Visualization of Nonclinical Standardized Data and the Fit for Use Pilot

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FDA Office of Computational Sciences

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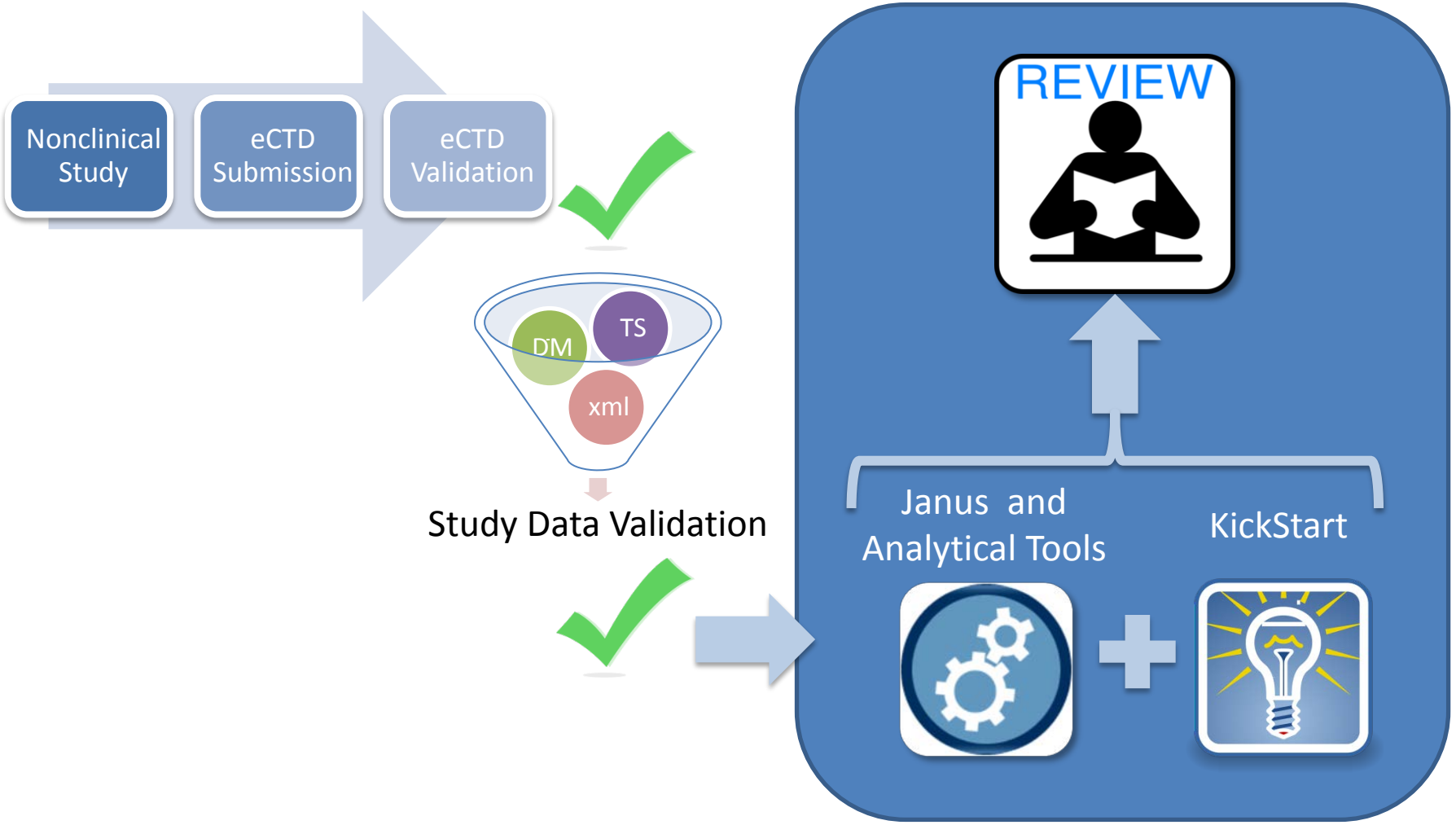
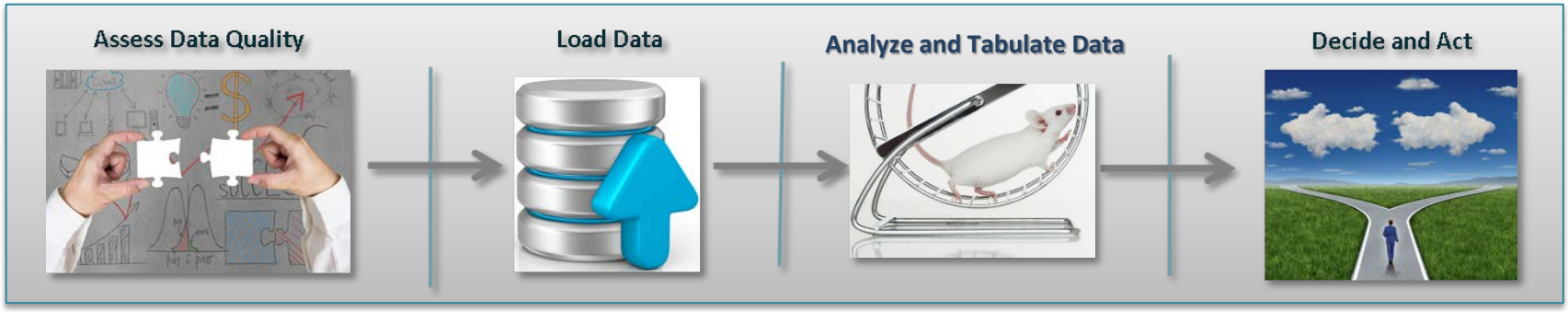
Disclaimer

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

Nonclinical Data Analysis

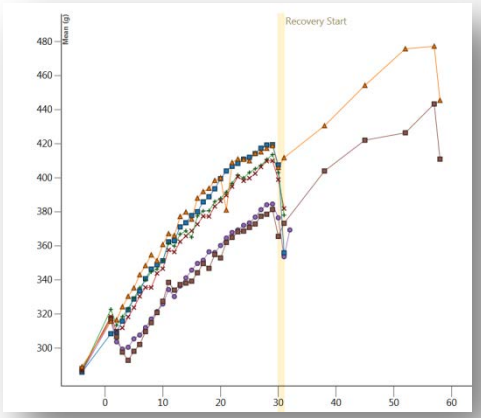


KickStart

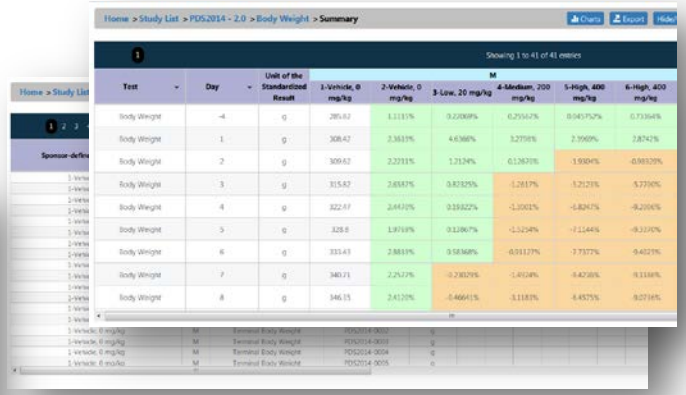


- OCS Nonclinical Review Service
- Reviewer with a first SEND submission
- Supports a consistent review process with nonclinical standardized data

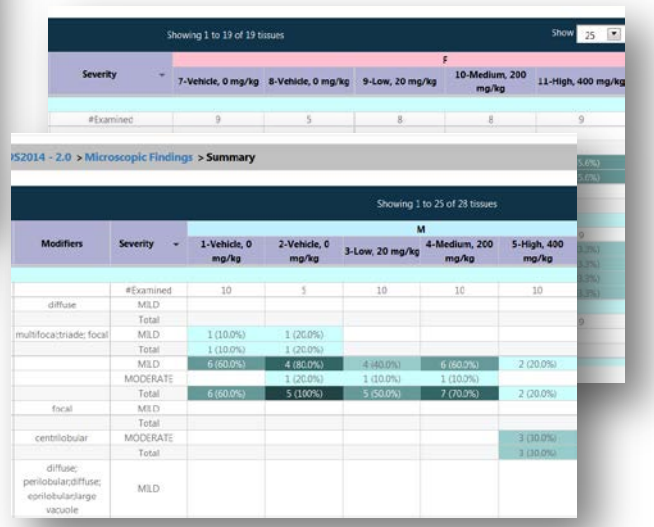
Janus Nonclinical Delivers Data to Reviewers



Graphs

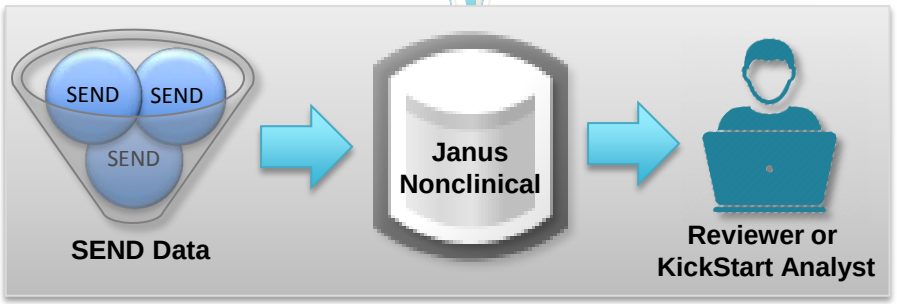


Tables

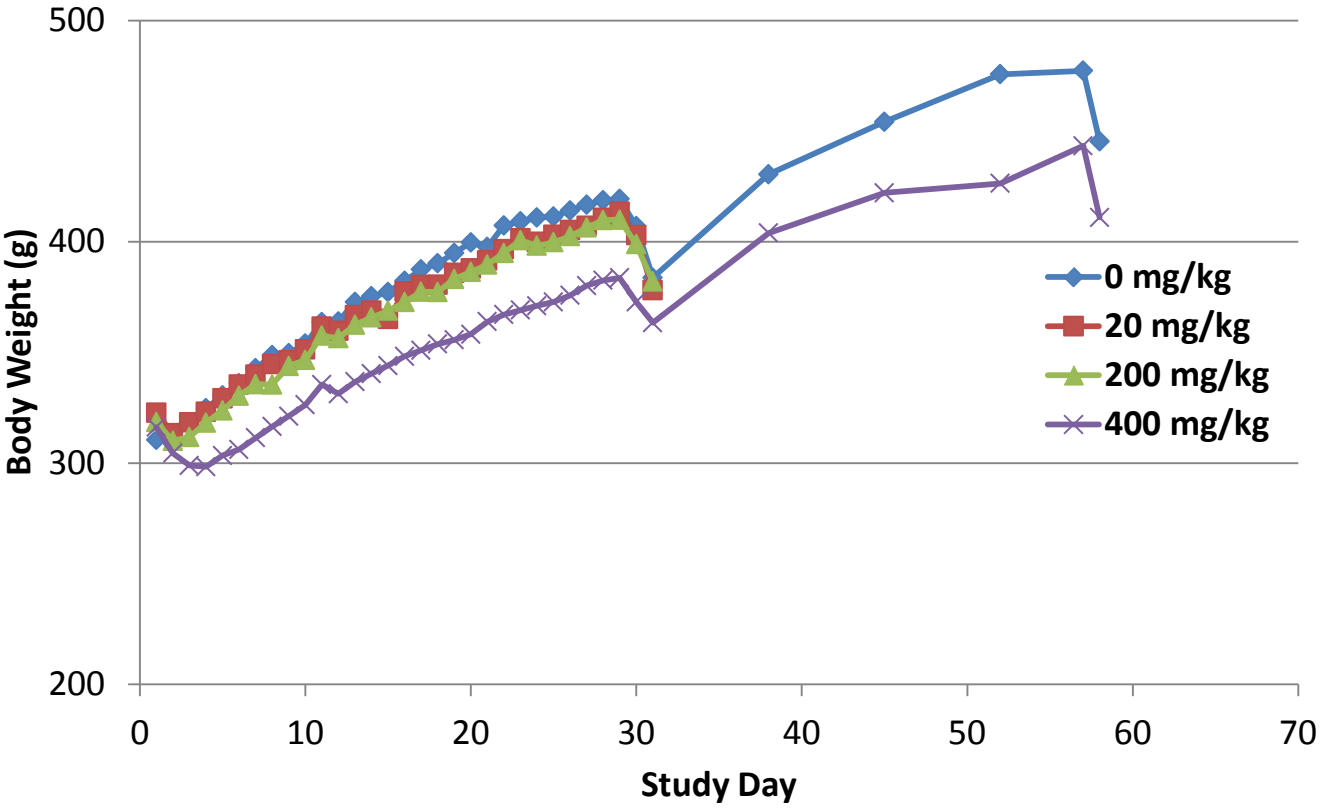


Visualizations

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							

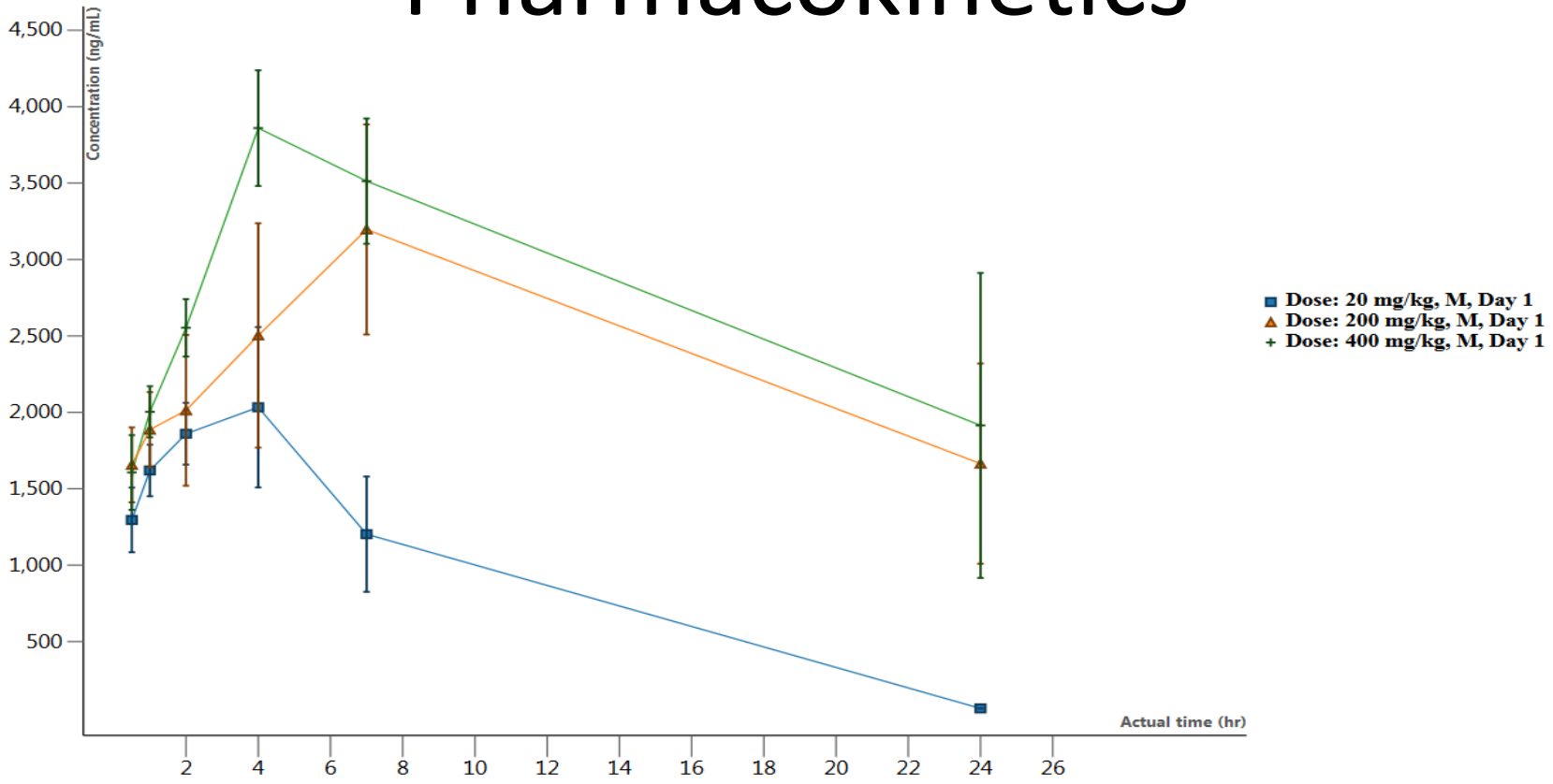
- **“Day Interval” indicates the range of study days**
- **Numbers are #observations / #animals**
- **Frequent observations appear at the top of the list**

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%)

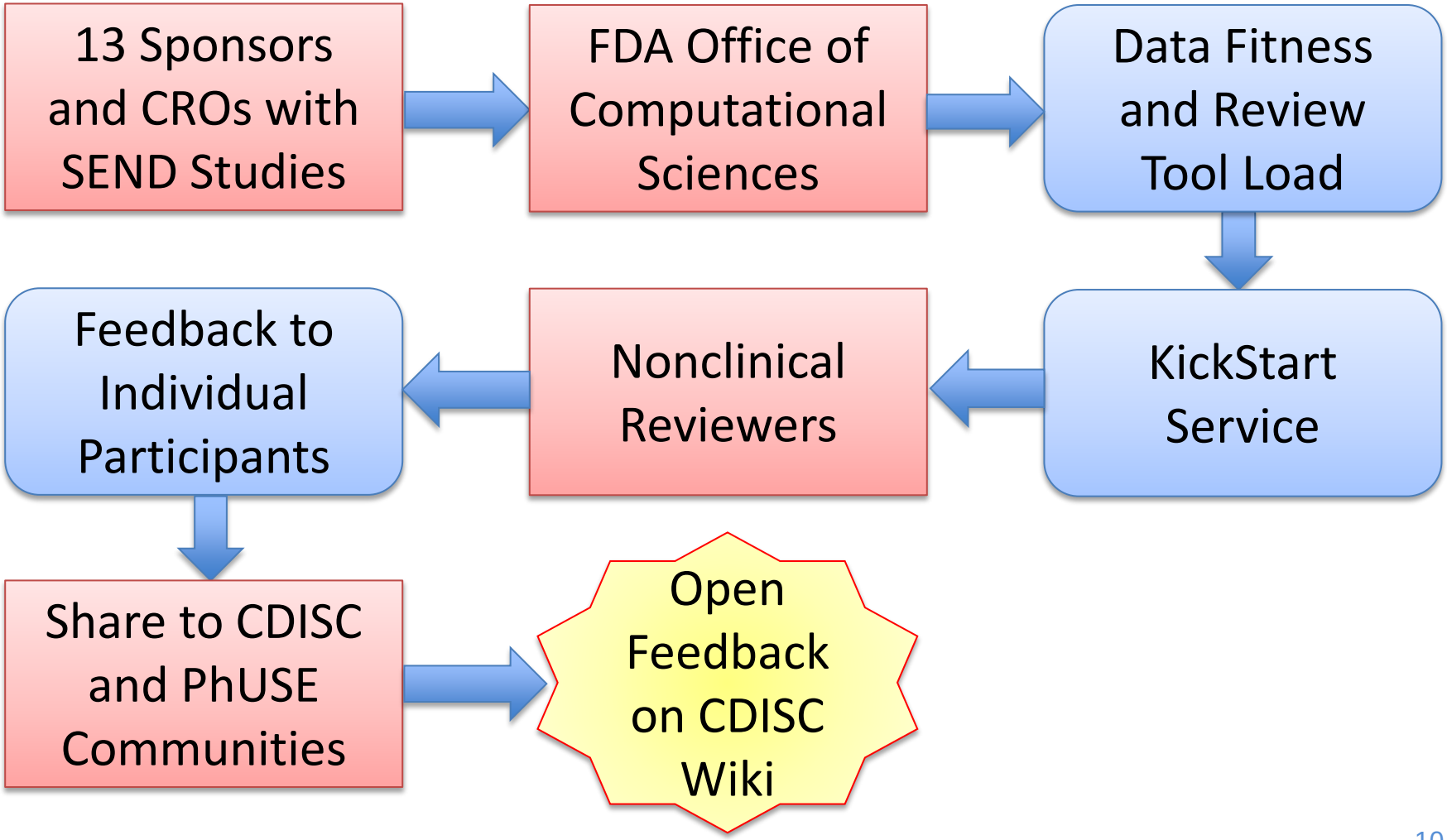
Heat map coloring on the incidence table helps reviewers spot frequent findings and dose dependent trends

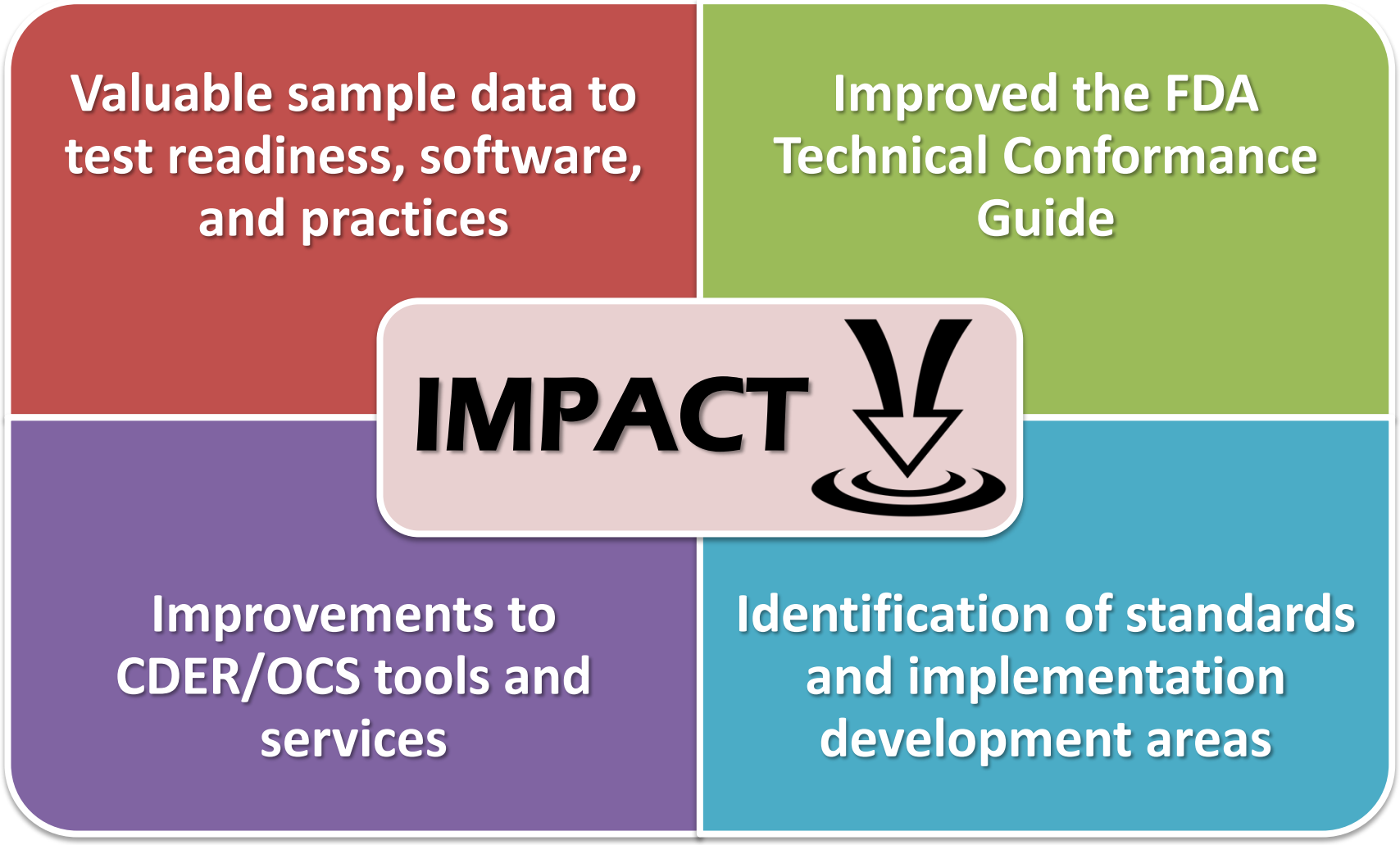
Pharmacokinetics



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

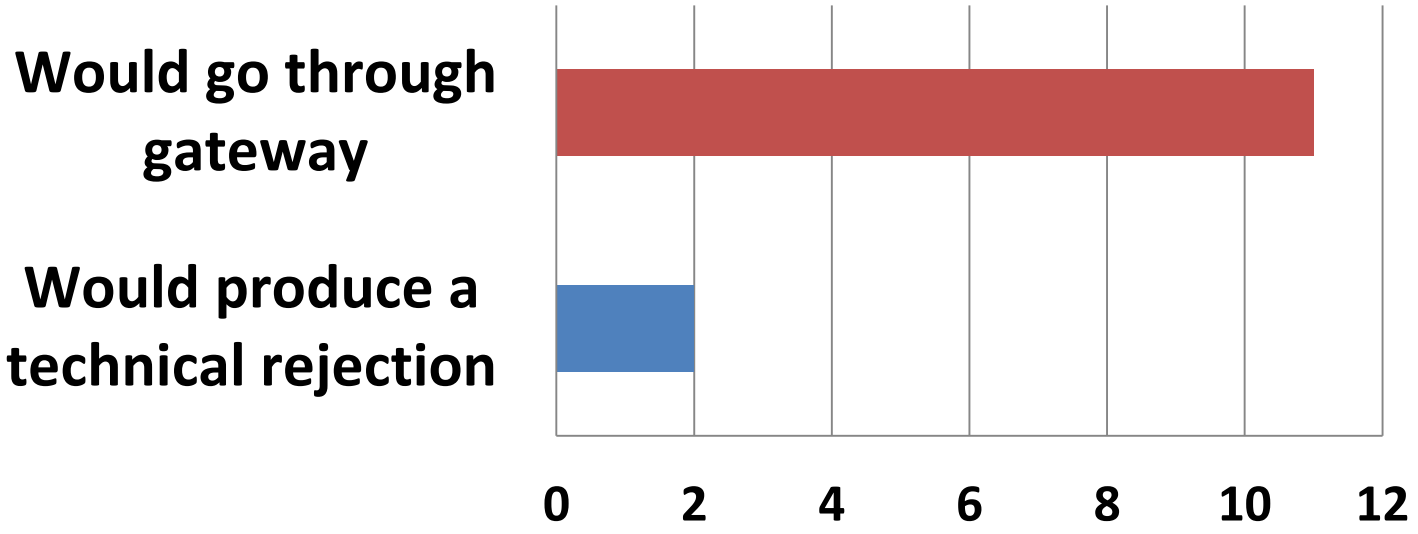
Follows the SENDIG

- Trial design is accurate and correct
- Correct Controlled Terminology

Agrees with and supports the Study Report

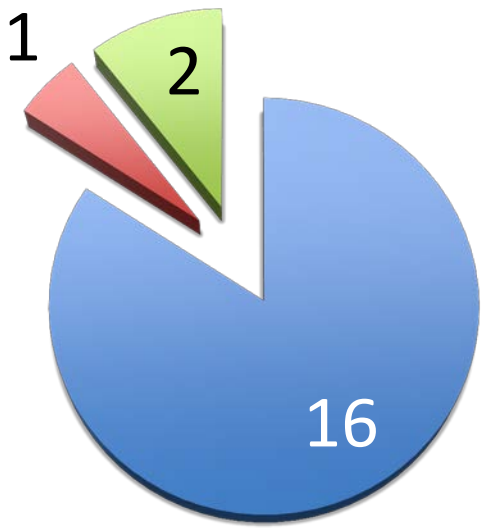
- Findings are standardized for incidence counts
- Dataset is complete
- Discrepancies or missing data are documented

Would the submission work?



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

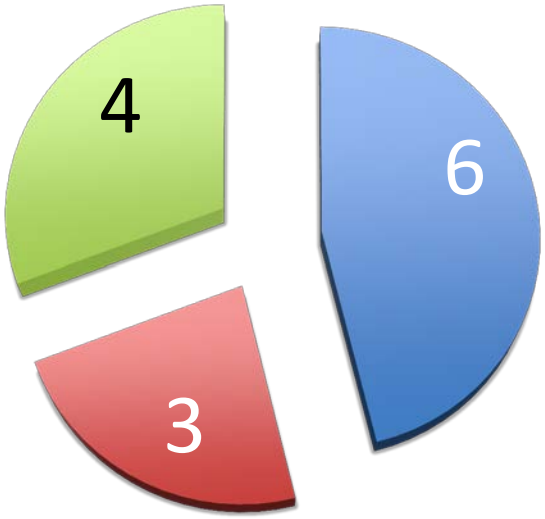
Data Integrity



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

One loaded without the comments

Submission Completeness



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

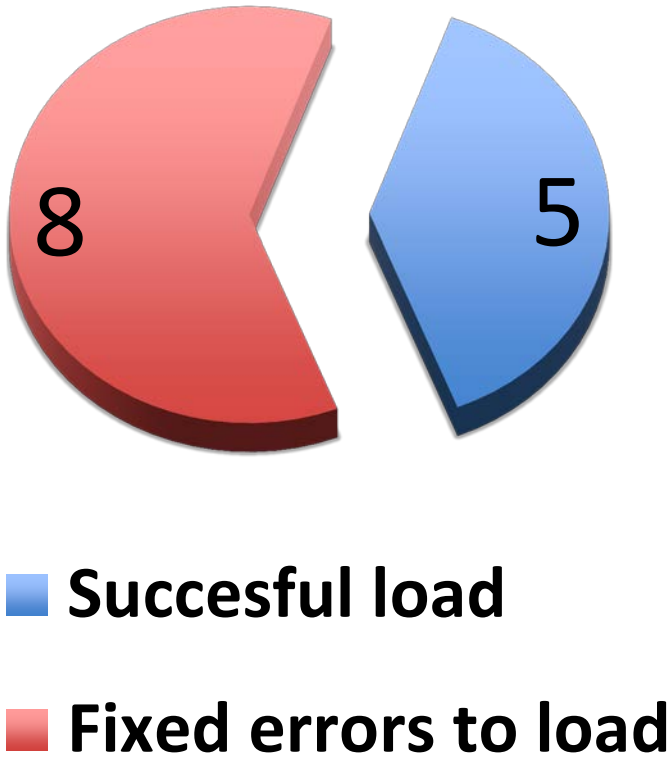
If data are modeled in SEND they should be included in the submission

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



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!

FDA/CDER

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