CDER Small Business and Industry Assistance (SBIA)
WEBINAR SERIES

FDA

COMMON ISSUES IN CDISC-SEND DATA IN FDA TOXICOLOGY REVIEW

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Today's Topics

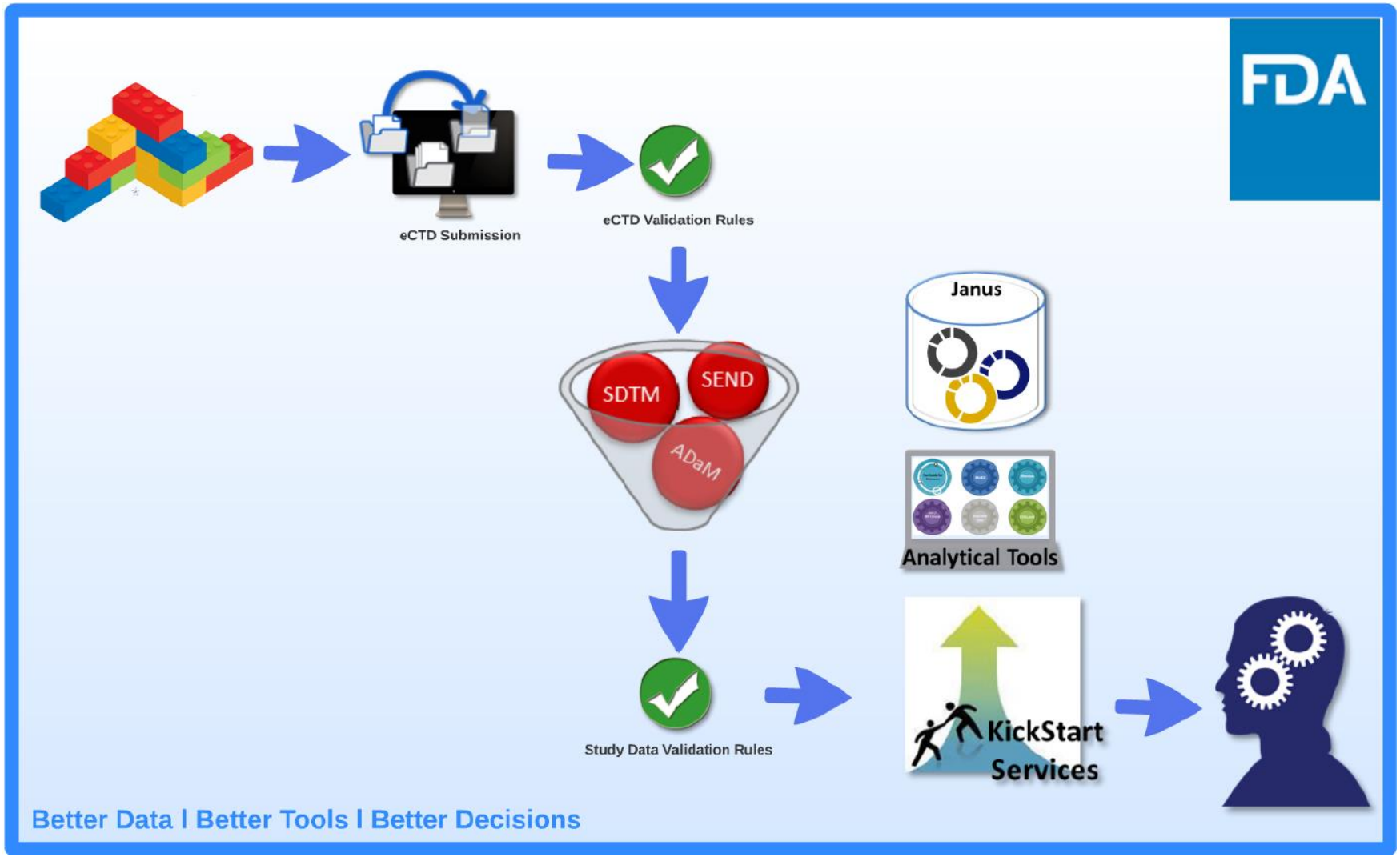
- SEND at the FDA
- Common SEND Data Fitness Issues
- FDA Communication on SEND

It All Starts with SEND

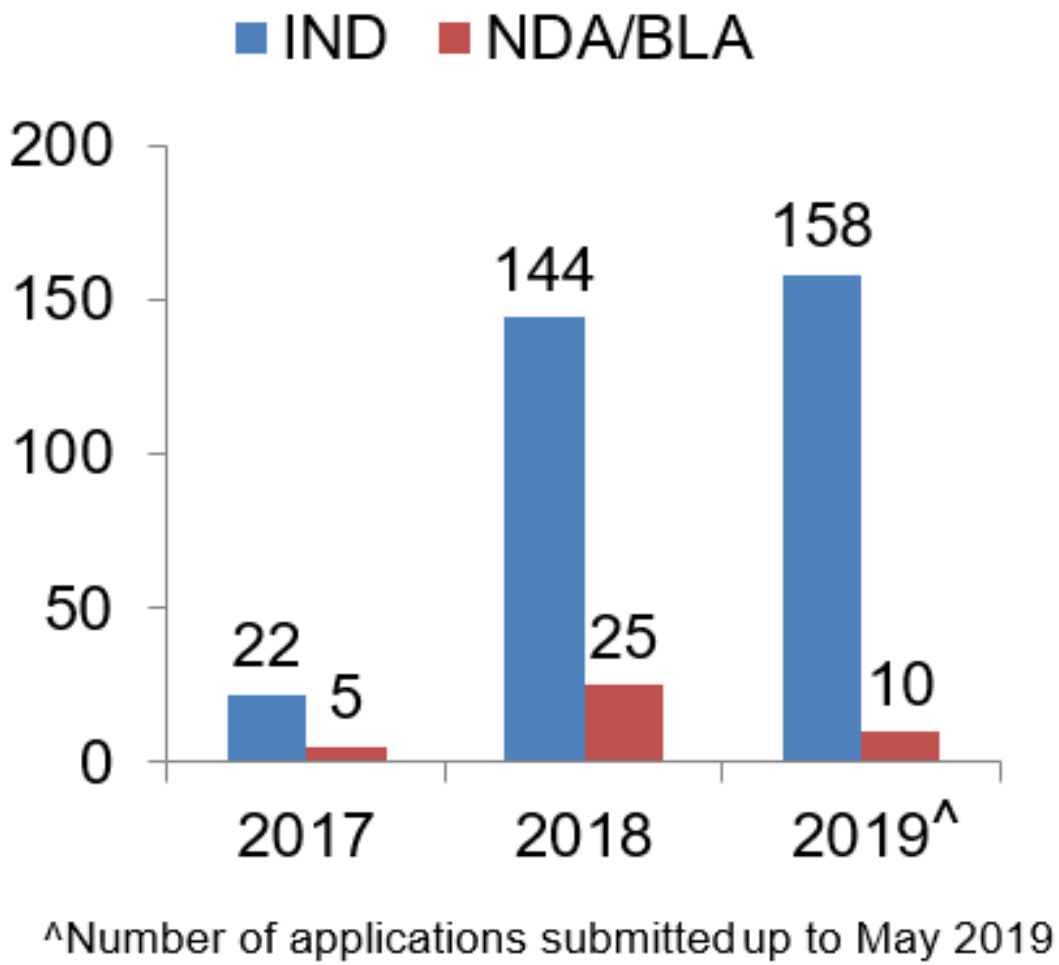
Key Concepts

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



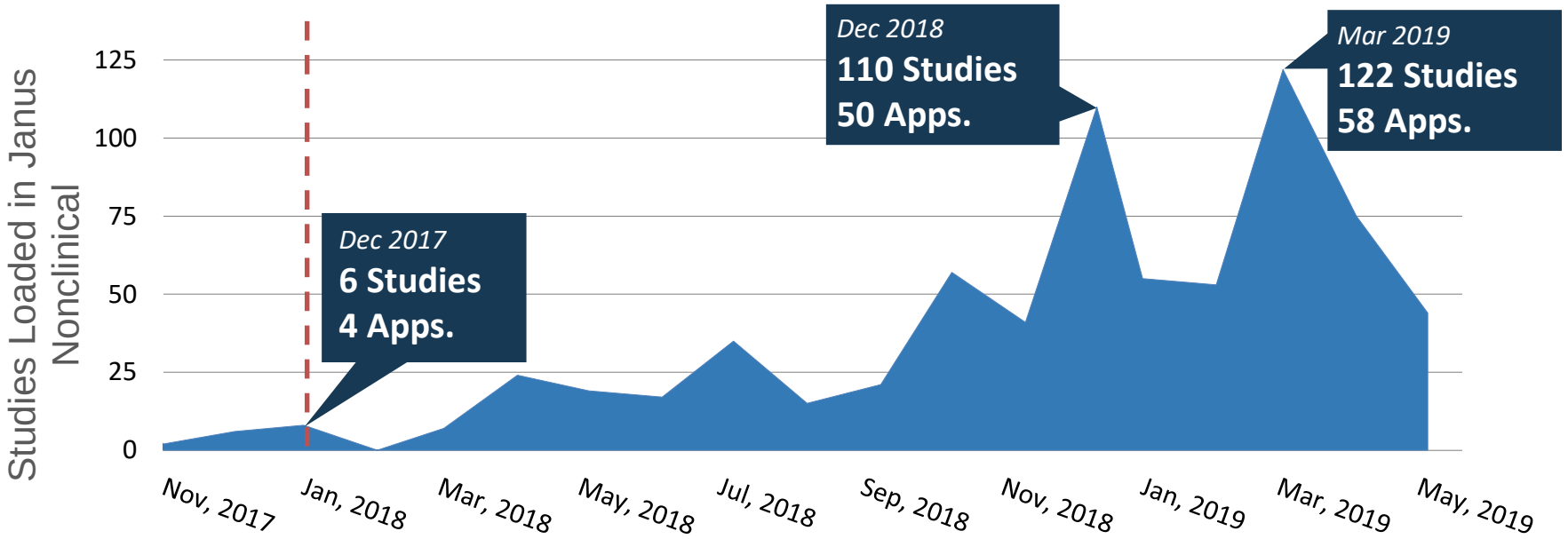
^Number of applications submitted up to May 2019

Janus Nonclinical

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 735 studies in Janus NC as of May 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 Study Data in Janus Nonclinical



	2017		2018		2019 (up to May)		Total in Janus
Studies Loaded	33	+	354	+	349	=	735+
Applications Loaded	25	+	173	+	167	=	365+

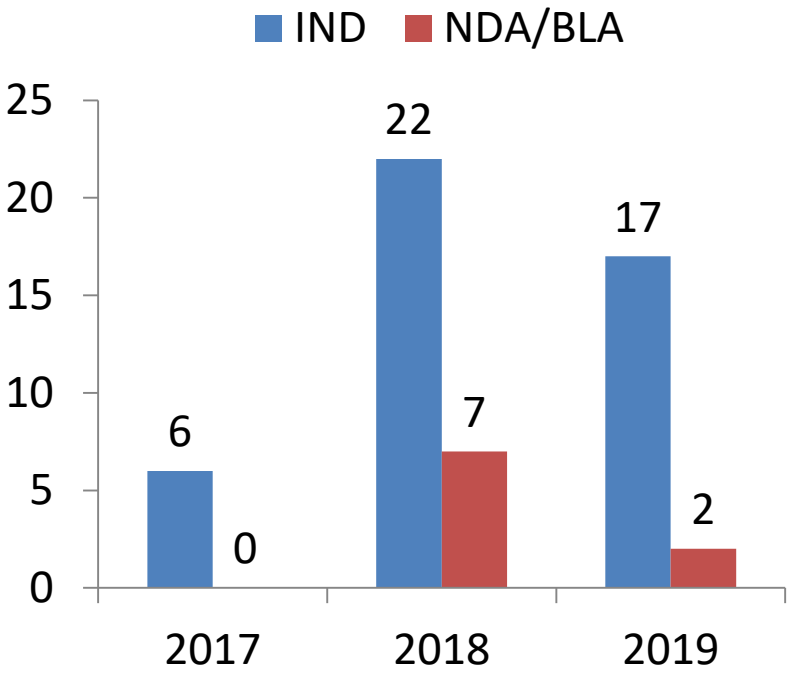
The KickStart Service

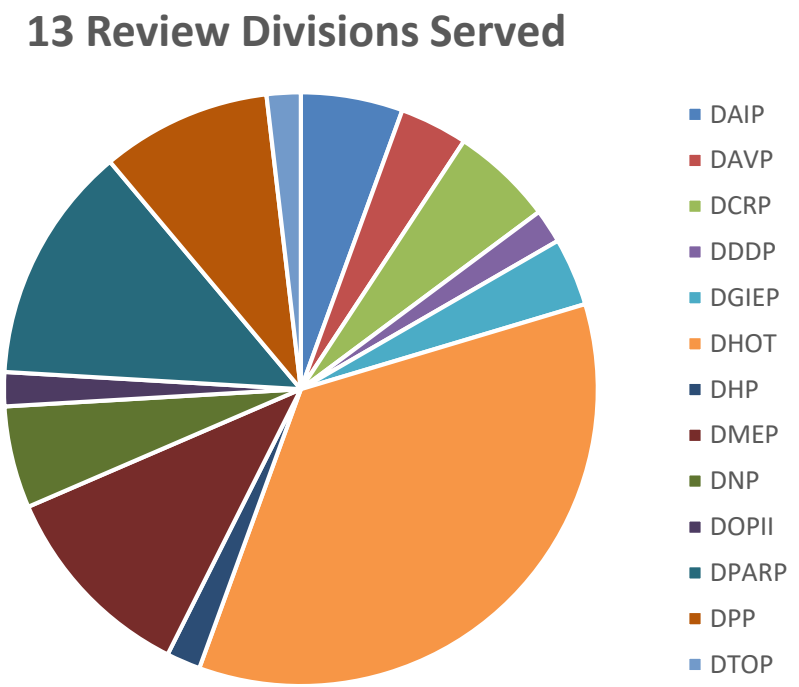
Key Concepts

1. KickStart is offered by OCS to all Pharm/Tox reviewers for their applications with preference given to reviewers who have never received a service.
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 Support Nonclinical Review

Applications Through May 2019

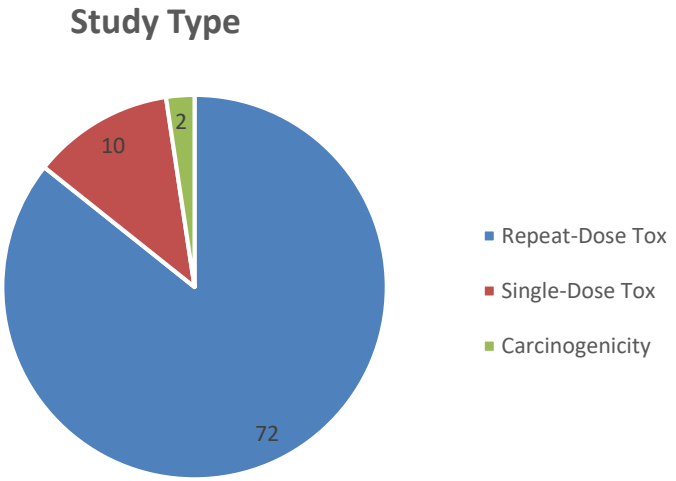


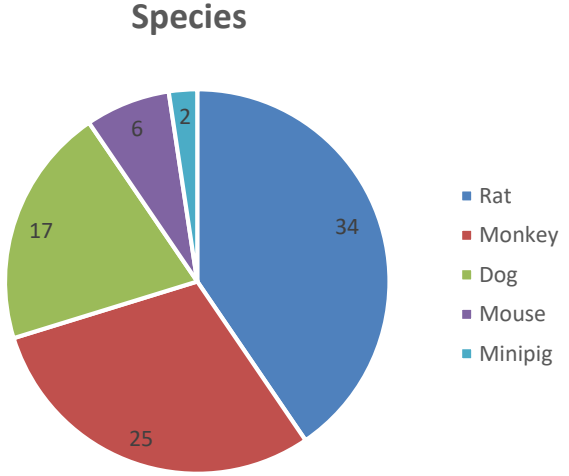


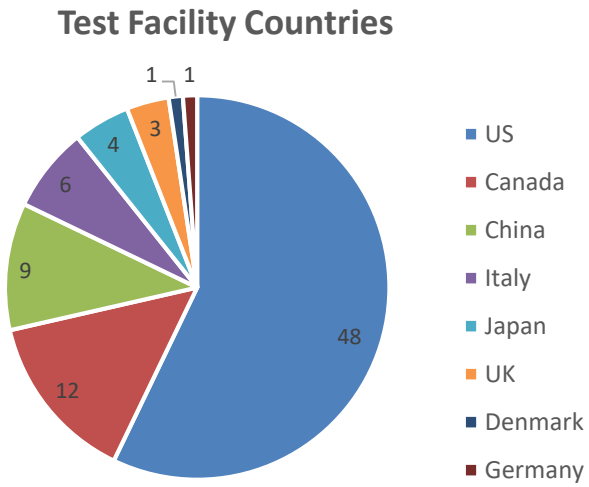
*Application must meet the following criteria:

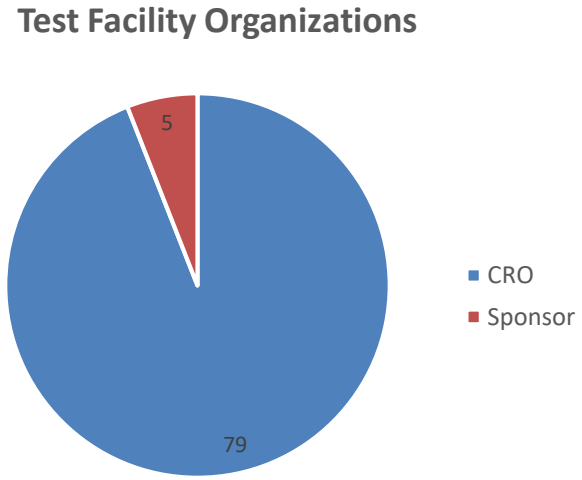
- Study loaded into Janus Nonclinical
- Reviewer requests service
- One or two studies per application generally reviewed

Studies Included in Kickstart Applications







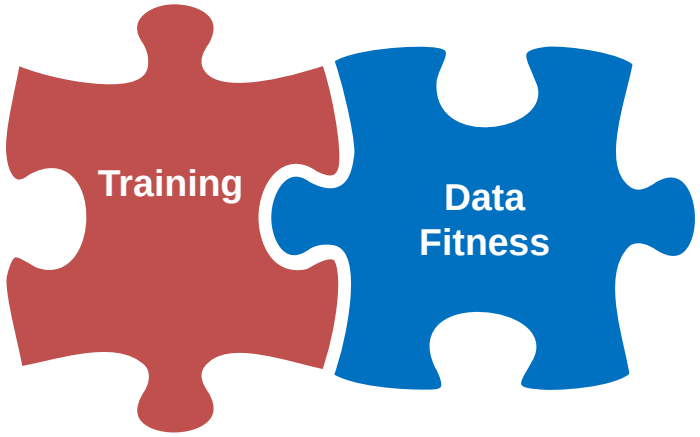


Pre-KickStart Training

- Provides reviewers 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

- Tutorial and 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

Common SEND Study Package Issues

Findings Data

- Timing, Categorical Data, Replacement Values

Study Design and Animal Assignments

- Removed Animals, Animal Set Assignments, Sets vs. Groups

Subject Elements

- Gaps, Overlaps, Data Outside Element, no SE

nSDRG Considerations

- Missing Key Information, Ambiguity, Unrelated Information

Define.xml

- StudyName does not match submission study ID

Common Findings Data Fitness Issues

- Through analysis of 79 studies across 54 applications, several data quality themes have emerged:
  - 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 text result

Data Fitness Issues with Standardization of Timing Variable

- Standardization issues related to a timing variable were found in nearly all of the studies reviewed
  - Reviewer could not use some submitted data in 10% of studies reviewed
    - Examples: Missing timing variables, timing does not align with report
  - Reviewer could use some data by applying work-arounds in Janus Nonclinical in 40% of the studies reviewed
    - Examples: Incorrect use of VISITDY for collection performed over multiple days and for 24-hr post dose result.

Data to be analyzed together is spread over multiple days in VISITDY
Days must be adjusted in FDA Tool views for summary analysis
VISITDY should align data with summary reporting

		Day -10	Day -9	Day -8	Day -7	Day 1 prior to the dosing		Day 8 2+/-0.5h postdose	Day 9 2+/-0.5h postdo…	Day 10 2+/-0.5h postdose	Day 26 2+/-0.5h postdose	Day 27 2+/-0.5h postdose	Day 53	Day 54	Day 55
2▲ Group	1▼ Sex	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Group 1…	Male		215.33		196.17							209.67			231.50
Group 2…	Male		226.25		192.00							218.50			
Group 3…	Male		196.50		214.25							228.25			
Group 4…	Male		233.00		231.67					231.60					260.00
Group 1…	Female	204.50		211.83							214.50			156.50	
Group 2…	Female	227.50		222.75							225.75				
Group 3…	Female	216.50		215.00							237.50				
Group 4…	Female	198.67		206.17		146.00	139.00	225.00	227.20				154.00	245.00	

Week -2

Week -1

Two unscheduled collections on one animal in SEND as scheduled

Group 4 Terminal

Week 4

Recovery

Schedule and Report

Twice during pretest (week -2, week -1)

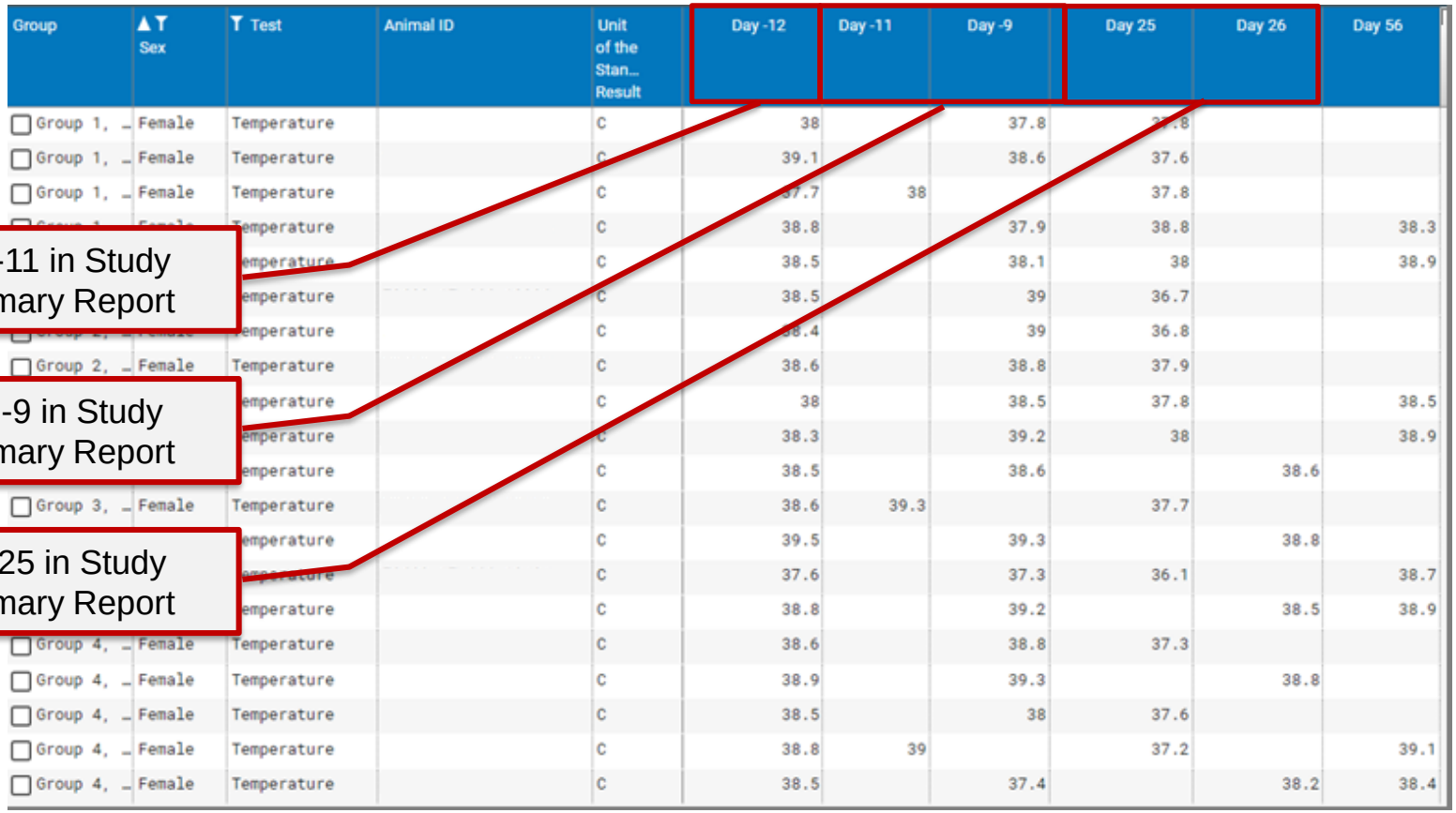
Last day of dose for group 4 (early termination),

Treatment week 4 for groups 1, 2, 3

Last week of Recovery all surviving animals

VISITDY is used to group records into a single planned study day as a label for reporting. This allows data that was collected based upon grace days to be reported in a single column on a report.

VISITDY Contains Day of Collection (shown in column headings)
Days for summarization on study report are different for each category of test
Days for each test must be adjusted in FDA Tool views for summary analysis



Group	Sex	Test	Animal ID	Unit of the Stan... Result	Day -12	Day -11	Day -9	Day 25	Day 26	Day 56
Group 1, _	Female	Temperature		C	38		37.8			
Group 1, _	Female	Temperature		C	39.1		38.6	37.6		
Group 1, _	Female	Temperature		C	37.7	38		37.8		
		Temperature		C	38.8		37.9	38.8		38.3
		emperature		C	38.5		38.1	38		38.9
		emperature		C	38.5		39	36.7		
		emperature		C	38.4		39	36.8		
Group 2, _	Female	Temperature		C	38.6		38.8	37.9		
		emperature		C	38		38.5	37.8		38.5
		emperature		C	38.3		39.2	38		38.9
		emperature		C	38.5		38.6		38.6	
Group 3, _	Female	Temperature		C	38.6	39.3		37.7		
		emperature		C	39.5		39.3		38.8	
				C	37.6		37.3	36.1		38.7
		emperature		C	38.8		39.2		38.5	38.9
Group 4, _	Female	Temperature		C	38.6		38.8	37.3		
Group 4, _	Female	Temperature		C	38.9		39.3		38.8	
Group 4, _	Female	Temperature		C	38.5		38	37.6		
Group 4, _	Female	Temperature		C	38.8	39		37.2		39.1
Group 4, _	Female	Temperature		C	38.5		37.4		38.2	38.4

Day -11 in Study Summary Report

Day -9 in Study Summary Report

Day 25 in Study Summary Report

To Match Report :

VISITDY in -12 in SEND has data from day -11 in report
VISITDY -11 and -9 in SEND have data from day -9 in report
VISITDY 25 and 26 in SEND have data from day 25 in report

Mismatched time point - label “24 hr” has elapsed time post dose P0D
0hr and 24hr data on Day 28 Cannot be Used for charting in Janus Nonclinical

VISITDY	PCTPT	PCTPTNUM	PCELTM
1	0.5h	0.5	P0DT30M
1	1h	1	P0DT1H
1	2h	2	P0DT2H
1	4h	4	P0DT4H
1	8h	8	P0DT8H
1	12h	12	P0DT12H
1	24h	24	P0D
28	0h0m	0	P0DT0M
28	0.5h	0.5	P0DT30M
28	1h	1	P0DT1H
28	2h	2	P0DT2H
28	4h	4	P0DT4H
28	8h	8	P0DT8H
28	12h	12	P0DT12H
28	24h	24	P0D

Elapsed Time - Day	Day	Plann... Time Point Name	Unit of the Stand... Result		Male High [Terminal...
0 Hrs - Day 1					
	1	24h	ng/mL	Mean	0.000
	1	24h	ng/mL	Std Dev	±0.000
	1	24h		N	5
0 Hrs - Day 28					
	28	0h0m	ng/mL	Mean	1,779.600
	28	0h0m	ng/mL	Std Dev	±1,400.693
	28	0h0m		N	5
	28	24h	ng/mL	Mean	0.000
	28	24h	ng/mL	Std Dev	±0.000
	28	24h		N	5

Elapsed Time Post Dose (PCELTM)

Label for Elapsed Time Post Dose (PCTPT)

ELTM used for Summary Table and Chart Organization for Times Post Dose In Janus Nonclinical

Incorrect VISITDY for 24hr sample (Day 1 dose has VISTDY 2)
Incorrect PCELTM for predose

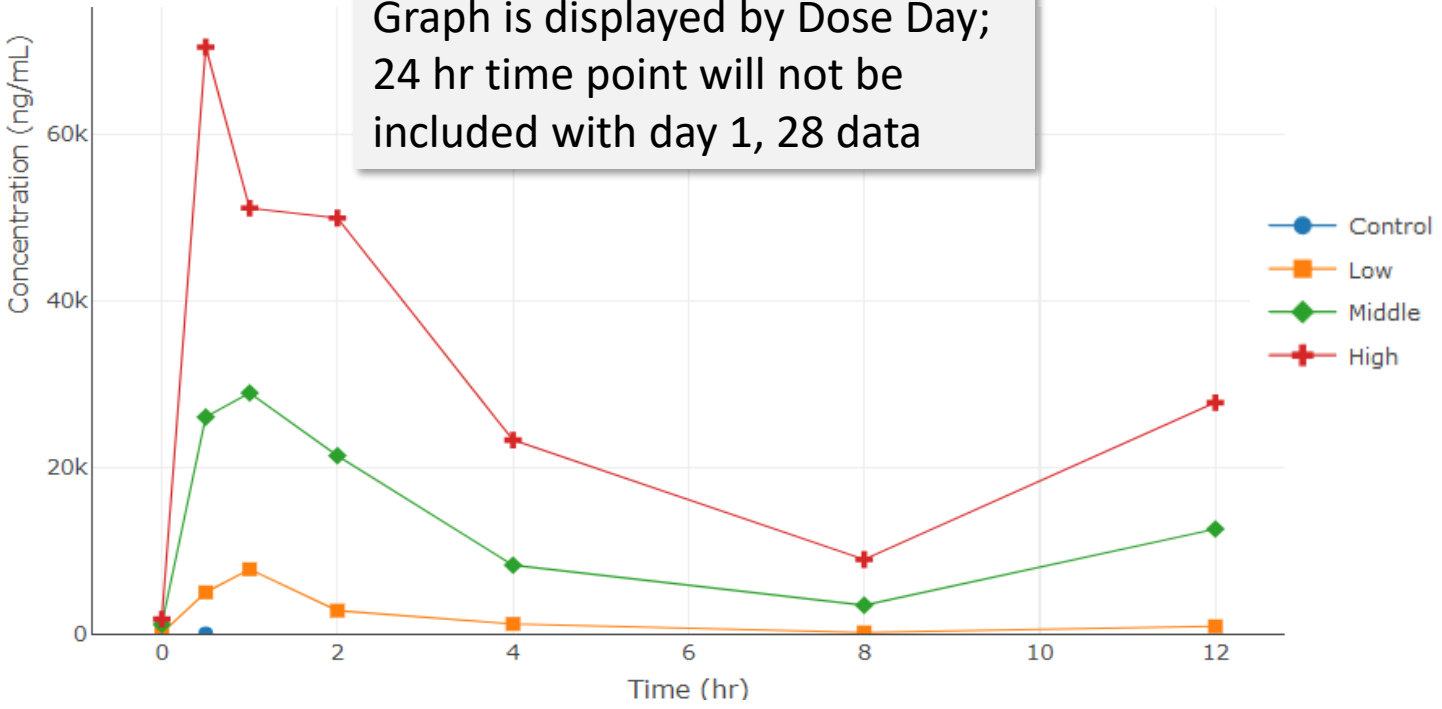
0.1 Hrs - Day 1	0.5 Hrs - Day 1	1 Hrs - Day 1	2 Hrs - Day 1	6 Hrs - Day 1	12 Hrs - Day 1	24 Hrs - Day 2

Predose

Day 1 24hr

Time points correctly sequence in tabular views in FDA Tools.

Graph is displayed by Dose Day; 24 hr time point will not be included with day 1, 28 data



Data Fitness Issues with Reporting of Categorical Test Results

- Improper reporting of categorical test results were found in nearly 60% of the studies reviewed
  - Most commonly seen in the Laboratory Test Results (LB) dataset for urinalysis and hematology tests with scored results on a discrete scale.
- Appropriate analyses cannot be automatically applied in Janus Nonclinical when these issues are present

Incorrect Standardization of Categorical Test Results

Day	Spec… Mate… Type	Category	Test	Unit of the Stan… Result		Male				
						0 mg/kg/day [Terminal,…	30 mg/kg/day - Terminal	100 mg/kg/day - Terminal	300 mg/kg/day [Terminal,…	1000 mg/kg/day - Terminal
29										
	SERUM	CLINICAL CHEMISTRY	Hemolytic Ind…		Mean	0.000 (Text)	0.000 (Text)	0.000	0.000 (Text)	0.000 (Text)
	SERUM	CLINICAL CHEMISTRY	Hemolytic Ind…		Std Dev	±0.000 (Text)	±0.000 (Text)	±0.000	±0.000 (Text)	±0.000 (Text)
	SERUM	CLINICAL CHEMISTRY								
57										
	SERUM	CLINICAL CHEMISTRY								
	SERUM	CLINICAL CHEMISTRY								
	SERUM	CLINICAL CHEMISTRY								

Animal ID	Day	Result	Result in Character
4001	29	0	Slight Hemolysis
4002	29	0	No Hemolysis
4003	29		No Hemolysis
4004	29	0	No Hemolysis
4005	29		No Hemolysis
4006	29		No Hemolysis
4007	29	0	No Hemolysis
4008	29	0	No Hemolysis
4009	29	0	Slight Hemolysis
4010	29	0	Slight Hemolysis

CLOSE | DAILY BY ANIMAL | ANIMAL DETAILS

Hemolytic Index results have LBSTRESN=0 for some results (not consistent with entry in LBSTRESC), no information provided in nSDRG. Janus Nonclinical automatically calculate summary means, standard deviations from values in LBSTRESN.

Incorrect Standardization of Categorical Lab Test Results

Day	Category	Test	Unit of the Standa... 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

CLOSE | DAILY BY ANIMAL | ANIMAL DETAILS

Semi-quantitative urine protein test are in SEND with the result range in LBSTRESC. When LBSTRESC “looks like” a numeric result, it is reported in LBSTRESN. This causes Janus Nonclinical to do means and standard deviations on those numeric results automatically.

Incorrect Standardization of Scored Lab Test Results

Specimen Material Type	Category	Test	Day	Unit of the Standardized Result	Male		
					Group 1 -	Group 2 -	Group 3 -
URINE	URINALYSIS	pH	-17		(Text)	(Text)	(Text)
URINE	URINALYSIS	pH	-11				
URINE	URINALYSIS	pH	33				

Animal ID	Day	Result	Result in Character
1001	-17		7
1002	-17		7
1003	-17		7.5
1104	-17		7

CLOSE | DAILY BY ANIMAL | ANIMAL DETAILS

Parameter:	Urine pH	DAY -17	DAY -11	DAY 33
GROUP	STATISTIC			
1	Mean	7.12	7.25	6.00
	SD	0.25	0.87	0.71
	N	4	4	4
2	Mean	7.20	7.25	7.62
	SD	0.62	0.87	1.49
	N	4	4	4
3	Mean	6.8	7.75	7.25
	SD	0.72	1.04	0.29
	N	4	4	4

pH group summary statistics included in study report;
SEND includes pH as categorical, with no LBSTRESN values.

Data Fitness Issues with Character Replacement Values

- Sponsor omitted character replacement values for use in PC or LB summary calculations in nearly 60% of the studies reviewed
  - Most commonly missing for plasma concentration results reported in the PC dataset
- Janus Nonclinical cannot replicate and use group mean results supplied in study report when replacement values are not submitted.

Supplemental Qualifier –CALCN Not Supplied for results <LLOQ

Day	Specimen Material Type	Sub Category	Test	Unit of the Stan… Result		Male 0 mg/kg	Male 1 mg/kg	Male 3 mg/kg	Male 10 mg/kg	Female 0 mg/kg	Female 1 mg/kg	Female 3 mg/kg	Female 10 mg/kg
29													
	PLASMA	Clinical Chemistry	Sorbitol Dehy…	U/L	Mean	1.500 (Text)							
	PLASMA	Clinical Chemistry	Sorbitol Dehy…	U/L	Std Dev	±0.577 (Text)							
	PLASMA	Clinical Chemistry	Sorbitol Dehy…		N	12 (Text)							
58													
	PLASMA	Clinical Chemistry	Sorbitol Dehy…	U/L	Mean	2.200 (Text)							
	PLASMA	Clinical Chemistry	Sorbitol Dehy…	U/L	Std Dev	±0.837 (Text)							
	PLASMA	Clinical Chemistry	Sorbitol Dehy…		N	6 (Text)							

Animal ID	Day	Result	Result in Character
10001	29	2	2
10002	29		<1.0
10003	29	1	1
10004	29		<1.0
10005	29	1	1
10006	29		<1.0
10007	29		<1.0
10008	29	2	2
10009	29		<1.0
10010	29		<1.0
10011	29		<1.0

CLOSE | DAILY BY ANIMAL | ANIMAL DETAILS

	U/L
	2.0
	0.5 }
	1.0
	0.5 }
	1.0
	0.5 }
	0.5 }
	2.0
	0.5 }
	0.5 }
	0.5 }
	0.5 }
n	12
Mean	0.83
S.D.	0.58

} : Below the LLOQ, represented as a half value of LLOQ

Study Report indicates that half of LLOQ is used for results <1.0. LBCALCN not supplied so results <1.0 eliminated from mean in Janus Nonclinical.

Key SEND Submission Issues in Foundational Datasets

- Animal(s) removed from a study and eliminated from all reporting are in SEND files with data not excluded
  - Study Report and FDA Summaries do not match; data for removed animal(s) must be manually excluded in Janus Nonclinical
- Animals assigned to wrong sets
  - Janus Nonclinical automatically groups data by set; this cannot be done when animals are not in the correct sets. Reviewers do not reassign animals to sets
- Sponsor group ID and/or label incorrectly assigned to a set
  - Janus Nonclinical reports certain data by sponsor group; this cannot be done when group assignments are inconsistent with study design. Reviewers can report by set, with merged sets possible if needed

Issues Seen in Subject Elements (SE)

Background:
SE is critical for identifying the epoch that data is collected for

- SE not submitted
  - Epoch cannot be assigned
- Overlapping dates across elements
  - Incorrect epoch may be assigned
- Gap between end date and next element's start date
  - Epoch for data collected within the gap is not assigned
- Last element date before some collection dates
  - Epoch for data after end of last element is not assigned

Example Use of Epoch in Janus Clinical Observations

High Dose Affected

			Male				Female			
			N = 15	N = 15	N = 15	N = 5	N = 15	N = 15	N = 15	N = 5
Category for Clinical Observations	Sign	Study Phase	Low - Terminal	Mid - Terminal	High - Terminal	High - Recovery	Low - Terminal	Mid - Terminal	High - Terminal	High - Recovery
OPHTHALMOLOGY	Retinal atrophy	Screening								
OPHTHALMOLOGY	Retinal atrophy	Treatment			1/1				11/11	4/4
OPHTHALMOLOGY	Retinal atrophy	Recovery								4/4

Treatment Affect Not Seen During Recovery

			Male				Female			
			N = 15	N = 15	N = 15	N = 5	N = 15	N = 15	N = 15	N = 5
Category for Clinical Observations	Sign	Study Phase	Low - Terminal	Mid - Terminal	High - Terminal	High - Recovery	Low - Terminal	Mid - Terminal	High - Terminal	High - Recovery
CLINICAL SIGNS	Salivation	Screening								
CLINICAL SIGNS	Salivation	Treatment	1/1	23/10	51/9	18/4		17/6	48/9	12/3
CLINICAL SIGNS	Salivation	Recovery								

Nonclinical Data Reviewers Guide

- Key (but not the only) use of the nSDRG is helps reviewers navigate and use the SEND study data alongside the study report
- Significant differences in quality (complete, correct, clear, specific to the study) from company to company
- PhUSE nonclinical nSDRG working group provides templates, instructions and samples
- KickStart team includes suggestions for improvement in sponsor data fitness reports when information needed for interpretation of the data is not present or is inaccurate

Nonclinical Data Reviewers Guide Most Common Issues

- List of Differences between SEND and Study Report is ambiguous, incomplete, and/or cannot be confirmed
- Information included that is not relevant to the study
- True validator findings written off as “false positives”
- No mention of results or observations not reported in SEND

Example Mapping of Collected Data to SEND

INDxxxx Study xxxx Methods	Location in Janus	
6.5 Toxicokientics		
Bioanalysis	PC	Pharmacokinetic Concentrations
Anti-Drug Antibodies – not submitted - out of scope		
Toxicokinetic Analysis	PP	Pharmacokinetic Parameters
6.6 Inlife Procedures		
Clinical Observations (Health Monitoring, Cageside, Detailed and Post-dose)	CL	Clinical Observations
Qualitative Food Consumption	CL	Clinical Observations
Body Weights	BW	Body Weights
Body Weight Gains	BG	Body Weight Gains
Functional Observation Battery –not submitted - out of scope		
Vital Signs: Body temperature, heart rate, respiration rate, and pulse oximetry	VS	Vital Signs
Ophthalmic Examinations	CL	Clinical Observations
Blood Pressure Measurements	VS	Vital Signs
6.7 Clinical Laboratory Procedures		
Hematology, Coagulation, Clinical Chemistry, Urinalysis	LB	Laboratory Findings
C-Reactive Protein	LB	Laboratory Findings
Peripheral Blood Immunophenotyping – Total Lymphocytes and Monocytes	LB	Laboratory Findings
Cytokine Sample Analysis	LB	Laboratory Findings

Define.xml StudyName

Study Data Technical Conformance Guide

4.1.3.2 General Considerations

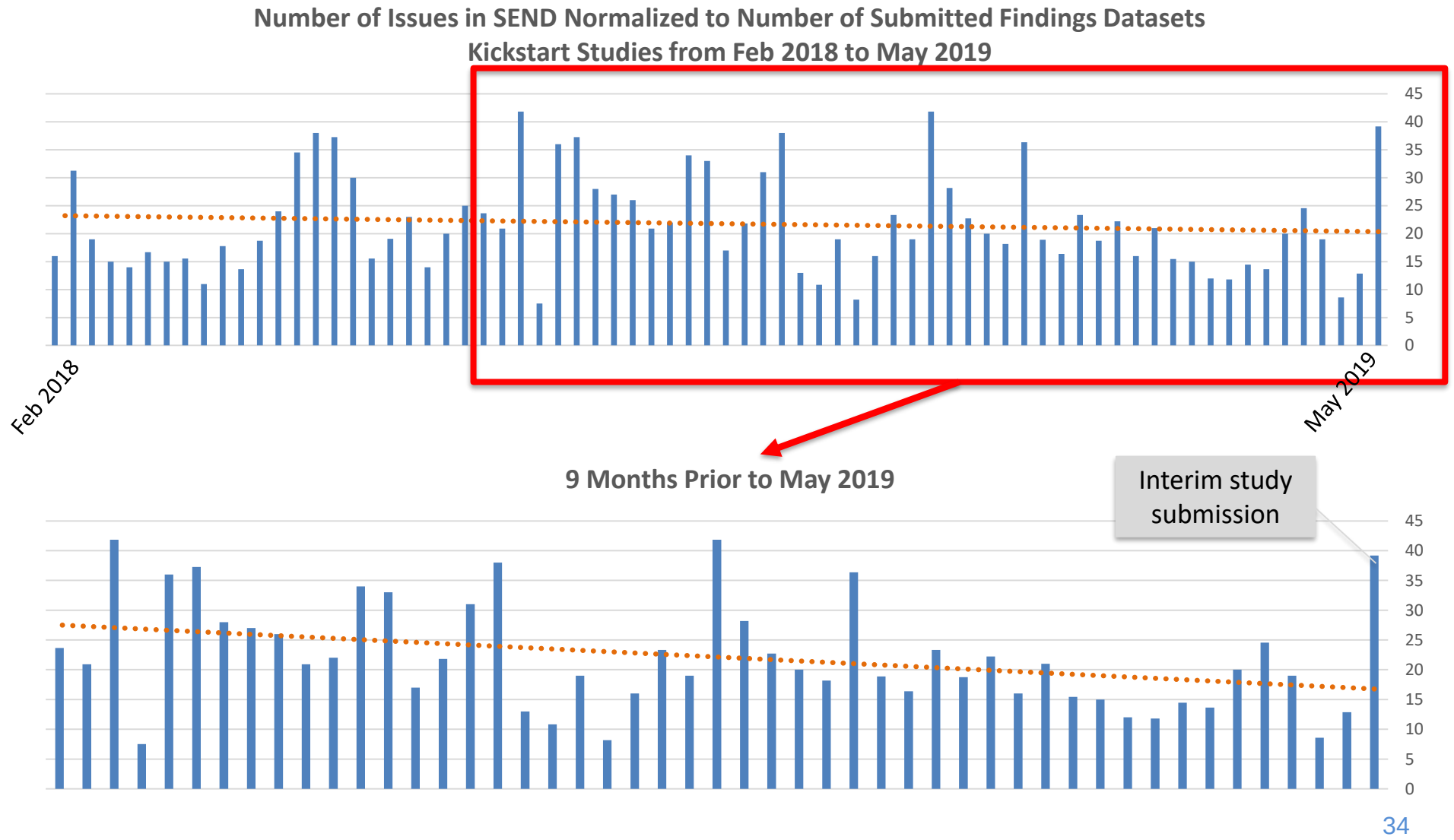
For nonclinical studies, the define.xml StudyName element value must contain the sponsor's study identifier, consistent with the study identifier used in the eCTD folder structure under Module 4; refer to Section 7.1 for additional information about the Module 4 folder structure.

StudyName Facts

- 40% of studies reviewed by Kickstart do not have the correct StudyName
- StudyName identifies the study within the application in Janus Nonclinical
- Correct use of StudyName aligns the application and study ID in Janus Nonclinical with the eCTD submission identifiers familiar to reviewers
- Incorrect StudyName can cause loading failures, for example when StudyName='UNKNOWN' for multiple studies in the application.
- StudyName may need to be updated by sponsor prior to submission

Quality Improvement in KickStart Studies

Trend Line Moving in the Right Direction!



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

FDA SEND Communications

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
   - This webinar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