SEND in the Review Template

CDISC-SEND Spring 2017 F2F

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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.

The Nonclinical Review Template

FDA is establishing our 21st Century Review Procedures

IND reviewers use standard templates

Findings are documented in a structured format that can be captured in a database

Trial Summary

6.2 Repeat-Dose Toxicity

Study Title: Click here to enter text.

Study no.:

Study report location:
Conducting laboratory and location:
Date of study initiation:
Duration:

Duration Units:
GLP compliance:
QA statement:
Drug, lot #, and % purity:

Target Organs:
Target Organs:
Target Organs:
Target Organs:
Target Organs:

When the TS domain is filled out, Janus Nonclinical provides this information to the reviewers to efficiently verify and document

Lot information from EX is also displayed in Janus Nonclinical

More Trial Summary

Methods

Doses:	
Frequency of dosing:	
Route of administration:	
Dose volume:	
Formulation/Vehicle:	
Species:	
Strain:	
Dedicated Juvenile Animal Study:	
Number/Sex/Group:	
Age:	
Weight:	
Satellite groups:	
Unique study design:	
Deviation from study protocol:	

More TS parameters

All of this is key information that must be verified and documented and can be captured in a review database

What was measured?

Parameters Measured (Optional section)

Clinical Findings:
Body weights:
Food consumption:
Ophthalmoscopy:
Hematology:
Clinical chemistry:
Urinalysis:
Gross pathology:
Organ weights:
Histopathology:

Adequate Battery: yes ( ), no ( )
Peer review: yes ( ), no ( )

Other:

Filters in Janus Nonclinical make it easy to identify which clinical chemistry was measured

MI, MA, OM show what postmortem data were collected

Mortality

- Premature deaths are reviewed and documented
- The DS table makes it easy!
- The DD table can provide needed details

(Optional sample table)

Mortality (animal #, study day, cause of death)		
Dose Group	**Males**	**Females**
Sample Table		

Clinical Signs

- Clinical Signs are next in the template
- Reviewers may choose to create a table to document findings
- This table was hand-typed; Janus Nonclinical can create this table from the CL domain

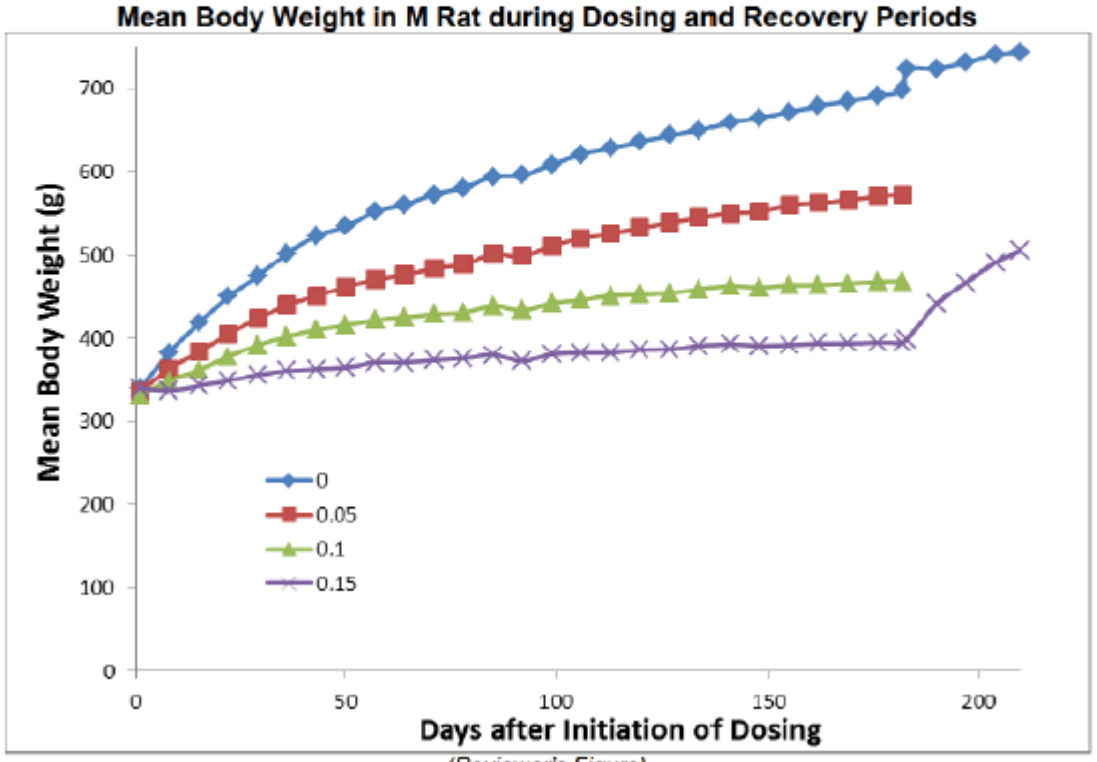
Effect of [redacted] on clinical observations (% of animals affected)								
Dosage (mg/kg/day)	0	0	0.05	0.10	0.15	0.30	0.5	1.0
Sex	M	F	M	F	M	F	M	F
Hyperactive	0/16	0/16	0/10	0/10	0/10	0/10	3/16 (19%)	0/16
Increased reactivity to stimulus	0/16	0/16	0/10	0/10	3/10 (30%)	0/10	1/16 (6%)	0/16

(Reviewer's Table)

Body Weight

Effect of [redacted] on body weight (% reduction vs. control)								
Dosage (mg/kg/day)	0	0	0.05	0.10	0.15	0.30	0.5	1.0
Sex	M	F	M	F	M	F	M	F
Body weight gain (Day 1-182)	0%	0%	34%	26%	62%	39%	85%	63%
Final body weight	0%	0%	18%	10%	33%	15%	43%	27%

(Reviewer's Table)



(Reviewer's Figure)

- If changes in body weight are observed they are documented next
- BW and BG domains provide this information
- SEND is a tremendous help – this graph was generated with OCR from the Study Report

Other In-life Observations in the Template

Food Consumption

- FW domain, a table may be provided to document changes in food or water consumption

Ophthalmoscopy

- CL Domain, any changes are noted

ECG

- EG Domain, a reviewer might make a table of major observations like tachycardia or Q/T prolongation

Labs – LB Domain

- **Hematology**
- **Clinical Chemistry**
- **Urinalysis**

Liver Markers, Males								
Dose, mg/kg	AST (U/L)		ALP (U/L)		ALT (U/L)		Bilirubin (µM)	
	wk 1	wk 4	wk 1	wk 4	wk 1	wk 4	wk 1	wk 4
Sample Table								

- Reviews typically contain a lot of LB documentation
  - Key for monitoring in clinical trials
  - Tables & graphs can be made from SEND to document changes
  - Reviewers search for data in the line listings

Postmortem Observations

- Gross pathology – MA is next in the template
- Organ Weights - OM are often documented in a table that can be created from SEND

Text Table 3.2: Test Article-Related Changes in Organ Weight Parameters - Recovery Sacrifice

	Sex	Males		Females	
	Dose Group	1	4	1	4
	Dose Level (mg/kg/day)	0	3.0	0	3.0
	Terminal body weights (g)	5200	88%	3550	87%
Adrenal					
	Absolute Weight (g)	0.588	79%	0.582	89%
	Body Weight Ratio (%)	0.0113	90%	0.0167	100%
	Brain Weight Ratio (%)	0.8602	73%	0.9450	91%
Spleen					
	Absolute Weight (g)	4.242	109%	4.831	60%
	Body Weight Ratio (%)	0.0814	125%	0.1360	69%
	Brain Weight Ratio (%)	6.1757	101%	7.7326	60%

Histopathology

Histopathology
Adequate Battery: (yes/no)
Peer Review: (yes/no)

Sampled organs can be listed from MI without retyping

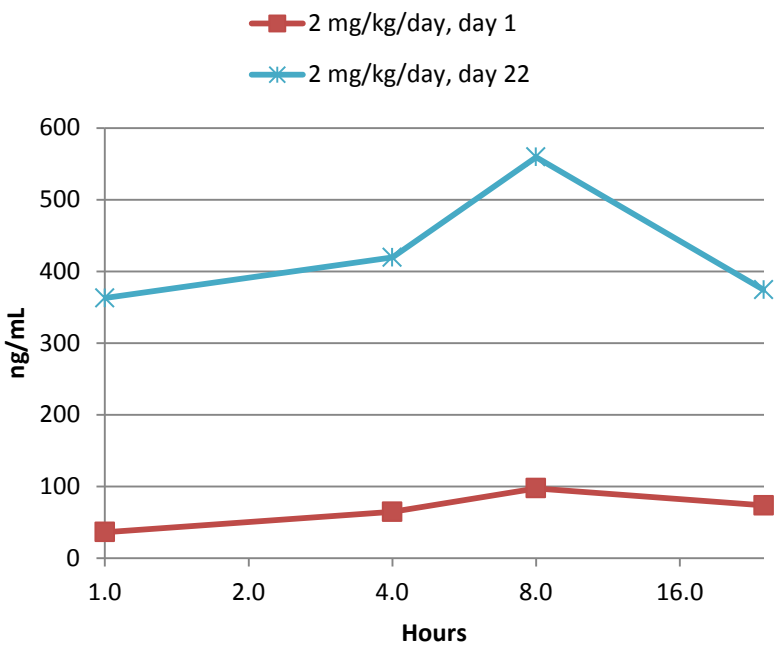
Histological Findings
(Optional sample table)

Male Histopathology, X week X Study							
Tissue	**Finding**	**Severity**	**0**	**0.1**	**0.4**	**1.6**	**6.4**
			n=10	**n=10**	**n=10**	**n=10**	**n=10**
Sample Table							
Tissue	**Finding**	**Severity**	**0**	**0.1**	**0.4**	**1.6**	**6.4**

MI makes it easy to make tables to document histopath findings

Toxicokinetics

- Reviewers independently estimate the NOAEL
- PP and PC support this section of the template
- Decisions can be documented with tables or visualizations



DOSE (mg/kg)	MALES		FEMALES	
	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng*hr/mL)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng*hr/mL)
0.1	63.2 ± 8.38	167 ± 7.06	15.0 ± 2.21	23.2 ± 2.55
0.3	155 ± 7.16	448 ± 25.2	50.1 ± 11.0	68.7 ± 11.6
1	680 ± 47.0	1340 ± 72.1	243 ± 71.9	640 ± 64.7

SEND Supports FDA Review

Strong alignment with FDA review process	Exploration and validation	Documentation of review decisions

Moving SEND Forward

Work streams from Fit for Use

SEND 3.1

- Cardiovascular & Respiratory Safety Pharmacology
- Nervous System in draft

DART – Development and Reproductive Toxicity

- Development of proof of concept scripts
- Community pilot to evaluate standard

Genetic Toxicity in draft

Voluntary SEND submissions warmly welcome