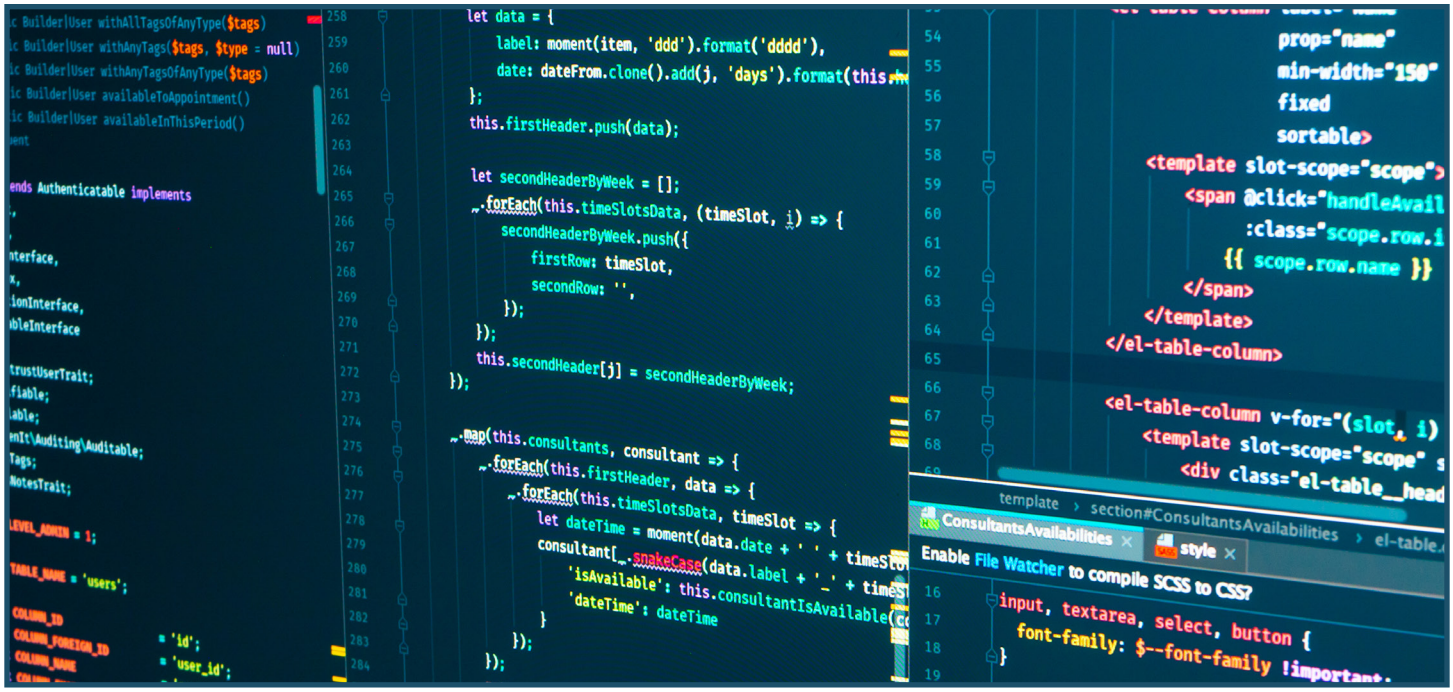

Understanding CDISC SEND Data and How to Be Compliant

Nonclinical study data submitted to the FDA must align with the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM). The version of data standards for nonclinical studies is known as the Standard for Exchange of Nonclinical Data (SEND).

SEND is chartered by CDISC, a globally recognized, not-for-profit organization that actively develops data standards with the collective knowledge and experience of individuals within the pharmaceutical industry. Under guidance provided in the FDA's Study Data Technical Conformance Guide, CDISC leads the ongoing efforts surrounding SEND for nonclinical data standards as well as standards for clinical data, such as SDTM and ADaM.

Why Was SEND Created?

SEND was created from the FDA's and other regulatory agencies' need to have a standard in place for nonclinical study data. The purpose of SEND is to align the organization, formatting, and structure of all nonclinical data across sponsors and studies and to help make the review process of nonclinical data more productive.

In 2010, the Center for Drug Evaluation and Research (CDER) commissioned the Data Standards Program to facilitate efficient review of data submitted to the FDA and to adhere to the Prescription Drug User Fee Act V. The FDA now requires SEND for most nonclinical studies and is receiving SEND data sets at a much higher rate than in previous years.

A CDER webinar given in May of 2021 stated that in 2017 there were 21 INDs and 4 NDAs/BLAs submitted with SEND, and only two years later in 2019, there were 493 INDs and 46 NDAs/BLAs submitted with SEND. The increase in SEND submissions demonstrates the importance for reviewers to receive standardized data, which will help save time and create a more efficient review process.

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Benefits of SEND

SEND data requirements are a relatively new concept compared to clinical data standards, which can lead to challenges. However, there are many benefits of integrating nonclinical studies into standardized data. Some of the main benefits of submitting SEND data sets include:

- Assisting agency reviewers in your application evaluation
- Removing ambiguity within results reported
- Cutting costs and timelines when it comes to the FDA submission and review process
- Guiding sponsors to collect and report raw data in a structured, standardized, and interpretable manner for a smooth exchange of data

Challenges of SEND Data Collection

There are a few challenges that sponsors may face when navigating regulations relating to SEND data standards. One challenge that many companies face is having a minimal understanding of SEND requirements in general. This is especially true if sponsors have not had any exposure to the clinical CDISC standards for SDTM and ADaM. Because of this, companies that strictly work in the nonclinical sector may need more time and assistance with implementing SEND.

Timing is another hurdle many companies are trying to navigate. With the recent changes in SEND requirements (and more to come over the next several years), some sponsors are unaware of the new requirements and find out they need SEND at the last minute. This causes delays in submission timelines and unplanned increases in costs.

One of the biggest challenges is the collection of laboratory data in an organized and readily usable format. Many times, we find that labs collect metadata with handwritten records of lab draw dates and times. When data scientists or analysts manually add handwritten lab data into electronic format from paper or PDFs, it leaves room for ambiguity. This incurs additional time and cost as the manual input of data into electronic format requires additional QC verification.

Having a data transfer agreement (DTA) in place is a large step to help avoid time consuming data queries. In addition, having a DTA between each company exchanging data helps give every party a clear expectation of the formatting, organization, and purpose of each dataset.

SEND Implementation Guide

The SEND Implementation Guide (IG) is a guide that describes how to prepare, manage, and structure data for FDA submission. The current version of the SEND IG includes details for the preparation of datasets for single-dose toxicity, repeat-dose toxicity, carcinogenicity, and cardiovascular/respiratory safety pharmacology studies. The most recent version of the FDA Study Data Technical Conformance Guide should be consulted in tandem with the IG for creating SEND datasets.

The most recent SEND IG version, 3.1.1, was published on March 30, 2021. The main difference between the 3.1.1 version and its predecessor, version 3.1, is additional examples and descriptions of variables, such as nominal timing. In addition, more examples are provided to model the relationships between domains which present concentration data, dosing, PK parameters, pooling data, and more. Other changes include:

- The Cardiovascular (CV) and Respiratory (RE) domains were added which enables the Vital Signs (VS) domain to solely report vital signs, unlike in previous versions
- Requirements of specific variables have been updated to reflect more informative information in the datasets
- Other variables have been added to provide consistent identifiers for data reported across multiple domains

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Creating SEND Data Files

To understand how SEND datasets are created and how to interpret them, it is crucial to review the respective domains and variable descriptions from the applicable version of the SEND IG and the FDA's Study Data Technical Conformance Guide for nonclinical studies. It is also helpful to know what domains are interventions, events, findings, trial design, relationship, and special-purpose classes within the IG. From there you want to identify which variables will provide you with identifying, qualifier, rule, or timing information. Each dataset has key variables used to identify unique records.

Some variables have what is called controlled terminology (CT). CT is beneficial because many terms are not extensible. This eliminates any room for misinterpretation of results, as each value must be set to fixed values for the sake of transparency. Understanding the domain classes, variable roles, and CT are merely the basis of understanding CDISC SEND. From there you can maneuver outward to see how all the SEND datasets are created, structured, and fit together.

As the requirement for SEND becomes more relevant for study data submitted to both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER), labs and sponsors will need to implement more technology earlier on in the process to streamline nonclinical study data, similar to what has been done for clinical studies. In response to this need, some companies are working on developing their software to be used for or with nonclinical CDISC datasets.

When is SEND Data Standardization Required?

The following table summarizes when SEND is required for different types of submissions as well as differences in date requirements for CBER versus CDER.

For CDER, SEND data is required for all studies that start after December 17, 2016 for NDAs, BLAs, and ANDAs and after December 17, 2017 for INDs. For CBER, SEND data is required for all studies that start after March 15, 2023 for NDAs, BLAs, ANDAs, and INDs.

SEND version 3.0 is applicable for any NDA, BLA, and ANDA studies that start after December 17, 2016 but before March 15, 2019. It is also applicable for IND studies that start after December 16, 2017 but before March 15, 2020. After these dates, SEND version 3.1 is required for all submissions.

After September 15, 2021, CBER and CDER will reject any electronic data submissions that do not meet the data specified criteria. In the meantime, CBER and CDER will send applicants warning messages for failed data submissions.

Type of Submission	Study Start Date	
	CBER	CDER
ANDA	After Mar 15, 2023	After Dec 17, 2016
NDA/BLA; SEND v3.0	After Mar 15, 2023	After Dec 17, 2016 for Single-Dose Toxicity, Repeat-Dose Toxicity, and Carcinogenicity Studies
NDA/BLA; SEND v3.1		After Mar 15, 2019 for Single-Dose Toxicity, Repeat-Dose Toxicity, Carcinogenicity, and Cardiovascular & Respiratory Safety Pharmacology Studies
IND, Commercial; SEND v3.0	After Mar 15, 2023	After Dec 17, 2017 Single-Dose Toxicity, Repeat-Dose Toxicity, and Carcinogenicity Studies
IND, Commercial; SEND v3.1		After Mar 15, 2020 for Single-Dose Toxicity, Repeat-Dose Toxicity, Carcinogenicity, and Cardiovascular & Respiratory Safety Pharmacology Studies

How to Be SEND Ready

One of the best ways to ensure your nonclinical SEND datasets are prepared efficiently and are ready for the FDA's assessment is to start thinking about them from the start. Each phase of the study should incorporate SEND standardization processes, beginning with protocol authorship through dosing administration, data collection, and data manipulation. The preparation of SEND does not always occur in-house or by the same team; therefore, organization and communication is key to ensuring everything is prepared as expected and within desired timelines and budgets.

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Conclusions

SEND is the standard for the exchange of nonclinical data and guides the organization, structure, and format of data from nonclinical studies. The SEND IG provides predefined domains and examples of nonclinical data based on the structure and metadata defined by the SDTM. SEND is required for many nonclinical studies submitted to the FDA and other regulatory agencies. As more changes and requirements come into effect for SEND, the more companies need to be ready for SEND implementation so that their data and submissions are not rejected.

Nuventra's SEND Data Implementation Support

Nuventra employs the utmost transparency and precision of data handling when it comes to SEND studies. Our programming and quality assurance units are very diligent with SEND implementation for GLP studies. Each dataset is subjected to rigorous data standards scrutinization and review.

Nuventra supports evolving SEND data standards due to our involvement and close following with CDISC, including working with the CDISC SEND PC and PP team to contribute to and help develop the PC and PP portions of the CDISC SEND IG.

With Nuventra's involvement as CDISC Gold members and as contributors to the SEND IG, we have a unique perspective on the implementation of CDISC standards for SEND studies. All these attributes allow us to stay ahead of anticipated changes and provide the best advice for our clients. Contact us today to learn more about CDISC and to see if your datasets are in compliance with the FDA's required CDISC standards.

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