SEND for CBER

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PharmaSUG 2021

Learning Objectives

- Describe CBER's requirement and support on SEND for CBER
- Know the important data points for CBER non-clinical studies
- Know the perspective from review's point of view
- Know the future development on SEND for CBER

SEND for CBER Requirement

"The Center for Biologics Evaluation and Research (CBER) intends to receive SEND datasets in future submissions."

Use	Data Exchange Standard	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)
Animal study datasets	SEND	3.1	CDER	08/21/2017		03/15/2019 [1] 03/15/2020 [2]
Animal study datasets	SEND	3.1	CBER	03/15/2021		03/15/2023

We are on the way!
Assessing, Analyzing, Recommending, Piloting, Implementing

Federal Register Notice was published in July 2020, announcing CBER's support and future requirement for SEND

PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Notice.

SUMMARY:

The Food and Drug Administration (FDA or Agency) Center for Biologics Evaluation and Research (CBER) is announcing support for the current version of Clinical Data Interchange Standards Consortium (CDISC) Standard for the Exchange of Nonclinical Data (SEND) and an update to the FDA Data Standards Catalog for the submission of nonclinical data in new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications (INDs). This update does not apply to noncommercial INDs for a product that is not intended for commercial distribution (research and investigator-sponsored INDs); INDs and BLAs for devices that are regulated by CBER as biological products under the Public Health Services (PHS) Act; and submissions for blood and blood components, including Source Plasma.

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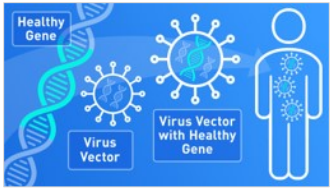
Important data points for CBER non-clinical studies

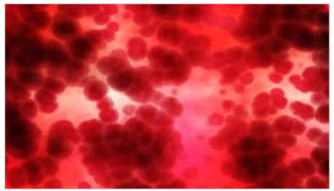
CBER Review Offices

- Office of Vaccine Research and Review (OVRR)

- Office of Tissues and Advanced Therapies (OTAT)



- Office of Blood Research and Review (OBRR)



• Office of Vaccine Research and Review (OVRR)

❖ Products Reviewed

- Vaccines for prevention or treatment of infectious disease indications only
- Allergenics
- Miscellaneous biologics:
  - Fecal microbiota transplants
  - Probiotics
  - Phage products

❖ Nonclinical Studies

- **Single and repeat dose toxicology**
- **Developmental and reproductive toxicology (DART)**
- **Genotoxicity, safety pharmacology (allergenics)**
- **Immunogenicity**
- Proof-of-concept, efficacy
- **Biodistribution**
- No chronic toxicity or carcinogenicity

❖ Data Consideration

- Timing of endpoints following vaccinations
- Draize Scoring
- Body temperature
- Acute phase reactants
- Immunogenicity/Serology Assays
- Injection site histology

Study and data types well aligned with SEND roadmap

• Office of Tissues and Advanced Therapies (OTAT)

❖ **Products Reviewed**

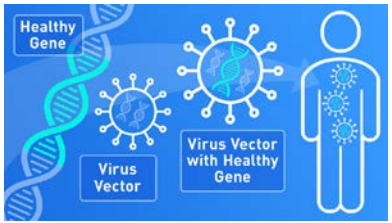
- Stem cell and stem-cell-derived products
- Somatic cell products
- Xenotransplantation products
- Certain devices and combination products
- Therapeutic vaccines
- Recombinant or plasma derived proteins
- Wound healing products
- Gene therapy

❖ **Nonclinical Studies**

- **Proof-of-concept/safety/toxicity**
- Cell-fate/biodistribution, typically no PK studies
- Differentiation/integration capacity
- Tumorigenicity: required for stem cell therapy
- Biocompatibility (implantable scaffolds)
- **Immunogenicity (therapeutic vaccines)**

❖ **Data Consideration**

- Animal model of disease/injury
- Hybrid safety and activity studies
- Distribution/biodistribution assessments
- Biocompatibility of devices



SEND for CBER Team will be working closely with CDISC on developing IS Domain for Nonclinical Immunogenicity Data

- **Office of Blood Research and Review (OBRR)**
  - **Products Reviewed**
    - Modified blood components
    - Hemoglobin-based oxygen carriers
    - Container-closure systems
    - Process-related impurities
    - Excipients
    - Pathogen reduction systems
  - **Nonclinical Studies**
    - Focused on biocompatibility
    - Extractables and leachables testing
    - Container closure systems
    - Occasionally see developmental or embryo-fetal toxicology for replacement proteins
    - Proof-of-concept
    - **Carcinogenicity**
  - **Data Consideration**
    - **GLP-compliant toxicology studies only requested on a case-by-case**
    - Most nonclinical studies received are not amenable to SEND data
    - Systemic toxicity (biocompatability, hemoglobin-based oxygen carriers),
    - Mutagenicity (impurities, extractables, leachables)

Most Nonclinical studies are not amenable to SEND data

Roadmap of SEND for CBER

Key Activities	June 2018-Dec 2019	Nov 2019 - Jun 2020	Jul-20	Dec-20	Mar 15 2021	Mar 15 2023
SEND IG 3.1 Review	Deep review of domains, examples, terminology					
Conduct Proof of Concept		Donated studies w/ team analysis on CDISC WIKI				
Develop Gap Analysis and Recommendations				Assessment Summary Report on CDISC WIKI		
FDA Federal Register Notice Docket No. FDA-2020-N-1313			FRN published		SENDIG V3.1 Supported	SENDIG V3.1 Required

- SEND for CBER Team was a strong collaboration between FDA and CDISC SEND Experts

FDA

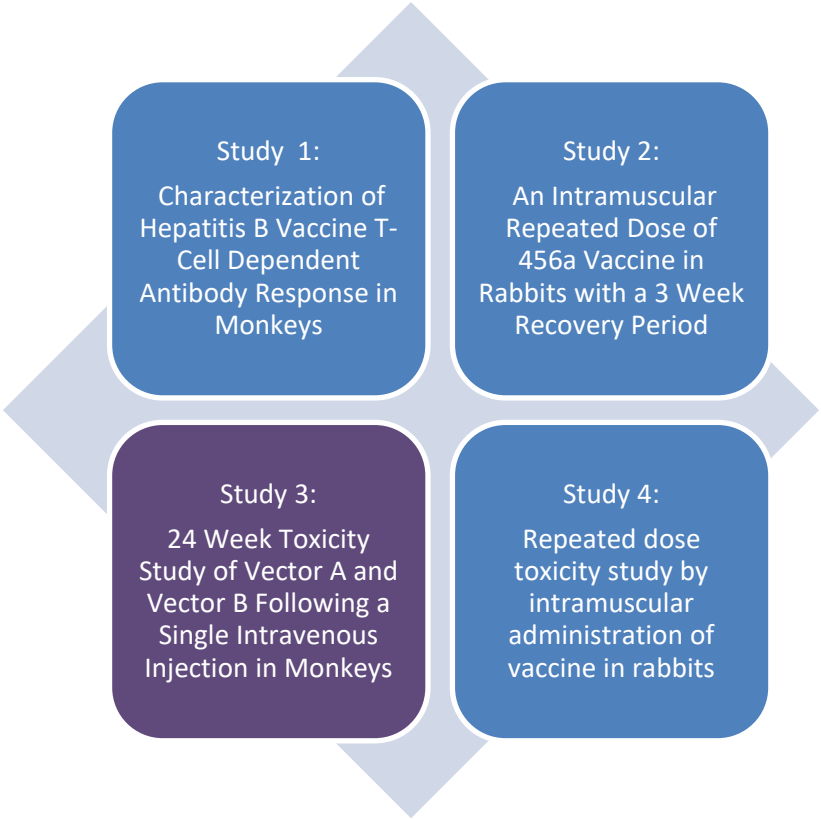
Drug/Vaccine Development Sponsors

CROs

Data Service Providers

Software Vendors

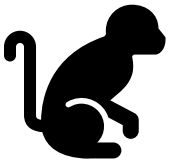
Proof of Concept Pilot Studies



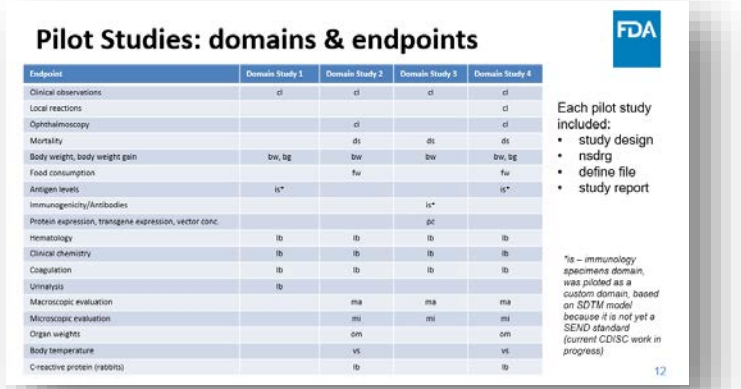
- Four Studies in two modalities were donated to the Pilot:
  - 3 Vaccine
  - 1 Gene Therapy
- No study suitable for OBRR consideration was donated

https://wiki.cdisc.org/display/SEND/Proof+of+Concept+Study+Reviews

Proof of Concept Pilot Endpoints



Endpoints evaluated:



- Clinical observations
- Local tolerance
- Ophthalmoscopy
- Mortality
- Body weight, Food consumption
- Plasma activity and antigen levels
- Immunogenicity/Antibody development
- Clinical pathology – standard hematology , clinical chemistry, urinalysis
- Terminal procedures: comprehensive macroscopic and microscopic evaluation
- Organ weight
- Body temperature
- Specifically noted for Vaccines: C-reactive protein (in rabbits)

Pilot Studies: domains & endpoints

Endpoint	Domain Study 1	Domain Study 2	Domain Study 3	Domain Study 4
Clinical observations	cl	cl	cl	cl
Local reactions				cl
Ophthalmoscopy		cl		cl
Mortality		ds	ds	ds
Body weight, body weight gain	bw, bg	bw	bw	bw, bg
Food consumption		fw		fw
Antigen levels	is*			is*
Immunogenicity/Antibodies			is*	
Protein expression, transgene expression, vector conc.			pc	
Hematology	lb	lb	lb	lb
Clinical chemistry	lb	lb	lb	lb
Coagulation	lb	lb	lb	lb
Urinalysis	lb			
Macroscopic evaluation		ma	ma	ma
Microscopic evaluation		mi	mi	mi
Organ weights		om		om
Body temperature		vs		vs
C-reactive protein (rabbits)		lb		lb

Each pilot study included:

- study design
- nsdrg
- define file
- study report

**is – immunology specimens domain, was piloted as a custom domain, based on SDTM model because it is not yet a SEND standard (current CDISC work in progress)*

Pilot Outcomes: *Study Findings Considerations*

KEY BENEFITS

Quick data overview

Consistent terms and units

Original results available

Alignment with Study Report

- Using SEND data enables quick overview of data, such as:

  Seeing differences between scheduled body weight measurements, Identifying body temperatures above normal, Determining key timepoints of collection relative to dosing (i.e. was CRP measured 24, 48 hrs postdose?)
- Correct mapping to controlled terminology and consistent units within/between SEND data, Study Report and nSDRG is helpful
- Use of variables in the SEND data needs to be consistent with SEND IG definitions, for clarity and utility
- Original result values in SEND (--ORRES) are very useful to see the full text of the observation as collected. Standardization of --ORRES parses content into parent domain variables or comment domain or supplemental qualifiers, such that sometimes difficult to reconstruct.
- Quantification of LOQ or BLQ values are useful when included in supplemental qualifiers

Pilot Outcomes: *SEND "Package" Considerations*

- **Study designs for single and repeat dose tox studies fit into SEND trial design domains**
  - Study design descriptions in nSDRG are very helpful
- **Important information dependencies:**
  - Clear description of differences between SEND dataset and study report in nSDRG
  - Consistency between Define file and dataset content
  - Explanation of extended terminology in nSDRG

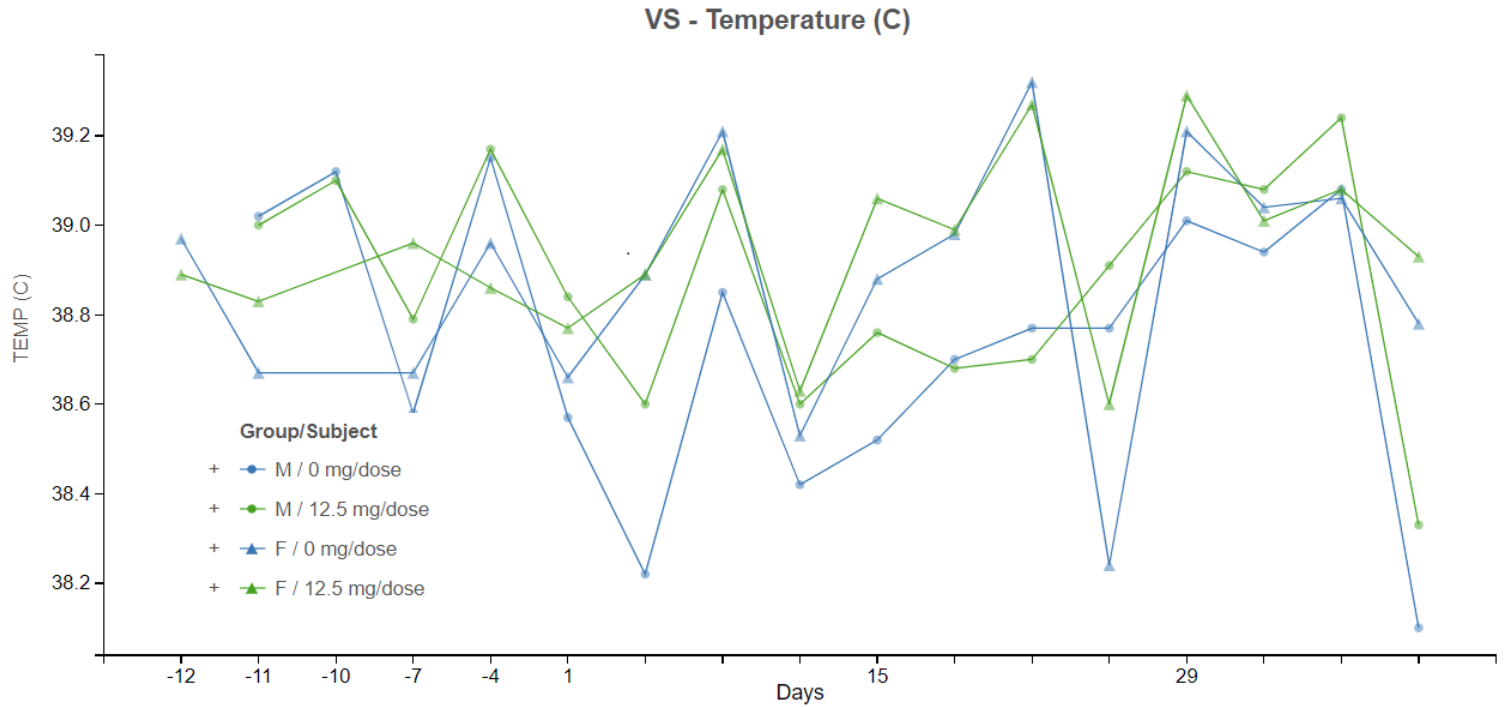
Pilot Outcomes: *Other Considerations*

- **Study "hybrid" e-data submissions are possible**
  - Nonclinical studies submitted to CBER can include some endpoints modeled in SEND and other endpoints not modeled in SEND
    - Efficacy endpoints within a tox study are not modeled in SEND IG 3.1
    - Not all endpoints for CBER studies are yet in scope of SEND
- **All data that can be submitted in SEND is helpful to the review**
  - Biodistribution data can be modeled using PC domain, though not specifically mentioned in SEND IG yet
  - "IS" Custom domain is not required, but can be accepted, or data (such as ADA) may fit in LB domain, under SEND IG 3.1
  - Clarify for Reviewers which data has been submitted in e-format or not, in nSDRG
- **As future SEND IG versions come into publication and adoption by CBER, e-data scope is expected to expand accordingly**

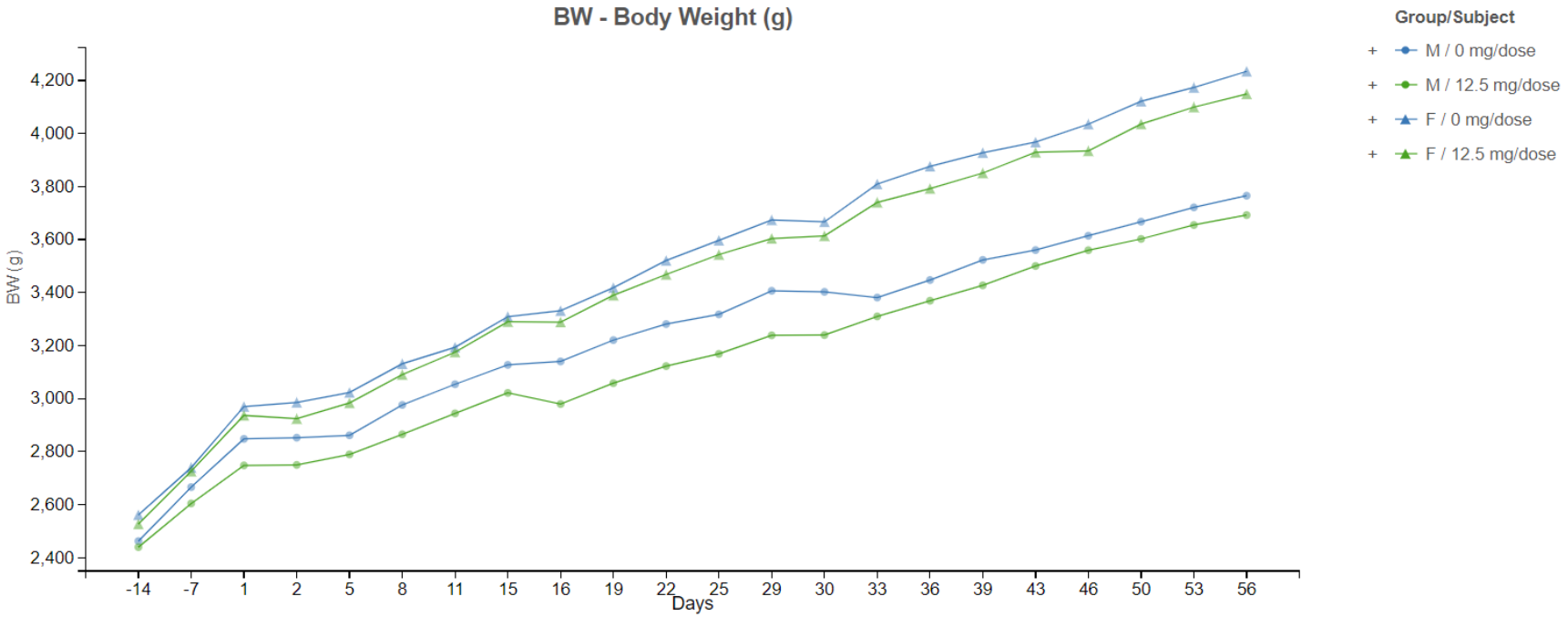
Reviewer's Point of View

- **CBER Reviewers' Training and Support**
  - ❖CDISC study data standards
  - ❖Analysis tools including JMP, JMP Clinical, SEND Explorer
  - ❖Going through data standards validation check
  - ❖Exploring data by using tools and evaluating define.xml and non-clinical study data reviewers guide

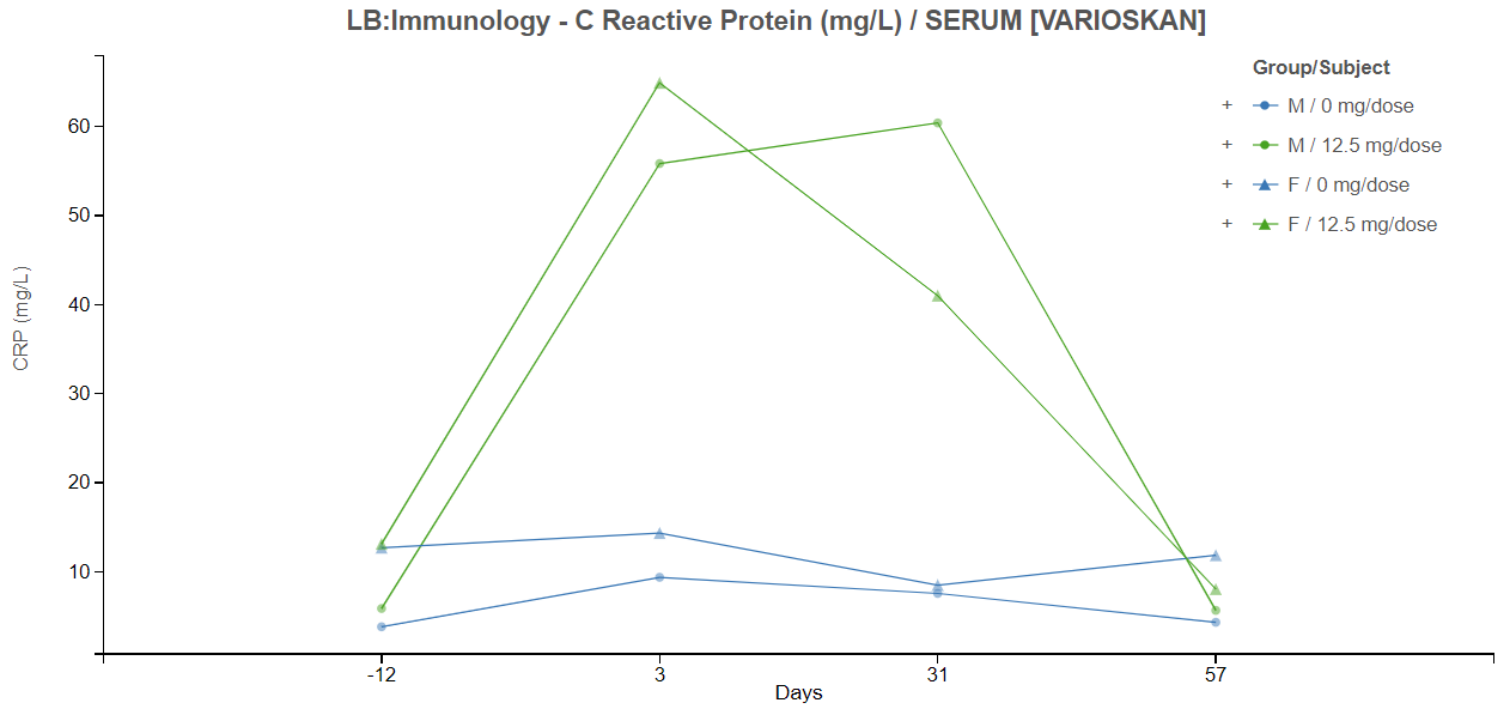
Temperature Levels



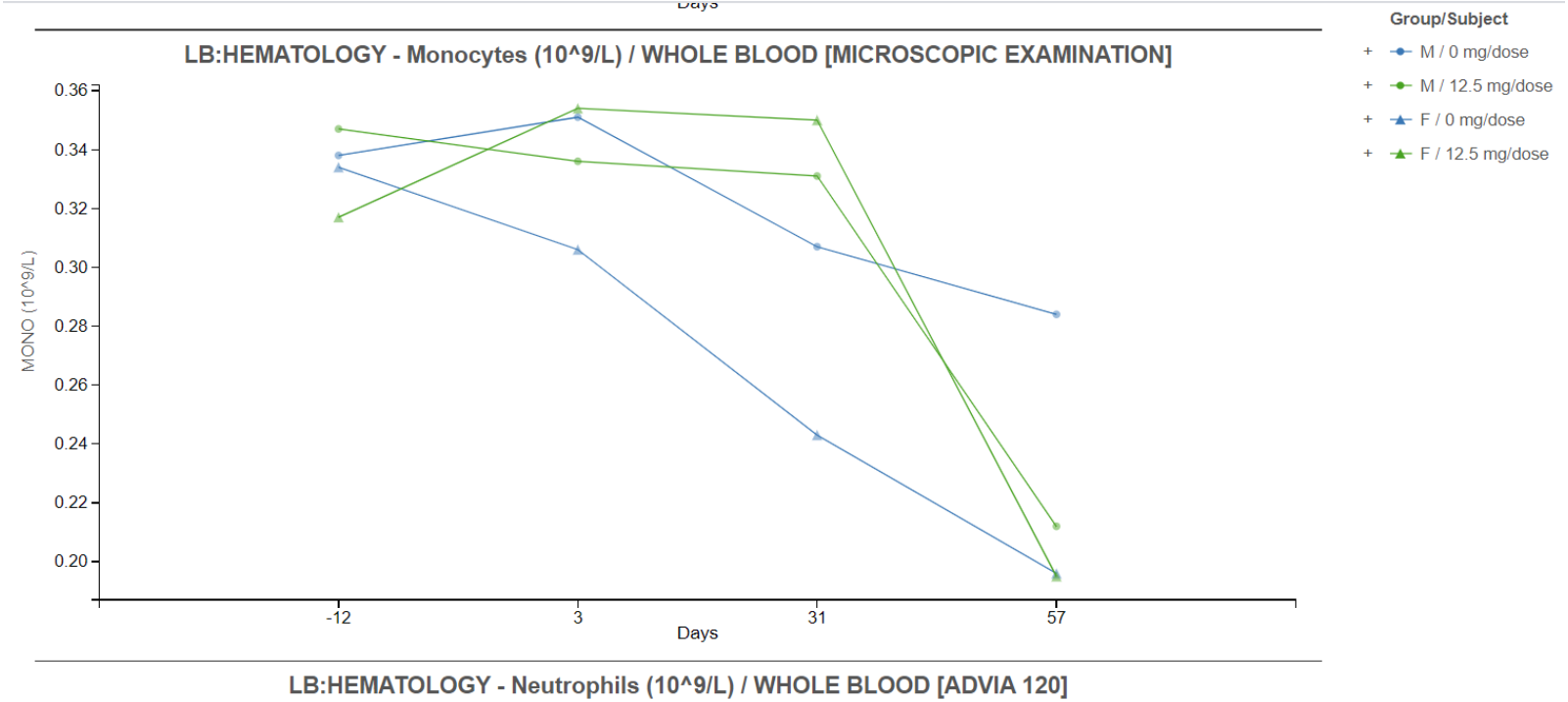
Body Weight Changes



C-Reactive Protein Levels



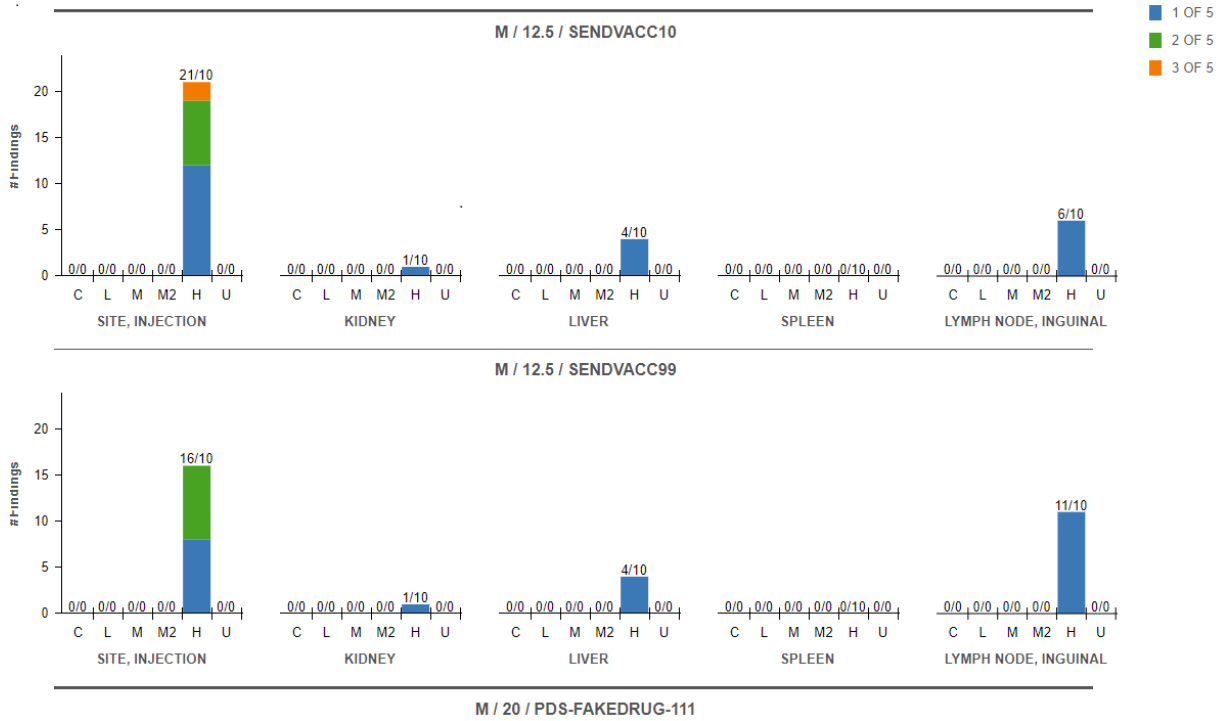
Monocyte Levels



Microscopic Findings-Table

LYMPH NODE, ILIAC	UNREMARKABLE				11	1	1	1	1	1	1	1	1	1	1	10										1	1
LYMPH NODE, ILIAC	Erythrocytosis	NON-NEOPLASTIC	1 OF 5		1											0								1			1
LYMPH NODE, ILIAC	Increased cellularity	NON-NEOPLASTIC	1 OF 5		2											0						1	1				2
LYMPH NODE, ILIAC	Increased cellularity	NON-NEOPLASTIC	2 OF 5		7											0	1	2	1	2	1			1	1		7
LYMPH NODE, ILIAC	Increased cellularity	NON-NEOPLASTIC	3 OF 5		2											0			1		1						2
				LYMPH NODE, ILIAC Examined:	20	1	1	1	1	1	1	1	1	1	1	10	1	1	1	1	1	1	1	1	1	1	10
LYMPH NODE, MESENTERIC	UNREMARKABLE				18	1	1	1	1	1	1	1	1	1	1	10	1	1	1	1		1	1		1	1	8
LYMPH NODE, MESENTERIC				NOT DONE	2											0					1			1			2
				LYMPH NODE, MESENTERIC Examined:	18	1	1	1	1	1	1	1	1	1	1	10	1	1	1	1		1	1		1	1	8
SITE, APPLICATION	UNREMARKABLE				20	3	3	3	3	2	3	3	3	3	3	10	1	2	1	1	1	3	1	3	3	2	10
SITE, APPLICATION	Cellular debris	NON-NEOPLASTIC	1 OF 5		1											0	1										1
SITE, APPLICATION	HEMORRHAGE	NON-NEOPLASTIC	1 OF 5		1											0	1										1
SITE, APPLICATION	HEMORRHAGE	NON-NEOPLASTIC	2 OF 5		2											0		1			2						2
SITE, APPLICATION	Infiltration, mixed cell	NON-NEOPLASTIC	1 OF 5		3											0	1		1	1							3
SITE, APPLICATION	Infiltration, mononuclear cell	NON-NEOPLASTIC	1 OF 5		5											0			1	1	1		2			1	5
SITE, APPLICATION	Inflammation, mixed cell	NON-NEOPLASTIC	2 OF 5		2											0				1	1						2
SITE, APPLICATION	Inflammation, mixed cell	NON-NEOPLASTIC	3 OF 5		2											0		1			1						2
SITE, APPLICATION	Inflammation, mononuclear cell	NON-NEOPLASTIC	1 OF 5		1					1						1											0
SITE, APPLICATION	Necrosis	NON-NEOPLASTIC	2 OF 5		1											0				1							1
SITE, APPLICATION	Necrosis	NON-NEOPLASTIC	3 OF 5		2											0		1			1						2
				SITE, APPLICATION Examined:	20	1	1	1	1	1	1	1	1	1	1	10	1	1	1	1	1	1	1	1	1	1	10
SPLEEN	UNREMARKABLE				11	1	1	1	1	1	1	1	1	1	1	10								1			1
SPLEEN	Increased cellularity	NON-NEOPLASTIC	1 OF 5		4											0					1	1	1			1	4
SPLEEN	Increased cellularity	NON-NEOPLASTIC	2 OF 5		5											0	1	1	1	1					1		5
				SPLEEN Examined:	20	1	1	1	1	1	1	1	1	1	1	10	1	1	1	1	1	1	1	1	1	1	10

Microscopic Findings-Graph



SEND For CBER Team Future *Ongoing Mission*

- **Support CDISC SEND Team to include CBER considerations in standards development by:**
  - Participating in domain working groups for Exposure, Immunogenicity Specimens and modeling of dermal/ocular findings
  - Contributing to relevant controlled terminology development
  - Contributing to CDISC SEND IG version 3.2 scope decisions and development
  - Remain engaged, as future SEND IG versions come into publication and adoption by CBER, scope is expected to expand accordingly (i.e. repro studies)
- **Support FDA's data standards efforts by:**
  - Developing recommendations for Technical Conformance Guide
  - Considering conformance and business rules applied to CBER e-data submissions
  - Communicating Proof of Concept Pilot and other team deliverables to industry stakeholders

Summary

- CBER is ready to support SEND data for non-clinical study submissions
- Requirement date of CBER SEND submission is March 15, 2023
- Future development on SENDIG for CBER

Resources

- *FDA Data Standards Catalog*
- *Federal Register Notice regarding SEND for CBER*
- *FDA Data Standards Program Action Plan*
- *SEND for CBER wiki site*

U.S. FOOD & DRUG ADMINISTRATION

Questions?

cber-edata@fda.hhs.gov