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The US FDA submission: A tactical approach towards new standards

For data submission of a given medicinal product, frequent discussions with the health authority at an early drug-development stage determine the approval success. Such interaction with health authorities ensures reduced revision cycles and data management. An early start also facilitates a relationship between the manufacturer and the health authority. Real-time strategy development and understanding could help organisations proceed with their submissions tactically with support documents. This editorial is to give the reader an in-depth insight into the US FDA eCTD submission process and the current version of approval, demonstrating the benefits of early HA involvement in eCTD submissions. Sonal Gadekar, Associate, Freyr Solution, reveals more about data submission

Over the years, pharmaceutical organisations have faced many challenges in adhering to and adapting to the dynamic submission requirements. Unfamiliarity with the current regulations can lead to delays in the approval process and, eventually, postponed time-to-market. Therefore, an agile submission strategy can help integrate the current US Food and Drug Administration (FDA) regulations and adopt uncertain feedback and requirements dictated by the USFDA on review.

Regulatory communication may include waiver requests for data standards and meetings, allowing sponsors to capitalise on the agreements before submission. The lack of data standards awareness may result in delays, especially in times when the FDA is enforcing a technical rejection. How familiar are you with the FDA data submission?

Information concerning Data Submission (Or) Anatomy of Data Submissions

The US FDA, in its guidance titled 'Study Data Technical Conformance Guide under sec. 2.1 - Study Data Standardization Plan (SDSP),' recommended providing Regulatory submissions in the electronic format to the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). The guidance suggests having a strategic plan dedicated to the submission of standardised study data at the time of the Investigational New Drug (IND) and updating it with any subsequent communication.

While strategising SDSP, clinical investigators must recognise the study submission standards, for instance, the detection of legacy study data formats. The investigators must establish early discussions with the Agency via frequent meetings and sharing the clinical data standards development. Additionally, this ensures prompt revisions when the reviewers have questions and supplementary requests during the review process.

The FDA also suggests considering the Pharmaceutical User Software Exchange (PhUSE) initiatives. The PhUSE is an independent, not-for-profit organisation run by volunteers that have developed an SDSP template and implementation guide. Both documents provide a general framework or foundation for sponsors to begin compiling their study data standardisation information. The SDSP is dynamic in nature, and it gets updated when required.

The updates usually include the following:

1. Latest studies
2. Data automation plan
3. Past document discussion with the USFDA
4. Non-conformity to the standards

Nothing is Obvious When one submits data packages to the agency

Sponsors can submit a sample of their data submission package to

CDER and CBER criteria for submissions:

CDER	CBER
BIMO package required for all pivotal studies	No BIMO package, but CBER uses the tabulations/SDTM data such as DM, DV, IE etc.
N/A	Recommends Vaccines Technical Specification Guidance for Office of Vaccine Research and Review (OVRR)
Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus (HIV) - 1 Infection	N/A
Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs	N/A
Technical Specifications—Comparative Clinical Endpoint Bioequivalence Study Analysis Datasets for Abbreviated New Drug Applications	N/A

the FDA (mock submission). It usually comprises one (01) study and may use real data. It is advisable to employ a study that involves some level of complexity, such as when the extensive transformation of legacy data is performed in the Study Data Tabulation Model (SDTM) or a study where a standard may have deviated and you want to seek the FDA validation for the same
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FDA rejection challenges and how to avoid them

Sponsors invest a lot of time in drafting electronic Common Technical Data (eCTD) submissions. To assist sponsors with the validation rules used by the FDA for conformance, the Technical Rejection Criteria (TRC) was developed in September 2021. The TRC obstructs submissions if the eCTD package doesn't comply with the validation rules. Let us see the top reasons for FDA rejection criteria, and how sponsors can avoid them:

Common Entry Submission Error Codes

When submitting an import entry to the FDA for approval, it is crucial to provide current, accurate, and comprehensive information. This expedites the decision-making process regarding the acceptability of medicinal products. Below are a few high-error codes mentioned in the FDA's eCTD updates published on June 06, 2022:

- Code 2034 – Submission type is invalid for the application type
- Code 2022 – Submission sub-type is invalid for submission type
- Code 1734 - A dataset named ts.xpt with information on the study start date must be present for each study in Module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4, and in Module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, and 5.3.5.2
- Code 1789 - A file has been submitted in a study section without providing a Study Tagging File (STF). STFs are not required for 4.3 literature references, 5.2 tabular listings, 5.4 literature references, and 5.3.6 post-marketing reports.
- Submission of incorrect product codes, quantity, or manufacturer information

Solution

Sponsors must ensure the resubmission of a modified leaf as per the latest guidance issued by the FDA. Even if one (01) component of the product code is inaccurate, it could lead products to enter the US market that may not comply with the FDA rules and regulations or cause the shipment to be unduly delayed for additional inspection. Care must be taken to ensure all the information is included with accurate codes as required by the laws and regulations.

Duplicate Sequence Number

When a submission is technically-rejected, the submission sequence is not transferred from the FDA Electronic Submission Gateway into the FDA electronic document rooms. Possibilities of receiving a duplicate sequence number are: