U.S. FOOD & DRUG ADMINISTRATION

CDISC-PhUSE Fit for Use Pilot

CDISC-SEND F2F October, 2016

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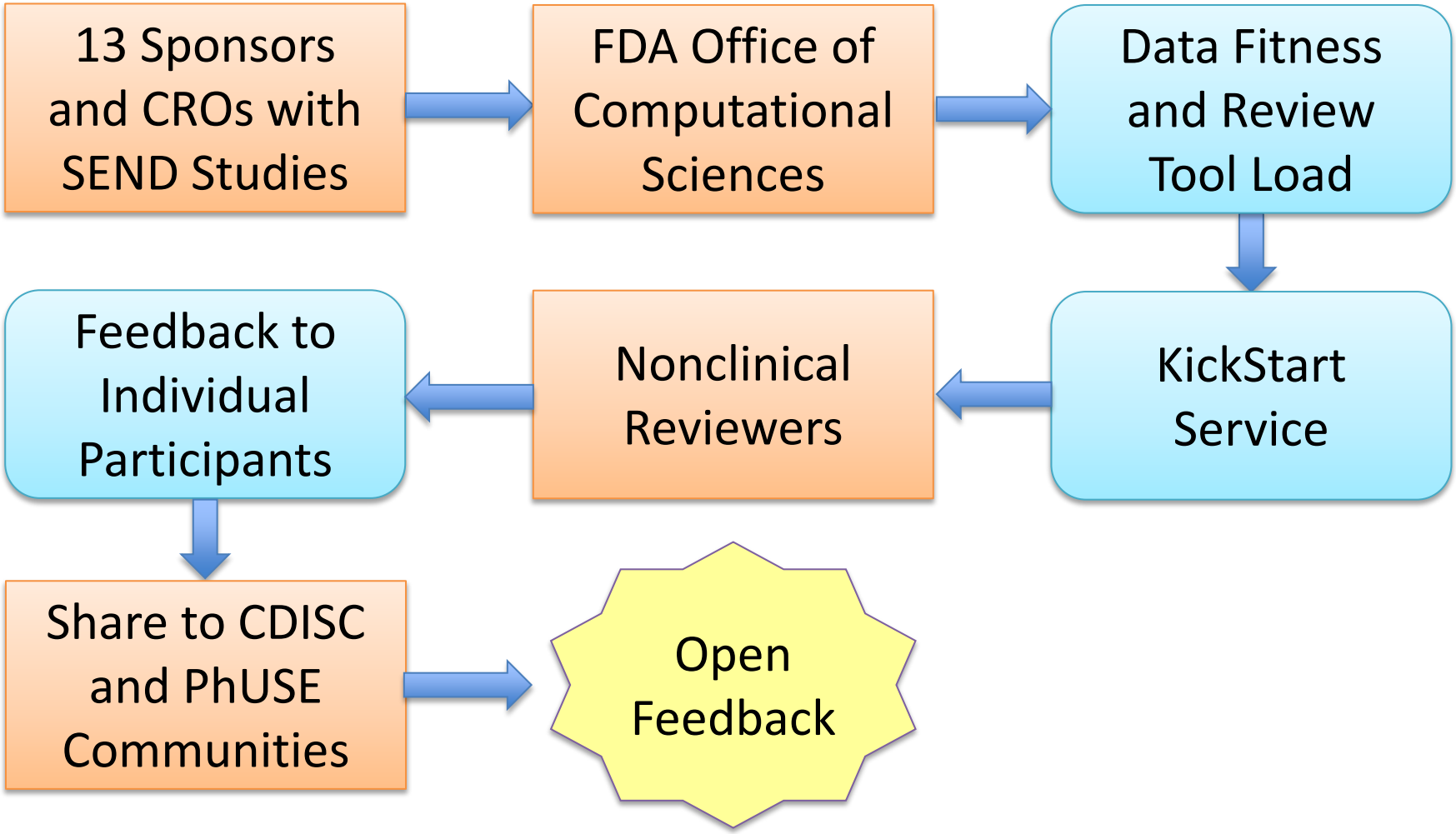
Office of Computational Sciences

Disclaimer

The views expressed are those of the speaker and do not necessarily reflect the policies and practices of the FDA.

What was the "Fit for Use" Pilot?



What did we learn "Fit for Use" means?

- Good integrity for loading to tools
- Complete
- Able to reproduce findings in the Study Report
- Documentation of limitations or discrepancies
- Close adherence to SENDIG so no manual programming is required for standard studies
- Good standardization and use of Controlled Terminology

Pilot Impact

- FDA received valuable sample data to test readiness, software, and practice
- Identified ten enhancements for our SEND visualization software
- Recommendations in FDA Technical Conformance Guide (still under internal review)
- Identification of software/standards development areas: MA, CL, PC domains
- Improvements to Office of Computational Science Datafit service

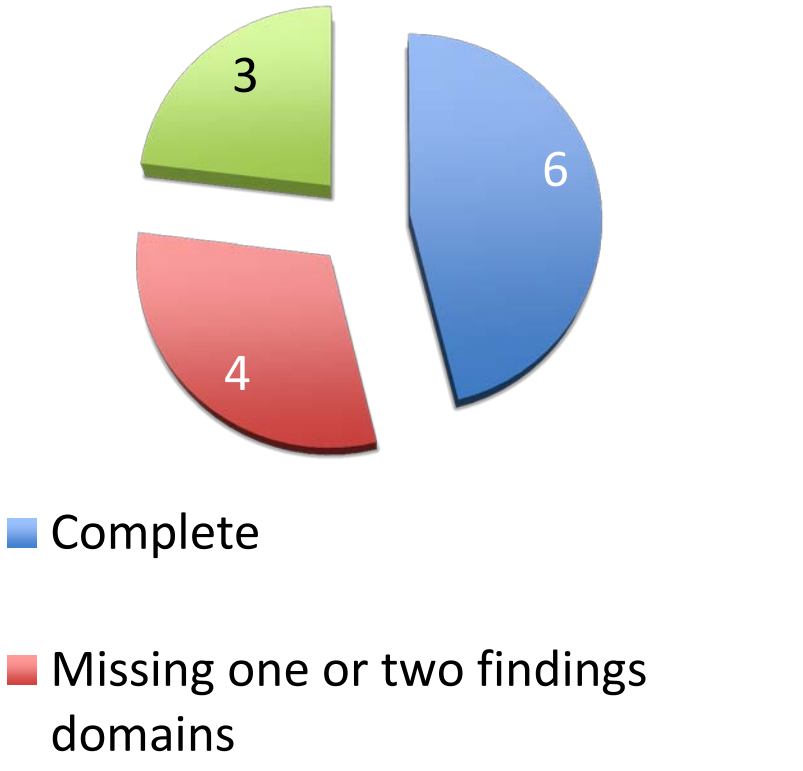
Review Readiness

- **Reviewers**
  - Nine reviewers gained experience with SEND
  - Five Pharm/tox divisions with reviewers prepared to train colleagues
- **KickStart**
  - Thirteen KickStart services performed to develop program
  - Received reviewer feedback to improve KickStart
- **OCS Training Team**
  - Concrete examples of the use of Janus Nonclinical in review provided to training team
- **Janus Nonclinical**
  - Ten software enhancements identified
  - Loading improved to support a broader variety of SEND data set and define.xml implementations

Fit for Use Pilot Metrics

- Data Completeness & Integrity
- Tabular Data Sets
- Reviewer feedback on NSDRG
- define.xml

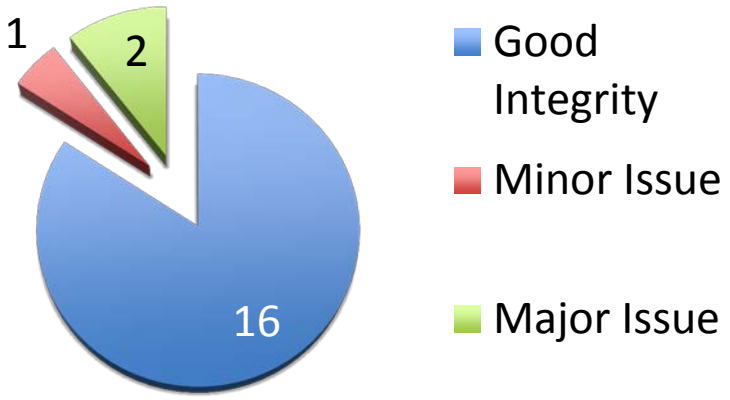
Submission Completeness



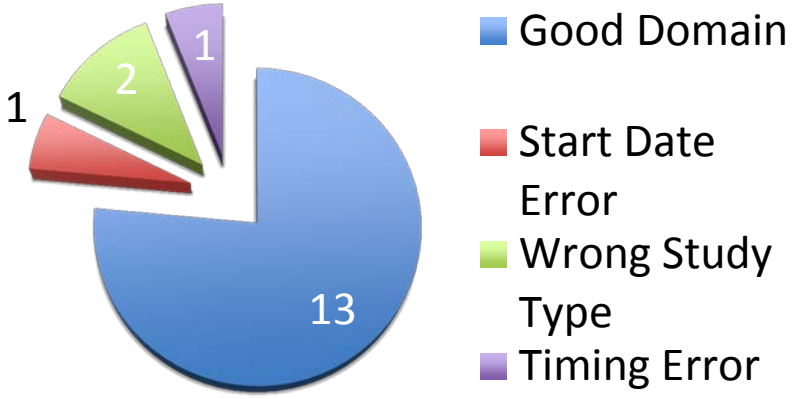
- Studies were compared to Study Reports to assess completeness
- Missing data were usually explained in the NSDRG
- Most of the missing data were due to challenges with legacy conversion

Data Integrity and TS

SEND Data Integrity



TS Dataset



- *Ensure that all SEND domains join and that the correct files are included*
- *TS accuracy will be important for submission through the eData gateway*

Fit for Use Pilot Metrics

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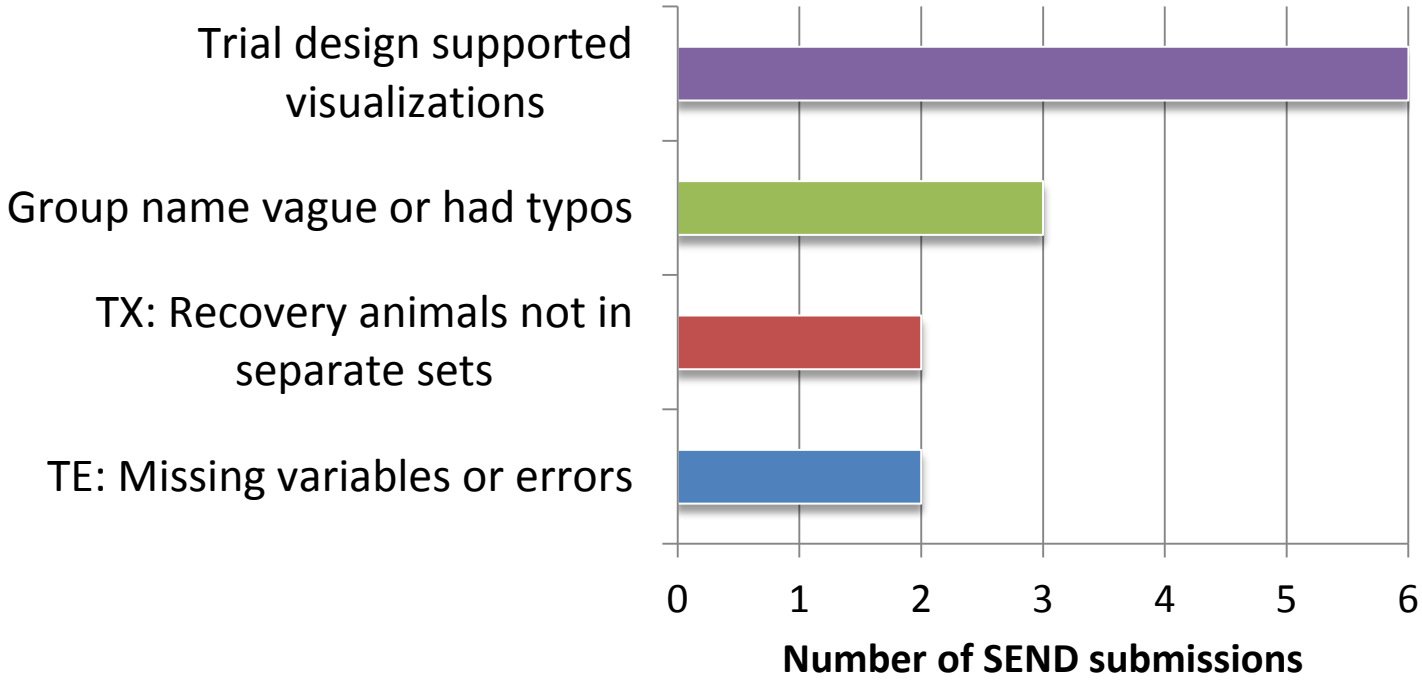
Trial Design Datasets

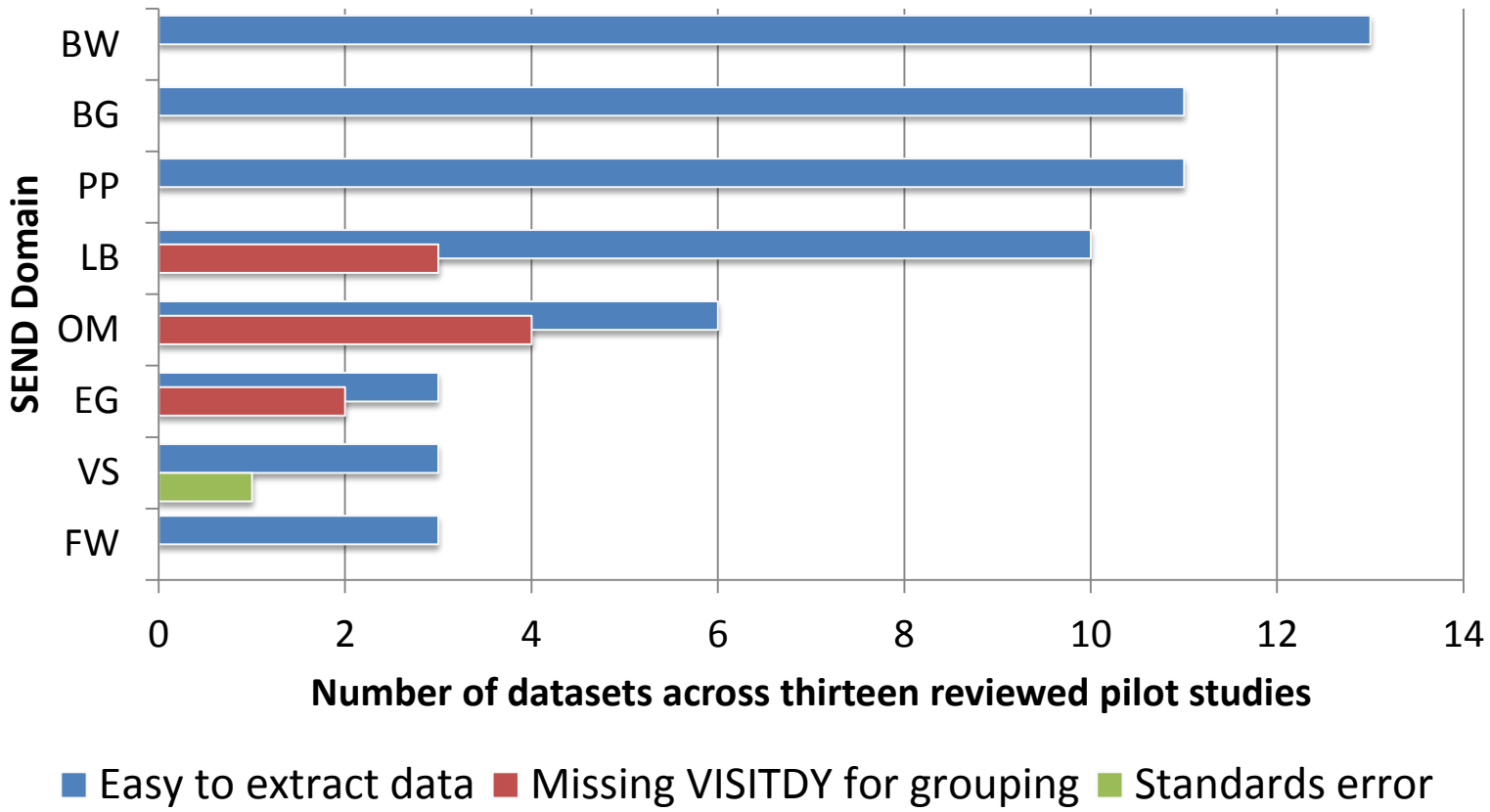


- *Not separating out recovery animals in TX makes the SEND datasets complicated to use – our software doesn't support it*
- *Group names are displayed to reviewers in our software*

Findings Domains

- Numeric domains BG, BW, FW, LB, PP, VS typically transmitted with good to excellent traceability to Study Reports
- CL, MA, MI could be difficult to reconcile to Study Reports because of standardization
- PC domains were often difficult to visualize
- Lack of VISITDY sometimes caused problems grouping observations in OM

Numeric Domains



- *The most common finding in numeric domains was VISITDY not included to group measurements collected on grace days*
- *A TX error and missing VISITDAY requires manual programming*

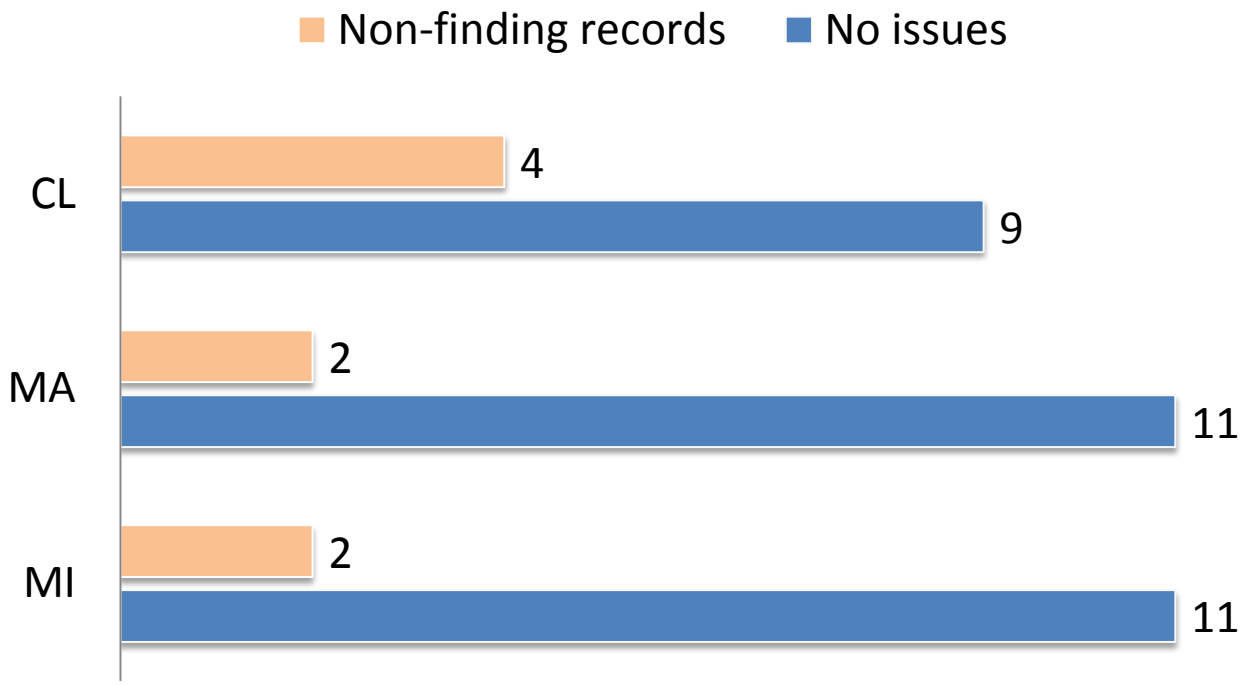
OM: Missing VISITDY Example

OMTESTCD	OMTEST	OMSTRESN	OMSTRESU	OMSPEC	OMDTC	OMDY
OWBW	Organ to Body Weight Ratio	3.916	%	LIVER	2016-01-01	59
OWBW	Organ to Body Weight Ratio	3.555	%	LIVER	2016-01-01	59
OWBW	Organ to Body Weight Ratio	3.512	%	LIVER	2016-01-02	60
OWBW	Organ to Body Weight Ratio	3.420	%	LIVER	2016-01-02	60

- Postmortem data collected on two days and averaged in Study Report
- This is an example of when VISITDY or SENDIG 3.1 OMNOMDY is very helpful – otherwise we have to write complicated code

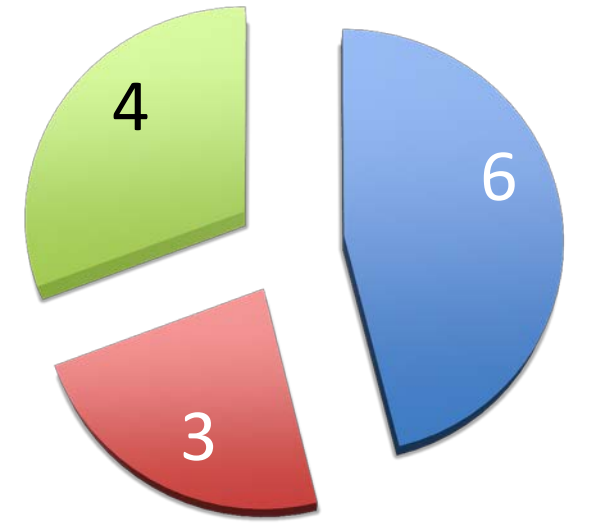
Two days at end of study

Non-Findings in Qualitative Datasets



Examples: "Refer to comment", "6 hours post dose"", "scheduled euthanasia", "Dose site tattoo"

Clinical Observations (CL)



- SENDIG allows multiple implementations
- Three had mixtures of implementations within the dataset, one study with a confusing choice of CLCAT
- CLSTRESC was less detailed than the Study Report in three studies

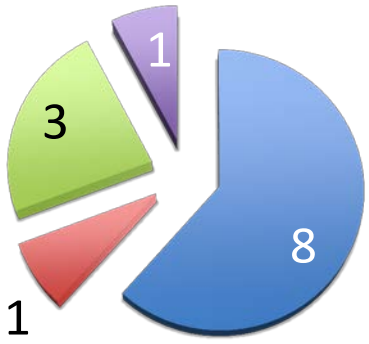
Too Little in STRESC

CLTESTCD	CLTEST	CLCAT	CLSCAT	CLORRES	CLSTRESC	CLLOC
GEN	General	PHYSICAL EXAM	Veterinary Clinical Observations	body temperature, body temperature, 102	body temperature	
GEN	General	PHYSICAL EXAM	Veterinary Clinical Observations	body temperature, body temperature, 103	body temperature	
SK	Skin	CLINICAL SIGNS	Clinical Observations	abnormal color, muzzle, red	abnormal color	muzzle
SE	Secretion/ Excretion	CLINICAL SIGNS	Clinical Observations	feces, unformed	feces	
SE	Secretion/ Excretion	CLINICAL SIGNS	Clinical Observations	feces, watery	feces	

- Important information is not captured in CLSTRESC
- Study Report finding was “elevated body temperature” and “feces, unformed”
- Prefer not to refer reviewers to CLORRES, cannot program on it

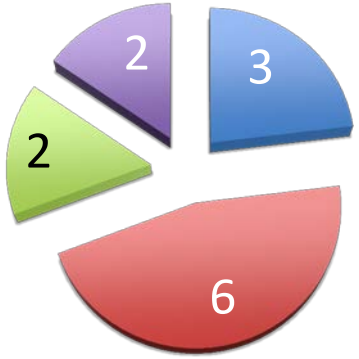
Histopathology (MI)

Main MI Dataset



- Good Traceability
- STRESC contained modifiers
- Severity mismatch to Study Report
- Mismatch in SPECIMEN CT

SUPPMI Dataset



- SUPPMI has easy Traceability
- Severities in SUPPMI
- Other reundant data in SUPPMI
- Missing SUPPMI when needed

CT to Study Report Mismatch

Study Report

Finding A	Control	20 mg/kg
Minimal	1	2
Slight	0	3
Mild	0	5

SEND Representation

Finding A	Control	20 mg/kg
MINIMAL	1	2
MILD	0	3
MODERATE	0	5

- Translation of severity to standard terminology in SEND submission does not agree with Study Report
- The level of severity in the SEND submission is of higher toxicological concern to reviewers

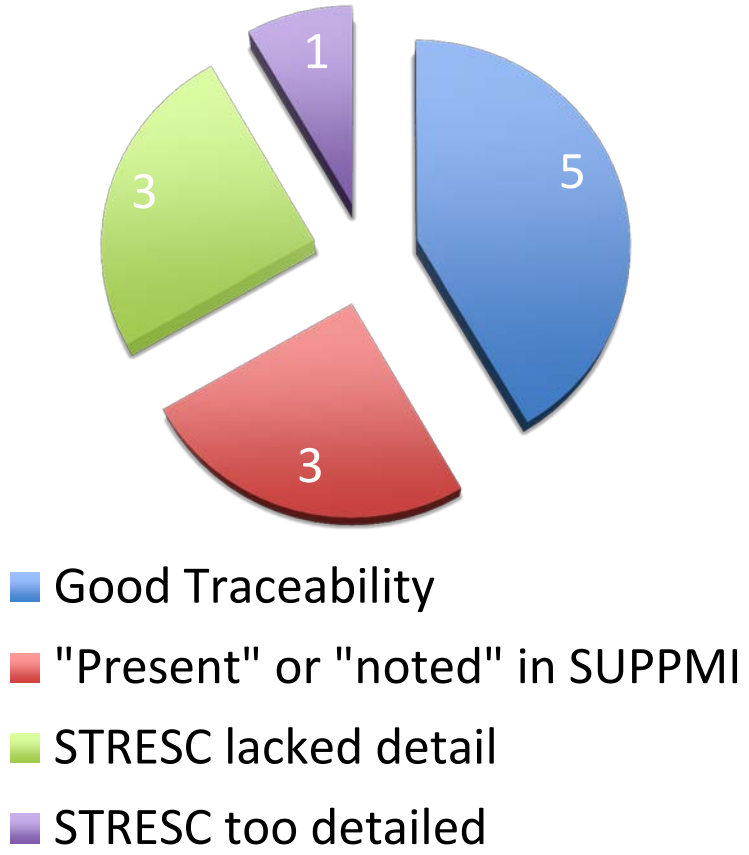
Histopathology (MI)

- SENDIG 3.1 will contribute to traceability of MI
  - Addition of Controlled Terminology
  - Modifiers are included in the main findings domain
  - Fewer submissions will require SUPPMI

- SEND 3.0 implementation wish list:
  - Match of MISTRESC to groupings in the Study Report
  - Match of MISPEC to the Study Report
  - Less redundant information in SUPPMI so it is easier to focus on relevant information

Gross Pathology (MA)

- SENDIG seems to lack sufficient explanation of how to standardize STRESC
- Best traceability when grouping by STRESC matches the Study Report
- Redundant “Present” in SUPPMI makes real modifiers hard to extract

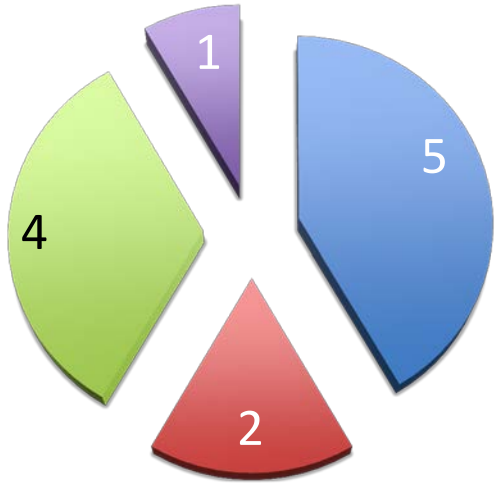


Too little in STRESC

MAORRES	MASTRESC	MASPEC	MODIFIERS
LUNG : Area; apical lobe; pale : right	Area	LUNG	APICAL LOBE; PALE : RIGHT
SKIN : Area; abdomen; ventral; dark : 40mm x 10mm	Area	SKIN	ABDOMEN; VENTRAL; DARK : 40MM X 10 MM
PANCREAS : Discolouration; pale	Discolouration	PANCREAS	PALE
LYMPH NODE : Discolouration; dark : thymic	Discolouration	LYMPH NODE	DARK : THYMIC

- "Area" is not detailed enough to be useful
- Discoloration is more meaningful, but still need the color to interpret
- SUPPMA modifiers are not standardized at all (per SENDIG) and often have too much information to extract details like colors

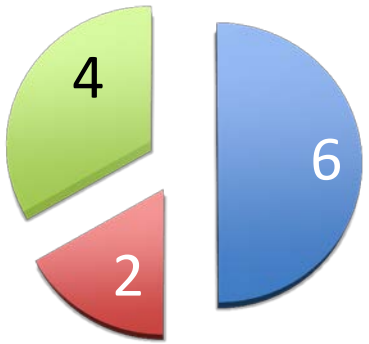
Pharmacokinetics Concentrations (PC)



- Determining related points is difficult unless VISITDY is used for grouping
- PCTPTNUM often not related to timings, ELTM often has nulls or is missing
- Below LLOQ records without STRESU require risky programming assumptions to determine sample sizes

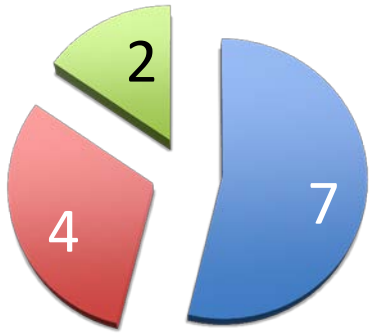
Intended PC timing variables

PCELTM



- All values provided
- Contains nulls
- Absent from dataset

PCTPTREF



- Allows Grouping
- "Most Recent Dose"
- Errors

Only two datasets of twelve had PCELTM/PCTPTREF implementations that fully supported automatic extraction of timings

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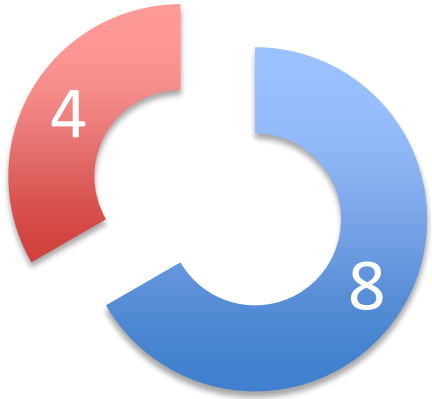
Nonclinical SDRG

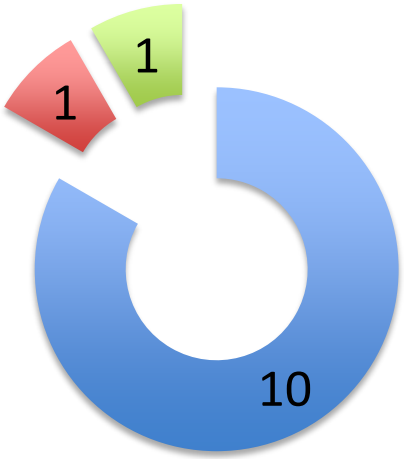
Was the NSDRG useful?



- In general, NSDRG content was very useful
- Most of the comments focused on the clarity and content of the study design section – it is very useful for quickly becoming familiar with a study

Level of information

Was there too much information?



- Not too much information
- Long list of unused CT extensions
- Unnecessary Study Report errors list

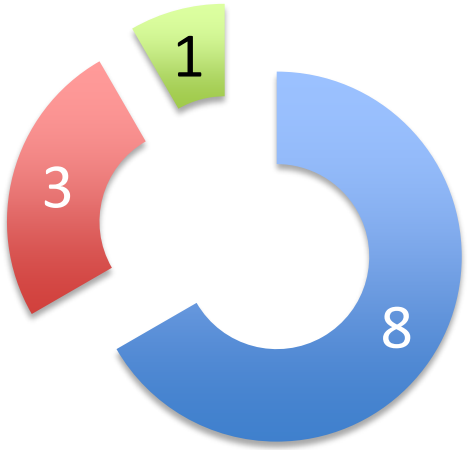
Was there too little information?

- Enough information
- Needed explanation of inconsistencies between the SEND data and study report
- No explanation for missing information or location of data
- Missing trial group explanation

Specific NSDRG Sections

How was the Study Report vs. Dataset Section?

How was the Validation Outcomes Section?



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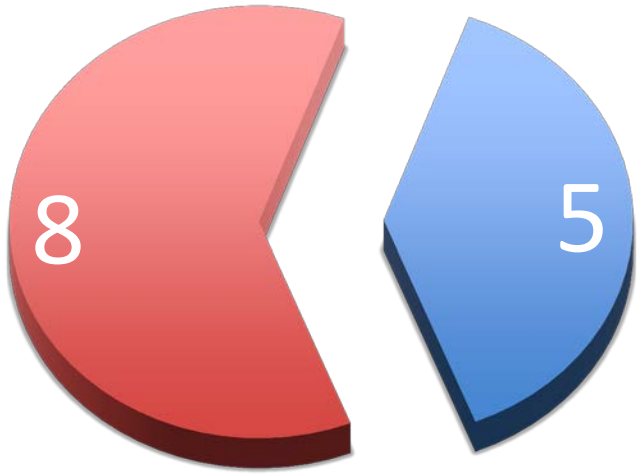
define.xml Loading Success



- We found OCS tools are “picky” about a few things in define.xml
- Loading a lot of the define.xml files required manually fixing minor issues
- OCS has taken the information from the pilot and improved our loading routines

Define.xml issues fixed

Error	Resolution
“SPECIAL-PURPOSE” or “Special-Purpose”	Corrected to follow GENRLOBSC or Define 1.0 standard by removing hyphen
Define.xml not named define.xml	Renamed file
Linked stylesheet missing	Supplied CDISC style sheet
Empty length attributes	Impute lengths from .xpt files
.xpt links have case mismatch	Matched links and .xpt file names
CLTPT with multiple ItemDef elements	Removed one
Missing ItemGroupDef purpose attribute	This can be imputed on core domains but not custom domains

Define.xml in general

- *OCS does not define agency requirements for data quality of define.xml*
- Certain errors like empty length attributes or a missing style sheet can be fixed with no impact on the traceability of the submission
- Big mismatches between define.xml and the SEND dataset can indicate errors in data preparation
- What do we do with define.xml? We load and warehouse study metadata, particularly CT versions and extensions

Participants

AbbVie
Bristol-Meyers Squibb
Celgene
Eisai
Genentech
GlaxoSmithKline
Janssen
Eli Lilly
Merck & Co.
MPI Research
Novartis
Pfizer
Sanofi

Thank you for participating!

FDA/CDER

Office of Computational Sciences
Office of Generic Drugs
Office of New Drugs
- OND Immediate Office
- Division of Anesthesia, Analgesia & Addiction Products
- Division of Psychiatry Products
- Division of Metabolism & Endocrinology Products
- Division of Pulmonary, Allergy & Rheumatology Products