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An Update on CDISC-SEND Data Submissions to FDA

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ABSTRACT

Over the past year, the US FDA received many electronic data submissions in CDISC-SEND format for nonclinical toxicology studies in new drug applications. Standardized data is used to quickly deliver key findings from nonclinical studies to pharmacology reviewers and aid in the efficiency of the review process. The FDA's KickStart team reviews a number of these CDISC-SEND submissions and reports on data quality issues identified during their review. The number and type of data quality issues identified in SEND submissions have changed over time, mirroring the success in industry-wide adoption of the SEND standard. If the industry addresses the most-frequently seen issues that may impact review, reviewers will be able to maximize the use of data submitted to the FDA for review.

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 can benefit from the use of an efficient and accurate review method.

Per the guidance issued by the US 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).[1] The FDA chose standards from the Clinical Data Interchange Standards Consortium (CDISC) as the required method for the sponsor's submission of clinical and nonclinical data to the FDA. Since this requirement began, the number of SEND submissions seen at the Agency has increased exponentially, requiring a significant expansion of resources to support the use of these data submitted to the Agency. To assist with this effort, the FDA CDER Office of Computational Science (OCS) continues to support reviewers' use of the SEND data by offering the KickStart service as well as additional tool and analysis support as needed.

SEND SUBMISSIONS UPDATE AT FDA

The SEND submissions seen at the US FDA increased rapidly after the SEND standard became required for INDs in 2017. As of December 2019, 1675 studies associated with 707 applications containing SEND data came to the FDA. More than one third of these studies (584) and applications (249) arrived at the FDA since September 2019. While Sponsors modeled most studies submitted in 2019 in the SEND Implementation Guide (SENDIG) v3.0, sponsors have been proactively submitting studies modeled in SENDIGv3.1 in support of several commercial INDs, despite SENDIG v3.1 not being required for commercial IND submissions.

The significant increase in SEND submissions to the Agency requires additional tool and reviewer support to process these submissions throughout the review cycle. In addition, the 30-day review timeline for INDs means this support should be provided as soon as possible to maximize reviewers' use of the data. FDA CDER OCS provides this support by performing the KickStart service on applications requested by the reviewer.

THE KICKSTART SERVICE

The increased number of commercial IND submissions together with the challenges of a short timeframe for review make KickStart an important service for the review of non-clinical data. KickStart uses the SEND data submitted by sponsors to increase the efficiency of the regulatory review process. The service is executed over the course of a 6-7 business days, after which two sessions are provided for the requester: a training session to introduce reviewers to key SEND concepts and the functionality of Janus Nonclinical (a proprietary system); and the KickStart session, which provides a data fitness assessments and an overview of the analysis capabilities based on the received data.

The KickStart Data Fitness Assessment highlights quality and usability issues that may impact the reviewer's use of standardized electronic data during the review of the drug application and provides 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. This Assessment provides two deliverables for studies receiving the KickStart service: (1) a summary presentation of issues that impact the reviewer's use of the study electronic data, and (2) 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 portion of the KickStart service 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 OCS analytical tools. The analysis outputs may be used for reference while writing the review. Additionally, this portion 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 into their reviews.

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 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.

Since inception, the KickStart team provided services to 124 studies for 81 applications. A breakdown of the studies analyzed through the service by division, test facility, and species are provided below.

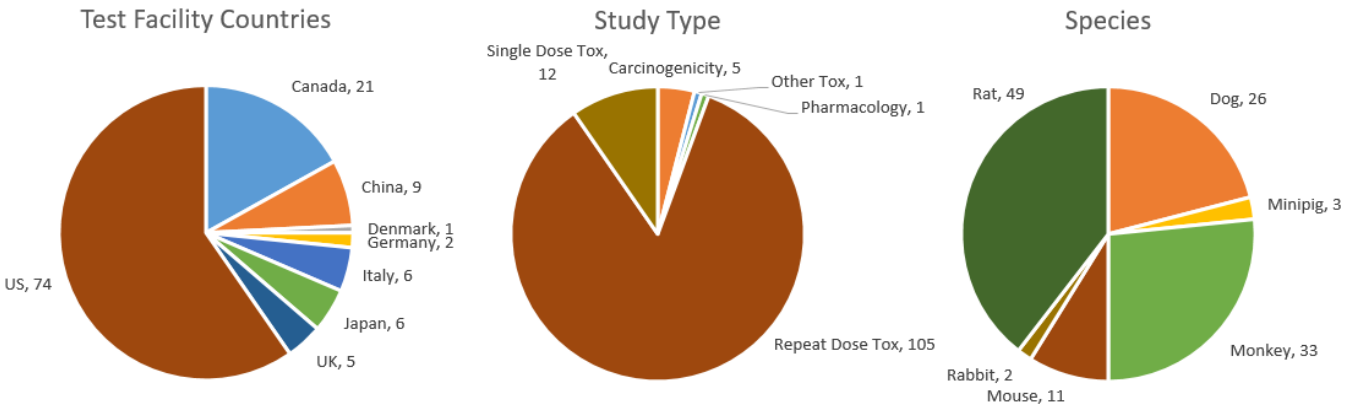

Figure 1 – KickStart Study Attributes

The two graphs below show the number of issues identified in SEND datasets reviewed for a KickStart service, with the first chart covering all studies since the inception of the service, and the second chart showing only studies reviewed in the fiscal year 2019. Each bar represents a single study with the height of each bar represents the number of issues identified in that study, normalized to allow comparison between studies with different designs. The increasingly negative slope in the trendline suggests that over time, studies are being submitted with fewer issues. Additionally, fewer studies have a significantly higher number of issues than the others, suggesting that companies are submitting more consistent datasets.

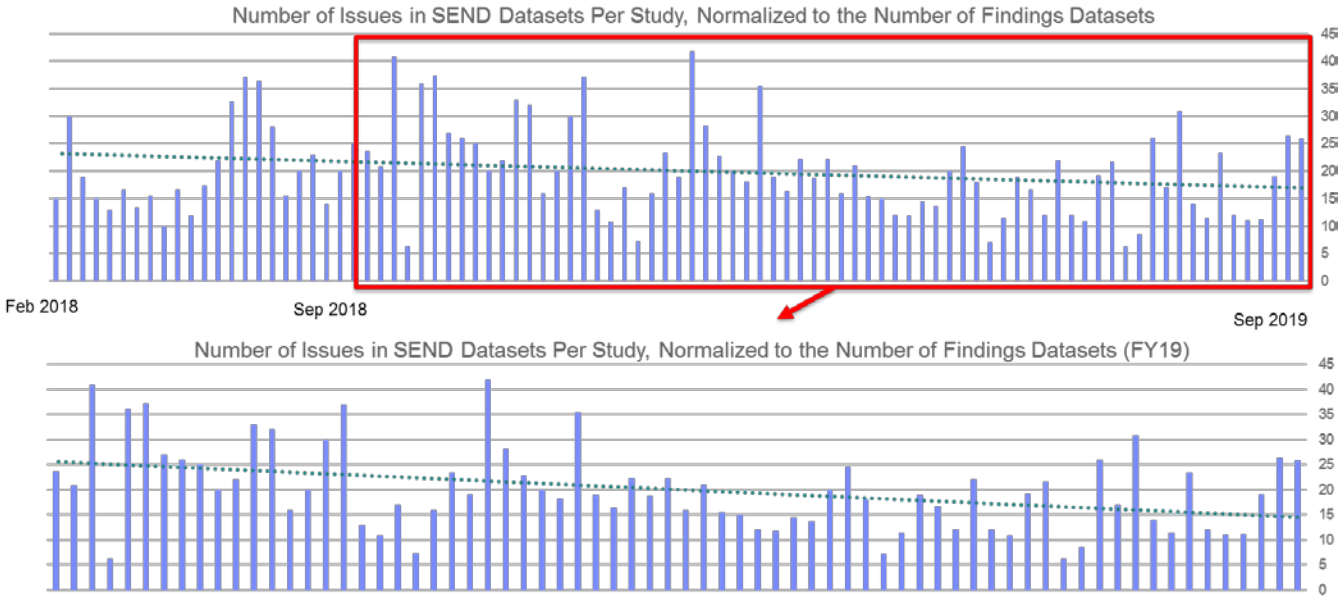

Figure 2 – Data Fitness Issue Occurrence Over TIme

COMMON DATA FITNESS ISSUES FOUND

The KickStart team tracks the specific data fitness issues identified as part of the service. Through analysis of the data fitness issues across 70 studies in 47 applications reviewed in Fiscal Year 2019, several data quality themes emerged:

- Incorrect reporting of timing variables needed for summarization and analysis of results
- Incorrect reporting of categorical data
- The omission of the numeric value to use in calculations as a replacement for text result
- Undefined codes/abbreviations included in datasets
- Issues with the alignment of organ/tissue names with the study report

Incorrect reporting of SEND Timing variables continue to be the most common issue seen in SEND datasets reviewed by the Kickstart team, with nearly all studies having at least one of the following issues:

- Planned day submitted does not align data with the study report summary
- Incorrect reporting of timing for tests or observations scheduled relative to dose
- Incorrect reporting of results from unscheduled tests or observations.

The following example shows how results are displayed to the FDA reviewer when the planned day submitted does not align with the study report summary. Figure 3 shows individual data (with animal numbers masked) for the one clinical chemistry test for the male control animals. The study report indicated that samples for clinical chemistry were collected once pretest and at necropsy. However, the Visit Day variable (VISITDY) reported does not align the data across animals into those two collection periods. Rather, the actual day of sample collection is reported in VISITDY, spreading the data for each collection period over multiple days:

GROUPED-SUMMARY : NUMERIC | GROUPED SUMMARY : NON-NUMERIC | **DAILY BY ANIMAL** | ANIMAL DETAILS

Filter table data by term...

Group	S...	Test	Animal ID	Unit of the Standa... Result	Day -13	Day -12	Day -11	Day 178	Day 179
1-Control ...	Male	Alanine Aminotransferase	1	U/L			21		17
1-Control ...	Male	Alanine Aminotransferase	2	U/L		34		26	
1-Control ...	Male	Alanine Aminotransferase	3	U/L	47			30	
1-Control ...	Male	Alanine Aminotransferase	4	U/L	23			30	
1-Control ...	Male	Alanine Aminotransferase	5	U/L			29		30
1-Control ...	Male	Alanine Aminotransferase	6	U/L			25		27
1-Control ...	Male	Alanine Aminotransferase	7	U/L		32			21
1-Control ...	Male	Alanine Aminotransferase	8	U/L	21			22	
1-Control ...	Male	Alanine Aminotransferase	9	U/L	18			14	

Figure 3 – Individual Animal View with Incorrect VISITDY

This results in group summarization, as shown in Figure 4 below, where it is evident (based on the N values) that the means for each day include only a subset of each group's animals. The FDA reviewer must merge the data from the three pretest days and from the two necropsy days together in Janus Nonclinical prior to using the data for analysis.

GROUPED-SUMMARY : NUMERIC | GROUPED SUMMARY : NON-NUMERIC | DAILY BY ANIMAL | ANIMAL DETAILS

Filter table data by term...

Group	S...	Test	Unit of the Standa... Result	Day -13 Mean	Day -13 N	Day -12 Mean	Day -12 N	Day -11 Mean	Day -11 N	Day 178 Mean	Day 178 N	Day 179 Mean	Day 179 N
1-Control...	Male	Alanine Aminotransferase	U/L	27.250	4	33.000	2	25.000	3	24.400	5	23.750	4
2-Low	Male	Alanine Aminotransferase	U/L	24.000	2	29.333	3	29.500	2	23.000	3	23.500	4
3-Mid	Male	Alanine Aminotransferase	U/L	28.000	2	28.500	2	27.000	3	46.333	3	25.750	4
4-High	Male	Alanine Aminotransferase	U/L	30.250	4	27.000	3	26.500	2	26.000	5	20.500	4

Figure 4 – Summary Animal View with Incorrect VISITDY

The next example illustrates incorrect timing for sample collection scheduled relative to dose. Figure 5 shows the reported timing from a sample scheduled for collection 24 hours after the day 1 dose reported with VISITDY=2 and Planned Elapsed Time (PCELTM) is PCELTM=PT0H, thus showing an Elapsed Time – Day value of "0 Hrs – Day 2" in this Janus Nonclinical summary view. The time post dose is evident only from the Planned Time Point Name (PCTPT) value, which is optional in this Janus Nonclinical summary view.

GROUPED SUMMARY | DAILY BY ANIMAL | ANIMAL DETAILS

Filter table data by term...

Elapsed Time - Day	Day	Planned Time Point Name
0 Hrs - Day 2		
	2	24 hr post

Figure 5 – Inconsistent timing relative to Dose day 1

This study, which had timed infusion dosing, had the added issue of having an --RFTDTC (the dose date/time) inconsistent with the study report and a non-specific –TPTREF (label for the dose date/time) entry. The study report indicated that the sample collection timing was relative to the end of the infusion while PCRFTDTC contained the start date/time of infusion, and PCTPTREF contained only "Day 1 Dose" without reference to the start or end of dose.

The most common issue with timing relative to dose in SEND is that the relevant timing variables are not reported at all. However, when they are reported, it is common to see issues such as those described above. These timing issues put additional burdens on the reviewer to both identify the issue prior to analysis and adjust the reported timing using capabilities in Janus Nonclinical in order to perform the required analyses. Additionally, analysis capabilities are more limited in Janus Nonclinical when certain timing information is not correctly provided in the submitted datasets.

Another common data quality issue is the improper reporting of categorical test results. While this has improved in studies reviewed in the past year, approximately 50% of studies reviewed still have this issue. This is most commonly seen in the Laboratory Test Results (LB) dataset for urinalysis and hematology tests with scored results on a discrete scale. For these results to be consistent with the study report, where they are recognized as scores that should be summarized as group incidence counts rather than means, categorical test results should not be reported as numeric data (i.e., Standardized Result in Numerical Format (LBSTRESN) should not be filled, as described in the SENDIG and the FDA Study Data Technical Conformance Guide).[2]

Figure 6 shows a selection of SEND variables for urine white blood cells (WBC) results, as seen through Janus Nonclinical. The Result as Collected (LBORRES) and Standardized Result in Character Format (LBSTRESC) shows results collected on a discrete scale. When the standardized result is zero, LBSTRESN is also filled; this is incorrect representation of such categorical results. Since SEND has no specific variable to distinguish a categorical test (for incidence summaries) from a

numeric test (for summary means) and the study had no define.xml codelist for the test to define the scale and put the results in context, Janus Nonclinical cannot automatically, with certainty, determine how to summarize such results.

Group	Sex	Animal ID	Category	Test Code	Test	Result or Findings as Collected	Unit of the Original Result	Standardi… Result in Character Format	Standardized Result in Numeric Format	Unit of the Standardized Result
1 -…	Male	1M005	Urine Sediment	WBC	Leukocytes	10-15	/HPF	10-15		/HPF
2 -…	Male	2M007	Urine Sediment	WBC	Leukocytes	1-3	/HPF	1-3		/HPF
2 -…	Male	2M010	Urine Sediment	WBC	Leukocytes	0	/HPF	0	0	/HPF
3 -…	Male	3M012	Urine Sediment	WBC	Leukocytes	0-1	/HPF	0-1		/HPF
1 -…	Female	1F023	Urine Sediment	WBC	Leukocytes	0	/HPF	0	0	/HPF
1 -…	Female	1F025	Urine Sediment	WBC	Leukocytes	0	/HPF	0	0	/HPF
3 -…	Female	3F032	Urine Sediment	WBC	Leukocytes	0-1	/HPF	0-1		/HPF
3 -…	Female	3F035	Urine Sediment	WBC	Leukocytes	5-10	/HPF	5-10		/HPF
3 -…	Female	3F035	Urine Sediment	WBC	Leukocytes	0-1	/HPF	0-1		/HPF
4 -…	Female	4F036	Urine Sediment	WBC	Leukocytes	1-3	/HPF	1-3		/HPF

Figure 6 - Results Collected on a Scale; Incorrect use of LBSTRESN

The KicKStart team has also seen a reduction in the number of sponsors that fail to provide a numeric replacement for a character value for use in calculations. Still, approximately 50% of studies reviewed have this issue, most commonly seen in plasma concentration results reported in the PC dataset, but also seen in the LB dataset. 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 specific to the study and analysis performed, the use of the electronic data without this substitute value can yield summary results that are inconsistent with the study report; it is, therefore, essential that it be provided.

Figure 7 illustrates this issue with results for a urine chloride test, with Janus Nonclinical summary to the left and the study report summary to the right, for one group and one day. The results include three animals with a value “<10”. The study report includes a value 10 in the mean for those three animals, while SEND excludes those three animals from the mean since LBCALCN was not supplied.

			Day 30 Urine		
Group	Test	Unit of the Standa… Result	Mean	Std Dev	N
G1 …	Chloride	mmol/L	16.143	±5.210	7

UCl mmol/L
Dosing
30

1/1/M	Mean	SD	N
	<14	5.2	10

Figure 7 - Missing --CALCN value

An emerging issue seen in studies reviewed by the KickStart team in 2019 is the use of codes and abbreviations in the SEND datasets either without a definition or with the nSDRG making a general reference to definitions in the study report. Almost 50% of the studies reviewed have this issue. Codes and abbreviations have been seen as result values, in reason fields, as finding modifiers and in comments. Undefined unit abbreviations (not part of the published UNIT codelist) have also been submitted. Use of codes and abbreviations in the electronic data add ambiguity to the review, requiring additional research and adding unnecessary time to the review.

Finally, in most submitted studies reviewed by the KickStart team, the representation in SEND of organs and tissues weighed and examined, and the alignment of those organ and tissue names in SEND variables has presented challenges. The study report list of tissues weighed and examined is typically very detailed, and SEND supports this level of detail. However, the KickStart team frequently sees the representation of the organs and tissues simplified in SEND datasets, missing important

details. Issues seen included a lack of laterality in SEND datasets when paired organs are weighed or examined, regions of a tissue scheduled for examination not defined in SEND datasets, and multiple tissues weighed or examined together not fully defined in SEND datasets. This again adds ambiguity to the study review and significantly limits the possibility of cross-study analysis.

Some examples from studies reviewed for a Kickstart service include:

- The study report indicates that thyroid and parathyroid glands are weighed together, but Specimen Material Type (OMSPEC) contains only “GLAND, THYROID”.
- The study report indicates that “Muscle (biceps femoris)” is required to be examined microscopically, but MISPEC contains only “MUSCLE, SKELETAL” with region unidentified.
- Multiple regions of the spinal cord are included in the study report list of tissues to examine; MISPEC contains multiple records per animal with MISPEC=”SPINAL CORD” with no information in MISPEC or Anatomical Region of Specimen (MIANTREG) to identify the region associated with each entry.

CONCLUSION

The US FDA continues to receive an increasing number of SEND submissions. 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.

REFERENCES

1. U.S. Food and Drug Administration. (2014). *Providing Regulatory Submissions in Electronic Formats – Standardized Study Data*. Retrieved from https://www.fda.gov/media/82716/download.
2. U.S. Food and Drug Administration. (2019). *Study Data Technical Conformance Guide v4.4.* Retrieved from https://www.fda.gov/media/131872/download.

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