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THE FDA ANIMAL RULE AND STANDARD FOR EXCHANGE OF NONCLINICAL DATA (SEND)

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Abstract

The Standard for Exchange of Nonclinical Data (SEND) is the newly required format for submissions of nonclinical data to the US Food and Drug Administration (FDA) for carcinogenicity studies, and single and repeat dose toxicity studies. The framework of SEND was modeled off the older Standard Data Tabulation Model (SDTM) used for clinical submissions; both were created by the Clinical Data Interchange Standards Consortium (CDISC) with the goal of standardizing and digitizing data for the FDA reviewer. SEND is not currently required for Animal Rule studies, however there is an increasing desire to use the SEND format for data visualization and warehousing purposes. Under the current SEND modeling paradigm, acute radiation syndrome (ARS) studies introduce several complications during the formation and review of the dataset. For example, SEND has no ability to include Day 0, which is counter to the traditional design of ARS studies that use Day 0 for challenge doses (i.e., day of radiation). Additionally, modeling the challenge agent and test article within the Trial Domains are not demonstrated within the current guidelines, making best practices and standardization across different studies and sites unachievable.. Since the current 3.0 guidelines do not allow the introduction of non-defined domains, information regarding challenge agent dosing, medical history, medical countermeasures, and microbiology samples will have to be included in existing domains, which will stretch their original purpose and incorporate non-controlled terminology. A CDISC Animal Rule team is currently working on drafting a guidance standard for Animal Rule studies. This guidance standard will be subject to FDA and public input prior to being issued as a requirement.

Current SEND Model

After the success of the implementation of SDTM for submissions to the FDA for clinical studies, a standardized electronic format was also requested for nonclinical studies. CDISC, a nonprofit organization that designed SDTM, adapted the model for nonclinical studies. This nonclinical model was named Standard for Exchange of Nonclinical Data (SEND), and the goal was to standardize submissions from all parties into one format. This standardization would allow for the warehousing and comparison of drugs in similar families, ultimately allowing for better analysis of drug candidates and shortening FDA decision time.

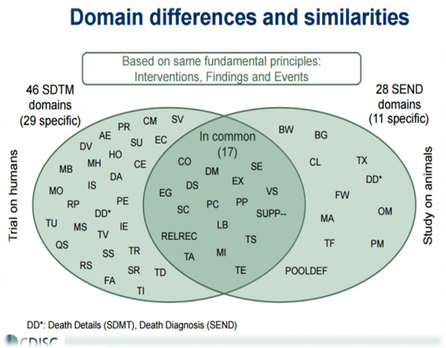

Figure 1: Venn Diagram depicting the similarities and differences between SDTM and SEND domains.

SEND 3.0

SEND version 3.0 was the first version to be accepted by the FDA for nonclinical submissions. Compared to SDTM, SEND has a narrow scope of supported study types (eCTD Filing Study Type):

- Single-dose general toxicology (eCTD Section 4.2.3.1)
- Repeat-dose general toxicology (eCTD Section 4.2.3.2)
- Carcinogenicity studies (eCTD sections under Section 4.2.3.4)

The narrow scope of SEND allows for all nonclinical studies being submitted outside these three eCTD filings to be excluded from SEND format requirements.

The implementation date requirements for SEND version 3.0 for FDA submissions can be found in the table below:

Table 1. SEND version 3.0 requirement dates for FDA

Submission Type	Support Start	Requirement Start	Requirement Ends
NDA, ANDA, and certain BLA submissions	March 13, 2011	Studies which start after December 17, 2016	Studies which start after March 15, 2019
Commercial INDs and amendments		Studies which start after December 17, 2017	Studies which start after March 15, 2020

Since SEND version 3.0 was the first version, some parameters that can be found in carcinogenicity studies, single dose, and repeat dose toxicity studies were excluded from scope, allowing them be incorporated into later versions. Some of the examples of non-supported parameters include:

- Reproductive assessments
- Neurological assessments
- Veterinary Treatments
- Flow cytometry
- Anti-Drug Antibody (ADA) measurements

SEND 3.1

SEND version 3.1 was subsequently released by CDISC on June 27, 2016. This version expands on the previous version in both scope and minor improvements, and supports the following study types (eCTD Filing Study Type):

- Single-dose general toxicology (eCTD Section 4.2.3.1)
- Repeat-dose general toxicology (eCTD Section 4.2.3.2)
- Carcinogenicity studies (eCTD sections under Section 4.2.3.4)
- Respiratory and cardiovascular safety pharmacology studies (eCTD Section 4.2.1.3)

Along with the addition of Safety Pharmacology studies to the scope, this version of SEND allows for the introduction of custom domains. This means that if a study contains information that has not been modeled in an established domain, a domain can be created or modified from a SDTM domain to fit the needs of the specific information.

The implementation date requirements for SEND version 3.1 for FDA submissions can be found in the table below:

Table 2. SEND version 3.1 requirement dates for FDA

Submission Type	Support Start	Requirement Start	Requirement Ends
NDA, ANDA, and certain BLA submissions	August 21, 2017	Studies which start after March 15, 2019	No end date at current time
Commercial INDs and amendments		Studies which start after March 15, 2020	

Future of SEND

Both SEND and SDTM are constantly evolving. Currently, there is a plan in place to have specific versions for the following study types:

- Dermal/Ocular
- Genetic Toxicology
- Developmental and Reproductive Toxicology (DART)
- Animal Rule

Modeling Issues

Although not currently required by the FDA for submissions, there has been an increased interest in integrating Animal Rule study data into SEND format. Even though a portion of the data for this study type is not modeled, SEND can be leveraged for visualizing, including pharmacodynamic to toxicologic parameters, and is useful for data warehousing purposes.

Both existing versions of SEND exclude Day 0 notation. Study days can be manually shifted post-export, but this requires a large amount of manually effort. Additionally, some of the Controlled Terminology (CT) that is established for SEND will have to be extended; this is specifically true for inclusion of Animal Rule studies with the upcoming standard.

SEND 3.0

Modeling within SEND version 3.0 creates a greater challenge than version 3.1. Since no non-defined domains can be used, information must be inserted into existing domains or excluded. If the data is to be included, there could be inconsistency between different test sites since there is no model for standardization. Additionally, this version requires more manual effort since information may not be recorded in an exportable fashion or not in an electronic system at all.

SEND 3.1

Since SEND version 3.1 allows for the use of non-defined domains, borrowing from established STDM domains that align more with endpoints like Medical History and Medical Countermeasures become possible to model in a more standardized form.

Future Model

Currently in the process of formation and review by CDISC, the Animal Rules version 1.0 model will be released for public review when available. Once approved, it will go through a review process at the FDA before being released for another public comment period. Only after all of these steps will it become regulation and officially a requirement after a two-year implementation period.

Like the SEND and SDTM standards, Animal Rule would not allow for Day 0 notation.

As of now, no Electronic Data Capture System (EDCS) has the ability to record all of the required data in a system that will be able to export in a validated, reproducible, and compliant fashion. Once the model has been accepted, software developers will have the option to build a system that would fit requirements as done with nonclinical and clinical studies in the past.

References

Scan me — CDISC Animal Rule webpage

Scan me — CDISC Standards Overview

Scan me — FDA Standards Resources

Note: The opinions expressed in this poster are those of the author and do not necessarily represent the opinions of their respective companies.

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