

Using CDISC-SEND Standardized Data in FDA Toxicology Review: The KickStart Service

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INTRODUCTION

One of the key regulatory tasks for the United States Food and Drug Administration (FDA) is to ensure drugs are safe and effective prior to entering the US market. The Investigational New Drug (IND) submission is the beginning of the life cycle of regulatory review. The review timeline for this type of submission is 30 calendar days. The pharmacologists tasked with reviewing these applications need a more efficient method for reviewing INDs while also ensuring the accuracy of the review.

Per the guidance issued by the FDA in December 2014 “Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act”, standardized electronic study data must be submitted for applications, including New Drug Applications (NDAs), Biologics License Applications (BLAs), and INDs, if the study was initiated after December 17, 2016 (for NDAs and BLAs) and December 17, 2017 (for INDs). The FDA chose standards from the Clinical Data Interchange Standards Consortium (CDISC) as the required method for submitting clinical and nonclinical data to the FDA for review. This represents a change in the review process for nonclinical reviewers in the Office of New Drugs (OND), who are responsible for reviewing each of these applications. The FDA CDER Office of Computational Science (OCS) began offering the KickStart service to support reviewers understanding of the quality of the submission study data and train them to use analytical tools.

THE KICKSTART SERVICE

The KickStart service uses SEND data submitted by sponsors to increase the efficiency of the regulatory review process. Given the 30-day review timelines for INDs, the team must provide this service as early as possible. The team provides two sessions: 1) Training session to introduce reviewers to key SEND concepts and the functionality of Janus Nonclinical (a proprietary system), and 2) the KickStart Session, which provides data quality assessments and a data exploration overview of the analysis capabilities. The Data Fitness portion of the service covers all aspects of the application, including a review of the nonclinical Study Data Reviewers Guide (nSDRG), define file, and datasets associated with the application. The data exploration portion of the service provides an overview of a reviewer’s SEND data in Janus Nonclinical to help reviewers become comfortable looking at the data and exporting it into their reviews. This information is disseminated to reviewers over the course of a 90-minute session, in which reviewers are oriented how to visualize their data further and are educated on data quality issues with their data that may impact their review.

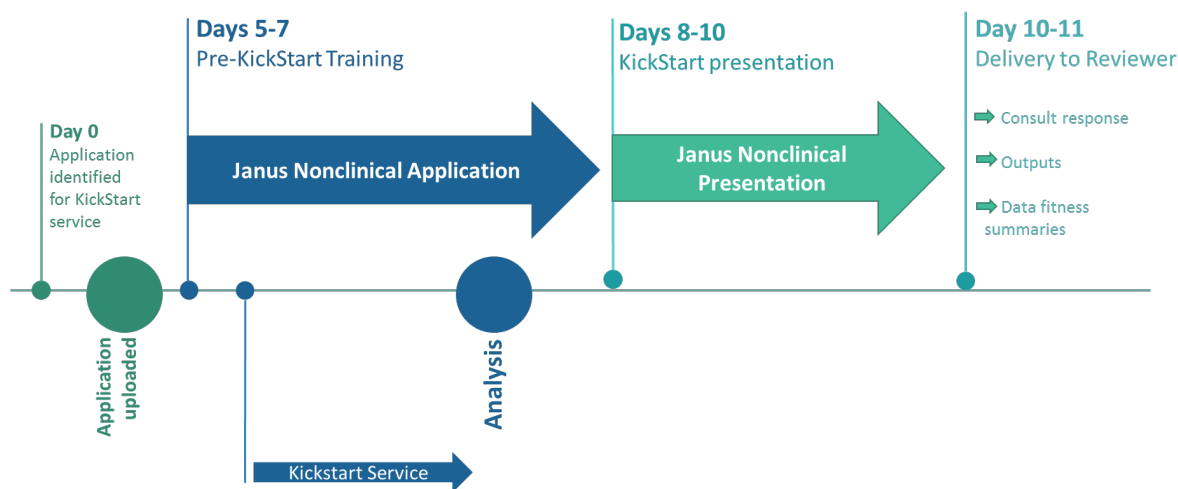


Figure 1: KickStart Service Overview

The KickStart service benefits reviewers in several ways. The data quality checks performed as part of the service help reviewers gain an understanding of SEND data and which analyses may be performed using these datasets. The data exploration assistance in Janus Nonclinical improves the review by providing orientation to data visualization of SEND and possible directions for how best to view the data within the tool. The team offers support and training for working with review tools and SEND standardized data which allows reviewers to learn how to automatically create tables and graphs for their reviews. Finally, the team supports review team communications regarding the sponsor's SEND data, including providing comprehensive data fitness assessment reports for each study which help resolve questions about the SEND submissions quickly.

PRE-KICKSTART TRAINING

To assist with the transition to working with electronic data, each KickStart session is preceded by a 60-minute Pre-KickStart Training that introduces reviewers to key SEND concepts and orients them to the features and functions of the Janus Nonclinical tool. This training covers the following SEND concepts:

- Domains
- Controlled terminology
- Overview of the nonclinical Study Data Reviewer's Guide (nSDRG)
- Introduction to the define file
- Janus Nonclinical overview

THE DATA FITNESS ASSESSMENT

The objective of the Kickstart Data Fitness Assessment is to highlight data quality and usability issues that may impact the reviewer's use of standardized electronic data during review of the drug application, and to provide feedback to the sponsor to encourage improvement of future submissions.

This assessment consists of automated and manual checks of the study SEND datasets and associated files to investigate the study's conformance to the CDISC standards.

The Data Fitness Assessment provides two deliverables for studies receiving the KickStart service:

- A summary presentation of issues that impact the reviewer's use of the study electronic data to assist the reviewer in their review of the application. This summary may include:

- A mapping of submitted electronic datasets with the study report result tables
 - A list of data collected but not submitted
 - An overall assessment of the quality of the submission
 - Identification of data that cannot be used, or can only be used with caution, due to data quality issues
 - Details of key data quality and usability issues with information about how the issue impacts use of the data and their ability to perform common analyses.
- A detailed report of quality issues identified in the submitted electronic study data that can be supplied to the study sponsor, with the objective of improving the quality of future submissions.

THE DATA EXPLORATION SESSION

The data exploration session provides reviewers with an interactive look at recommendations on how to best visualize the SEND data for their studies based on the issues identified in the data fitness portion of the session and the unique functionality of Janus Nonclinical. The KickStart team utilizes Janus Nonclinical to show key outputs extracted from SEND datasets, including the histopathology, labs, body weight, clinical observations, and pharmacokinetics datasets. The outputs may be used for reference while writing the review and may include a study summary, details on animal deaths, body weight graphs, a histopathology heat map, tables of study-specific findings, pharmacokinetic concentration graphs, and a table of pharmacokinetic parameters.

The Data Exploration portion of the KickStart service provides reviewers with an overview of their data and a tutorial on how to view SEND-specific study data and prepare example outputs. As reviewers become more comfortable with conducting analyses using SEND data, they will no longer require the KickStart service to provide this orientation and will be able to incorporate the automated analyses from Janus Nonclinical into their reviews.

COMMON DATA FITNESS ISSUES FOUND

As part of the service, the KickStart team tracks data fitness issues. Through analysis of the data fitness issues across 40 studies in 27 applications, several data quality themes have emerged:

- Incorrect reporting of timing variables needed for summarization and analysis of results
- Incorrect reporting of categorical data
- Omission of the numeric value to use in calculations as a replacement for text result

Standardization issues related to a timing variable were found in 87% (35 of 40) of the studies submitted.

- Issues in standardization of timing variables that caused a reviewer to be unable to use submitted data in Janus Nonclinical included data that could not be aligned with the reported timing, missing or incorrect elapsed time post dose for plasma concentration results, and missing time point labelling for multiple sessions of data in a day (25% (10 of 40)).
- Other standardization issues allowed the reviewer to summarize and analyze consistent with the study report but only after using the capabilities of Janus Nonclinical to align the submitted data with the reported timing. The types of standardization issues that could be overcome by Janus Nonclinical included, incorrect use of the planned day variable for a scheduled collection event performed over multiple days and reporting of 24-hr post-dose result under the collection day rather than the dosing day (62% (25 of 40)).
- Additionally, some standardization issues of timing variables were identified such as mislabeling time points within a day, missing information for tests scheduled relative to dose, and incorrect reporting of unscheduled results, which create ambiguity.

In order to prevent these standardization issues, sponsors submitting this data should perform quality control activities on submitted datasets to ensure timing variables are consistent across each dataset.

Another common data quality issue is the improper reporting of categorical test results in 70% (28 of 40) of submitted studies. This is most commonly seen in the Laboratory Test Results (LB) dataset for urinalysis and hematology tests with scored results on a discrete scale. In these cases, some scores are being reported as a numeric value, triggering group mean calculations from those results in FDA tools, which is inconsistent with the summary data in the study report. In order for these results to be recognized as scores that should be summarized as incidence counts, categorical test results should not be reported as numeric data (i.e., LBSTRESN should not be filled). A similar, but less common problem has also been seen in the Clinical Observations (CL) dataset, where scored observations such as Draize Test, functional observation battery, and body condition scoring are submitted in a manner that does not support incidence summary by score. Appropriate standardization of categorical data is necessary to permit the FDA reviewer to do a meaningful analysis of the change in incidence across dose levels and time.

Additionally, some studies have been submitted where the study report shows numeric results with group means that were submitted as categorical data in the SEND datasets. This includes submission of numeric data in the Clinical Observations (CL), and submission of numeric lab test results without a value in the LBSTRESN variable. Sponsors should ensure variables are filled in with the correct information to prevent this error in future submissions.

Finally, in 80%, or 32 of 40 studies, sponsors fail to provide a numeric replacement for a character value for use in calculations. This issue is most commonly seen in plasma concentration results reported in the PC dataset but has also been seen in immunology data reported in the LB datasets. Submission of this replacement value is necessary when group summary descriptive statistics include a replacement value for a text result such as "BLQ" rather than excluding that result from the statistics. Since that replacement is generally specific to the study and analysis performed, use of the electronic data without this substitute value will generally yield summary results that are inconsistent with the study report; it is therefore essential that it be provided.

CONCLUSION

The KickStart service provides data quality assessments and support with using analytical capabilities in the regulatory review. The KickStart service also allows the identification of common data standard implementation issues. Addressing these common errors helps both sponsors and FDA reviewers in ensuring an effective review.