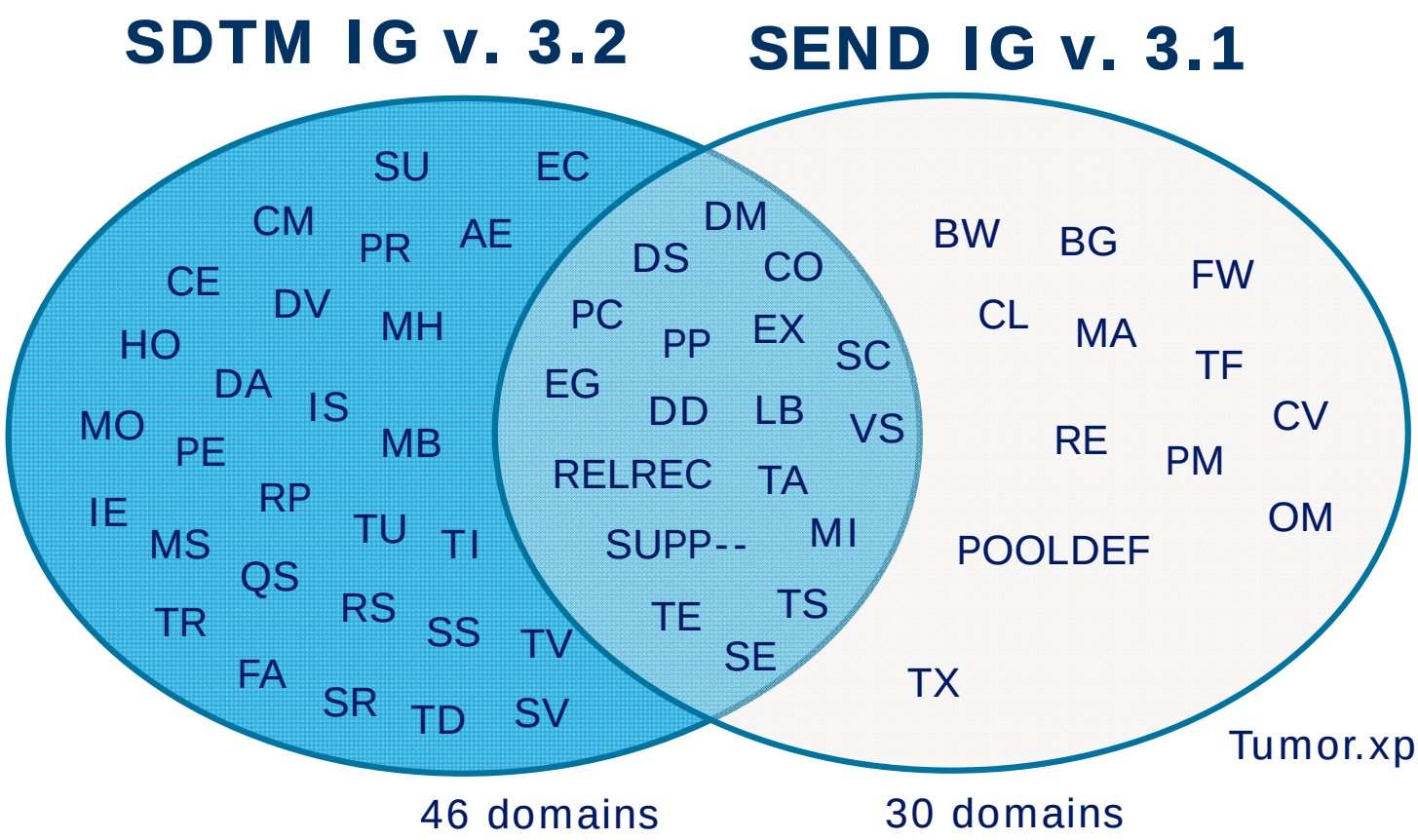
SEND and SDTM: The SDTM rules apply for both

- IG arranged into domains built of SDTM defined variables
- Consistent use of variables, e.g. shared terminology
- No new sponsor defined variables and no renaming or modification for novel usage
- Data include both “raw” (as captured by the data provider) and derived values (standard units or computed)
- Permissible variables may be dropped
- Science and regulation determines what to collect

- *Not all variables and domain types in the SDTM Tables are appropriate for all implementations*

DATA STANDARDS DECISIONS

SENDIG and SDTMIG: Domain overview



DATA STANDARDS DECISIONS

Study design: SEND trial design

- Based on SDTM – foundation in clinical trial design
- Concepts unknown or unuseful for non-clinical
- Nonclinical often have other parameters than treatment with study drug that distinguish study groups

Variable Name	Variable Label	Type	Controlled Terms, Codelist, or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	TA	Identifier	Two-character abbreviation for the domain.	Req
ARMCD	Planned Arm Code	Char		Topic	Short name of a specific ARM (may be up to 20 characters) used for sorting and programming. Should be populated in Demographics when Arms have been defined in this domain.	Req
ARM	Description of Planned Arm	Char		Synonym Qualifier	Descriptive name given to a specific Trial Arm (e.g., Low Dose, Mid Dose, 10 mg/kg/day dose, 3rd Arm).	Req
TAETORD	Order of Element within Arm	Num		Timing	Number that provides the order of the planned Element within the Arm. This value should be an integer.	Req
ETCD	Element Code	Char		Record Qualifier	Short name of the Element. The same Element may occur more than once within an Arm. Maximum 8 characters. The values of ETCD used in the Trial Arms dataset must match values for the same Element in the Trial Elements dataset.	Req
ELEMENT	Description of Element	Char		Synonym Qualifier	The name of the Element. The same Element may occur more than once within an Arm.	Perm
TABRANCH	Branch	Char		Rule	Conditions subjects meet, occurring at the end of an Element, which cause an Arm to branch off from other Arms (e.g., randomization to control group).	Perm
TATRANS	Transition Rule	Char		Rule	If the study design allows for a subject to transition to an Element other than the next sequential Element, as defined by TAETORD, then the conditions for transitioning to those other Elements, as well as the alternative Element sequences, are specified in this rule (e.g., TATRANS = 'Subject with Hypoactivity Transitions to Rest Period to Treatment 2').	Perm
EPOCH	Trial Epoch	Char		Timing	Name of the study Epoch with which this Element of the Arm is associated (e.g., Treatment, Screen). Equivalent to 'Phase' or 'Period.'	Exp

DATA STANDARDS DECISIONS

Study design: Nonclinical

Group Number	Group Label	Dose Level (mg/kg/day)	Number of Animals (M+F)			
			Main animals		Toxicokinetic	
			No recovery	Recovery	No recovery	Recovery
1	Group 1, Vehicle control	0	12	12	0	0
2	Group 2, 100 mg/kg	100	12	0	6	0
3	Group 3, 500 mg/kg	500	12	12	6	6

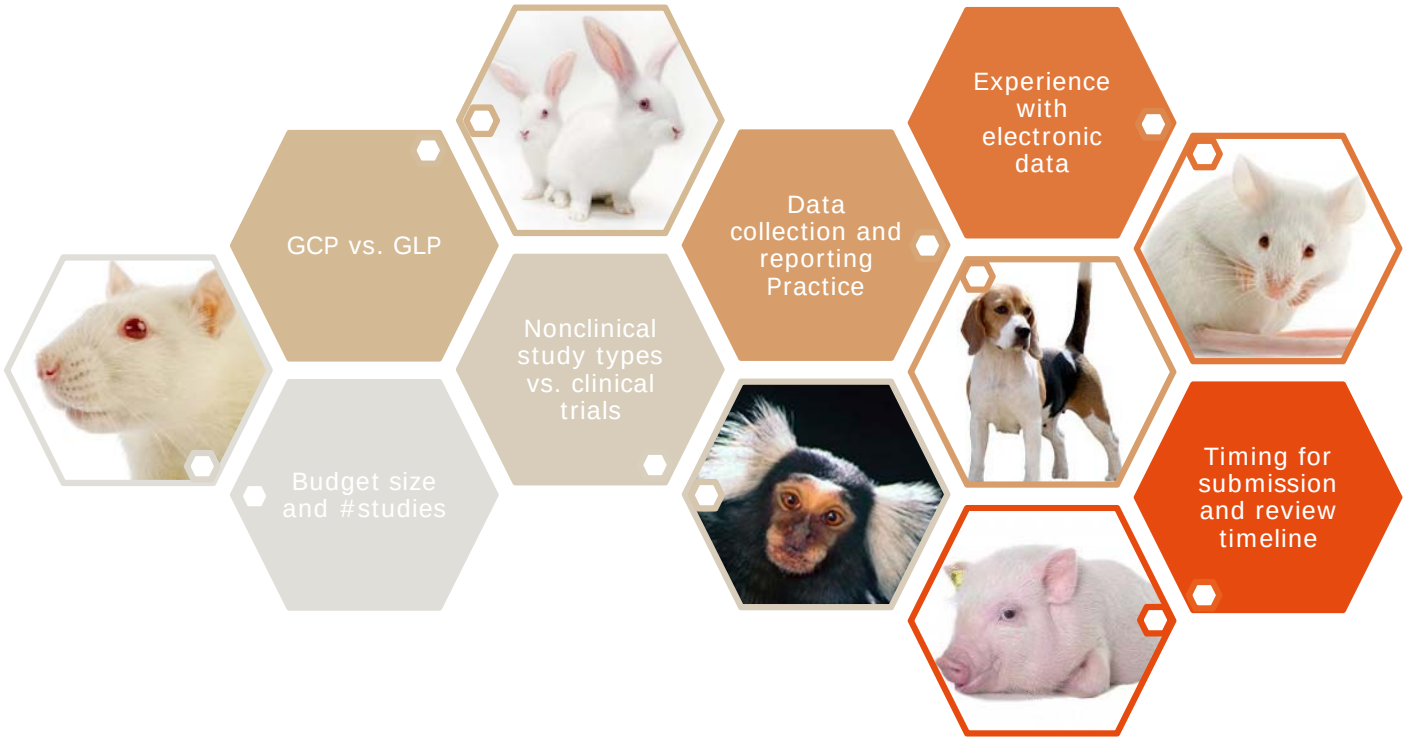
DATA STANDARDS DECISIONS

SEND and ADaM

- There is no ADaM for Nonclinical
  - SEND datasets are not processed for further analysis
  - Statistics and study reports are created ‘out-of-the-box’ by data collection systems on raw data
  - SEND datasets are created similarly, although ‘maturation’ in the industry is still ongoing
  - Generally, the SEND team considers SEND datasets ‘analysis-ready’
    - More derived information in SENDIG than in SDTMIG
    - Analysis-type variables found in SENDIG, e.g. Exclusion Flag and Reason

DATA STANDARDS DECISIONS

Summary: Notable differences



DATA STANDARDS DECISIONS

References

1. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC pharmacology & toxicology 14(1):1 · January 2013.
2. US FDA Regulatory Submissions: Receipt, Process, Review and Approval (or not) *by* Steve Wilson, Ron Fitzmartin, Ginny Hussong. CDISC Europe Interchange Workshop 2015.
3. European Patient's Academy. https://www.eupati.eu/non-clinical-studies/general-toxicity-studies/

DATA STANDARDS DECISIONS

Thank you for your attention

- Contact us for further information:

  SENDsupport@datastandardsdecisions.com

  www.datastandardsdecisions.com

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