CDER Small Business and Industry Assistance (SBIA)
WEBINAR SERIES

FDA

COMMON ISSUES WITH SEND DATA SUBMITTED FOR SAFETY PHARMACOLOGY STUDIES

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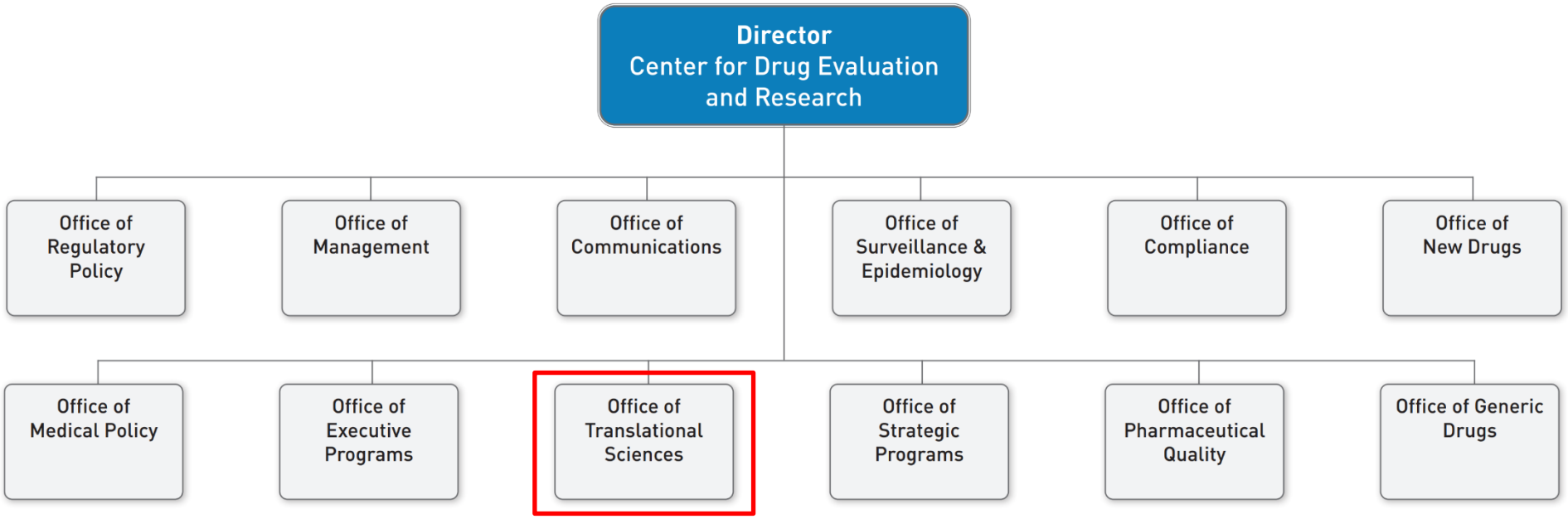
November 16, 2023

Agenda

- Background
- OCS Nonclinical Services Overview
- Common Data Issues for SENDIGv3.1

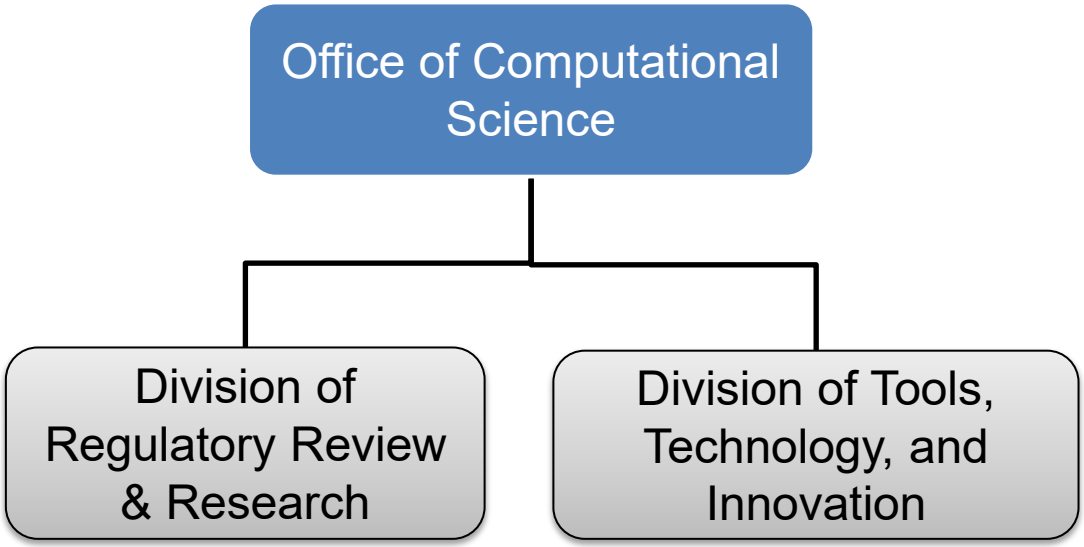
BACKGROUND

CDER Organization Chart



- OCS is under the Office of Translational Sciences in CDER
- OCS supports multiple Offices across the Center
- Interacts with other Offices within Center for various initiatives

OCS Mission and Vision



- Provide CDER reviewers solutions that improve the scientific review process by integrating data, tools, and training
- Drives modernization of CDER's scientific review process through the implementation of tools, services, and training to enable reviewers to apply their expertise to information

The KickStart Service

Key Concepts

1. KickStart is offered by OCS to all Pharm/Tox reviewers for their applications.
2. Pre-KickStart Training includes overviews of:
   - The SEND Standard
   - Nonclinical Study Data Reviewers Guide (nSDRG)
   - Define.xml
   - FDA Tool features
3. The KickStart Service covers:
   - A data fitness assessment with sponsor report and details to reviewer for issues that impact use of data
   - Shows reviewers how to explore study data using FDA tools and how to produce tables and graphs that can be used in review documents
   - Prepare graphs and tables for key analyses using FDA tools

OCS NONCLINICAL SERVICES OVERVIEW

OCS Nonclinical Services Background

- The vision for OCS Nonclinical Services is to provide CDER nonclinical review teams with a collection of services that enable an effective evaluation of a new drug or biologic application using submitted electronic data.
- Services include
  - SEND data quality assessment
  - Assistance with generating safety analysis visualizations
  - One-on-one SEND analysis tool walkthroughs
  - Issue diagnosis and resolution for loading data to SEND analysis tools
- New version of the OCS Nonclinical service, began October 2022

OCS Nonclinical Services by Tier

Tier 1A	Proactive service providing preliminary data quality overview to SEND users
Tier 1B	Proactive service demonstrating the utility of SEND by providing reviewers with visualizations of findings/trends **not** clearly reflected in the study report
Tier 2	Training-focused request-based service providing one-on-one tool walkthroughs, Q&A, and deep data quality analysis

Tier 1A: Proactive Preliminary Data Fitness Assessment

- A Tier 1A OCS Nonclinical Service is provided for original IND applications received for review by FDA CDER.
- The service is provided study applications that have been submitted with electronic data that has been loaded for use with OCS analytical tools.

Tier 1B: Proactive Visualizations Service

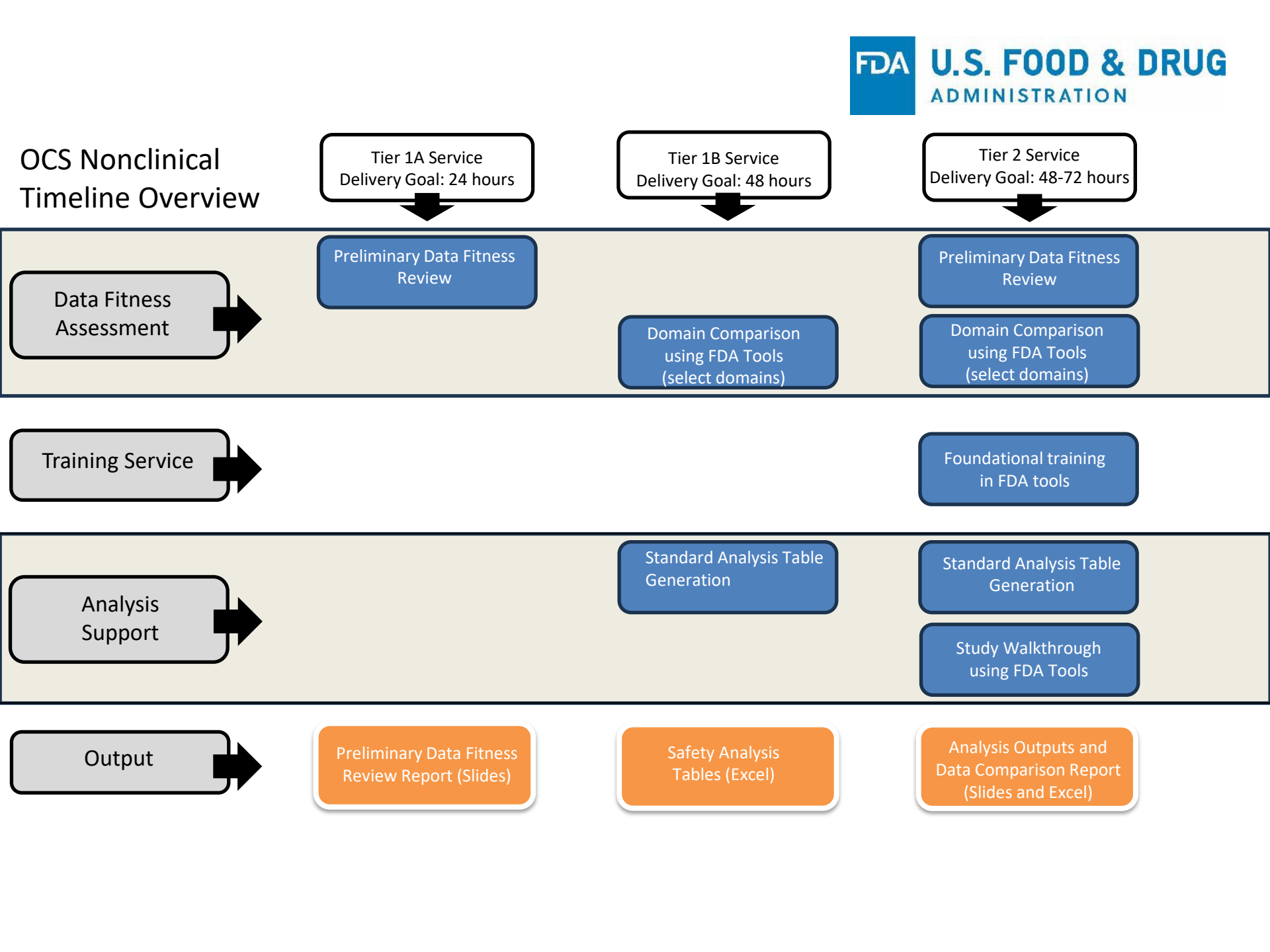
- A Tier 1B OCS Nonclinical Service is provided for original IND applications received for review by FDA CDER.
- The service is provided only for studies that have been submitted with electronic data that has been loaded for use with OCS Nonclinical analytical tools and only for reviewers not actively using review tools.

Tier 2: Proactive Visualizations Service

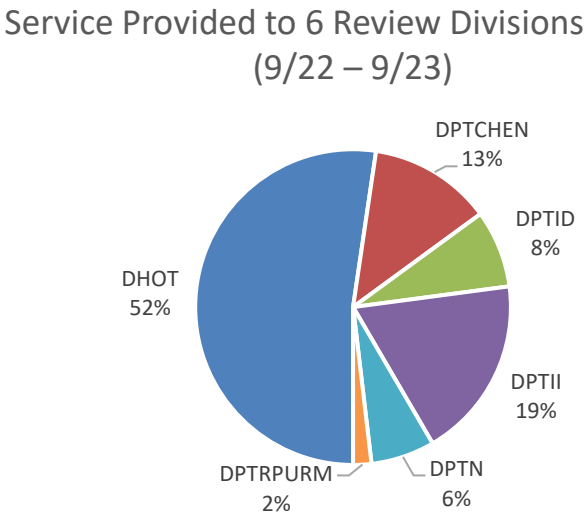
- OCS Nonclinical Services only accepts study data that conforms to a SEND standard version supported by the FDA for animal study datasets, as described in the published FDA Data Standards Catalog.

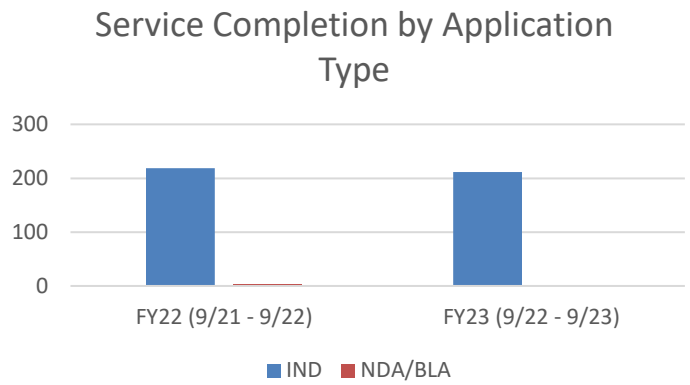
Training

- For first Tier 2 service, the OCS Nonclinical Services team offers reviewers a general training on the SEND topics, including:
  - Domains
  - Controlled Terminology
  - Overview of the nSDRG
  - Introduction to the define file

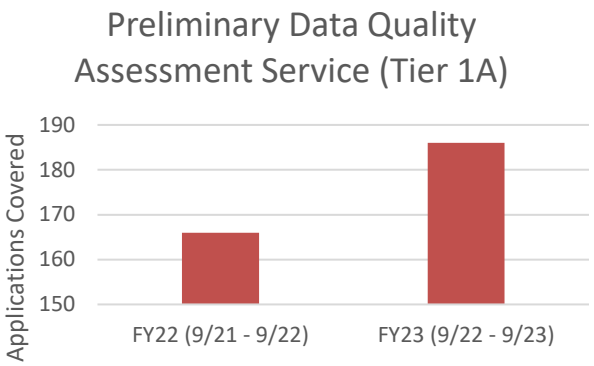

U.S. FOOD & DRUG ADMINISTRATION
OCS Nonclinical Timeline Overview
Tier 1A Service Delivery Goal: 24 hours
Tier 1B Service Delivery Goal: 48 hours
Tier 2 Service Delivery Goal: 48-72 hours
Data Fitness Assessment
Preliminary Data Fitness Review
Domain Comparison using FDA Tools (select domains)
Preliminary Data Fitness Review
Domain Comparison using FDA Tools (select domains)
Training Service
Foundational training in FDA tools
Analysis Support
Standard Analysis Table Generation
Standard Analysis Table Generation
Study Walkthrough using FDA Tools
Output
Preliminary Data Fitness Review Report (Slides)
Safety Analysis Tables (Excel)
Analysis Outputs and Data Comparison Report (Slides and Excel)

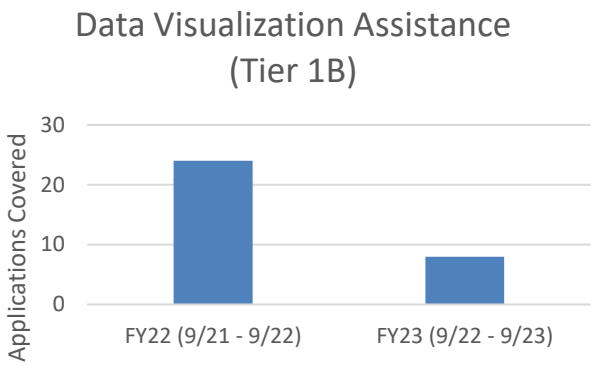
OCS Nonclinical Services

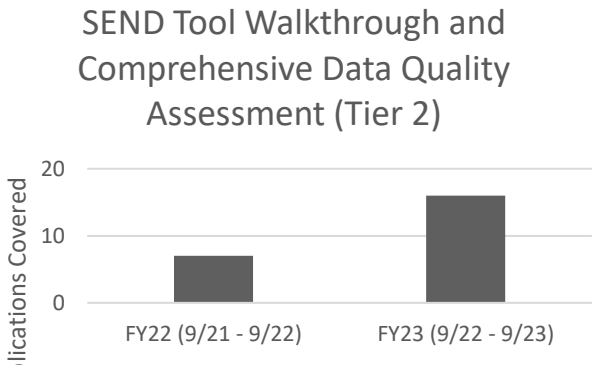




OCS Nonclinical Services by Tier and FY







Key Points

- FDA saw significant increase in number of studies containing SEND datasets over the past 5 years
- Complete and correct SEND datasets are critical for seamless, confident use of SEND datasets by FDA reviewers
- Some common issues in a SEND dataset can complicate or even prevent FDA reviewers use of those SEND datasets
- OCS Nonclinical Services team offers tiered assistance to Pharm/Tox reviewers to provide the most appropriate level of support for a reviewer's SEND experience to allow them to maximize these submitted data. Supporting services include:
  - SEND data quality assessment
  - Assistance with generating safety analysis visualizations
  - One-on-one SEND analysis tool walkthroughs
  - Issue diagnosis and resolution for loading data to SEND analysis tools

COMMON ISSUES WITH SEND DATA SUBMITTED FOR SAFETY PHARMACOLOGY STUDIES

Material to be Covered

- FDA CDER has supported SENDIG v3.1 for more than 6 years and now receives about 200 studies/year designated as crossover design cardiovascular safety pharmacology studies
- OCS assessed a selection of SEND dataset packages submitted for cardiovascular safety pharmacology studies with Latin square or other cross-over design
- That assessment looked at conformance to the SEND standard, consistency in implementation and the ability to use the study in FDA analysis tools

- This presentation describes the review performed and findings of the review
  - Study selection methodology and summary of reviewed studies
  - Differences seen in SEND Implementation across studies and across domains within a study
  - Errors encountered that impact ability to use these studies for review

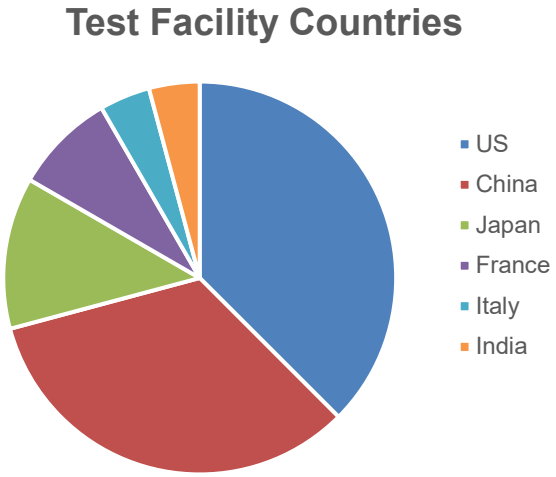
Review of Cardiovascular Safety Pharmacology Studies at FDA CDER

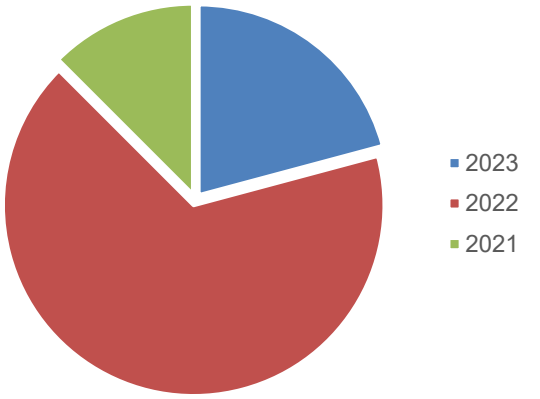
- 24 Studies Reviewed
  - Only Dog studies selected
  - Studies submitted by August 5, 2023 were considered
  - One study per Test Facility companies selected to maximize the potential for variability
  - Most recent study, based on study start date, was selected per company

- Focus on implementation of SENDIG 3.1 specific to cardiovascular safety pharmacology with Latin square or other cross-over study design
  - TS Study Type, Category, Design, Dose Frequency
  - Trial Design and Subject Elements domains
  - EX (Dose Documentation) content
  - Consistency of implementation across safety pharmacology findings domains
  - Baseline flag use in safety pharm findings domains
  - Timing variable use in safety pharm findings domains

Study Breakdown

- Studies submitted between August 5, 2022 and August 4, 2023
- Study start between February 2, 2023 and October 12, 2021
- All studies had 4 dose levels
- 15 studies males only; 9 both males and females
- 21 studies oral gavage dosing, 1 IV Bolus, 1 Subcutaneous, 1 capsule
- 21 studies had 1 dose each treatment day, 3 studies with 2 doses
- 19 studies have 4 animal/sex
- 21 studies had approximately 24 hrs. Post Dose Assessment
  - 8 hours with 72 hrs. follow up: 2 studies
  - 48 hours: 1 study

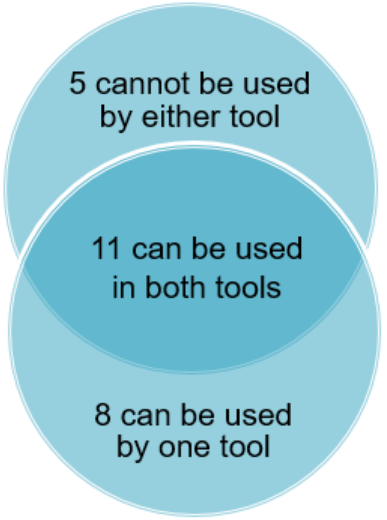




Use of Studies at FDA

- FDA Pharm/Tox Reviewers have access to two tools for analysis of SEND
- Tools have both tabular and graphic representations of summary results
- Each tool uses a different method of identifying dose level and timepoint relative to dose for summarization of findings

Studies in FDA Tools



- SEND Issues impacting single study review/analysis include:
  - Incorrect element definitions
  - Dose day/date is not present in the findings record for matching to EX or SE
  - Actual rather than nominal times relative to dose reported as timepoints
  - Same timepoint label has different timepoint numbers on different days
  - Postdose interval uses --ELTM=PT0H

Other Issues Noted

- Other SEND Issues noted that did not impact use in FDA tools for single-study analysis
  - Incorrect study type (STYP), study category (STCAT)
  - Multiple study category values
  - Incorrect use of EPOCH
  - Set code and set label do not have a one-to-one relationship
  - Concurrent treatment and subsequent rest/washout elements based on start date/time (SESTDTC)

- Issues/Ambiguities in the SENDIG that can impact consistency for Crossover Design Studies
  - No defined variable for dose level under which results should be summarized
  - Elements and/or Epochs are not defined as treatment / non-treatment
  - Expected scope of a treatment element unclear when treatment is followed by rest/washout period
  - How to interpret Baseline flag when multiple change from baseline calculations included in study report
  - Ambiguity in dose frequency variable definition and controlled terminology
  - Ambiguity in Epoch definition
  - The option used for the content of –ELTM (which is generally also in –TPT) is not defined

Study Type, Category, Design in TS

- 1 study has “TOX” as value for STCAT (Study Category), Rest had “SP”
  - All submitted in eCTD section 4.2.1.3 Safety Pharmacology
- All but 1 study had “CARDIOVASCULAR PHARMACOLOGY” as all or part of SSTYP (Study Type)
  - 1 study has “REPEAT DOSE TOXICITY”
- 21 studies had “LATIN SQUARE” as value for SDESIGN (Study Design)
  - 3 have "CROSSOVER" in value for SDESIGN
    - 6x4 “Modified Latin Square” in the study report: 1 study
    - 4x4 “Randomized dose design” in the study report: 2 studies

CROSSOVER	Participants receive one of two or more alternative intervention(s) during the initial epoch of the study and receive other intervention(s) during the subsequent epoch(s) of the study.
LATIN SQUARE	A type of crossover study in which the subject receives every treatment during the study. The treatments are administered in a prespecified order in such a way that each subject receives each treatment and each treatment is in each study phase.

Study Category when Respiratory Endpoints Present

- 10 studies were combined cardiovascular and respiratory safety pharmacology studies
  - 7 studies had a single STCAT entry “CARDIOVASCULAR PHARMACOLOGY”
  - 2 studies had a second record for “RESPIRATORY PHARMACOLOGY”
  - 1 study had “CARDIOVASCULAR PHARMACOLOGY, RESPIRATORY PHARMACOLOGY”

- SENDIG 3.1 states, *“The most appropriate single value, as defined by the sponsor, should be included for Trial Summary purposes.”*

Illustrates some difficulty with studies with multiple objectives with no defined order of precedence or importance and a single published term does not describe them all

Elements

- 21 studies with one treatment element per dose level
  - All ELEMENT values for treatment elements contained dose level with units
  - Other information included test article name, dose frequency, level number (1=control, 2=low, etc.), dose duration (P1D)
- 13 of 21 included rest/washout elements
  - Remainder had sequential treatment elements that cover the entire study period (no rest/washout period) even though all but one explicitly mentioned a washout period in the study report

SENDIG Permits Either Organization of Elements

Description of Element	Start Date/Time of Element	End Date/Time of Element
Screening	2022-07-21	2022-07-26
3 mg/kg, …	2022-07-26	2022-07-27
Wash-out	2022-07-27	2022-07-29
6 mg/kg, …	2022-07-29	2022-07-30
Wash-out	2022-07-30	2022-08-01
12 mg/kg, …	2022-08-01	2022-08-02
Wash-out	2022-08-02	2022-08-04
0 mg/kg, …	2022-08-04	2022-08-05

Description of Element	Start Date/Time of Element	End Date/Time of Element
Screen	2022-05-02	2022-05-15
100 mg/kg	2022-05-16	2022-05-18
500 mg/kg	2022-05-19	2022-05-22
250 mg/kg	2022-05-23	2022-05-25
0 mg/kg	2022-05-26	2022-05-27

Element, Arm, and Set Definitions

- 21 studies had one arm/set per dose sequence
  - 1 study with males/females having same dose sequence in same arm and **same set label, different set numbers/sex**
- 3 studies had **incorrect elements**, used to build arms/sets
  - 1 study – one element covering treatment, one arm, one set
  - 1 study – one element per dose sequence, one arm and set per sequence
  - 1 study – one treatment element per animal per dose level (16 elements for 4 dose levels and 4 animals), one arm and set per animal
- Most studies included the dose level sequence in the arm and/or set label making it easy to see the intent of the arm/set organization
  - 3 studies had only numeric arm and set labels and no description in the nSDRG
  - 1 study had the animal numbers in the labels
  - Other treatment components also included in labels: group number, test article name, dose frequency, TK notation, other text

SENDIG v3.1: "an Element is defined by the treatment (or lack of treatment) to be administered to subjects during the Element, as well as either the planned duration or start/end rules of the Element"

--DTC in Subject Elements with Rest/Washout

- 3 Different Approaches Seen
  - Start/End of Treatment and Start of Washout have the same value (4)
  - End of Treatment and Start of Washout have the same date/time (6)
  - No overlaps between treatment and washout - consecutive dates (3)
- Compare dose date/day in a finding record with subject element dates
  - 4 studies had the same date for the treatment and following rest/washout
  - 3 studies assessed did not include --RFTDTC (not required)
  - 3 studies did not use dosing day in --NOMDY
- Ambiguity in definition of the treatment elements - should all SP data collected be included in the treatment element or only the dose?

What Treatment Element is the Data Associated With?
Accurate Look-Up from Data into Subject Elements should be Possible

Description of Element	Start Date/Time of Element	End Date/Time of Element
0 mg/kg	2022-04-28	2022-04-28
Rest	2022-04-28	2022-05-05
450 mg/kg	2022-05-05	2022-05-05
Rest	2022-05-05	2022-05-12
150 mg/kg	2022-05-12	2022-05-12
Rest	2022-05-12	2022-05-19
50 mg/kg	2022-05-19	2022-05-20

Description of Element	Start Date/Time of Element	End Date/Time of Element
3 mg/kg	2022-07-26	2022-07-27
Wash-out	2022-07-27	2022-07-29
6 mg/kg	2022-07-29	2022-07-30
Wash-out	2022-07-30	2022-08-01
12 mg/kg	2022-08-01	2022-08-02
Wash-out	2022-08-02	2022-08-04
0 mg/kg	2022-08-04	2022-08-05

Epoch Associated with Elements

- Treatment Elements
  - Common Epoch name across all treatment elements like “Treatment” or “Dosing” – 13 studies
  - Epoch name changes by dose sequence – 7 studies

Animal 1	Control	Rest	Low Dose	Rest	Mid Dose	Rest	High Dose
Animal 2	Low Dose	Rest	Mid Dose	Rest	High Dose	Rest	Control
Animal 3	Mid Dose	Rest	High Dose	Rest	Control	Rest	Low Dose
Animal 4	High Dose	Rest	Control	Rest	Low Dose	Rest	Mid Dose

Epoch Key
Treatment 1
Treatment 2
Treatment 3
Treatment 4

  - Epoch name changes by dose level – 1 studies

Animal 1	Control	Rest	Low Dose	Rest	Mid Dose	Rest	High Dose
Animal 2	Low Dose	Rest	Mid Dose	Rest	High Dose	Rest	Control
Animal 3	Mid Dose	Rest	High Dose	Rest	Control	Rest	Low Dose
Animal 4	High Dose	Rest	Control	Rest	Low Dose	Rest	Mid Dose

SENDIG 3.1 states: “For example, in a three-period crossover study of three doses of Compound X, each treatment Epoch is associated with Compound X, but not with a specific dose” and example in Section 7.5.5 has different epochs per dose sequence, so either of the first two methods appears to be acceptable.

Dose Frequency in TS and EX

- One dose per treatment day (21 studies)
  - TS PDOSFRQ (Planned Dose Frequency)
    - "ONCE" – 16 studies, "1 TIME PER WEEK" – 2 studies, "INTERMITTENT" – 1 study
    - parameter not included – 2 studies
  - EXDOSFRQ (Dose Frequency for the interval) is the same as TS PDOSFRQ except:
    - When TS PDOSFRQ not included, EXDOSFRQ=ONCE in 2 studies
    - When TS PDOSFRQ="ONCE", EXDOSFRQ="INTERMITTENT" in 1 study
    - When TS PDOSFRQ="1 TIME PER WEEK", EXDOSFRQ="ONCE" in 1 study

Illustrates issues with definition of published terms and frequency variables for cross-over design studies

- Two doses per treatment day (3 studies)
  - TS PDOSFRQ (Planned Dose Frequency)
    - "BID" – 2 studies
    - Parameter not included – 1 study
  - TS PDOSFRQ (Planned Dose Frequency) is the same as TS PDOSFRQ except:
    - When TS PDOSFRQ not included, EXDOSFRQ="2 TIMES PER CYCLE"

Content of EX (Dose Documentation)

- All but one study included one record per animal per dose administered
  - 1 study with 2 doses/day had one record for both doses in a day
- EXDOSE/EXDOSU contains dose level (mg/kg) in 17 studies
- EXDOSE/EXDOSU contains test article amount (mg) in dose volume given in 7 studies

SENDIG 3.1 EXDOSE Information

EXDOSE CDISC Note: “Amount of treatment administered”.
EXDOSU CDISC Note: “Qualifier Units for EXDOSE or EXDOSTXT. Examples: ng, mg, or mg/kg”
EXVAMT CDISC Note: “EXDOSE refers to the amount of test material administered to the subject.”
EX Assumption 4: “EXDOSE: the sponsor’s data definition file should indicate whether the values in EXDOSE represent **intended or actual dose levels”**
All EX examples have EXDOSU with a /kg unit, indicating a dose level

Findings Domains in Studies

- Safety Pharmacology Data
  - Cardiovascular measurements for all studies – all submitted in CV and EG
  - ECG morphologies in study report for 16 studies (4 with no non-normal findings) – **not submitted in 11**
  - Temperatures in 17 studies – all submitted
  - Respiratory Results in 10 studies – all submitted
  - Activity counts in 4 studies – all submitted in CV
- Plasma Concentrations in 8 studies
  - 5 studies had separate dosing day(s) after the safety pharm testing specifically for the TK bleeds, PP included
  - 5 studies had bleeds at limited timepoints at each safety pharm dose
  - 2 studies had both
- LB Domain Submitted in 5 studies
  - Chemistry, Hematology, Coagulation for pretest screening – 2 studies
  - Oxygen saturation at safety pharm timepoints – 2 studies
  - Complete blood gas analysis 2-4 hrs. post each dose – 1 study
- Clinical Signs collected on all studies but one – **CL not submitted in 3** (all had non-normal signs in report)

Findings Domains in Studies

For the Endpoints Submitted:

- No missing records detected
- No inconsistencies in results between SEND and study report detected

Use of Baseline Flag (--BLFL) in Safety Pharm Findings Domains

- 2 studies with no predose timepoints submitted so no baseline flags expected
- 3 studies with predose timepoints but no –BLFL value
  - 1 study has analysis of change from predose baseline values for each dose in study report
- 5 studies with –BLFL=Y for predose first dose only
  - 2 studies has analysis of change from Predose for each dose in study report
- 15 studies with –BLFL=Y for predose each dose

* 1 study used different methods depending on domain, so total count by use is 25, not 24

For some studies, the study report included analyses for both time-matched changes from a pretest collection period to each treatment period, and predose to postdose value change within each treatment period.

Use of Timing Variables in Safety Pharm Findings

- Nominal Day (--NOMDY) was not the dosing day in 3 studies
  - Data collection day reported so data collected relative to one dose had two different nominal days
- All studies used --TPT/--TPTNUM filled for all records
- All but 3 studies used –ELTM, --TPTREF, and --RFTDTC
- Planned evaluation interval start and end --STINT/--ENINT were used in 15 studies
- Planned duration of evaluation interval –EVLINT never used
- All studies had --DTC filled for all records; contents were difficult to interpret
- 8 studies had –ENDTC filled

- 2 studies used different approaches for filling timing variables between CV and EG

Use of Timing Variables in Safety Pharm Findings – Timepoints, Intervals

- --TPT for Postdose intervals
  - Contains text with a single value to describe planned time relative to dose that aligns with –ELTM

    Example: When interval was 1-2 hrs. postdose, --TPT="2 hr. post", ELTM=PT2H
  - 2 studies contained the start and end times (ex: "1-2 hrs. postdose") as an unambiguous label for the timepoint

    Consistent with --STINT/--ENINT, with --ELTM contained the end of the interval when populated

- 1 study used actual end of the selected assessment interval in –TPT and –ELTM rather than planned
  - summary analysis was not possible, different animals had different actual assessment interval end times within an allowable range

- 1 study used different --TPTNUM values for the same --TPT labels on different days
  - All FDA tools use a combination of –TPT and –TPTNUM when organizing data by timepoint relative to dose

Use of Timing Variables in Safety Pharm Findings – Timepoints, Intervals

- SENDIG indicates that –ELTM can be the use of start of interval, end of interval, or "somewhere in the middle" of the assessment interval
  - All methods were used in reviewed studies
  - 1 study used start of interval predose, end of interval postdose
  - 2 studies that used start of interval labelled the **first postdose interval as PT0H**
  - Interval labelling is clearer when –STINT/--ENINT are filled (15 studies)
    - Only 1 study without –STINT/--ENINT filled describes content of –ELTM in nSDRG

Understanding Time Point Labelling During Review
Allows alignment with Cmax times
Enables Cross-Study Comparisons
Identifies PT0H as pre or post dose
Helps identify gaps in the data submission

Summary

- FDA has been supporting cardiovascular safety pharmacology studies in SEND for more than 6 years
- 24 recently-submitted crossover design cardiovascular safety pharmacology studies in dogs have been assessed, each from a different test facility company
- The assessment looked at conformance to the SEND standard, consistency in implementation and the ability to use the study in FDA analysis tools
- Some issues in SEND implementation prohibits use of FDA tools for study analysis
- Some inconsistencies in implementation of the standard both across and within a study were observed that cannot be attributed to study design or SENDIG language
- Some variation in SEND is permitted by the SENDIG and some appear to be the result of ambiguity in the standard
- Adherence to the SEND standard with consideration for analysis of the resulting SEND files would enable FDA to more easily use this data for safety analysis