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The Impact of SEND Data on FDA Review of Nonclinical Studies

Matthew Whittaker, Ph.D., U.S. Food and Drug Administration, Silver Spring, MD, USA

Kevin Snyder, Ph.D., U.S. Food and Drug Administration, Silver Spring, MD, USA

ABSTRACT

In accordance with the final guidance issued on December 17, 2014, *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*, study reports for certain toxicology studies initiated on or after December 17, 2016 for new drug applications (NDA) or December 17, 2017 for investigational new drug applications (IND) must be submitted with standardized electronic datasets. The FDA Data Standards Catalog indicates that these datasets are required to be formatted in accordance with the Clinical Data Interchange Standards Consortium (CDISC) Standard Exchange for Nonclinical Data (SEND), which currently supports single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. As a result, nonclinical pharmacology/toxicology reviewers at the FDA are beginning to receive standardized electronic SEND datasets along with traditional toxicology study reports. New software tools will allow reviewers to quickly visualize study results from multiple perspectives as they will no longer be limited by the single perspective presented by the static tables and figures in study reports. Analysis of SEND datasets at FDA will be an important step forward for the agency, increasing both the efficiency and thoroughness of the nonclinical study review process.

INTRODUCTION

All Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics License Applications (BLAs) received by the FDA Center for Drug Evaluation and Research (CDER) are evaluated by a multi-disciplinary team of reviewers.

Table 1. Review disciplines included in evaluation of INDs/NDAs/BLAs in CDER

Discipline	Office
Regulatory project manager	Office of New Drugs
Clinical	Office of New Drugs
Nonclinical	Office of New Drugs
Chemistry, Manufacturing &	Office of Pharmaceutical Quality
Clinical Pharmacology	Office of Translational Sciences – Office of Clinical Pharmacology
Biostatistics	Office of Translational Sciences – Office of Biostatistics

Within each discipline, a single primary reviewer is responsible for critically assessing all relevant study reports while a secondary reviewer acts to ensure that the review is conducted appropriately. Nonclinical reviewers evaluate pharmacology and toxicology studies submitted by drug sponsors to support the testing of a drug product in humans. The inclusion of SEND datasets with nonclinical study reports in regulatory submissions presents many opportunities for enhancing the review process for all nonclinical reviewers in the FDA Office of New Drugs (OND). Nonclinical review staff in OND and staff from the FDA Office of Computational Science (OCS) are collaborating to develop tools and technologies to use SEND data to improve the efficiency and quality of nonclinical reviews.

NONCLINICAL REVIEW PROCESS IN CDER OFFICE OF NEW DRUGS

There are approximately 250 nonclinical reviewers in the Office of New Drugs, divided among 17 Review Divisions that are defined by disease indication. Review Divisions in OND are comprised of clinical reviewers (medical officers), nonclinical reviewers, and regulatory project managers.

The FDA's decision to approve a drug for a particular disease indication is based on the sponsor's evidence for the safety and efficacy of their drug product in clinical studies conducted in humans. Prior to initiating any studies of a drug in humans under an IND, sponsors must conduct nonclinical toxicology studies in animals. Nonclinical toxicology studies are conducted to define potential toxic effects of a drug in humans, as well as the doses at which these effects might be expected to occur.

The specific types of nonclinical studies required to support clinical development, and the general timing of submission of these studies to the FDA, are shown in Figure 1. It is notable that a large portion of the nonclinical development program for a drug product is conducted prior to the initial submission of the IND.

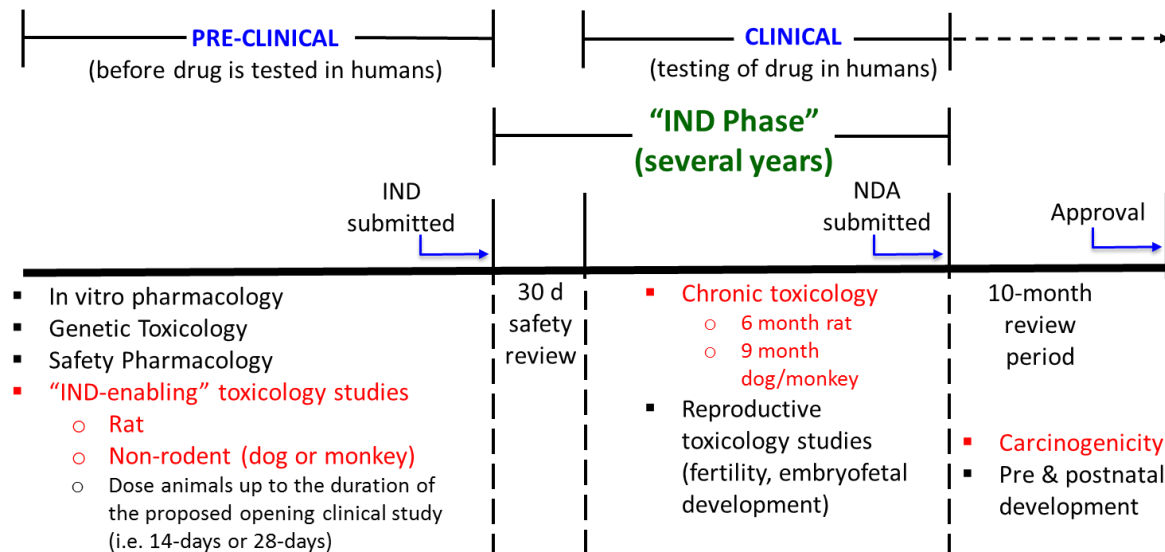


Figure 1. Nonclinical study types required to support the clinical development of a drug product. Study types listed in red are modeled in SEND 3.0.

BASICS OF CURRENT NONCLINICAL REVIEW PRACTICES

The primary responsibility for nonclinical reviewers at FDA is to determine whether sponsors have demonstrated adequate support for the safety of all of the doses that are proposed for use in a clinical setting. A major part of that decision is based on defining the Limit Dose in general toxicology studies. The ICH M3(R2) and ICH S6 Guidances outline for Industry the general requirements for nonclinical support of clinical doses for small molecules and biologic products, respectively.

Historically, nonclinical reviewers have accessed pdf files of nonclinical study reports (NCSRs) submitted to the Agency. Sponsors present all of the data collected for each animal in the study in the form of summary tables, individual line listings, and figures. NCSRs also include detailed Methods as well as Discussion and Conclusions sections where sponsors provide their interpretation of the evidence. Reviewers use the information in the study report to define a Limit Dose and determine whether the doses and duration of a proposed clinical trial are supported by the nonclinical data. The review process is intended to capture all of the relevant study data for each NCSR in a standardized IND Review Template used across OND. Reviewers must include all information necessary to support and explain their decision on the Limit Dose. Review documents generally consist of tables (Microsoft Word, Excel) presenting important findings from a study and text describing the reviewer's interpretation of the findings. Analysis of study data (i.e. calculation of % change from control) requires manual re-entry of data into an appropriate analytical tool.

CHALLENGES WITH THE CURRENT APPROACH TO NONCLINICAL STUDY DATA SUBMISSION AND REVIEW

- (1) Nonclinical reviewers spend significant time re-typing values presented in pdf nonclinical study reports in order to conduct analyses or view the data in a way that is sensible to them.
- (2) There is no uniform format for study data presentation in NCSRs that sponsors are required to adhere to. Therefore, the organization of study reports varies widely between different sponsors. Reviewers must spend significant time navigating through a pdf document and marking the document up to be able to efficiently access data.
- (3) The FDA is a repository for a tremendous amount of nonclinical study data. However, these data are not readily searchable.

ELECTRONIC STUDY DATA REGULATIONS

Per the Food, Drug & Cosmetic Act Section 745A(a): Sponsors must submit study data using the data standards defined in the FDA Data Standards Catalog starting 24-months after final guidance is issued for a specific submission type. The relevant dates pertaining to SEND are shown in the table below.

Table 2. Summary of relevant dates for requirement of submission of SEND datasets with regulatory submissions to the FDA. Dates are derived from the FDA Data Standards Catalog v5.2 (<https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm#Catalog>)

Standard	Application type	Dates that standard is accepted	Dates that standard is required*
SEND 3.0	NDA/BLA/ANDA	6/13/11 – 3/15/19	12/17/16
	Commercial IND	6/13/11 – 3/15/20	12/17/17
SEND 3.1	NDA/BLA/ANDA	8/21/17 -	3/15/19
	Commercial IND	8/21/17-	3/15/20

*Requirement dates refer to the nonclinical study initiation date (not the date that the study is submitted to the Agency)

The nonclinical study types modeled in SEND 3.0 include single and repeat-dose general toxicology studies, as well as carcinogenicity studies. The number of submissions to the FDA with SEND datasets sharply increased in 2018 (Table 3) and is expected to increase even further in 2019. The majority of SEND submissions have been in support of IND applications. This is expected, given that IND applications far outnumber NDA/BLA applications. Secondly, the vast majority of nonclinical studies are completed and submitted during the IND phase, prior to NDA/BLA submission. Generally, the only nonclinical studies submitted with an NDA/BLA are carcinogenicity studies and pre-postnatal development studies. Approximately 80% of the SEND datasets received to date have been for repeat-dose toxicology studies. To date, all SEND submissions to the FDA have been in SEND 3.0.

Table 3. Total number of nonclinical studies with SEND data submitted to the FDA

Application type	Total SEND studies*	2016	2017	2018
Commercial IND	360	4	47	309
NDA	54	8	8	38
BLA	3	0	1	2

*As of 12/28/18

WHY IS FDA DEVELOPING ITS OWN SEND VISUALIZATION APPLICATION?

There are multiple benefits to developing an FDA-specific software application for the visualization and analysis of SEND datasets:

- (1) Janus Nonclinical is designed to meet the specific needs of nonclinical reviewers at FDA. The application is designed to visually present tables and figures in a way that is useful to all nonclinical reviewers. Furthermore, the application is being developed to allow for the export of outputs (i.e. tables & figures) that are consistent in format and content with the general practices of nonclinical reviewers at FDA and that are readily compatible with the IND Review Template.

Use of the Janus NC application will eliminate the current review practice of manual transcription of study data from pdf files to Word or Excel documents. Production of tables and figures in Janus NC will allow for formatting in review documents to be consistent across reviewers and review divisions.

- (2) Janus Nonclinical will be used to interface with the IND Smart Template. The IND Smart Template project represents another collaboration effort between OND Pharm/Tox and OCS. Briefly, the Smart Template is a Word template that contains text fields and dropdown menus that capture all of the elements of a review. Current good review practice in OND is that all reviews of nonclinical studies submitted to INDs are to be completed using the Smart Template.

Ongoing development of Janus Nonclinical will allow for pre-population of required fields in the Smart template with SEND data derived from the Janus database.

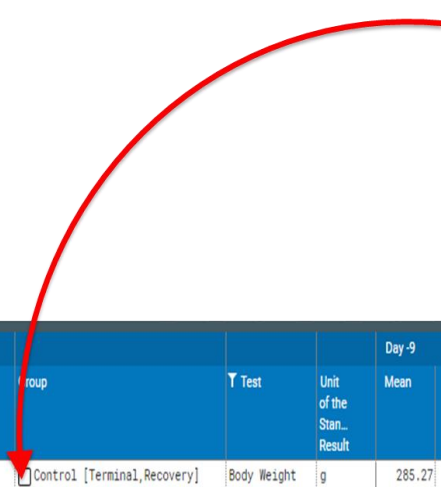
- (3) Future development of Janus NC will allow for analysis of nonclinical study results from the same drug across multiple studies within a development program. For example: reviewers could use the tool to analyze toxicities observed in rodent vs. non-rodent species as well as in studies of different dosing durations (i.e. acute vs. chronic toxicology studies). The ability to conduct such analyses within a single software application would represent a significant improvement in capability over existing practices.
- (4) The availability of electronic standardized study data, both from clinical and nonclinical sources, opens the possibility for better prediction of toxicities in humans. Janus NC could be used to correlate adverse events in clinical studies with toxicities observed in nonclinical studies. These types of analyses would not be possible using commercially available analysis tools for standardized clinical or nonclinical datasets.

WAYS THAT JANUS NONCLINICAL ENHANCES REVIEW OF NONCLINICAL DATA NOW

- (1) A major advantage to using Janus NC to analyze nonclinical study data is the ability to dynamically filter and sort data in summary tables. This allows users to identify dose-related trends much more quickly than by reading through hundreds of pages of static tables in pdf files.
- (2) Janus NC allows users to switch from Mean $\pm$ SD view to % change from control view in 2 clicks for body weight, clinical chemistry, hematology, urinalysis, and organ weight summary data. This functionality allows reviewers to quickly see the magnitude of differences from concurrent control animals. Conducting such an analysis using traditional review methods requires re-typing relevant values and conducting % change analyses in Excel. This process is both time-consuming and prone to human error.
- (3) Another important functional feature of Janus NC is that mean values in Summary Tables contain the underlying individual animal data values (accessible by clicking on the mean value). Accessing individual animal data in a pdf study report requires navigation away from the summary table and several additional steps to view the data that one is looking for.
- (4) Janus NC has a Dashboard that allows for users to assign attributes (Alias, Set Type, reference group) to each treatment group and define how the SEND data is presented in summary tables across all domains within the application.
- (5) Users can re-name dose groups in the Group Alias column in the Dashboard in a way that makes sense to them. The Group Alias replaces the sponsor's Group Label throughout Janus Nonclinical.
- (6) Janus NC has default settings for each domain that define which Set Types to combine for calculation of mean $\pm$ SD values. For example, mean values in summary tables for in-life data such as body weight, clinical chemistry, hematology, urinalysis, and clinical signs are comprised of values for Terminal and Recovery sets. Values from toxicokinetic animals and satellite animals (if reported) are excluded from mean calculations for these domains. Default settings are different for post-mortem domains including MA, MI, OM, and TF (set types are not combined) as well as for the toxicokinetic domains PP and PC (all set

types combined). Figure 2 shows a representative example of body weight data presented in a summary table of an NCSR and the Janus NC representation of the associated SEND data. Default summary tables in Janus NC are prepared automatically and require no user-intervention beyond assigning set types at the Dashboard page.

- (7) Janus NC allows for significant customization of how study data is presented in summary tables. Within a summary table, users can define the specific Set Types to combine in the calculation of means for each treatment group. Users can also define the specific Set Types that are shown/hidden in the table. Finally, columns can be dragged and dropped to allow the user to set up the table in a way that visually makes sense.



Group / Sex		-9	-1	4	7
1M	Mean	285.3	352.8	388.5	411.9
	SD	9.6	15.2	21.3	24.5
	N	15	15	15	15
2M	Mean	286.1	352.1	386.1	407.6
	SD	5.5	15.4	21.7	25.8
	N	10	10	10	10
	%Diff G1	0.3	-0.2	-0.6	-1.1
3M	Mean	285.6	354.0	387.2	406.9
	SD	6.1	10.7	17.1	16.7
	N	10	10	10	10
	%Diff G1	0.1	0.3	-0.3	-1.2
4M	Mean	284.9	353.9	381.2	395.5
	SD	9.3	14.0	14.5	18.1
	N	15	15	15	15
	%Diff G1	-0.1	0.3	-1.9	-4.0

Sex	Group	Test	Unit of the Stan. Result	Day -9			Day -1			Day 4			Day 7		
				Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	N
Male	☐ Control [Terminal, Recovery]	Body Weight	g	285.27	±9.61	15	352.80	±15.17	15	388.47	±21.32	15	411.93	±24.47	15
Male	☐ Low dose - Terminal	Body Weight	g	286.10	±5.49	10	352.10	±15.38	10	386.10	±21.69	10	407.60	±25.84	10
Male	☐ Mid dose - Terminal	Body Weight	g	285.60	±6.08	10	354.00	±10.72	10	387.20	±17.14	10	406.90	±16.68	10
Male	☐ High dose [Terminal, Recovery]	Body Weight	g	284.93	±9.34	15	353.87	±13.96	15	381.20	±14.52	15	395.53	±18.07	15

Figure 2. Representative example of body weight summary data presented in a sponsor's nonclinical study report (above) and the SEND data represented in Janus Nonclinical (below). Default settings for set types to include in mean $\pm$ SD calculations allow Janus NC to present summary data that is consistent with what is presented in the nonclinical study report without user intervention.

FUTURE DEVELOPMENT INITIATIVES

Much of the development effort for Janus NC in the past year has been devoted to presenting SEND data in a way that is sensible to reviewers. Effort was also directed toward including functionality to allow users to customize the way that the data is presented. These efforts will continue with the goal of optimizing data presentation for all domains modeled in SEND.

An exciting direction for future development lies in graphing and visualization of SEND data. This will allow users to see trends and evaluate data in ways that are not possible using traditional review methods. One specific example is visualization of clinical observation incidence over time. Improved graphing and visualization could also be expected to be used to great effect in analyzing data in the LB domain.

CURRENT USE OF JANUS NONCLINICAL IN CDER

Janus NC is available to those reviewers who are assigned to an IND that includes studies with associated SEND datasets. Reviewers must request a Kickstart training service from OCS to gain access to Janus NC. A Kickstart training service, delivered to a single reviewer by a team of analysts, is comprised of instruction on the basics of SEND and on use of the Janus NC tool.

Experience has shown significant time savings in using Janus NC over traditional review methods. The most significant advantage to using Janus NC over transcribing data from the pdf NCSR is the ability to use filtering strategies to quickly isolate dose-related findings. This is particularly relevant in the LB domain when there are a

large number of endpoints collected over multiple timepoints throughout the course of a study. Generation of a table showing relevant treatment-related findings on clinical chemistry endpoints takes approximately 30 minutes in Janus NC. Generating the same table using traditional review methodologies might take 2-3 hours or more. Janus NC is also particularly useful for visualization of histopathology data. Preparation of a histopathology table showing only the relevant treatment-related findings for a small molecule with multiple toxicities has been reported to take less than 2 hours using Janus NC. Preparation of the same table by reading the pdf and manually entering the data into a word table could be expected to take up to 6 – 8 hours.

CONCLUSION

Sponsor submission of nonclinical study data in SEND format allows for the development of review tools and strategies at FDA that can alleviate many of the existing inefficiencies associated with current and past practices of nonclinical review in OND. OCS and OND are closely collaborating to develop Janus NC into a review tool that can truly enhance the efficiency and quality of nonclinical review at FDA. In order to achieve the maximum user adoption of the tool in the nonclinical reviewer community, it is of the utmost importance that the application is simple to use, and that the data presented in Janus NC is consistent with the data in the NCSR.

Janus NC will provide users with multiple advantages over the traditional methods of reviewing nonclinical study data. Currently, these advantages include rapid filtering/sorting of data and % change calculation capabilities. Users can interact with the data in ways that are not possible when reviewing pdf study reports. Users can hide/show and drag/drop columns in summary tables. Individual animal data underlying mean values is available in a single click. In the near term, enhanced graphing capability will allow users to visually examine data in ways that were not previously possible. This functionality is intended to allow reviewers to identify physiologically relevant findings more quickly.

The impact of SEND data submissions to FDA is expected to extend beyond improving the efficiency of the review of nonclinical study reports at the level of the individual reviewer. Janus is a warehouse of datasets that are all formatted according to the same rules. This database could be queried to address questions relevant to regulatory decision-making for a specific product or class of products. Careful scrutiny will be required for such cross-study analyses to ensure that the questions being asked are being approached in a scientifically appropriate way.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Matthew Whittaker, Ph.D.
Company: United States Food and Drug Administration
Address: 10903 New Hampshire Avenue
City / Postcode: Silver Spring, MD 20993
Work Phone: 301-796-4868
Email: matthew.whittaker@fda.hhs.gov

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