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Study data standards leading to efficient legacy conversion

Study data standards lead to effective legacy conversions, which form the basis of the initial submission for medicinal product approval. In this article, ***Dr SD Devendra Raj,*** *Senior Manager, Freyr Solutions, looks at the different study data standards endorsed by the FDA and their relevance in creating structured legacy submissions*

The first step towards ensuring the safety and efficacy of a medicinal product is to conduct clinical trials. Manufacturers rely greatly on study data to ensure the safety of a particular drug. Clinical study data is briefly defined as information about a human participant in clinical trials. Some attributes included in study data are demography, diagnosis, laboratory tests, medical treatment, participants' progress, etc. The data is termed non-clinical if the same attributes are used for animal testing.

The exchange of clinical and non-clinical data is crucial for study data analysis and clinical assets submission. For the exchange of clinical and non-clinical research data among computer systems/programmes, a standardised method has been proven to be the best approach. If these data standards are not met, the competent Health Authorities (HAs) may not consider the data to be viable.

For instance, the United States (US) Food and Drug Administration (FDA) may Refuse-to-File a New Drug Application (NDA)/Biological License Application (BLA) and Refuse-to-Re- ceive an Abbreviated New Drug Application (ANDA) if the study data submitted to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) is not as per the specified data standards.

Study data standards lead to effective legacy conversions, which form the basis of the initial submission for medicinal product approval. In this article, we will look at the different study data standards endorsed by the FDA and their relevance in creating structured legacy submissions.

FDA-approved study data standards

The pyramid below represents the list of study data standards developed together by the FDA and the Clinical Data Interchange Standards Consortium (CDISC) for effective legacy conversions (see Figure 1.1):

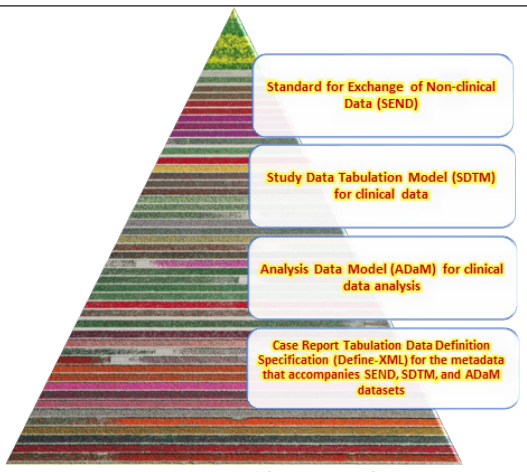


Figure 1.1: A List of Study Data Standards

Standard for Exchange of Non-Clinical Data (SEND): One of the required standards for data submission to the FDA, SEND specifies the method to collect non-clinical data in a compatible format.

Study Data Tabulation Model (SDTM): Used for clinical data, SDTM is a standard for organising and formatting data to restructure processes of collection, management, analysis, and reporting. It is used for clinical and non-clinical data, med- ical devices, and pharmacogenomics/genetics studies. Here are a few advantages of this standard:

- Helps in data aggregation.
- Encourages mining and reuse.
- Enables data-sharing.
- Helps in performing due diligence and other major data review activities.
- Enhances the Regulatory review and approval process.

Analysis Data Model (ADaM): ADaM is one of the required standards for data submission to the FDA and the Pharmaceu- ticals and Medical Devices Agency (PMDA), Japan. It supports the following:

- Effective generation, reproduction, and review of clinical trial statistical analyses.
- Traceability among analysis results, analysis data, and data represented in the SDTM.

Table 1.1: What is Contained in the Data Packages?

SEND Data Package	SDTM Data Package	ADAM Data Package
• acrf.pdf	• acrf.pdf	• .xpt files
• .xpt files	• .xpt files	• Define.xml
• Define.xml	• Define.xml	

What are legacy conversions?

The process of converting the entire study data into a submis- sion-ready format is called a legacy conversion. A legacy submis- sion is interchangeable with the initial submission made to the HA. Once this submission is done, the applicant can file additional sub- missions such as renewals, changes, etc. The legacy submission applies to NDAs, BLAs, and ANDAs.

Traceability and Legacy Data Conversions

The conversion of legacy data (also known as source/raw data) to standardized data comes with several challenges. The most prevalent among them is traceability. Maintaining the source data's integrity in clinical trials is important. Therefore, effectively managing the data collected is essential for Regulatory approval. The following are the key factors for ensuring traceability:

- Verification of the origin/location.
- Use of a well-defined measurement method (calibration).
- Establishing a foolproof chain of custody.

Every clinical trial facility needs a Legacy Data Conversion Plan (LDCP) to help the Regulatory reviewers understand the conversion details and ensure the traceability of the source data. The LDCP is the first issue that should be addressed so that the applicant follows the specific study data formats and streamlines their clinical studies right from the product development stage. An infallible LDCP sub- sequently leads to relevant, complete, and compliant initial submis- sions.

How does the format impact FDA's submission review?

Using a standardised study data format has the following advantag- es (see Figure 1.2):

Figure 1.2: Benefits of a Standardized Study Data Format

A standard study data format makes the process much easier since it helps the submission reviewers get complete traceability. The submissions contain consistent information all through, and several related studies can be merged easily to save time. With standard study data formats, the submissions contain suitable explanations for the processes applied, the inconsistencies, and consequently, the conclusions.

The Study Data Technical Conformance Guide, which was last up- dated in March 2022, provides further information on preparing and submitting data and relevant documents to the FDA, based on the specified data standards.

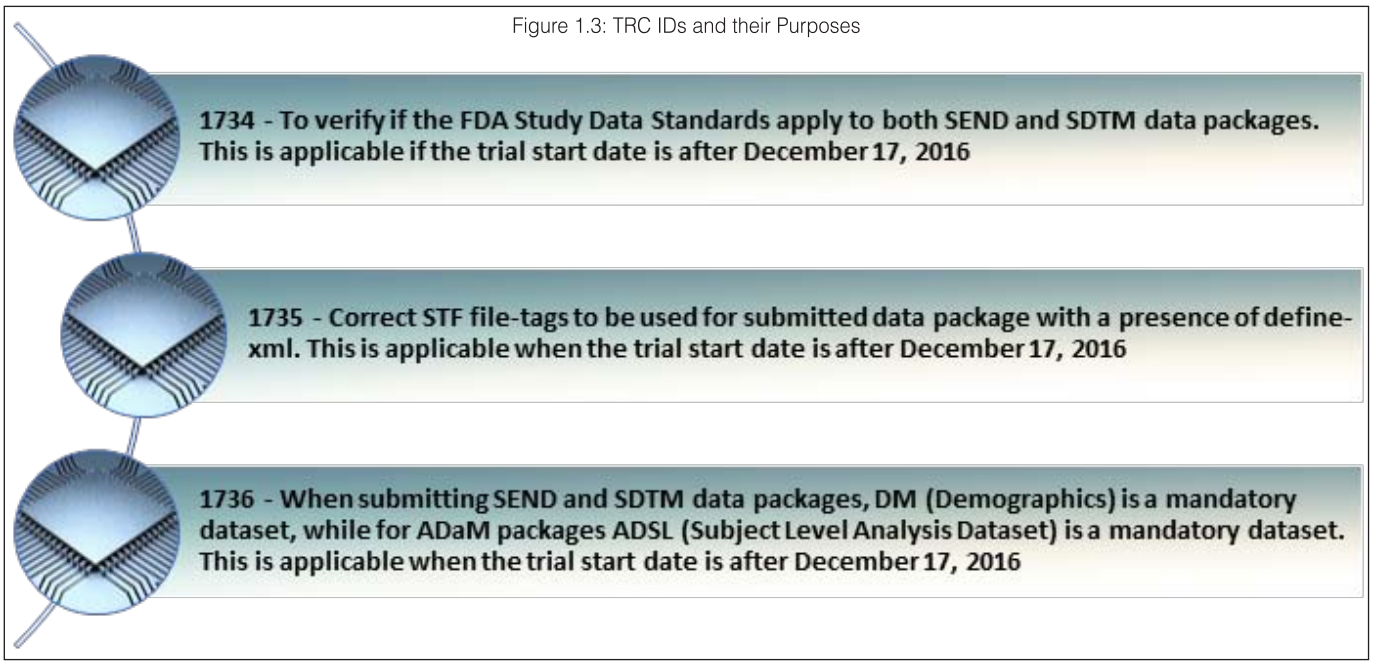
FDA study data Technical Rejection Criteria (TRC)

The FDA uses electronic Common Technical Document (eCTD) validations to check the conformance of the study data. Every drug application sponsor must use the standards defined in the FDA Data

Standards Catalog, which was last updated in March 2021.

The TRC are automated validations carried out by the CDER/CBER inbound processing system, which use the specifications outlined in the FDA's 'Specifications for eCTD Validation Criteria' to ensure compliance with the requirements for submitting electronic standardised study data. The FDA implemented the TRC on September 15, 2021. Post this date, the TRC can block any submissions if the respective eCTD package fails in any of the three (03) TRCs specified. The current TRC Identification numbers (IDs) that applicants/sponsors need to abide by are 1734, 1735, and 1736. The following are the purposes of each of these IDs:

Figure 1.3: TRC IDs and their Purposes



Out of these, the most common error found in all application types is 1734. According to the FDA's database, 58 per cent of the errors across all application types belong to TRC 1734, out of which 62 per cent of the errors belong to Investigational New Drug (IND) applica- tions.

To help first-time sponsors/applicants avoid these errors, the FDA allows sample data submissions to check if the latter accepts the data submitted. For this, the sponsors must have an NDA, an IND, a BLA, an ANDA, or a Drug Master File (DMF) number and need to file an actual submission within twelve (12) months of the sample submission.

Give study data standards their due prominence for error-free submissions!

The FDA's study data standards have been developed to provide a consistent structure for organizing and managing study data. There are separate templates for datasets, standard names for variables, appropriate terminology, and a standard calculation method with common variables. Once the study data is converted into a submis- sion-ready format using the specified standards, it becomes easier to create the ideal submission, based on the application type.

Data standards help reviewers access, organize, process, and ar- chive submissions faster and more effectively. The FDA encourag- es applicants to incorporate study data standards very early in the product development lifecycle so that these standards can be used to design, conduct, and analyse clinical trial studies. Sponsors/ap- plicants must collaborate/consult with the FDA right from the LDCP stage to understand the study data standard requirements and en- sure efficient legacy conversions for error-free submissions.

Disclaimer: *Before Christmas 2022, the US Congress lifted the requirement that all new drugs need to be tested on two (02) animal species. Though the law will not stop animal testing immediately, medicinal product manufacturers will have to prove to the FDA that the safety and efficacy of drugs are not being compromised by replacing animal testing with a suitable alternative. Sponsors are still waiting for detailed instructions from the FDA on this matter.*