# Study Data Standards Update for CBER:
## Your Guide To A Successful Submission

## October 2022

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# Overview

- Non-Clinical Data:
  - CBER requirements for Standard for Exchange of Nonclinical Data (SEND) and Technical Rejection Criteria (TRC)
  - SEND data common issues
- Clinical Data:
  - CBER Study Data standards validation Process
  - Common data validation issues
- Resources

# Non-Clinical Data:
# CBER requirements for Standard for Exchange of Nonclinical Data (SEND) and Technical Rejection Criteria (TRC)

# "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) [10] [11] |
|---|---|---|---|---|---|---|
| Animal study datasets | SEND | 3.1 | CDER | 08/21/2017 | | 03/15/2019 [1]<br>03/15/2020 [2] |
| Animal study datasets | SEND | 3.1 | CBER | 03/15/2021 | | 03/15/2023 |

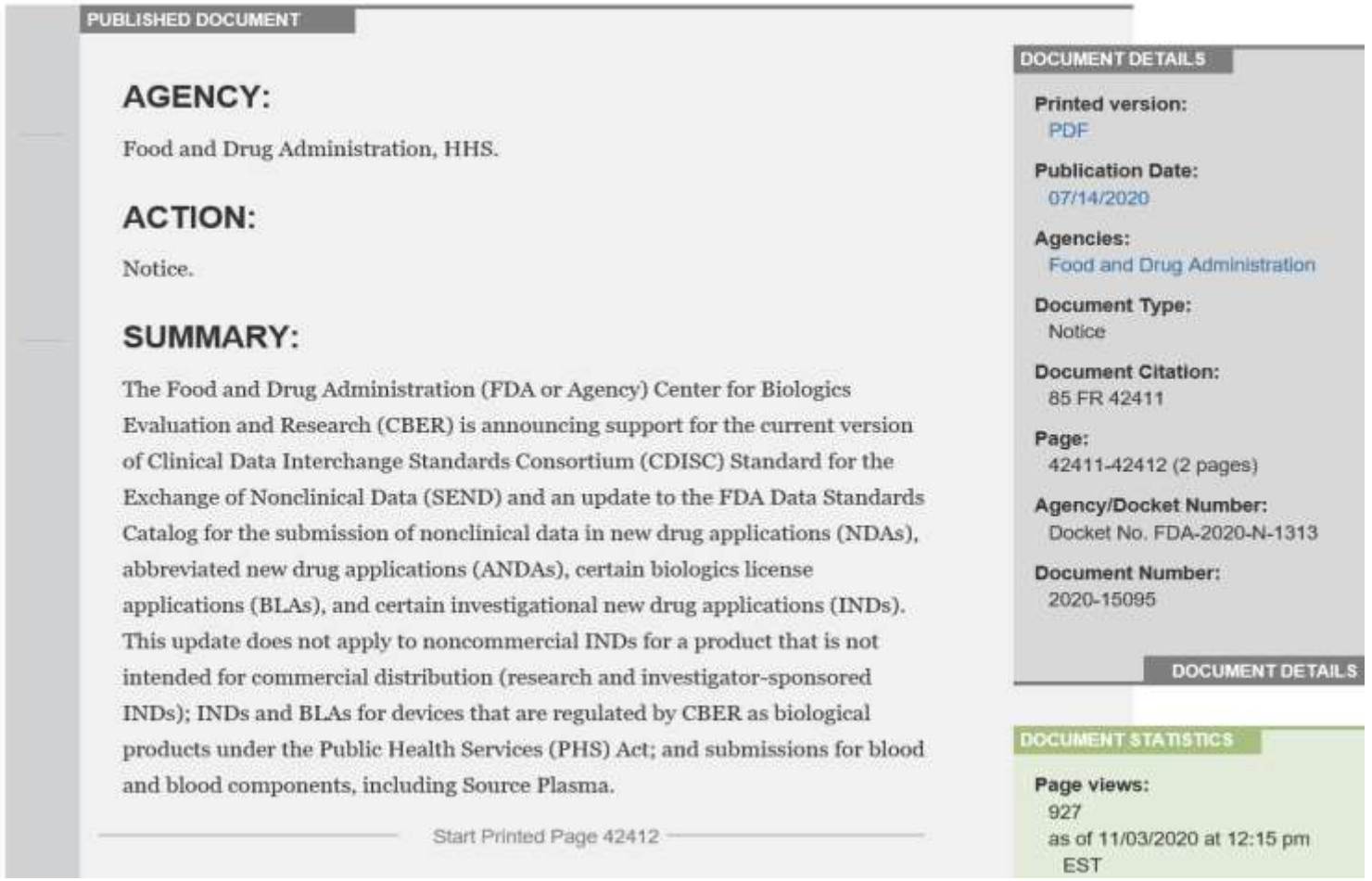
cdisc + FDA

## WE ARE ON THE WAY!
## ASSESSING, ANALYZING, RECOMMENDING, PILOTING, IMPLEMENTING

[1] Jhttps://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources (July 2022)

# Nonclinical studies that start after March 15, 2023 must be in SEND format for submission to CBER

*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.

Start Printed Page 42412

DOCUMENT DETAILS

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https://www.federalregister.gov/documents/2020/07/14/2020-15095/electronic-submissions-data-standards-support-for-standard-for-the-exchange-of-nonclinical-data

# FDA Technical Rejection Criteria For Study Data

| | |
|---|---|
| 1734 | • Trial Summary dataset (ts.xpt) must be present for each study in eCTD. |
| 1736 | • DM dataset and define.xml must be submitted in module 4. |

**CBER WILL BEGIN VALIDATION ON MARCH 16, 2023.**

# Non-Clinical Data:
# SEND data common issues

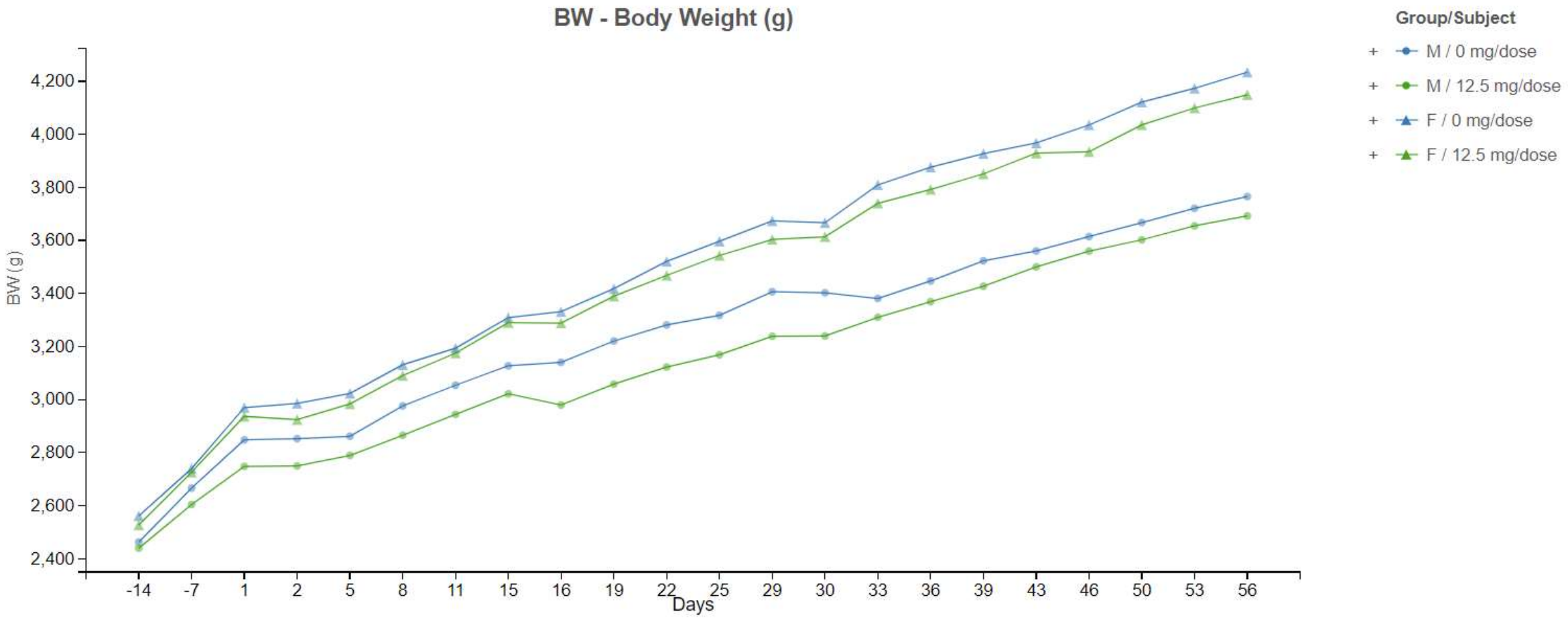
# SEND Data Exploration

- Data standards group loads SEND data in SEND Explorer immediately after receiving the submission data

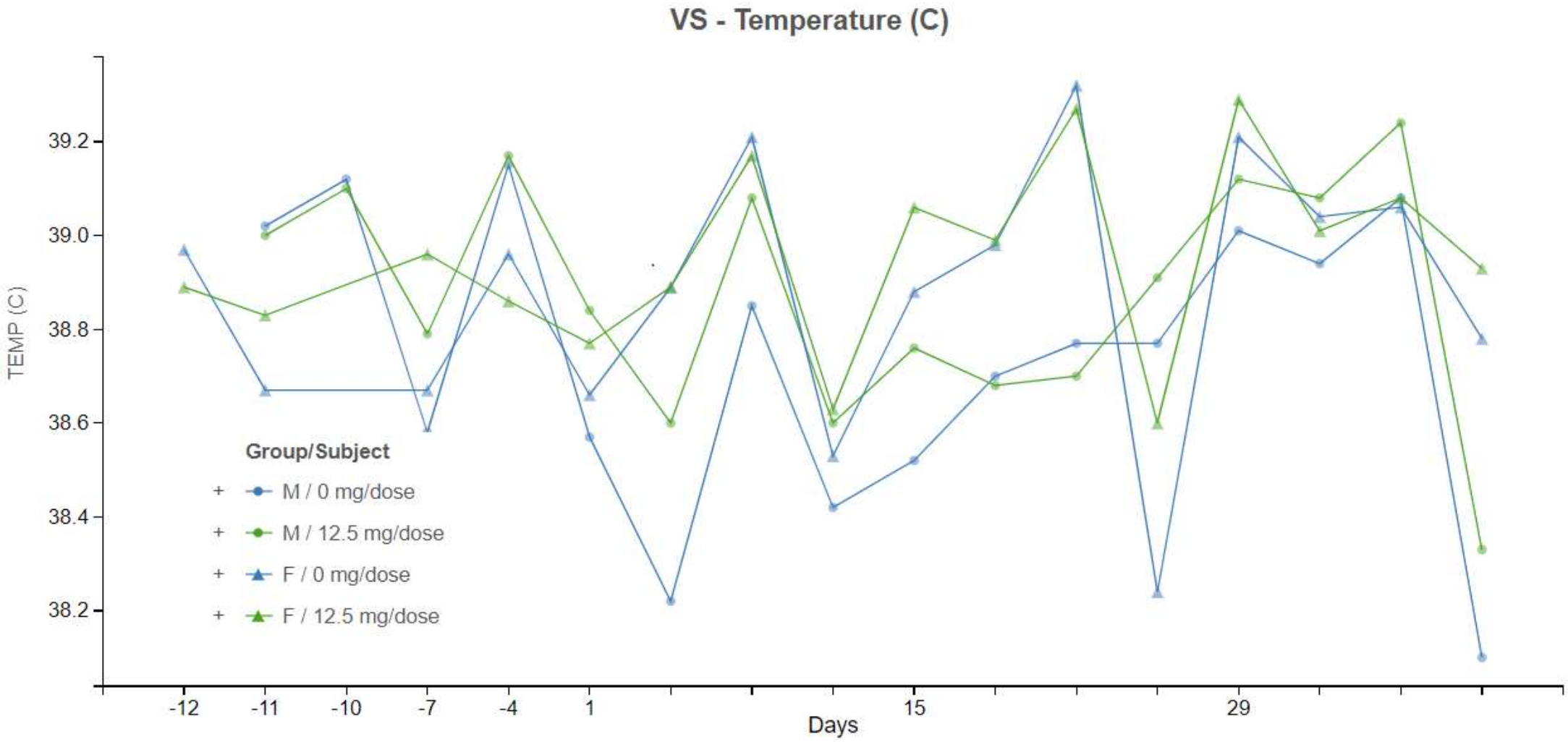
- Data standards group grants access to reviewers to SEND explorer

- Reviewers use SEND Explorer and JMP/JMP Clinical for visualization, query and data summarization

# Body Weight Changes



# Temperature 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 |

# SEND Data Loading Issues

Upload Study Data  Next Scheduled Load: 2/1/21 12:00 AM

Presets ▼  Save as Preset

◀◀ ◀ 1 of 6 ▶ ▶▶ | Rows 108 of 3,413 | Select Columns | Reset | Export ▼ | Study Dashboard

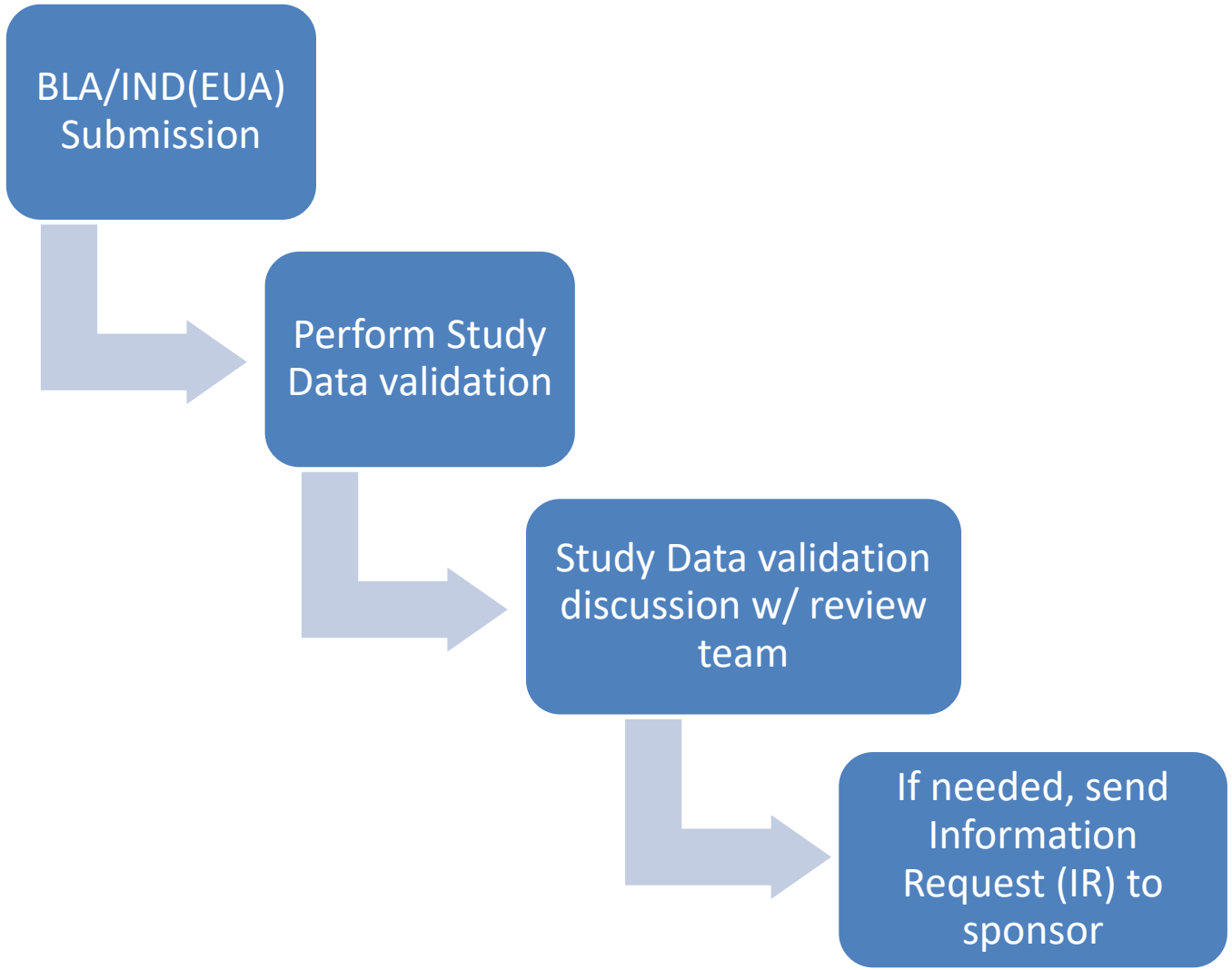
| Application ID | Study ID | Sponsor Reference ID | Treatment | Species | Study Title | Study Type | Study Start Date | Domains | Last Loaded Date | Load |
|---|---|---|---|---|---|---|---|---|---|---|
| IND 12345 | OPQ | NOT APPLICABLE | TRPC-05 | DOG | TRPC-05: 28-Day Oral Dose Toxicity and Toxicokinetic Study in Beagle Dogs with 28-Day Dose-free Recovery | REPEAT DOSE TOXICITY | 1/23/19 | BW, CL, DM, DS, EG, EX, FW, LB, MA, MI, OM, PC, PP, RELREC, SE, SUPPMA, SUPPMI, SUPPPC, TA, TE, TS, TX | 6/10/22 11:27 AM | ☐ |
| IND 54321 | ABCD | NOT APPLICABLE | 7HP349 also called MPTHE-09 | RAT | MPTHE-09:28 DAY REPEAT DOSE ORAL GAVAGE TOXICITY AND TOXICOKINETICS STUDY IN SPRAGUE-DAWLEY RATS WITH 28-DAY RECOVERY PERIOD | REPEAT DOSE TOXICITY | 7/31/17 | BG, BW, CL, CO, DM, DS, EX, FW, LB, MA, MI, OM, PC, POOLDEF, PP, SE, SUPPMA, SUPPMI, TA, TE, TS, TX | 6/10/22 11:27 AM | ☐ |

# SEND Data Loading Issues

- Domains with duplicate IDs (in pooldef, pp – Pharmacokinetic Parameters, fw – food and water consumption domains)
- TS (Trial Summary) or TX (Trial Sets) domains were not submitted
- Missing RFSTDTC (Reference Start date)

# Clinical Data:
# CBER Study Data standards validation Process

# Study Data Validation Process



# Study Data Validation Process: Common Issues

## AE related issues

- Inconsistency coding of the exact same term value

| aeterm | aellt | aedecod | aehlt | aehlgt | aebodsys |
|---|---|---|---|---|---|
| **ELEVATED BLOOD GLUCOSE** | BLOOD GLUCOSE INCREASED | BLOOD GLUCOSE INCREASED | CARBOHYDRATE TOLERANCE ANALYSES (INCL DIABETES) | METABOLIC, NUTRITIONAL AND BLOOD GAS INVESTIGATIONS | INVESTIGATIONS |
| **ELEVATED BLOOD GLUCOSE** | HYPERGLYCEMIA | HYPERGLYCAEMIA | HYPERGLYCAEMIC CONDITIONS NEC | GLUCOSE METABOLISM DISORDERS (INCL DIABETES MELLITUS) | METABOLISM AND NUTRITION DISORDERS |

# Study Data Validation Process: Common Issues

## AE related issues:

- No severity or toxicity grade populated
- SDTM AE that are not present in ADAE and vice versa
- Treatment emergent flag in SDTM is not consistent with ADaM treatment emergent flag
- ADAE.TRTEMFL not equal to Y, but ASTDT is within treatment period
- Serious adverse events are missing seriousness criteria
- AEOUT is inconsistent with AEENDTC

# Study Data Validation Process: Common Issues

## CE related Issues:

- CESTDTC, CEENDTC, or CESTRTPT (ongoing not flagged) not provided for reactogenicity data
- Clinical Events have neither severity or toxicity grade provided
- CE duration determined inaccurately
- Multiple rows for one event one subject (maybe due to different severity)

# Study Data Validation Process: Common Issues

## DM related issues:

- Subjects present in another domain but not found in DM domain
- Missing sex/race/country for treated subjects
- Missing important dates in DM

## MH related issues:

- Inconsistent value for MHDECOD

# Study Data Validation Process: Common Issues

## LB related issues:

- Standard units missing
- Inconsistent unit values
- Missing Reference Range Upper/Lower Limit
- LBNRIND = NORMAL, but result is greater than normal range high

# Study Data Validation Process: Common Issues

## Dates related issues:

- Medical history events dates are after treatment start dates
- Records in different domains with dates happen after end of participation date in DM
- Events are missing start and end time-point

# Study Data Validation Process: Common Issues

## Documentation (aCRF, define, reviewers' guide) related issues:

- Incorrect file name, such as reviewers-guide.pdf or adifine.xml instead of csdrg.pdf or define.xml
- Documentation located in the wrong place
- No bookmarks or wrong bookmarks (SDTM Reviewer's Guide or Define.xml)
- No annotations in aCRF

# Study Data Validation Process: Common Issues

## Documentation (aCRF, define, reviewers' guide) related issues:

- Inconsistent version of MedDRA listed in Define.xml and SDTM Reviewer's Guide
- Variable listed as derived, but no computational method is provided
- Derivations reference variables in raw data, but raw data was not submitted

# Study Data Validation Process: Common Issues

## Documentation (aCRF, define, reviewers' guide) related errors:

- Domain referenced in define.xml but dataset is missing
- ADaM datasets were submitted, but are not listed in the ADaM define.xml
- Define.xml for a different study
- No explanations of issues in reviewer's guide

# Study Data Validation Process: Common Issues

## Other issues:

- Inconsistent variable length
- Study subjects with missing baseline flags
- Data submitted in the wrong folder
- Missing values for one or more MedDRA variables
- Comments provided in other domains instead of CO

# Summary

- CBER is ready to support SEND data for non-clinical study submissions
- SEND is required for studies that **start after March 15, 2023**
- CBER validation process for clinical data, common issues should be avoided

# Resources

- *Federal Register Notice regarding SEND for CBER*
- *FDA Data Standards Catalog*
- *Study Data Technical Conformance Guide*
- *FDA Study Data Standards Resources*

# Questions?

*Email:* cber-edata@fda.hhs.gov for any questions regarding study data submissions to CBER