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Developing SEND for CBER - Collaborative Workstream Initiative

Lisa Lin, FDA, White Oak, MD, USA

Susan DeHaven, Sanofi US Inc., Bridgewater, NJ, USA

ABSTRACT

The Center for Biologics Evaluation and Research (CBER) within FDA intends to receive SEND datasets in future submissions. However, implementations currently defined in published and planned SEND Implementation Guides do not fully provide data models needed for representing certain study types (including study design) or endpoints typically received in a CBER submission. Endpoints related biodistribution, immunogenicity, test article characterization and hybrid activity/safety trial designs need to be evaluated with the current SEND domain models available to understand gaps and possible new requirements. To address the intention of CBER, a team has been developed, and project work strategy defined, to evaluate essential SEND data tabulation needs for supporting CBER submissions. This team will recommend proposals for modeling enhancements and solutions (e.g., implementation guidance and any new domain(s), variables, and CT codelist needs) to enable SEND for CBER.

INTRODUCTION

SEND (Standards for Exchange of Nonclinical Data) is an implementation of the SDTM standard for nonclinical studies. FDA Data Standards Catalog V5.1 (08-2-2018) and Study Data Technical Conformance Guide states The Center for Drug Evaluation and Research (CDER) requires SEND submission for single-dose general toxicology, repeat-dose general toxicology and carcinogenicity studies. Since implementations currently defined in published and planned SEND Implementation Guides do not fully provide data models needed for representing certain study types (including study design) or endpoints typically received in a Center for Biological Evaluation and Research (CBER) submission, a joint working team among CDISC, CBER non-clinical reviewers and industry experts has been formed to evaluate essential SEND data tabulation needs for supporting CBER submissions. This team will recommend proposals for modeling enhancements and solutions (e.g., implementation guidance and any new domain(s), variables, and CT codelist needs) to enable SEND for CBER. In the FDA Data Standards Action Plan, this project is listed as "Evaluation and Testing of the SEND Standard for CBER" to improve efficiency in the review process for nonclinical toxicology studies for CBER.

DEVELOPING SEND FOR CBER

THE PROJECT

The SEND for CBER team began their work in June 2018, with the objectives to:

- to develop a team and project work strategy
- to evaluate SEND data tabulation needs for supporting CBER submissions, which are aimed toward identifying modeling and controlled terminology gaps (with respect to published and planned SEND implementation models) - essentially, a "gap analysis"
- to develop a recommendation of proposed solutions for mitigating the gaps (e.g., implementation guidance and any new domain(s), variables, and CT codelist needs).

Additional project(s) and/or CDISC workstream activities will be defined to fulfill any standards gaps identified, based on this team's recommendations for modeling solutions needed to enable CBER to require SEND submissions.

The team is a highly collaborative group with roles from across the drug development stakeholder community which are needed to fulfill the project objectives:

- Project Co-Leads representing Industry and FDA
- FDA scientific subject-matter experts and reviewers
- CDISC SEND/SDTM modeling and controlled terminology subject matter experts
- Industry Pharmacologists and Toxicologists
- Computerized tools developers
- CDISC representatives providing standards governance guidance



Three CBER Offices are represented on the team: Office of Vaccines Research and Review (OVRR), Office of Tissues and Advanced Therapies (OTAT), Office of Blood Research and Review (OBRR).

The project is planned for approximately 16 months duration (see Figure 1.)

ID	Task Name	Start	Finish	Duration	Q3 18				Q4 18				Q1 19			Q2 19			Q3 19			Q4 19	
					Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov		
1	SEND Orientation	6/28/2018	7/31/2018	4.8w																			
2	SEND Domain Reviews Includes unpublished domains: IS and IA	7/31/2018	3/29/2019	34.8w																			
3	Gap Analysis	9/28/2018	5/28/2019	34.6w																			
4	Recommendation	6/3/2019	9/2/2019	13.2w																			

Figure 1: SEND for CBER Project Plan

The SEND for CBER project is conducted through bi-weekly teleconferences hosted by CBER and facilitated by the Project Co-Leads. Generally, one or two domains are presented for the team to evaluate per meeting. For published domains, information materials used for the domain presentations can include: the domain specification from the SEND Implementation Guide (SENDIG), an example domain.xpt file from a sponsor provided study intended for CBER submission, an associated individual listing table such as traditionally provided in the Study Report.pdf and the associated CDISC Controlled Terminology codelists. For domains of interest that are not yet published for SEND, relevant development team members were invited to present the new concepts and rationale for the new domains to the SEND for CBER team. Materials provided for these reviews are slide presentations by domain developers, draft domain specifications with examples and any proposed controlled terms (CT) supporting the new domains. CBER Reviewers assess the domains by comparing their expectations of data based on their experience, to what would be available if provided in the SEND domains. This assessment provides the basis of the gap analysis. The SEND subject matter experts are able to listen to the CBER Reviewers assessment, ask questions during the teleconferences and together, determine gaps. An additional reference, currently in draft is the Confirmed Data Endpoints for Exchange (CoDEX) for SENDIG v3.1 Data, used to support the gap analysis. The CoDEX reference provides a listing of data types or study design topics that are considered by the CDISC SEND Team to be “confidently modeled” by SENDIG v.3.1 specifications, because they are either directly included in the examples or the modeling has been successfully demonstrated to the CDISC SEND Team. This reference is currently available, in draft status as of January 2019, on the CDISC WIKI site (see References section.)

Following each domain assessment, a summary is prepared containing the possible gaps found, learnings derived regarding both use of SEND and CBER needs, and any actions decided by the team. The summary accumulated within a SEND domain review feedback document is being maintained throughout the project. This working document will be the basis for the gap analysis for SEND domains.

To aid in the determination of what kind of studies and data need to be modeled for CBER submissions, the three CBER Offices compiled a list of CBER study types and endpoints by offices. A current CDISC Controlled Terminology Codelist for study types was used as a template, and CBER Reviewers selected which of those study types can be included in a CBER Submission. CBER Reviewers provided a list of expected endpoints for their respective offices. Assessment of this information will be included in the gap analysis.

The team will prepare a recommendation detailing the full scope of exchange standard definition required to enable sufficient SEND implementation in CBER and proposed/developed mitigations of gaps found in the assessment of currently published and drafted standards. Within the recommendation for mitigating gaps, the team may include some developed solutions, some recommendations for further standards development and recommendations for handling unfulfilled gaps.

PROJECT PROGRESS

The team achieved significant progress in key information topics essential for defining the full scope of work necessary to accept and use SEND submissions in CBER. First, understanding the current SEND model enabled CBER reviewers to recognize and characterize where to find data of primary interest, how to reference information across domains, what is useful, and ultimately to identify possible gaps between SENDIG v.3.1 and CBER needs. A domain by domain review was started in July 2018 and has progressed through a portion of published nonclinical SEND domains (Table 1), some yet unpublished domains for SEND (Table 2) and an overview of Developmental and Reproductive Toxicity (DART) domains. Table 3 lists domains still under review as of January 2019.

Table 1: Published SENDIG v3.1 Domains Reviewed by Team



CL	Clinical Signs		BG	Body Weight Gain		VS	Vital Signs
BW	Body Weights		LB	Laboratory Measurements		EX	Exposure
MA	Macroscopic Observations		MI	Microscopic Observations			
TF	Tumor Findings (determined not needed by CBER)		OM	Organ Measurements			

Table 2: Not Yet Published (for SEND) Domains Reviewed by Team

IS	Immunogenicity Specimens		OE	Ophthalmic Examination		AG	Procedural Agents
IA	Irritation Assessments		AT	Allocation to Treatment		DART	See footnote ¹

¹. A general overview of SENDIG-DART v.1.1 domains were done in fall 2018. Detailed assessments are not planned at this time.

Table 3: Domains Still Under Review by Team (as of January 2019)

FW	Food and Water Consumption		SE	Subject Elements		DM	Demographics
EG	ECG Test Results		CO	Comments		TX	Trial Sets
DS	Disposition		RELREC	Related Records		TE	Trial Elements
PC	Pharmacokinetic Concentrations		SUPP--	Supplemental Qualifiers		TA	Trial Arms
PP	Pharmacokinetic Parameters		POOLDEF	Pool Definition		TS	Trial Summary

RESULTS SO FAR

Of the domains reviewed so far by the team, the gaps between CBER needs and SENDIG v.3.1 are significant but, in our opinion, are quite manageable and solutions are expected to be consistent with current modeling norms.

Generally, gaps identified so far are:

- Needs for added controlled terms have arisen for the clinical signs subcategory, laboratory test names and categories, and appropriate reproductive toxicology study type.
- Need to assure handling of injection site reactions and irritation assessments that ensures clear context and tabulation.
- Need for broader capability to handle immunogenicity assessments, beyond current Laboratory Measurements domain specifications. The "IS" domain available in SDTM, but not yet published for SEND, plus custom variables currently being proposed by the CDISC Microbiology Team are of interest to represent immunogenicity assessment data (for example: binding agent.)
- Study design concepts that are being developed for Dermal and Ocular study types are needed also to properly model some study designs received by CBER (for example: designs with Control and Treatment applied to one animal at different anatomic sites.)
- Need for additional reproductive toxicity domains, which are still in development by CDISC, for fertility and developmental toxicity. Commonly, CBER receives combination reproductive toxicity studies, in which multiple reproductive toxicity assessments (fertility, embryo-fetal and developmental toxicity) are conducted within one study. The currently published SENDIG-DART v.1.1 handles only embryo-fetal toxicity assessments.

Still to do, as of January 2019 is to complete the domain assessments listed in Table 3, to complete the gap analysis for data and study design domains. Additionally, an overview and assessment of the Nonclinical Study Data Reviewers' Guide will be done to include CBER feedback on this component of the SEND data package in the gap analysis and recommendation. There is not a plan at this time to do the same for the DEFINE file, Standard Data Submission Plan (SDSP) or Validation Rules, so the recommendation may include thoughts of the team regarding future work needed on these components for successful implementation in CBER.

It is planned for the SEND for CBER Team's recommendation to be available at the end of 3rd quarter 2019. The deliverables of this recommendation will include:

- The result of the gap analysis between CBER submission expectations of nonclinical study data and SENDIG v.3.1
- Recommendations for mitigating gaps
- Definition of full scope of exchange standard definition required to enable sufficient SEND implementation in CBER
- Development of solutions for gaps, as possible



Further deliverables may be identified or refined by the team, based on gap analysis and full scope decisions.

NEXT STEPS

SENDIG V.3.1 PILOT PARTICIPATION

Once the gap analysis is finished, CBER will consider some type of fit-for-use pilot to have sponsors submit some sample submissions to test out before the requirement of SEND submission for CBER. The scope of testing and format/content of feedback for these sample submissions will be determined by the CBER participants Sponsor organizations providing the sample studies will be able to choose, if and how this feedback will be shared with the public.

A Pilot would have its own charter and would be managed as an activity with feedback made publicly available. The planned approach will be to collaborate with a CDER Fit for Use Pilot, planned for 2019. The Pilot plan for the SEND for CBER participation will be developed by the team with a study and data scope appropriate for their first Pilot experience.

Key points that will be included in the Pilot plan:

- Clear description of stakeholders' participation: expectations for reviewers' activities and feedback coordination of reviewers' participation
- Clear definition of pilot scope and actions

CBER aims to achieve several goals through the "real-world" experience that a Pilot can provide. The Pilot will provide Reviewers the opportunity to explore data domains, the Nonclinical Study Data Reviewers' Guide and DEFINE file included in a SEND dataset package, as they might in a real review, without any actions required for a real submission. Previous pilots have shown that open discussion among the reviewers and with SEND Subject Matter Experts yields valuable information on the feasibility and impact of requiring SEND for submissions.

CDISC ACTIVITIES TO RESOLVE GAPS

CDISC, and the CDISC SEND Team, provide an operational framework which can support anticipated SEND model development activities identified by the SEND for CBER project. Following the recommendation, the SEND for CBER Team will work with the CDISC SEND Team to plan the standards development work needed through CDISC workstreams or subteams. Some workstreams, subteams and processes are already in place within the CDISC framework, such the SEND Controlled Terminology Team (CT Team.) New working groups may need to be formed, depending on the work needed.

An example of CDISC framework in place to facilitate the goals of SEND for CBER is the established processes in place for new terminology request, deliberation, public review and decision, managed by the CT Team. The CT is routinely updated on a current schedule of 4 times a year in March, June, September and December. The SEND for CBER Team or any Workstreams with activities related to their requests for terminology can use the established CT request process.

The final recommendations of the SEND for CBER Team will be presented to the CDISC SEND Core Team for assessment on what CDISC support will be needed to address the SEND IG gaps for CBER. It is expected that the operational resources of the CDISC SEND Team, along with the SEND Controlled Terminology Team and an SDTM subteam will be needed to manage the development and implementation of all mitigations recommended to fulfill the gaps for CBER. So far, it is certain the following support will be needed from the CDISC SEND Core Team, CT Team and specific Workstreams noted:

- 1) Dermal Ocular Workstream: Publication of the domains developed, initially for Dermal and Ocular Toxicity studies, contain specific concepts needed by CBER.
- 2) Animal Rule Workstream: Publication of the domains and terminology developed, initially for studies conducted under the "Animal Rule", contain specific concepts needed by CBER.
- 3) SDTM Subteam for Immunogenicity Specimen Assessment: Publication of the IS domain in a SEND IG is needed to formally enable handling of some needed tests and terminology.
- 4) Controlled Terminology Team: Management of new terminology requests from the SEND for CBER Team for future versions of published CDISC Controlled Terminology.



New Workstream work may still be identified, as the full gap analysis is not yet done as of January 2019. If new domains or new variables, not yet in development are proposed in the final recommendation from the SEND for CBER Team, the SEND Core Team will consider new Workstream definition or may decide to fit the requests into existing Workstreams, as appropriate.

PREPARING FOR FUTURE IMPLEMENTATION

CBER has started providing CDISC study data standards training for all reviewers, routinely, twice a year to give reviewers basic knowledge about study data standards. CBER also provides some tool training including JMP, JMP Clinical, JReview to help reviewers to use tools that enable robust utilization of SEND data for their reviews. CBER continues looking for specific tools for non-clinical data.

The FDA Data Standards Catalog (Catalog) lists the data standards and terminologies that FDA supports for use in regulatory submissions to better enable the evaluation of safety, effectiveness, and quality of FDA-regulated products. In addition, the FDA has the statutory and regulatory authority to require certain standards and terminologies and these are identified in the Catalog with the date the requirement begins and, as needed, the date the requirement ends, and information sources. The submission of data using standards or terminologies not listed in the catalog should be discussed with the Agency in advance. Once CBER has participated in a SEND fit for use pilot and determines it covers CBER's needs, the support and requirement status could be added to the Catalog in future.

CONCLUSION

Through the strong and well-resourced collaboration between the CDISC SEND Team and CBER offices of FDA, the SEND for CBER Team is expected to achieve a robust assessment of SEND IG 3.1 for implementation use on CBER submissions. From this assessment, a detailed recommendation will be developed with a goal to enable a roadmap of SEND development activities to enable eventual, routine use by CBER reviewers of SEND data received in INDs and BLAs, by CBER Reviewers. SEND Workstream activities for governance approval, public reviews and publication are ongoing for domains already drafted for Dermal, Ocular and Animal Rule study types that are of significant interest for CBER. Additional activities for existing or new Workstreams and controlled terminology requests will be defined by the CDISC SEND Core Team, upon receipt and assessment of the SEND for CBER final recommendation. In the meantime, the SENDIG v.3.1 Fit for Use Pilot activities are expected in mid-late 2019. This will be an excellent opportunity which will greatly contribute to the steering of development activities and give needed experience to both the CBER Reviewers and participating Sponsors.

Based on industry and regulatory experience with the implementation of data standards, the SEND for CBER Team members understand SEND development and maintenance will be a continuing effort, until and beyond the initial implementation of SEND for CBER. The team will maintain a close relationship with the CDISC SEND Team and evolve its' resources to fit the needs for fulfillment of the FDA Data Standards Action Plan related to implementation of SEND for CBER.

Because work is ongoing, additional participation from industry is possible and welcome. If you are interested to join the SEND for CBER Team, contact the team leaders who will determine if participation is feasible.

REFERENCES

[FDA Data Standards Program Action Plan](#)

[FDA Data Standards Catalog](#)

[Confirmed Data Endpoints for Exchange \(CoDEx\) for SENDIG v3.1 Data, available on the CDISC WIKI](#)

[Nonclinical Fit for Use Workstream](#) – deliverables of CDER Fit for Use Pilot conducted for SEND IG v3.0 in Oct 2016.

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RECOMMENDED READING

Green, Martin David; Al-Humadi, Nabil Hussain. A Comprehensive Guide to Toxicology in Preclinical Drug Development; Preclinical Toxicology of Vaccines, pp 691-631. <http://dx.doi.org/10.1016/B978-0-12-387815-1.00025-3>

CONTACT INFORMATION

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

Author Name: Susan DeHaven
Company: Sanofi, US Inc.
Address: 55 Corporate Drive, MailSlot: 55C-325
City / Postcode: Bridgewater/ 08807
Work Phone: 908-981-3347
Email: susan.dehaven@sanofi.com
Web: www.sanofi.com

Author Name: Lisa Lin
Company: FDA
Address: 10903 New Hampshire Ave
City / Postcode: Silver Spring, MD 20993
Work Phone: 301-796-5059
Email: wei.lin@fda.hhs.gov
Web: www.fda.gov