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IND Toxicology Study Report and SEND Dataset Requirements

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Introduction

Drug development is a stepwise evaluation process on both animal and human efficacy and safety information. Nonclinical toxicology studies play pivotal roles in estimating an initial safe starting dose and dose range for the human clinical trials and in identifying parameters for clinical monitoring for potential adverse effects.[1] For an IND application, ideally it is expected that sponsors submit final, quality-assured toxicology study reports. In addition, FDA requests Standard for Exchange of Nonclinical Data (SEND) for specific types of toxicology studies and safety pharmacology studies to be submitted in the IND. There are specific acceptable submission scenarios for toxicology study reports and SEND datasets that meet FDA requirements.

Toxicology Study Report

The primary objective of the nonclinical safety evaluation is to characterize toxic effects with respect to target organs, dose dependence, relationship to exposure, and when appropriate, potential reversibility. Toxicology studies are considered essential to support the clinical development in estimating the first dose in humans, characterizing potential adverse effects that might occur in clinical studies, and supporting the risk-benefit assessment for a proposed clinical trial.[1] Generally, the toxicology studies that should be conducted prior to human clinical trials include general toxicity studies, genotoxicity studies, and other studies on a case-by-case basis to assess phototoxicity, immunotoxicity, local tolerance, etc.

Ideally, it is expected that sponsors submit "final fully quality-assured" toxicology study reports in the IND submission as well as corresponding datasets required by FDA. However, there are occasions where the time to prepare final quality-assured individual reports from unaudited draft toxicologic reports may result in months-long delay in the IND submission.[2] As a result, FDA has developed a guidance to clarify when sponsors should submit final, quality-assured toxicology reports and/or update the Agency on any changes in findings since submission of the unaudited draft toxicology reports or reports based on non-quality-assured data.[3] Aleon recommends that sponsors submit INDs only after all documents have been finalized. However, we understand that there may be instances in which a sponsor may choose to submit an IND without having finalized one or more toxicology study reports. Should the sponsor choose to proceed in this manner, there are basic requirements to be met as discussed below.

Sponsors may submit an unaudited draft toxicology report in lieu of a final toxicology report as long as the final toxicology report is available upon FDA's request within 120 days of receipt of the IND.

If the final, fully quality-assured individual study report is not available at the time of IND submission, submitting an unaudited draft toxicology report may be an option. If the sponsor decides to submit a draft report, in addition to the integrated summary and full data tabulation, the following information should be provided as well: 1) a copy of the study protocol and amendments

or a description of the study and methods; 2) detailed tabulation of data, including individual data points for each animal, as well as summary tabulations of these data points to be suitable for review; and 3) a signed pathology report for FDA to determine if the nonclinical data supports the IND submission.[2,3]

What are the risks of submitting draft toxicology study reports and corresponding datasets at the time of IND submission?

FDA may request final toxicology study reports and datasets at any time within the 120-day period, at which point the sponsor must be prepared to submit these documents to FDA. Should FDA make this request, there is no way to be certain of the deadlines the Agency will establish (i.e. FDA may give you a day, week, etc. to provide the final toxicology reports and datasets from the time of the request). Due to the uncertainty regarding how much time will be granted by FDA to prepare final documents after the request is made, sponsors risk being unprepared. As a regulatory representative, Aleon will assist sponsors to maintain an open line of communication with FDA to decrease this risk.

Standard for Exchange of Nonclinical Data (SEND) Datasets

The Standard for Exchange of Nonclinical Data (SEND) is the standard nonclinical data format to fulfill IND submission requirements. For commercial INDs, SEND datasets are required to be submitted along with nonclinical study reports for study types that are modeled in the SEND Implementation Guide (SENDIG) version 3.0 and version 3.1. The SENDIG version 3.0 supports the modeling of single dose and repeat dose toxicity studies and carcinogenicity studies. The SENDIG version 3.1 supports the modeling of respiratory and cardiovascular safety pharmacology studies.[4] Additionally, the SEND implementation guides continue to add domains to the standard with the growing need for new versions.

FDA requires commercial INDs to include SEND datasets for those studies that started after December 17, 2017. Requirements vary based on study start date as detailed in the table below.

Study Started Date	**Requirement**
Prior to December 17, 2017	Simplified *ts.xpt* datasets for single dose and repeat dose toxicity studies and for carcinogenicity studies
After December 17, 2017	SEND datasets for single dose and repeat dose toxicity studies and for carcinogenicity studies
After March 15, 2020	SEND dataset for additional stand-alone cardiovascular and respiratory safety pharmacology studies and for cardiovascular and respiratory test results collected during repeat dose toxicity studies

FDA is in the process of implementing rejection criteria for nonclinical study data. Aleon has a great wealth of experience in validating datasets to meet FDA requirements and avoid rejection. Also, we follow the most up-to-date FDA requirements regarding SEND datasets to assist sponsors in finding the best solutions.

4. References

- Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010)
- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (November 1995)
- Guidance for Industry Q & A Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products (October 2000)
- Study Data Standards Resources