BRIEFING

US FDA requirements for nonclinical data

This article provides a brief overview of what the FDA expects in terms of nonclinical data standards in regulatory submissions

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What are data standards?

In the US when sponsor companies are providing regulatory submissions to the FDA for either drug or certain biologic products, data from the clinical and nonclinical studies must be accessible to FDA reviewers. This data must be formatted according to specific standards that were developed by the Clinical Data Interchange Standards Consortium (CDISC) in collaboration with the FDA, industry, software vendors and contract research organisations (CROs).

These data standards apply to both clinical (human) and nonclinical (animal) studies and provide a consistent general framework for organising study data, provide standard names for variables and identify appropriate controlled terminology. They may also include standard methods for calculations with common data variables. Before the use of data standards, reviewers at the FDA had to enter the data manually into their own systems, which was an inefficient use of their time.

More broadly data standards also help the FDA receive, process, review, and archive submissions more efficiently and effectively and allow the Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER) to warehouse the data from which they can utilise software to perform their review, create visualisations and analyses. There are required standards for data submissions made to the FDA which are part of investigational new drug (IND) applications, new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologic license applications (BLAs), specifically those for therapeutic biologics that are formatted as BLAs but reviewed by the CDER. The Agency may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, any electronic submission that does not have study data that conform to the required standards.

What is SEND?

SEND (Standard for Exchange of Non-clinical Data) allows for the interchange of data between organisations such as sponsors and CROs and for submission to regulatory authorities. Data that would normally be presented in tabular format (eg, tabulations that comprised volumes of data) must follow the Study Data Tabulation Model (SDTM) and SEND is the implementation of the SDTM standard that is used for nonclinical studies. SEND specifies the way to collect and present nonclinical data in a consistent format and is intended to provide a structured representation of information included in study report appendices. SEND data are organised into domains or individual datasets that contain a specific grouping of data, such as food and water consumptions (FW) and organ measurements (OM). The SEND data standards initially focused on endpoint data, such as body weights for toxicology studies and tumour data for carcinogenicity studies. These data standards are evolving including the area of embryo-fetal developmental (EFD) toxicity studies.

SEND relies on the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) for most of the terminology used and there are implementation guides available (SENDIG) which provide a set of instructions and examples of how to structure data into the SEND format.

Currently, products regulated by the CDER should provide nonclinical data as outlined in the Technical Rejection Criteria (TRC), however, products regulated by the CBER are not currently required to be submitted as SEND in INDs or BLAs. The “transition” date for CDISC SEND for CBER was initially set for 15 March 2021, which means the date the requirement would begin would be 15 March 2023. However these dates are currently under review. SEND will not be required for non-commercial INDs (eg, research- and investigator-sponsored INDs); or for INDs and BLAs for devices regulated by the CBER as biological products under the Public Health Services (PHS) Act; or for submissions for blood and blood components. However, the CBER is accepting SEND now on a voluntary basis, encouraging sponsors to begin using it in submissions.

What kind of studies will require SEND?

According to SENDIG, the model is designed to support data generated in single and repeat dose toxicology studies, as well as carcinogenicity studies. In addition, safety pharmacology studies that look at respiratory and cardiovascular effects can also utilise SEND and the latest implementation guide (SENDIG v3.1) includes these domains (respiratory and cardiovascular). There are also SEND Implementation Guides for Developmental and Reproductive Toxicology Studies (SENDIG-DART v1.1) and one for studies conducted under the animal rule (SENDIG-AR v1.0).

The CDISC website has additional information on the models, implementation guides and conformance rules that can help companies, including contract laboratories and research organisations, to ensure the data they are generating conform to the standards.

TABLE 1

Sample study data standardisation plan (SDSP) table

Study identifier	Study start date	Study duration	Tabulation	Analysis	Terminology (CDISC)	Terminology (Events)	Terminology (Medication)	Define XML	PDF	Other standards *-Optional-*
	mm/dd/ ccyy	‹# of years›	SDTM IG ‹version› SEND ‹version›	ADaM IG ‹version›	‹date›	MedDRA ‹version›	WHODrug ‹version›	‹version›	‹version›	Standard Name ‹version›

Timing of studies and SEND

Sponsors submitting a commercial IND and nonclinical study started before or on 17 December 2017 must submit a simplified trial summary (File name = ts.xpt) file even when there are no other data files for the study. If the study started after 17 December 2017, the agency will be expecting standardised data in the SEND format.

For sponsors submitting a marketing application as a NDA or BLA to the CDER, and the studies started before or on 17 December 2016, the agency will expect to see the simplified trial summary (File name = ts.xpt) dataset for nonclinical data regardless of whether other data files (legacy datasets) are being submitted. If the nonclinical study started after 17 December 2016, the agency will expect to receive standardised datasets in SEND format.

Identifying and communicating study requirements

It is important for sponsors to meet with their nonclinical stakeholders, whether internal or external, to determine which studies are impacted and which study identifiers will be utilised within the study report and the data. The study identifiers used within the datasets must match those used in the eCTD (electronic common technical document) metadata; if the information does not match, it can trigger further questions from the agency.

One of the best ways to document and communicate nonclinical study requirements is to create a Study Data Standardisation Plan (SDSP) that outlines all the studies that are being included in the submission. Study start dates must be addressed in the plan to rationalise the presence of the trial summary files, legacy data and/or standardised data packages.

For INDs, sponsors can aim to submit the SDSP with the General Investigational Plan. For NDAs/BLAs, the SDSP can be submitted to the IND with your pre-NDA package. It is important to note that sponsors must provide the SDSP to the CBER for review no later than the End-of-Phase 2 meeting.

As the sponsor fills in the SDSP, the study start date will determine how the rest of the table (see Table 1) is completed. The table should give the agency enough information to understand what the sponsor is submitting while addressing their initial questions in advance of the submission.

Another critical area to communicate is what, in addition to the datasets themselves, is required as part of the data package. For studies submitted using the SEND format there will need to be a data definition file (File name = define.xml), a corresponding reviewer's guide highlighting any errors, warnings, or other nuances in the data (File name = nsdrg.pdf) and the datasets, submitted as SAS transport files that must include a trial summary dataset (ts.xpt) and a demographics dataset (dm.xpt).

How important is it to follow the SEND specifications?

As part of the processing through the FDA Electronic Submission Gateway (ESG), a series of automated validation checks are performed and submissions are only accepted if the acceptance criteria are met. In October 2019, the FDA updated its technical rejection criteria for study data. These validation measures are based on the FDA specifications for eCTD validation criteria. They ensure sponsors are submitting standardised data in a CDISC compliant format when applicable for clinical (SDTM and ADaM [analysis data model]) and nonclinical studies (SEND). If a submission does not conform to the technical validation criteria it will automatically be rejected, possibly resulting in delays getting the submission in front of an agency review team. In 2019, there were four additional conditions added to the existing validation criteria. These apply to both clinical and nonclinical data but only references to SEND are included here.

- **Validation #1734** This validation check is looking for a dataset named ts.xpt within the electronic submission. This is also referred to as the trial summary dataset. It is one of the most important datasets in an application because it informs the agency of the actual study start date for a study. This date triggers a comparison to the study start dates listed above. If the study start date is prior, the agency will not expect to receive the standardised data packages. If the start date falls after the prescribed dates, the agency will expect SEND-compliant data.
- **Validation #1735** This validation ensures that the sponsor is using the correct study tagging files when submitting standardised data in SEND-compliant formats. This validation also checks that the define files and any corresponding information is tagged correctly.
- **Validation #1736** This validation targets the study demographic and subject level data. It confirms that the demographic data and define.xml is included in the standardised data packages in SEND and SDTM format.
- **Validation #1789** This validation criteria ensures that each study submitted within a programme has a corresponding study tagging file. This means that if a report does not have a corresponding study tagging file (STF), the submission will be rejected rather than receiving a warning and an opportunity to fix the error. These updates to the technical rejection criteria apply to the following nonclinical study sections of the eCTD: M4.2.3.1 Single dose toxicity, M4.2.3.2 Repeat dose toxicity, and M4.2.3.4 Carcinogenicity.

FDA resources

The FDA Study Data Resources page (see Resources #2) includes required items and helpful tools for submission of study data to FDA's CBER, CDER and Center for Devices and Radiological Health (CDRH). There are explanations and links to the FDA Data Standards Catalog, FDA guidance documents and technical guides, as well as FDA business and validator rules. ■

RESOURCES

- FDA. SEND for CBER – What you need to know. 4 December 2020. Available at: www.fda.gov/drugs/news-events-human-drugs/send-cber-what-you-need-know-12042020-12042020 (accessed 19 February 2021).
- FDA. Study data standards resources. Available at: www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources (accessed 22 February 2021).
- FDA. Technical rejection criteria (TRC). Available at: www.fda.gov/media/100743/download (accessed 22 February 2021). (Please note the TRC has not been updated with current CBER dates.)