

CDISC-SEND COMMON ISSUES AND CDER POLICY UPDATES

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PART I: COMMON ISSUES WITH CDISC-SEND DATA

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Today's Topics



SEND at the FDA



Common SEND Data Fitness Issues



FDA Communication on SEND

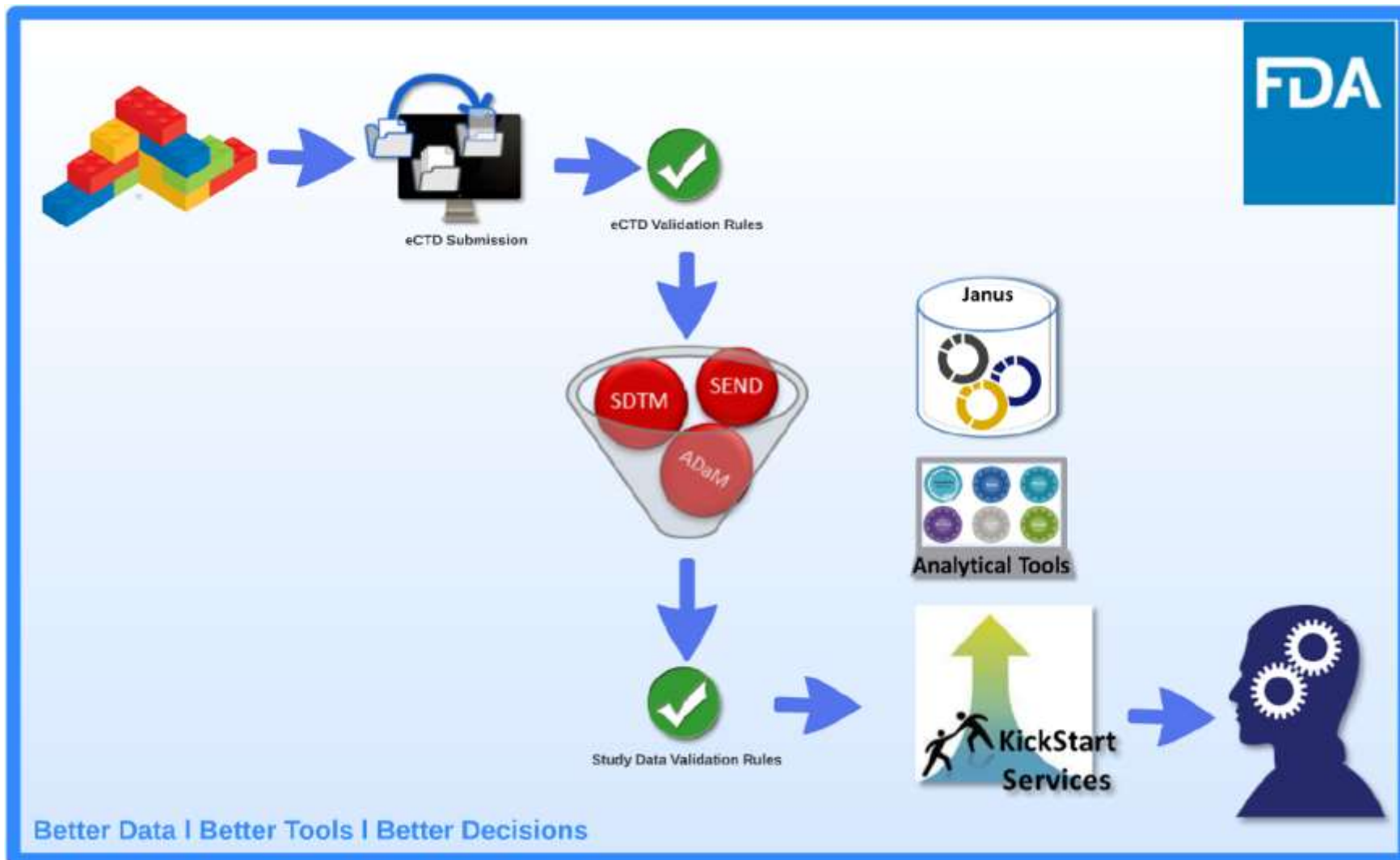
It All Starts with SEND



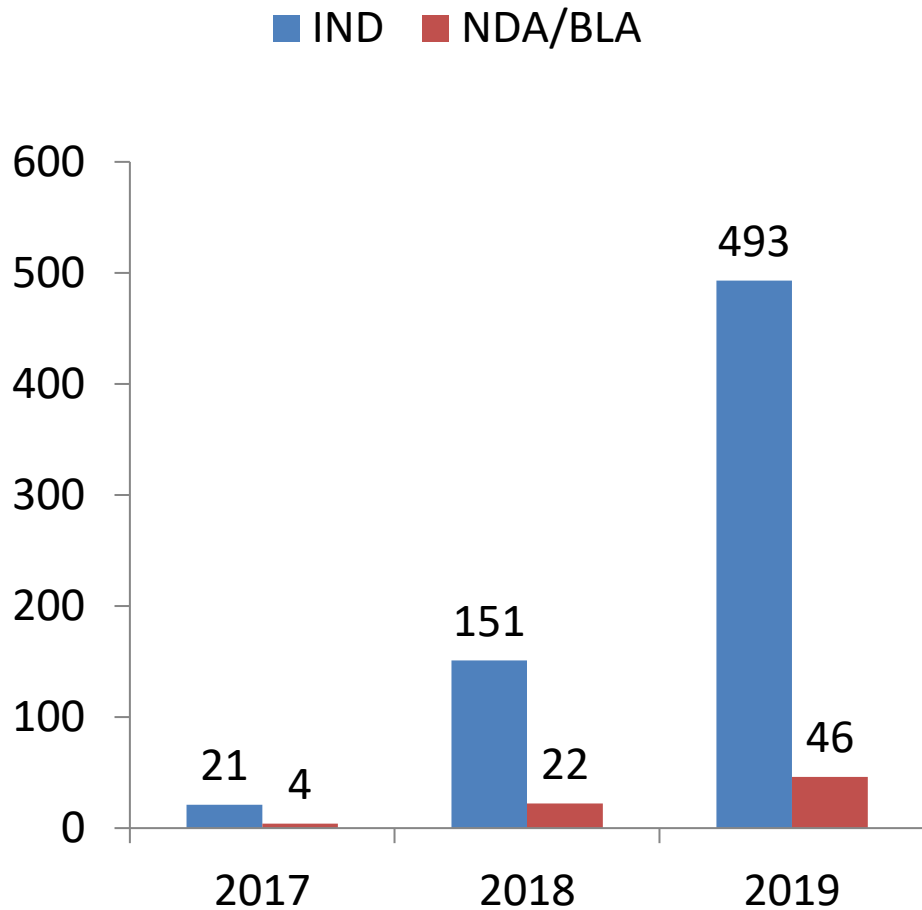
Key Concepts

1. Carcinogenicity, single-dose and repeat-dose toxicity, and cardiovascular and respiratory safety pharmacology currently covered by SENDIGv3.0 and SENDIGv3.1 in the FDA Data Standards Catalog.
2. SEND should present nonclinical data in a consistent and predictable manner.
3. SEND allows exploration of study data and automated creation of tables and graphs.
4. Use of SEND electronic data is a process change for the reviewer community within a short timeline for many submissions.
5. OCS KickStart service and resources support reviewer use of SEND electronic data.

Nonclinical Regulatory Review



Applications Received with SEND



Number of Applications Per Calendar Year

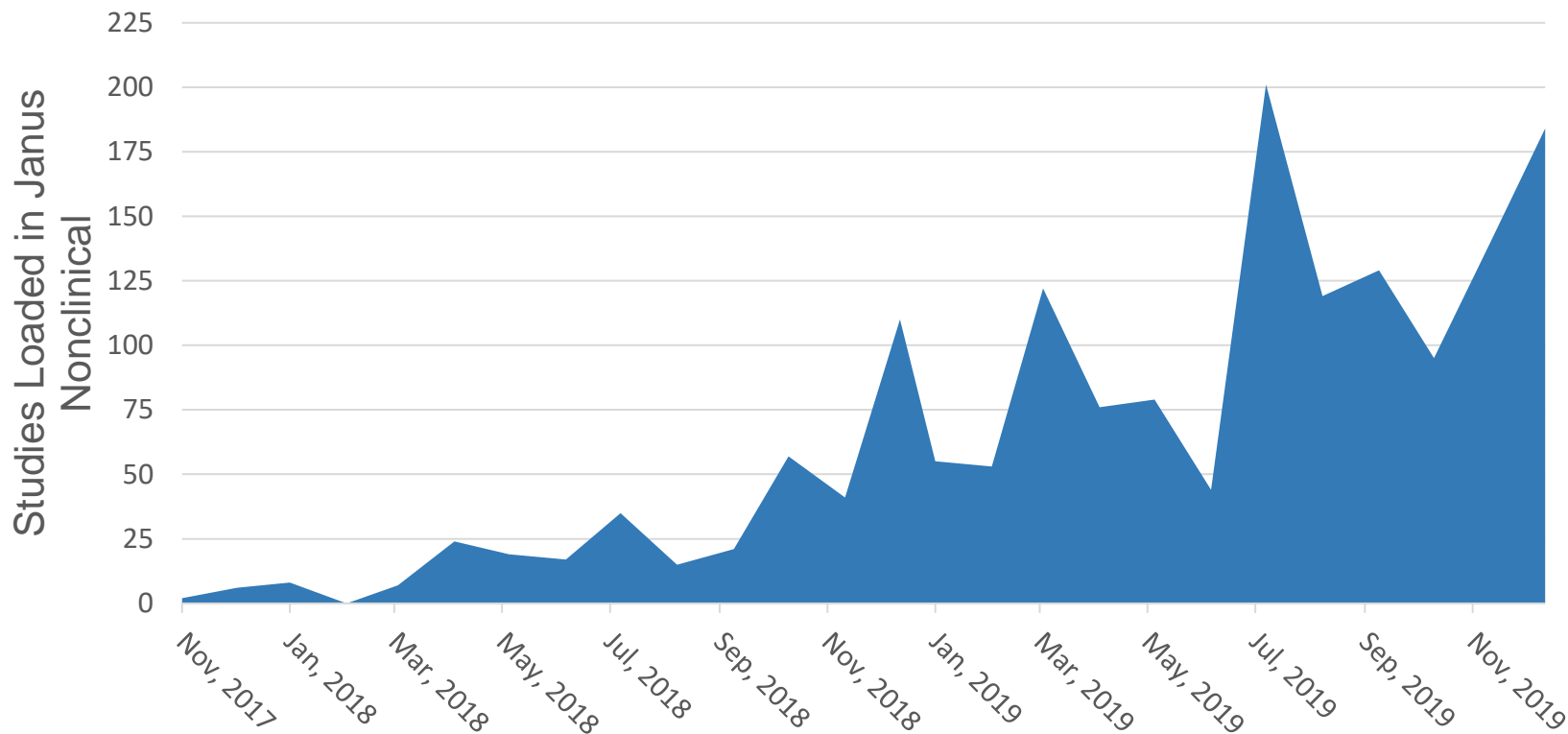
The types of studies included Repeat-Dose Toxicity, Single-Dose Toxicity, and Carcinogenicity. FDA has received 735 applications with SEND data during this time period.





Key Concepts

1. Janus Nonclinical is a database and system that allows reviewers to use SEND datasets for their reviews
2. Every SEND study received in an application goes through Janus loading process automatically
3. More than 1,740 studies loaded as of Dec. 2019
4. Reviewers may request a Kickstart Service to help them with their application in Janus Nonclinical consisting of:
 - One-on-one training
 - Data Fitness Analysis
 - Help with study data exploration and analysis
5. Reviewers may also receive support from the Office of Computational Science (OCS) Service Desk

SEND Studies in Janus Nonclinical



	2017	2018	2019	Total in Janus
 Studies Loaded	33	354	1359	= 1740+
 Applications Loaded	25	173	539	= 735+

The KickStart Service

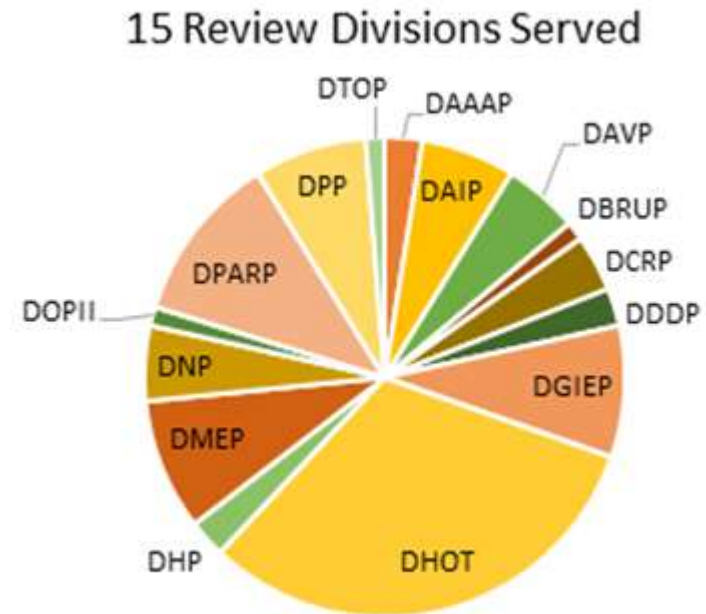
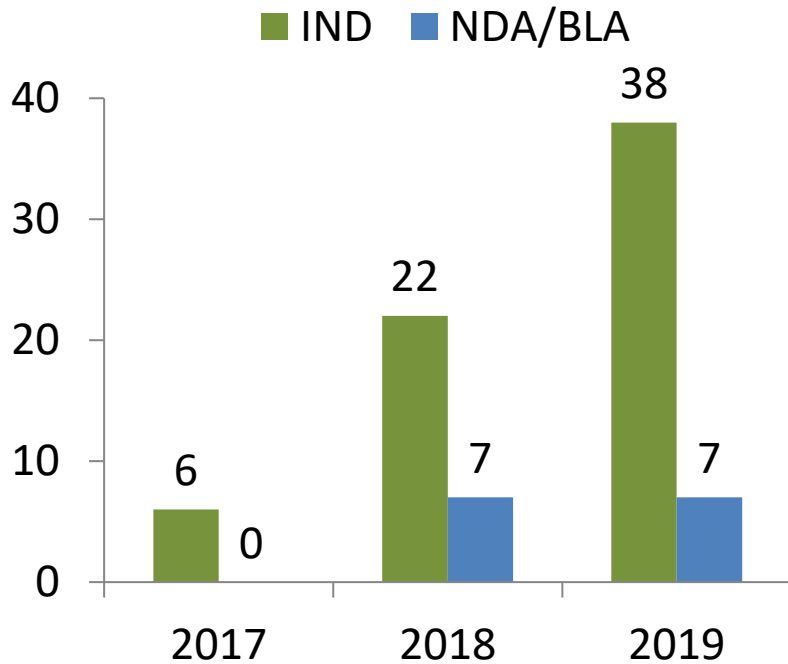


Key Concepts

1. KickStart is offered by OCS to all Pharm/Tox reviewers for their applications.
2. Pre-KickStart Training includes overviews of:
 - The SEND Standard
 - Nonclinical Study Data Reviewers Guide (nSDRG)
 - Define.xml
 - Janus Nonclinical features
3. The KickStart Service covers:
 - A data fitness assessment with sponsor report and details to reviewer for issues that impact use of data
 - Shows reviewers how to explore study data using Janus Nonclinical and how to produce tables and graphs that can be used in review documents
 - Prepare graphs and tables for key analyses using Janus Nonclinical

KickStart Services for Nonclinical Review

Applications Through End of December 2019



Calendar Year Counts

Kickstart service provided when:

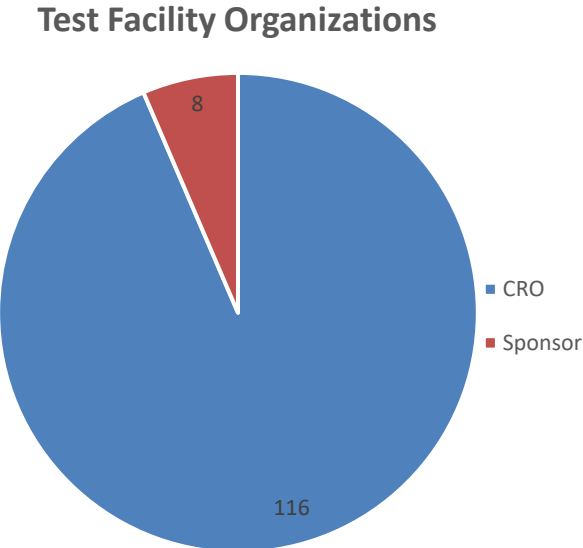
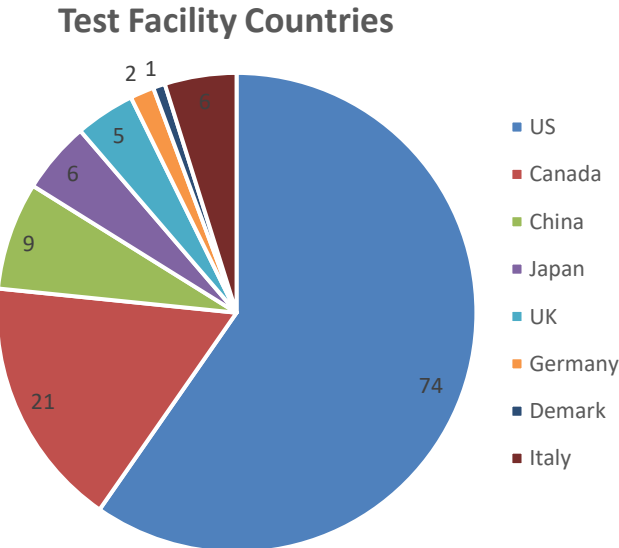
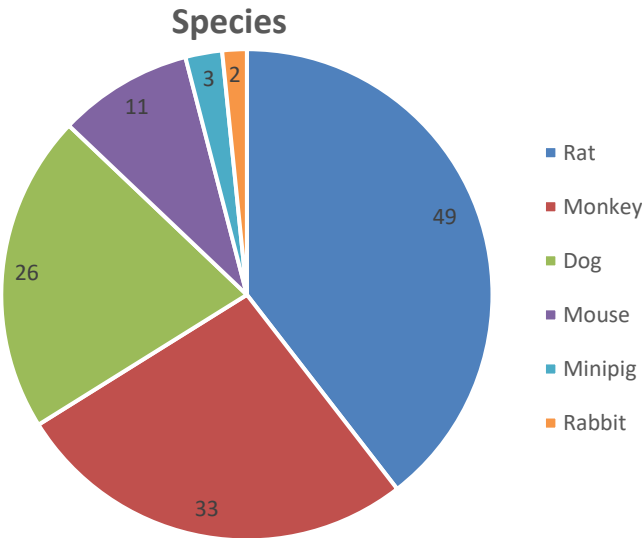
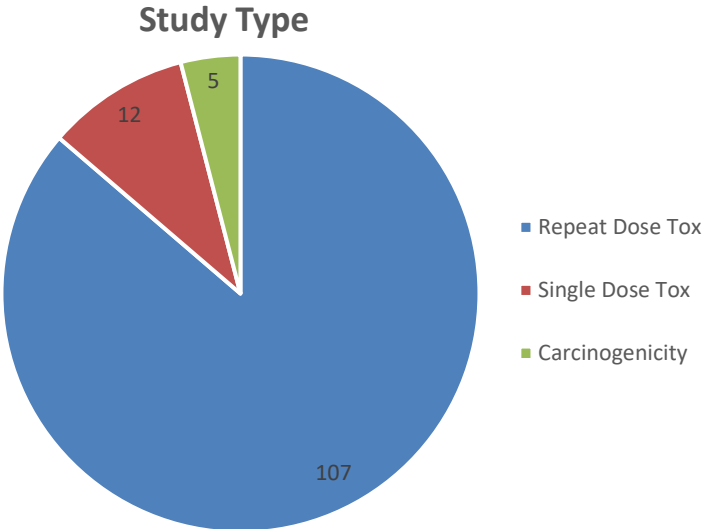
- Study loaded into Janus Nonclinical
- Reviewer requests service

One or two studies per application generally reviewed

Studies Included in KickStart Applications



Through End of December 2019



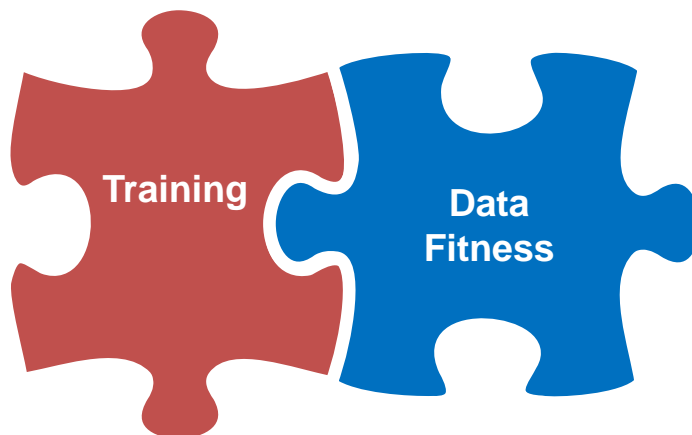
Pre-KickStart Training

- For first KickStart service, the KickStart team provides reviewers with general training on the SEND topics, including:
 - Domains
 - Controlled Terminology
 - Overview of the nSDRG
 - Introduction to the define file
 - Introduction to Janus Nonclinical



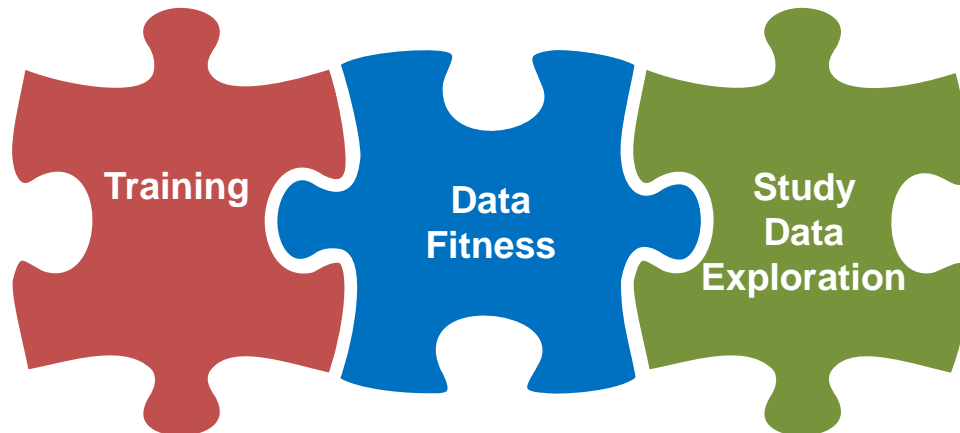
KickStart Data Fitness Assessment

- Automated and manual review of SEND datasets and associated nSDRG and define.xml files
 - Verify compliance with standards and FDA rules/recommendations
 - Confirm and document data not submitted
 - Check consistency across study files and documents
 - Ensure summarizations included in study report can be reproduced
- Issues that affect data analysis are discussed with reviewer
- Sponsor data fitness report details all issues identified

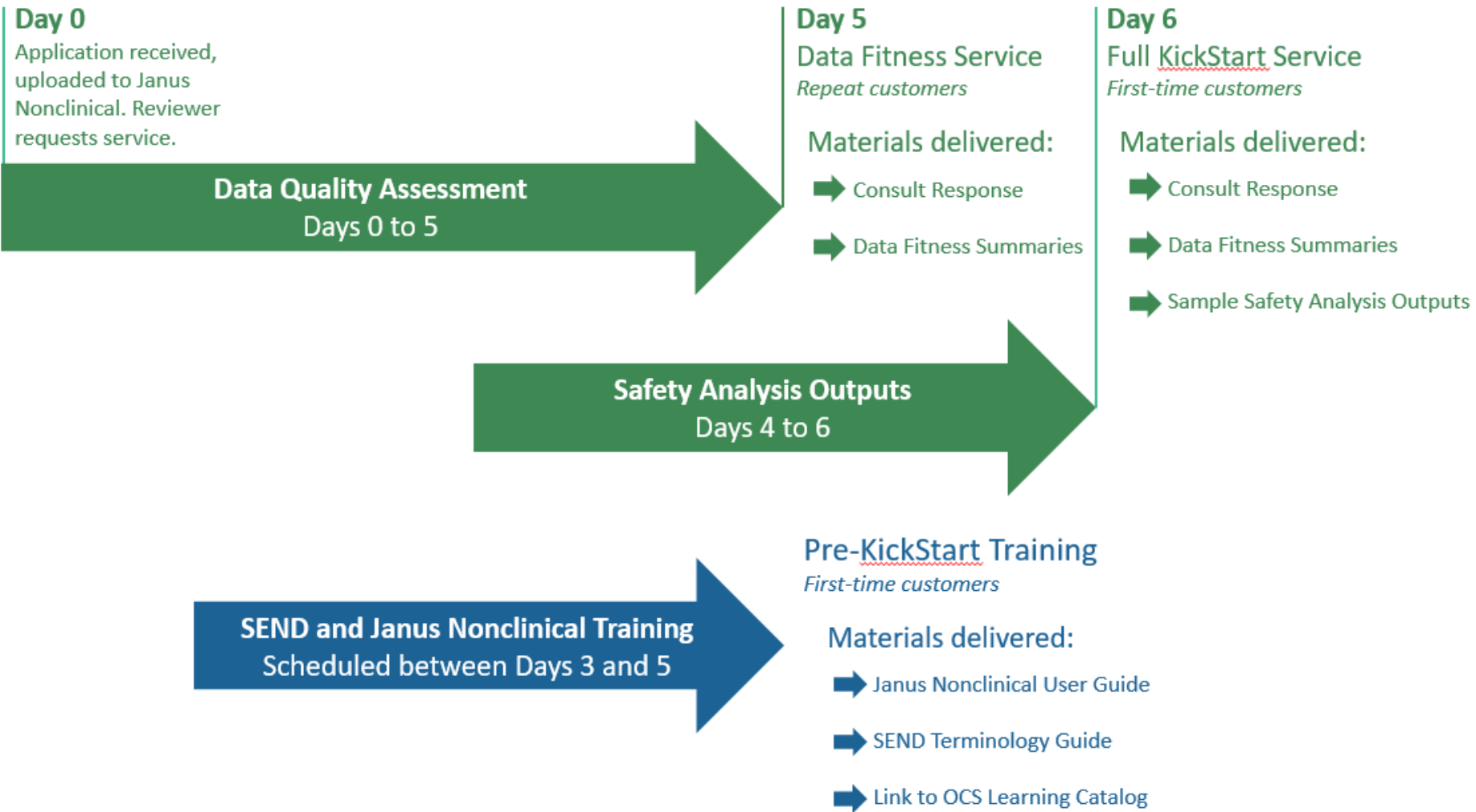


KickStart Data Exploration Session

- Interactive look at the best way to interact with application study data using Janus Nonclinical
- Show tables and graphs from key domains with findings aligned with study report when possible
- Provide outputs may be used as part of application review documents



KickStart Timeline Overview



SEND Study Package Issues for Discussion

Define.xml

- Submission Files, File Naming, StudyName Attribute

ISO8601 Values

- Dates, Date/Times, Durations

Standardization of Timing Variables

- VISITDY/--NOMDY, timing relative to dose, unscheduled tests

Categorical Results

- LBSTRESN and the FDA Study Data Technical Conformance Guide

Replacement Values for Results Outside Limit of Quantitation

- Submission of --CALCN

Codes and Abbreviations

- Impact on reviewers when these are undefined

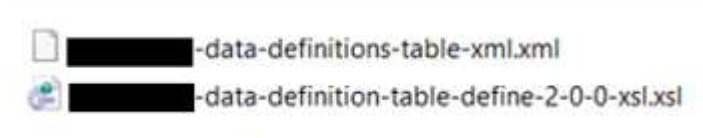
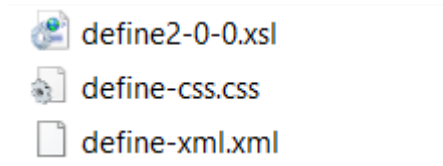
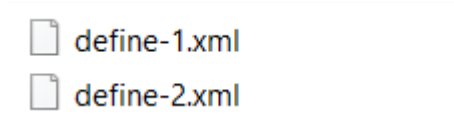
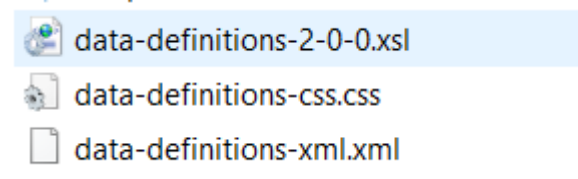
File Naming – define.xml

- Use “define.xml”
- Required stylesheet name is included in the define.xml file:

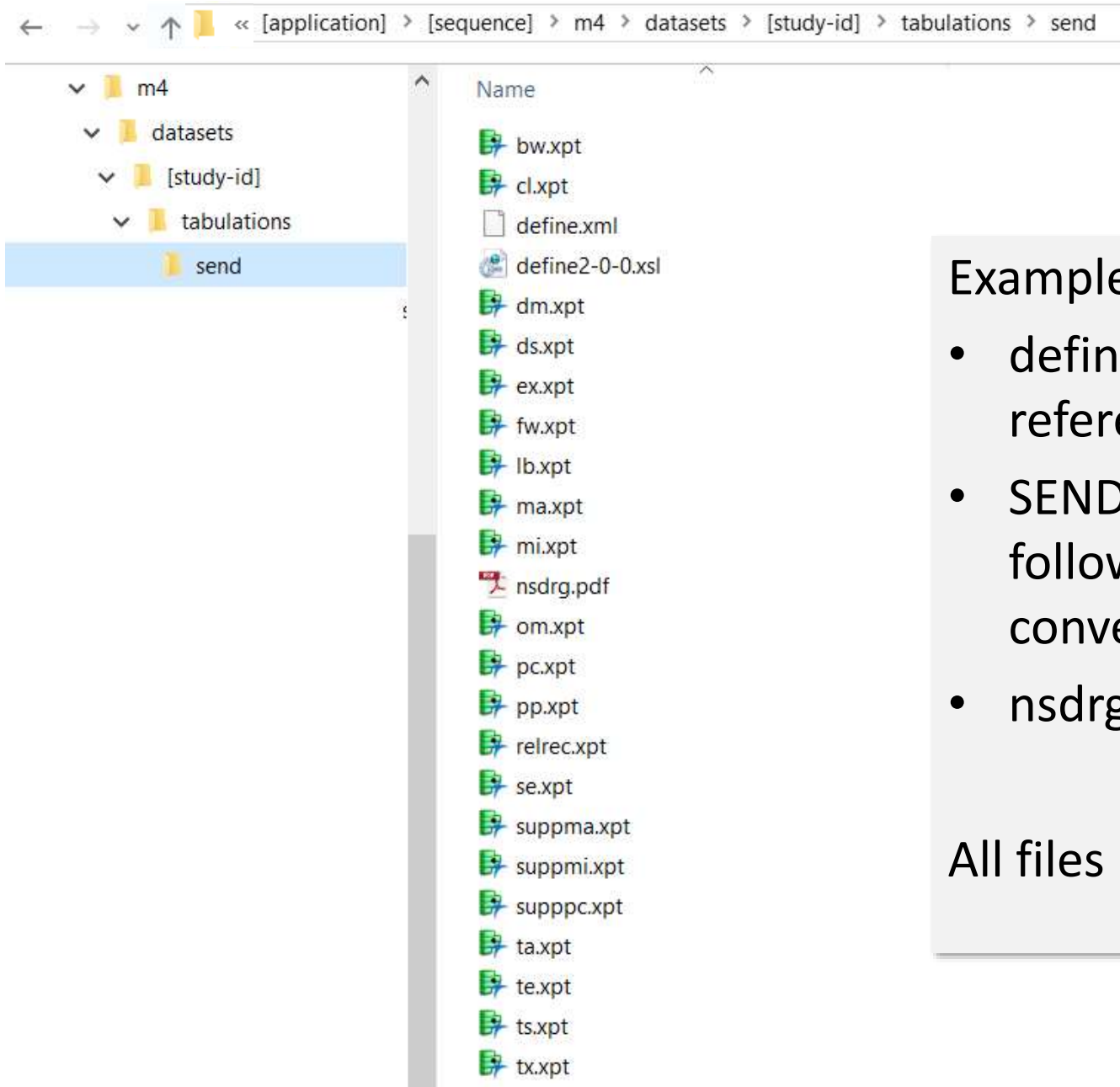
```
xml-stylesheet type="text/xsl"
href="define2-0-0.xsl"
```

- Some older stylesheets also reference define.css
- Submit the files in the study tabulation/send folder with the datasets

Some incorrect naming seen....



define.xml enables loading of data into Janus Nonclinical



Example SEND Package

- define.xml and referenced stylesheet
- SEND dataset files follow naming convention in SENDIG
- nsdrg.pdf

All files in the same folder

Define.xml StudyName

Study Data Technical Conformance Guide

4.1.3.2 General Considerations

For nonclinical studies, the define.xml StudyName element value must contain the sponsor's study identifier, consistent with the study identifier used in the eCTD folder structure under Module 4; refer to Section 7.1 for additional information about the Module 4 folder structure.

StudyName at FDA

- In 44% of studies reviewed by Kickstart in calendar 2019, StudyName does not conform to the Technical Conformance Guide
- StudyName identifies the study in the SEND files to Janus Nonclinical
- StudyName, when aligned with the eCTD submission study identifier, gives a reviewer a consistent identifier for the study
- StudyName may need to be updated by sponsor prior to submission

ISO 8601 Values

- ISO 8601 format in SEND
 - Dates and/or Times
 - Intervals and Durations of Time
- Certain domain variables use ISO 8601 format
- Some TS/TX Parameters use ISO 8601 format for –VAL
- SENDIG indicates when ISO 8601 format is used

Include only ISO 8601 formatted text when the SENDIG indicates that this format is used and no other formats.

Common Data Fitness Issues



Analysis of Kickstart Data Fitness Results for 68 studies in 45 applications in calendar 2019 identified a number of key themes:

- Incorrect reporting of timing variables needed for summarization and analysis of results
- Incorrect reporting of categorical data
- Omission of the numeric value to use in calculations as a replacement for a text result
- Undefined codes/abbreviations included in datasets

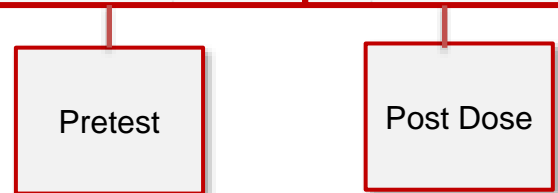
Common Issues with Standardization of Timing Variables

- Planned/nominal day does not align data with the study report summary
- Incorrect reporting of timing for tests or observations scheduled relative to dose
- Incorrect reporting of result from unscheduled tests or observations.

VISITDY/--NOMDY Used for Analysis

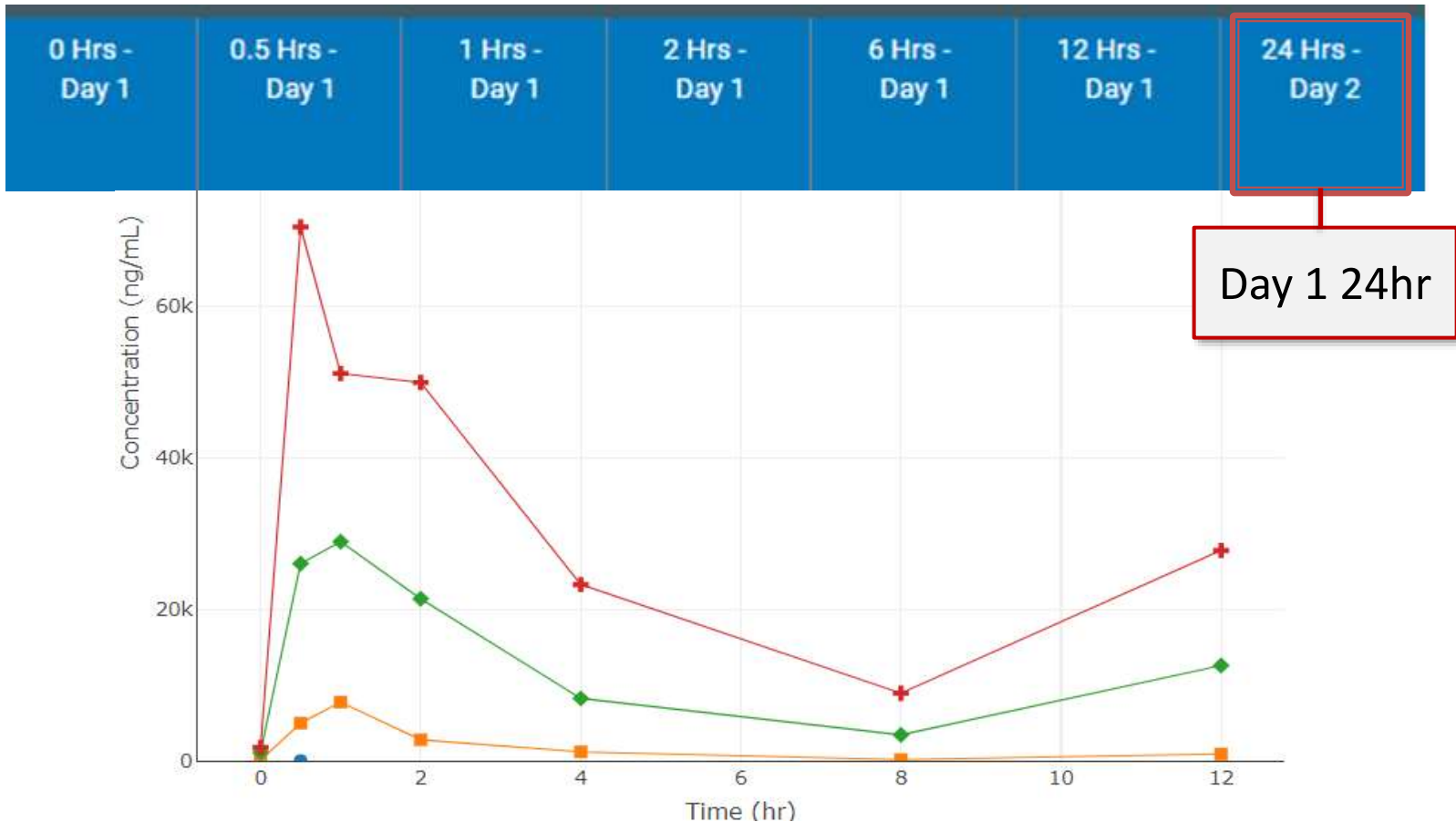
Example: Study Schedule indicates each animal has two sample collections: One pretest and one at the conclusion of dosing. Sponsor reported actual collection day in VISITDY. Reviewer must adjust days prior to use of data in summary analyses.

GROUPED-SUMMARY : NUMERIC			GROUPED SUMMARY : NON-NUMERIC			DAILY BY ANIMAL		ANIMAL DETAILS	
Group	S...	Test	Animal ID	Unit of the Standa... Result	Day -13	Day -12	Day -11	Day 178	Day 179
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	1	U/L			21		17
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	2	U/L		34		26	
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	3	U/L	47			30	
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	4	U/L	23			30	
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	5	U/L			29		30
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	6	U/L			25		27
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	7	U/L		32			21
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	8	U/L	21			22	
<input type="checkbox"/> 1-Control ...	Male	Alanine Aminotransferase	9	U/L	18			14	



VISITDY/--NOMDY and –ELTM Use for Analysis

Example: Sponsor reported sample collection day in VISITDY when samples collected at times relative to dose. Tabular data is therefore mislabeled; graphs of results relative to dose do not include data for timepoints > 24 hrs post dose



Timing Relative to Dose

- Elapsed Time --ELTM
 - uses ISO8601 duration format
 - describes amount of time relative to the dose event
- Time Point Reference --TPTREF
 - Description of the dose event that the elapsed time --ELTM is relative to
 - Consider the dosing regimen for the study in --TPTREF
 - For timed infusion, inhalation, or other dosing over time, include whether elapsed time is relative to start or end of the dose
 - For multiple doses per day, include which dose the elapsed time is relative to

From the SENDIG: It is recommended that --TPTREF be as descriptive as possible so the reference time point can be inferred without looking at other variables.

Timing Relative to Dose

Example: 1 hr infusion, twice per day.

Sample collection 2 hrs after start of 1st infusion day 1 and 2 hrs after start of 2nd infusion day 28.

Use --ELTM=PT2H to represent 2 hours post dose

Common issue: --TPTREF is not specific to the specific dose during the day or to the start/end of the dose .

For example if --TPTREF is “Day 1 Dose” and “Day 28 dose”

--ELTM and --TPTREF together would not match the study report:

“2 hours after Day 1 Dose” and “2 hours after Day 28 Dose”

Be specific in --TPTREF: “Start of 1st Day 1 Dose” and “Start of 2nd Day 28 Dose”

From the SENDIG: It is recommended that --TPTREF be as descriptive as possible so the reference time point can be inferred without looking at other variables.

Unscheduled Tests/Observations

- Results from unscheduled tests or observations are generally tabulated separately in the study report tables.
- In SEND, for an unscheduled test result or observation:
 - SENDIG 3.0, VISITDY with no value identifies an unscheduled result
 - In SENDIG 3.1, --USCHFL="Y" identifies an unscheduled result
- Correct flagging of unscheduled results in SEND allows reviewer to align results with study report.
 - Unscheduled data can be included/excluded
 - Using only text variables to label unscheduled results is not sufficient

VISITDY	LBDC	LDY	LBPT	LBPTNUM
15	2018-01-23	15	Unsch Vet Request	6
22	2018-01-30	22		•
22	2018-01-30	22		•
22	2018-01-30	22		•



Data Fitness Issues with Reporting of Categorical Test Results

- Seen in the Laboratory Test Results (LB) dataset
- Issue with including LBSTRESN for categorical results
 - Refer to the FDA Technical Conformance Guide, section 4.1.3.3
 - SEND has no specific flag for categorical results
 - Define-xml value-level metadata inconsistently reported
 - Janus attempts to identify non-numeric tests using LBSTRESN

Example Incidence Counts for LB in Janus



GROUPED SUMMARY : NUMERIC		GROUPED SUMMARY : NON-NUMERIC		DAILY BY ANIMAL		ANIMAL DETAILS				
Filter table data by term...										
Category	Test	Day	Value	Female						
				Control [Terminal,Recove...	Low [Terminal,Recove...	Mid [Terminal,Recove...	High [Terminal,Recove...			
URINALYSIS	Protein	29	N	19	19	19	20			
URINALYSIS	Protein	29	0.3 (g/L)	7	4	4				
URINALYSIS	Protein	29	1 (g/L)		1					
URINALYSIS	Protein	29	Negative	4	2	4	14			
URINALYSIS	Protein	29	Trace	8	12	11	6			
URINALYSIS	Protein	43	N	10	10	9	10			
URINALYSIS	Protein	43	0.3 (g/L)		2	3	2			
URINALYSIS	Protein	43	1 (g/L)							
URINALYSIS	Protein	43	Negative	3	1	4	2			
URINALYSIS	Protein	43	Trace	7	7	2	6			

Tests with no LBSTRESN reported with summary incidence counts in Janus Nonclinical

Example of Incorrect Standardization



Day	Category	Test	Unit of the Standard Result		Male			
					Group 1,0mg/kg/d... [Terminal,R...	Group 4,600-400mg/kg/- [Terminal,R...	Group 2,60mg/kg/- - Terminal	Group 3,200mg/k... - Terminal
-8	URINALYSIS	Protein	g/L	Mean	0.000 (Text)	0.000 (Text)	0.000	0.000 (Text)
	URINALYSIS	Protein	g/L	Std Dev	±0.000 (Text)	±0.000 (Text)	±0.000	±0.000 (Text)

Animal ID	Day	Result	Result in Character
1001	-8	0.0	
1002	-8	0.0	
1003	-8	0.0	
1004	-8	0.3-0.7	
005	-8	0.0	
1006	-8	0.1-0.2	

Semi-quantitative urine protein test are in SEND with the result range in LBSTRESC and with values incorrectly in LBSTRESN. This causes Janus Nonclinical to report means and standard deviations on those numeric results rather than incidence counts.

Data Fitness Issues with Character Replacement Values

- Sponsor omitted character replacement values for use in PC or LB summary calculations in approximately half the studies reviewed:
 - Most commonly missing for plasma concentration results reported in the PC dataset.
 - Should be reported in SUPP-- dataset, with --CALCN in the QNAM variable and the replacement value in QVAL.
 - For example SUPPPC would have entries with PCCALCN.
- Use of group mean results supplied in study report is impaired when replacement values are not submitted.

Undefined Code/Abbreviations included in the Dataset



- Almost 50% of studies have codes/abbreviations in the SEND datasets in variables where they are not expected.
 - Frequently without a definition
 - For some studies, the nSDRG notes generally that abbreviations are defined in the study report.
- Codes and abbreviations have been seen as result values, in reason fields, as finding modifiers and in comments.
- Undefined unit abbreviations (not part of the published UNIT codelist) have also been submitted.

Examples of Undefined Code/Abbreviations



Test	Sign	Location of a Finding	Comments
Clinical Observation	scaly skin	dose site	D

Organ/Tissue	Test	Exclusion Flag	Reason for Exclusion
GLAND, THYROID/GLAND, PARATHYROID	Weight	Y	E

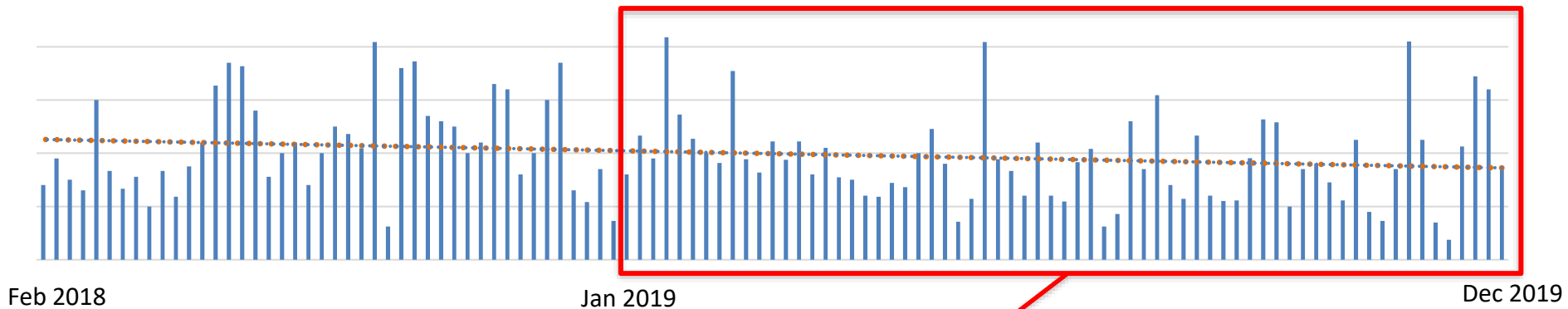
Category	Test Code	Test	Standardized Result in Character Format
URINALYSIS/URINE CHEMISTRY	COLOR	Color	CO

Category	Test Code	Test	Standardized Result in Character Format	Unit of the Standardized Result
URINALYSIS	CREATVOL	Creatinine Volume	115.4	umol/cp
URINALYSIS	GLUCVOL	Glucose Volume	9.5	umol/cp

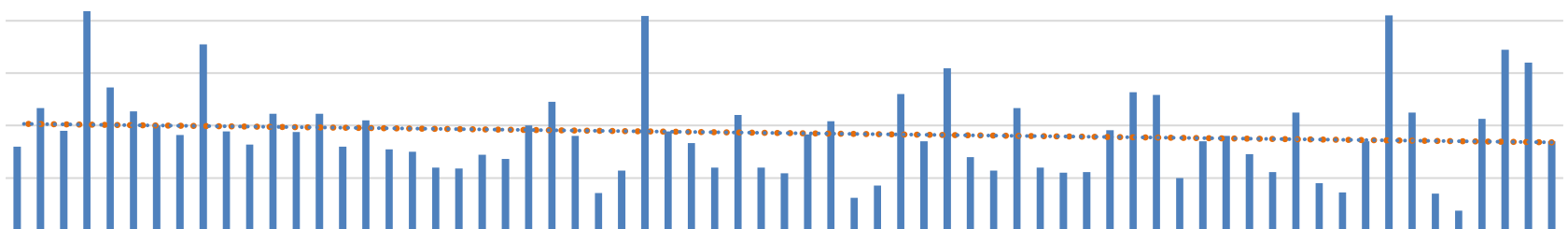
SEND Data Quality Assessment



Relative Number of Issues in SEND Datasets Per Study, Normalized, All Kickstart Studies



Relative Number of Issues in SEND Datasets Per Study, Calendar 2019 Only



Key Points



- FDA saw significant increase in number of studies containing SEND datasets in the past year
- FDA Pharm/Tox Reviewers transitioning to utilize SEND datasets alongside the study report
- Complete and correct SEND datasets are critical for seamless, confident use of SEND datasets by FDA reviewers
- Some common issues in a SEND dataset can complicate or even prevent FDA reviewers use of those SEND datasets
- The FDA KickStart team identifies issues in SEND data to communicate with industry, identify trends, and help reviewers maximize use of their SEND datasets



How We Communicate

1. Responses to questions sent to eData@fda.hhs.gov
2. Technical Conformance Guide Updates
3. FDA Business Rule Updates
4. Sponsor-Specific Study Data Fitness Reports
5. PhUSE Presentations, Papers, and Posters
 - PhUSE US Connect
 - PhUSE Computational Science Symposium (CSS)
6. CDISC Collaborations
 - CDISC-SEND Face-to-Face (F2F) Public Forums