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Developing SEND for CBER - Collaborative Workstream Initiative Update

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ABSTRACT

The Center for Biologics Evaluation and Research (CBER) within Food and Drug Administration (FDA) intends to receive Standards for Exchange of Nonclinical Data (SEND) datasets in future submissions. However, implementations currently defined in published and planned SEND Implementation Guides had not been evaluated regarding data models needed for representing certain study types (including study design) or endpoints typically received in a CBER submission. The SEND for CBER team was formed to evaluate endpoints related biodistribution, immunogenicity, test article characterization and hybrid activity/safety trial designs 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 followed to evaluate essential SEND data tabulation needs for supporting CBER submissions. This team has reviewed all SENDIG 3.1 domains plus a few SDTM domains and is undergoing a proof-of-concept pilot using donated study datasets. The team will recommend proposals for modeling enhancements and solutions (e.g., implementation guidance and any new domain(s), variables, and codelist needs) to enable submission of electronic data in SEND format to CBER.

INTRODUCTION

This presentation gives you the update status of SEND for CBER project so you can be aware of the requirement expected in future submissions. SEND is an implementation of the SDTM standard for nonclinical studies. FDA Data Standards Catalog V6.1 (09-9-2019) 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 guidance regarding 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 the Clinical Data Interchange Standards Consortium (CDISC), CBER non-clinical reviewers and industry experts was 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 Control Terminology 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 these objectives:

- 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 can 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 SEND for CBER project is planned to support the Proof of Concept activities and finalization of the recommendations in 2Q2020 (see Figure 1.)

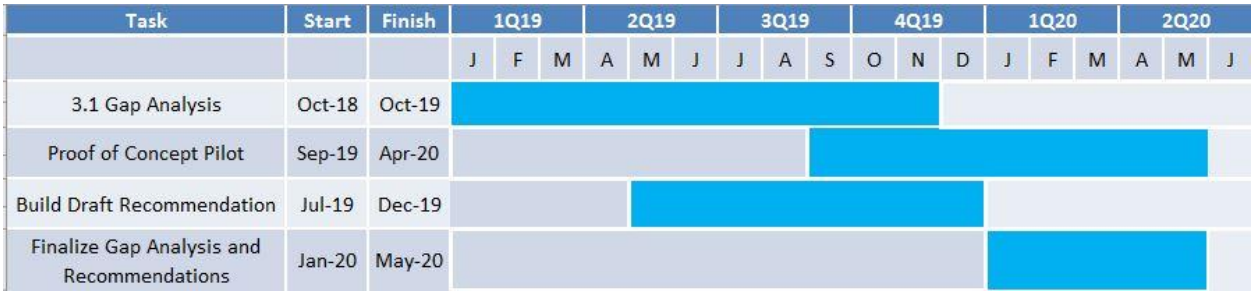

Figure 1: SEND for CBER Project Plan

The SEND for CBER project is conducted through bi-weekly teleconferences hosted by CBER and facilitated by the Project Co-Leads. During the Gap Analysis phase, generally, one or two domains were presented for the team to evaluate per meeting. For published domains, information materials used for the domain presentations included: 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 were slide presentations by domain developers, draft domain specifications with examples and any proposed controlled terms (CT) supporting the new domains. CBER Reviewers assessed 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 provided the basis of the gap analysis. The SEND subject matter experts were able to listen to the CBER Reviewers assessment, ask questions during the teleconferences and together, determine gaps. An additional reference, 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, on the CDISC WIKI site (see References section.)

Following each domain assessment, a summary was 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 final gap analysis and recommendations 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 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 that was started in July 2018 and has progressed through all 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 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			
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

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.

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 sign 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.

The SEND for CBER Team’s draft recommendations are available on the CDISC Wiki site. The deliverables of this recommendation includes:

- 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.

SENDIG V.3.1 PILOT EVALUATION

Currently, CBER has received 4 pilot studies to support conducting a Proof-of-Concept (POC) for implementation of SEND for submissions to FDA CBER offices. 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. The pilot also allows reviewers using tools in development at FDA (JMP, JMP Clinical, SEND Explorer), confirming the gap analysis identified during domain review and finalize the recommendation to CDISC on how to ensure SEND meets CBER needs and to FDA on how to implement a SEND requirement for CBER. The Pilot feedback will be made publicly available once it is finished.

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:

1) Dermal Ocular Workstream: Publication of the domains developed, initially for Dermal and Ocular Toxicity studies, contain specificconcepts 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 interesting to 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 Worksteam work may still be identified, as the final gap analysis is not yet done as of January 2020. 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, SEND Explorer to help reviewers to use tools that enable robust utilization of SEND data for their reviews.

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 finished Proof-of-Concept 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. 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 Proof-of-Concept Pilot activities are expected to be finished at the end of March 2020. This is an excellent opportunity which greatly contributes to the steering of development activities and gives 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 relationship with the CDISC SEND Team and work towards fulfillment of the FDA Data Standards Action Plan as it relates 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

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