

Visualization of Nonclinical Standardized Data and the Fit for Use Pilot

Elaine Thompson, Ph.D.

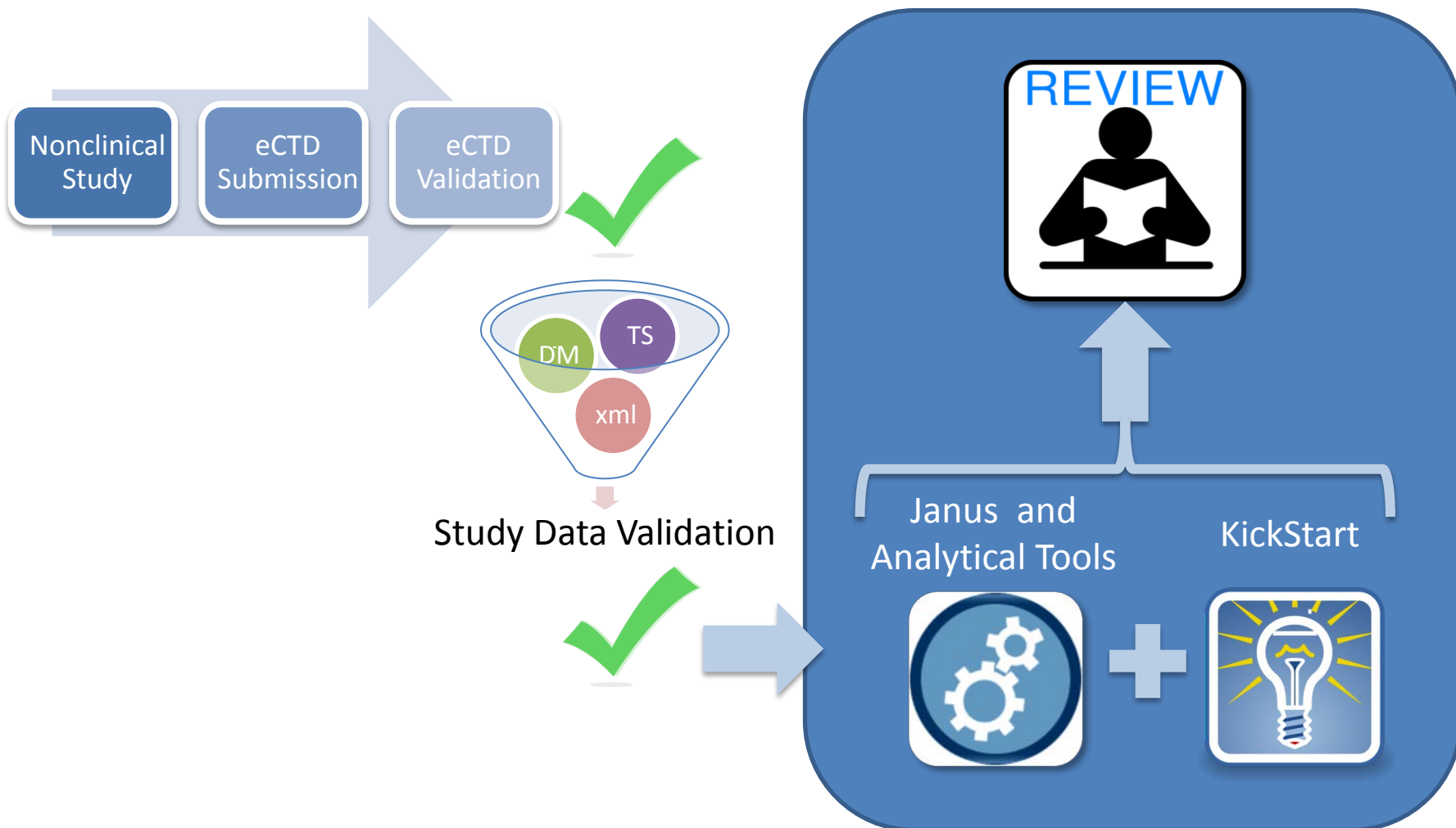
FDA Office of Computational Sciences

PhUSE CSS, March 2017

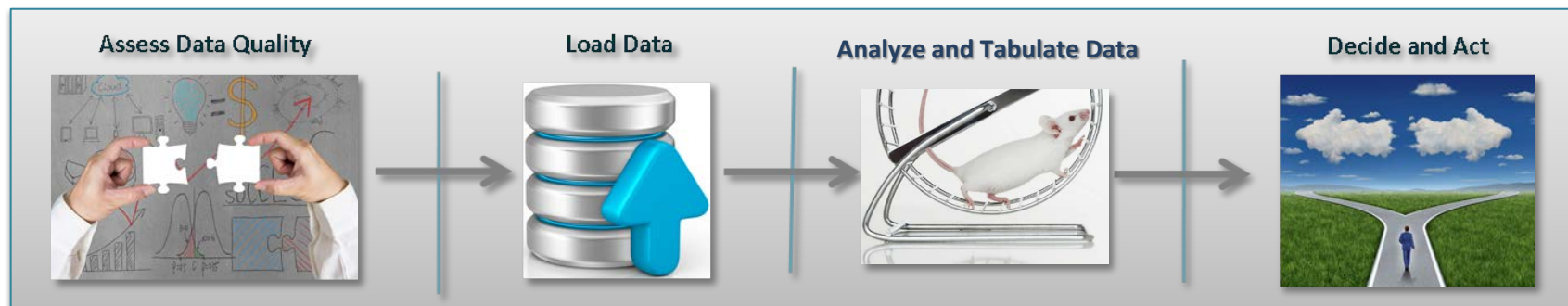
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The views expressed are those of the speaker and do not necessarily reflect the policies and practices of the FDA.

Nonclinical Data Analysis

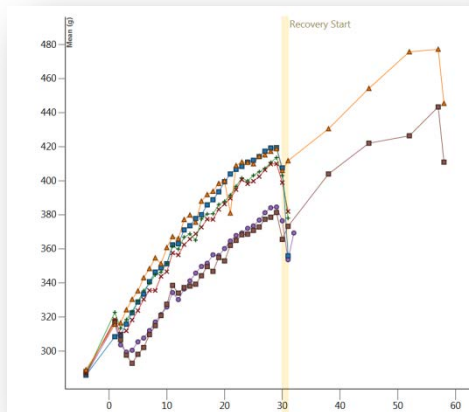


KickStart



- OCS Nonclinical Review Service
- Reviewer with a first SEND submission
- Supports a consistent review process with nonclinical standardized data

Janus Nonclinical Delivers Data to Reviewers



Graphs

Home > Study List > PD52014 - 2.0 > Body Weight > Summary

Showing 1 to 41 of 41 rows

Test	Day	Units of the Standardized Result	1-Vehicle, 0 mg/kg	2-Vehicle, 0 mg/kg	3-Low, 20 mg/kg	4-Medium, 200 mg/kg	5-High, 400 mg/kg	6-High, 400 mg/kg
Body Weight	-4	g	285.62	1.1115%	0.22009%	0.25547%	0.045757%	0.77354%
Body Weight	1	g	308.47	2.5631%	4.6366%	3.2798%	2.3909%	2.8747%
Body Weight	2	g	309.62	2.2711%	1.2124%	6.1267%	1.9004%	6.9832%
Body Weight	3	g	315.82	2.6887%	0.80325%	-1.2817%	-1.2121%	5.7790%
Body Weight	4	g	322.97	2.6419%	0.19322%	-1.0021%	-6.8417%	-8.2001%
Body Weight	5	g	328.8	1.9789%	0.10617%	-1.3234%	-17.144%	-9.3207%
Body Weight	6	g	333.43	2.5631%	0.10368%	0.31127%	7.7377%	9.4027%
Body Weight	7	g	340.71	2.2572%	-0.23029%	-1.4534%	0.4238%	8.1108%
Body Weight	8	g	346.15	2.4120%	-0.46641%	-1.1183%	4.4575%	8.0738%

Tables

Showing 1 to 19 of 19 tissues

Severity	7-Vehicle, 0 mg/kg	8-Vehicle, 0 mg/kg	9-Low, 20 mg/kg	10-Medium, 200 mg/kg	11-High, 400 mg/kg
#Examined	9	5	8	8	9

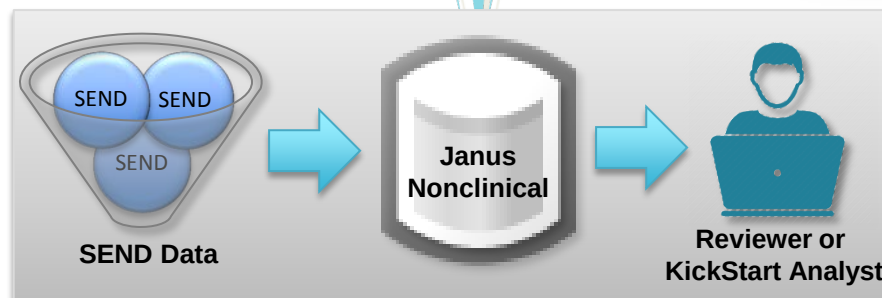
PD52014 - 2.0 > Microscopic Findings > Summary

Showing 1 to 25 of 28 tissues

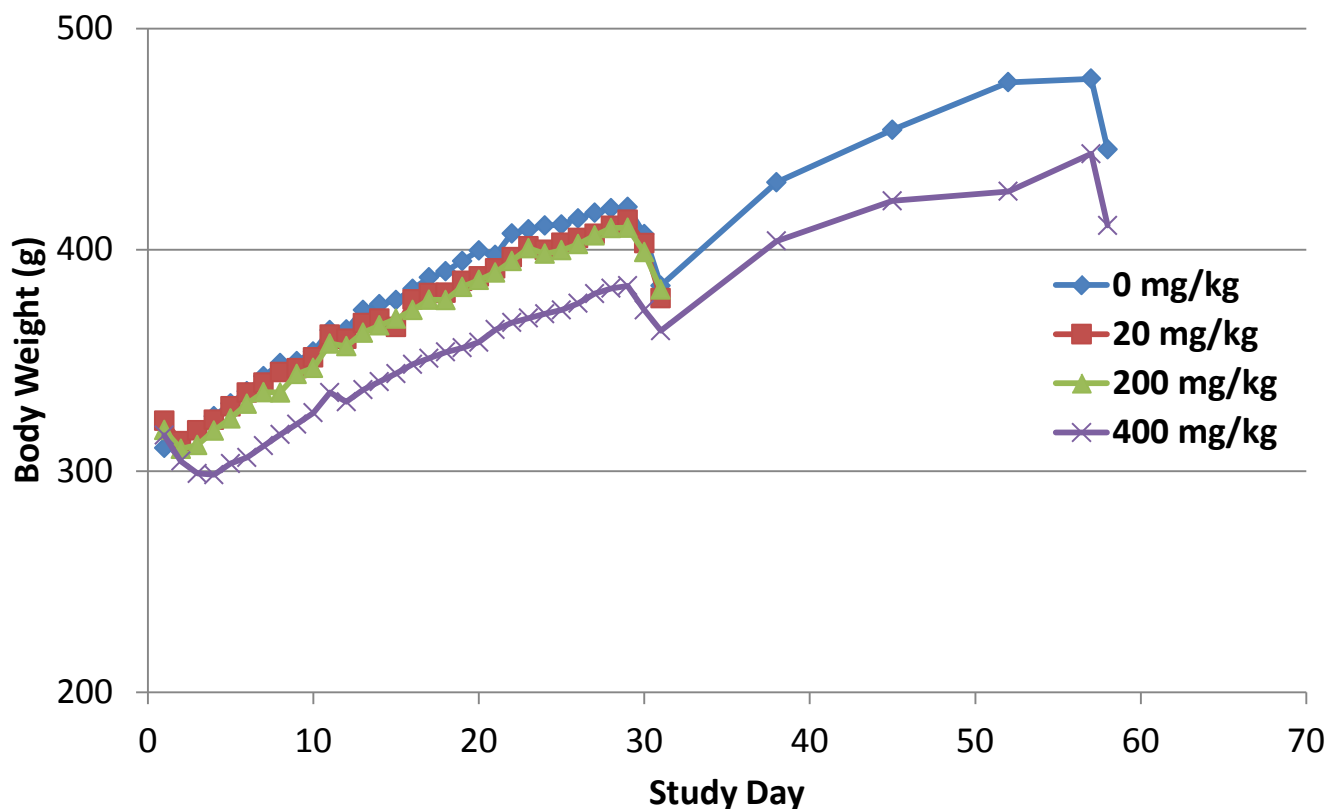
Modifiers	Severity	1-Vehicle, 0 mg/kg	2-Vehicle, 0 mg/kg	3-Low, 20 mg/kg	4-Medium, 200 mg/kg	5-High, 400 mg/kg
diffuse	#Examined	10	5	10	10	10
	MILD					
	Total					
multifocal/triade: focal	MILD	1 (10.0%)	1 (20.0%)			
	Total	1 (10.0%)	1 (20.0%)			
	MILD	6 (60.0%)	4 (80.0%)	4 (40.0%)	6 (60.0%)	2 (20.0%)
	MODERATE	1 (10.0%)	1 (20.0%)	1 (10.0%)	1 (10.0%)	
	Total	6 (60.0%)	5 (100%)	5 (50.0%)	7 (70.0%)	2 (20.0%)
focal	MILD					
	Total					
centrilobular	MODERATE					1 (10.0%)
	Total					1 (10.0%)
diffuse: perilobular/diffuse; epilobular/large vacuole	MILD					

Visualizations

Analysis-Ready Views



Time Series for Visualization of Trends



Time series graphs from Janus Nonclinical allow reviewers to see trends in clinical chemistry or body weights across a study

Incidence Counts of Clinical Observations

Sign	Day Interval	Male				Female			
		0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg	0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg
Skin Abnormal	1-31	75/5							
Cataract	-1-56	6/3			11/4				2/1
Corneal Opacification	-1-56	6/3			3/1				5/2
Haircoat Abnormal	27-31	5/1							
Persistent Hyaloid Artery	-1-28	2/1			2/1				
Preretinal Bleeding	-1-56	4/3							
Persistent Pupillary Membrane	-1-56	3/1							
Retinal Hyperreflectivity	-1-56	3/1							
Vitreous Hemorrhage	-1-28					2/1			
Ocular Discharge	-1--1	1/1							

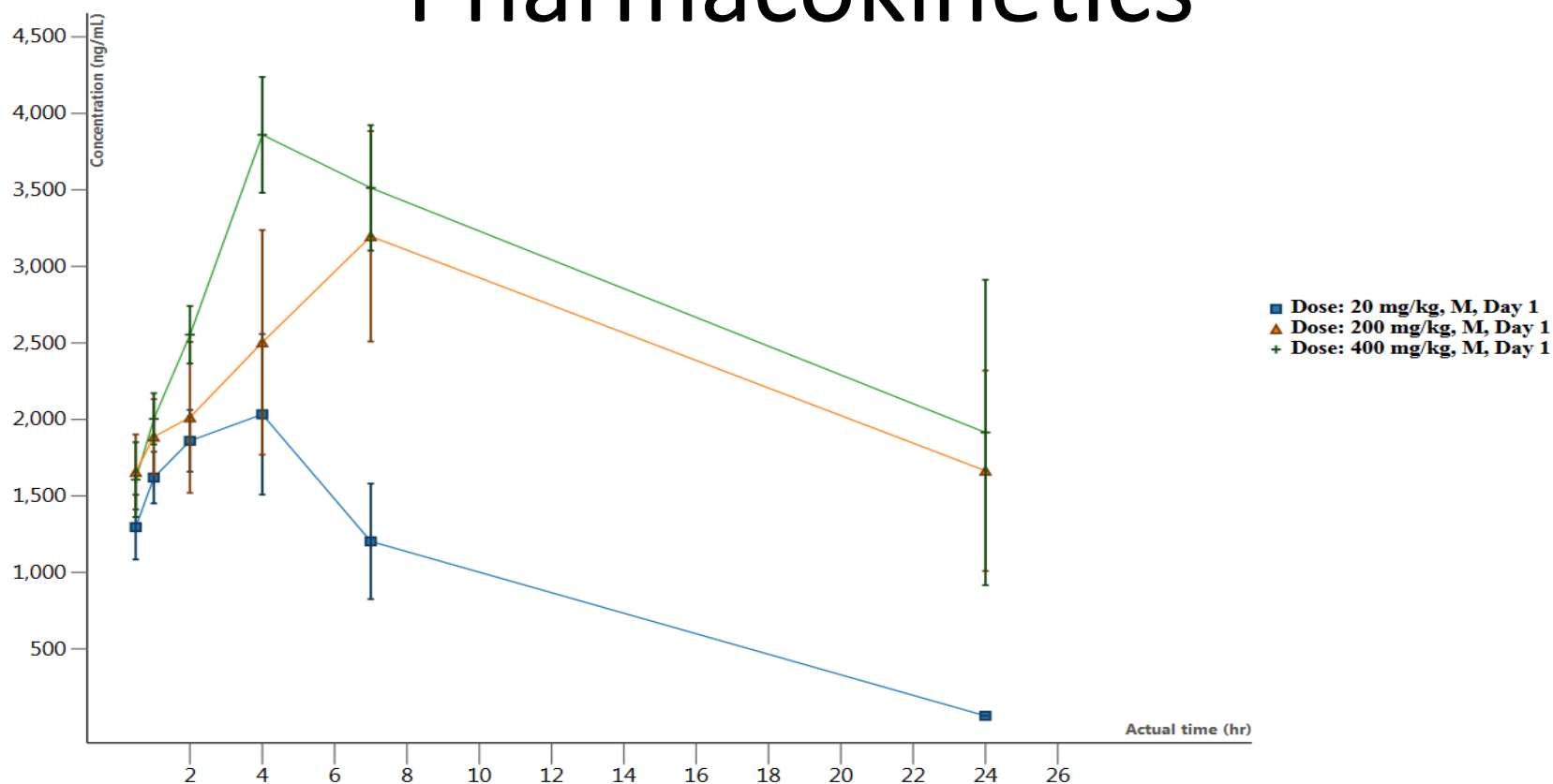
- “Day Interval” indicates the range of study days
- Numbers are #observations / #animals
- Frequent observations appear at the top of the list

Histopathology Heat Map

Finding	Severity	Males			
		0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg
LIVER					
	#Examined	10	10	10	10
MPS-aggregates multifocal	MILD	7 (70%)	4 (40%)	6 (60%)	4 (40%)
	MODERATE	1 (10%)	1 (10%)	1 (10%)	1 (10%)
Necrosis	MILD				
	MODERATE				2 (20%)
Vacuolization	MILD				
Vacuolization hepatocellular	MODERATE				
GLAND, ADRENAL					
	#Examined	10	10	10	10
Hemorrhage	MILD			1 (10%)	1 (10%)
Hypertrophy	MILD	1 (10%)	1 (10%)		
Vacuolization	MILD	1 (10%)	2 (20%)	7 (70%)	8 (80%)

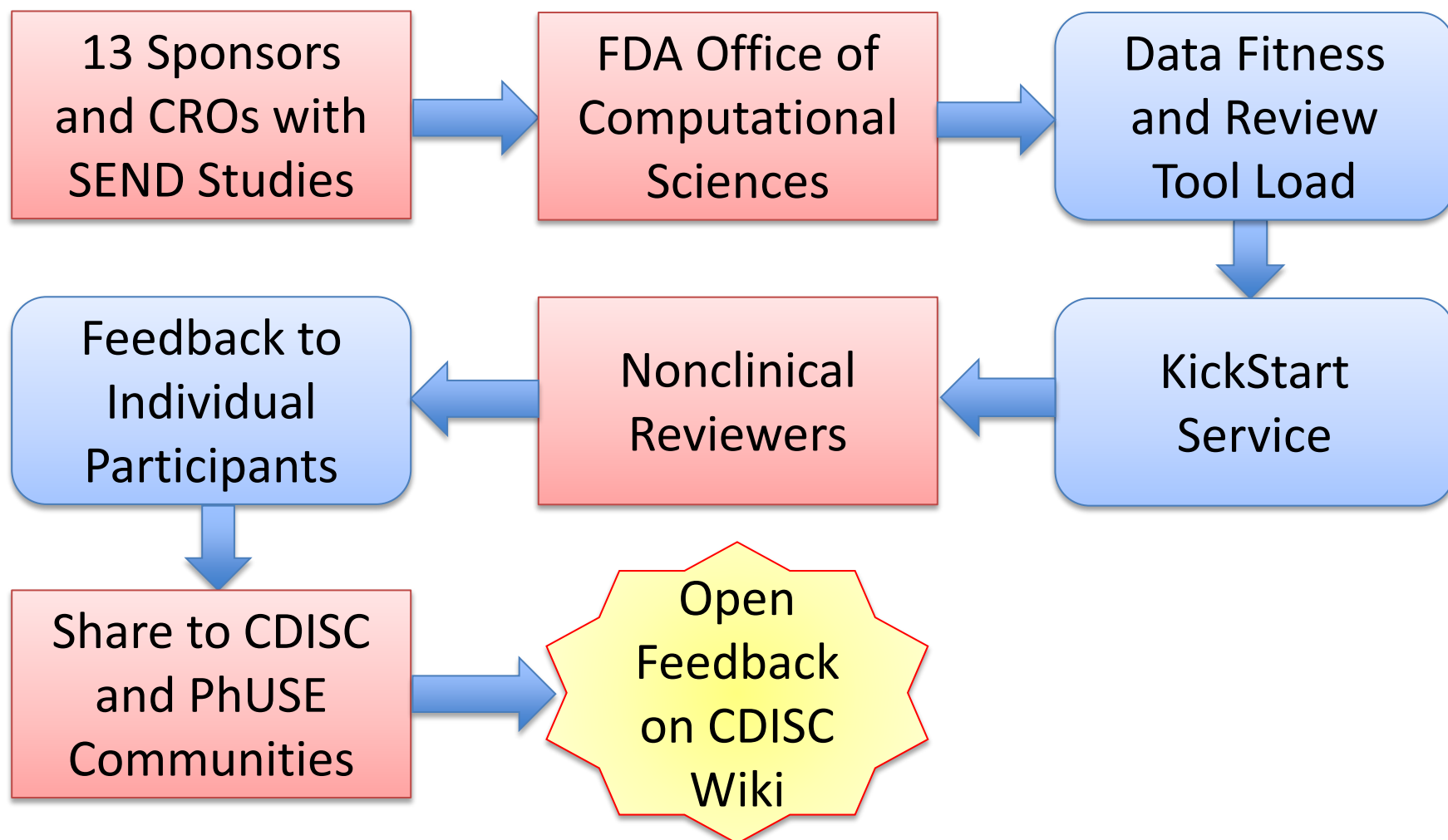
Heat map coloring on the incidence table helps reviewers spot frequent findings and dose dependent trends

Pharmacokinetics



Automatically generated pharmacokinetic graphs allow reviewers to focus on data interpretation, instead of on making graphs

What was the “Fit for Use” Pilot?



**Valuable sample data to
test readiness, software,
and practices**

**Improved the FDA
Technical Conformance
Guide**

IMPACT



**Improvements to
CDER/OCS tools and
services**

**Identification of standards
and implementation
development areas**

Improved Review Readiness

Reviewers

- Nine reviewers experienced with SEND
- Five Pharm/tox divisions prepared

KickStart

- Piloted KickStart Service
- Reviewer feedback improved KickStart

Training

- Captured examples of Janus in use for development of training

Janus Nonclinical

- Identified ten enhancements
- Improved data loading routines

What did we learn “**Fit for Use**” means?

Data Integrity

**Follows the
SENDIG**

**Agrees with and supports
the Study Report**

Trial design is
accurate and
correct

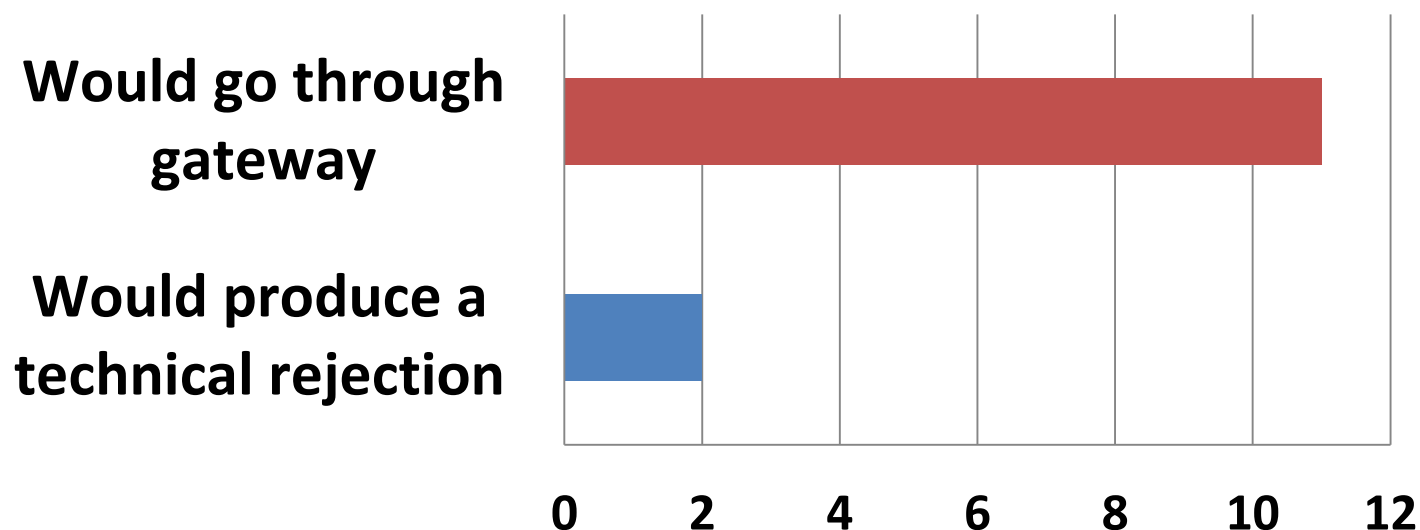
Correct
Controlled
Terminology

Findings are
standardized
for incidence
counts

Dataset is
complete

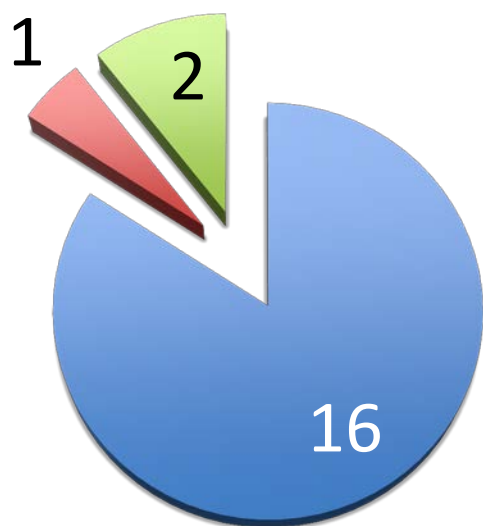
Discrepancies
or missing
data are
documented

Would the submission work?



Two of the thirteen submissions had errors that would have produced a technical rejection

Data Integrity

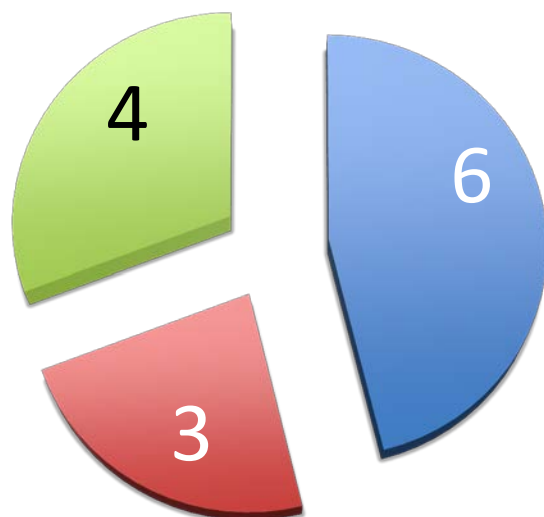


- Good Integrity
- Minor Issue
- Major Issue

Two of nineteen studies could not be used at all because tables did not join

One loaded without the comments

Submission Completeness



- Complete
- Missing some findings
- Missing whole domains

Fewer than half had all of the Study Report data included in the SEND dataset

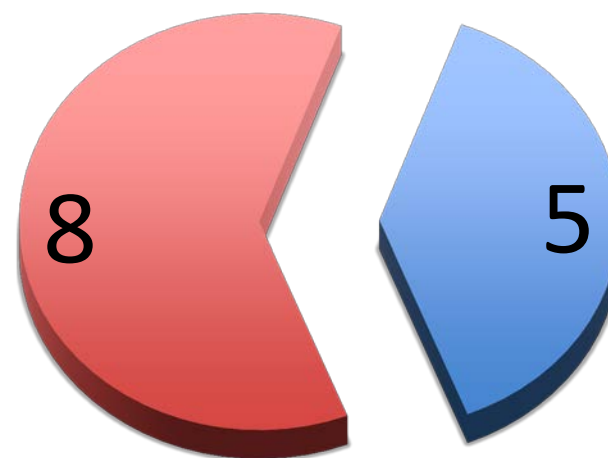
If data are modeled in SEND they should be included in the submission

Define.xml

More than half of the submissions had problems with define.xml

Multiple problems with define files were fixed

- empty attributes
- errors in referenced files
- multiple or missing elements



■ Successful load

■ Fixed errors to load

Severity Mismatch in Histopathology

Study Report

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

SEND Tabulation

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

Ensure that the SEND and study report match. Avoid submitting conflicting data.

Other common issues

Histopathology * Gross Pathology

- Results not standardized well
- Severities different from the Study Report

Pharmacokinetics *

- Multiple problems with timings
- Units missing for LLOQ

Clinical Observations *

- Hard to create incidence counts
- Too much diversity in implementations

Timings

- Grace days could not be grouped
- Dates in the wrong format

Trial Design

- Recovery animals not in separate trial sets
- Vague group names

*** CDISC or PhUSE work stream chartered**

Moving SEND Forward

Work streams from Fit for Use

DART – Development and Reproductive Toxicity

- **Need sample data sets**
- **Development of proof of concept scripts**
- **Community pilot to evaluate standard**

SEND 3.1

- **Cardiovascular & Respiratory Safety Pharmacology**
- **Nervous System in draft**

Genetic Toxicity in draft

Voluntary SEND submissions warmly welcome

Fit for Use Participants

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

Thank you for participating!

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