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FDA CBER Data Standards Activity Update

Lisa Lin, FDA, Silver Spring, MD, USA

ABSTRACT

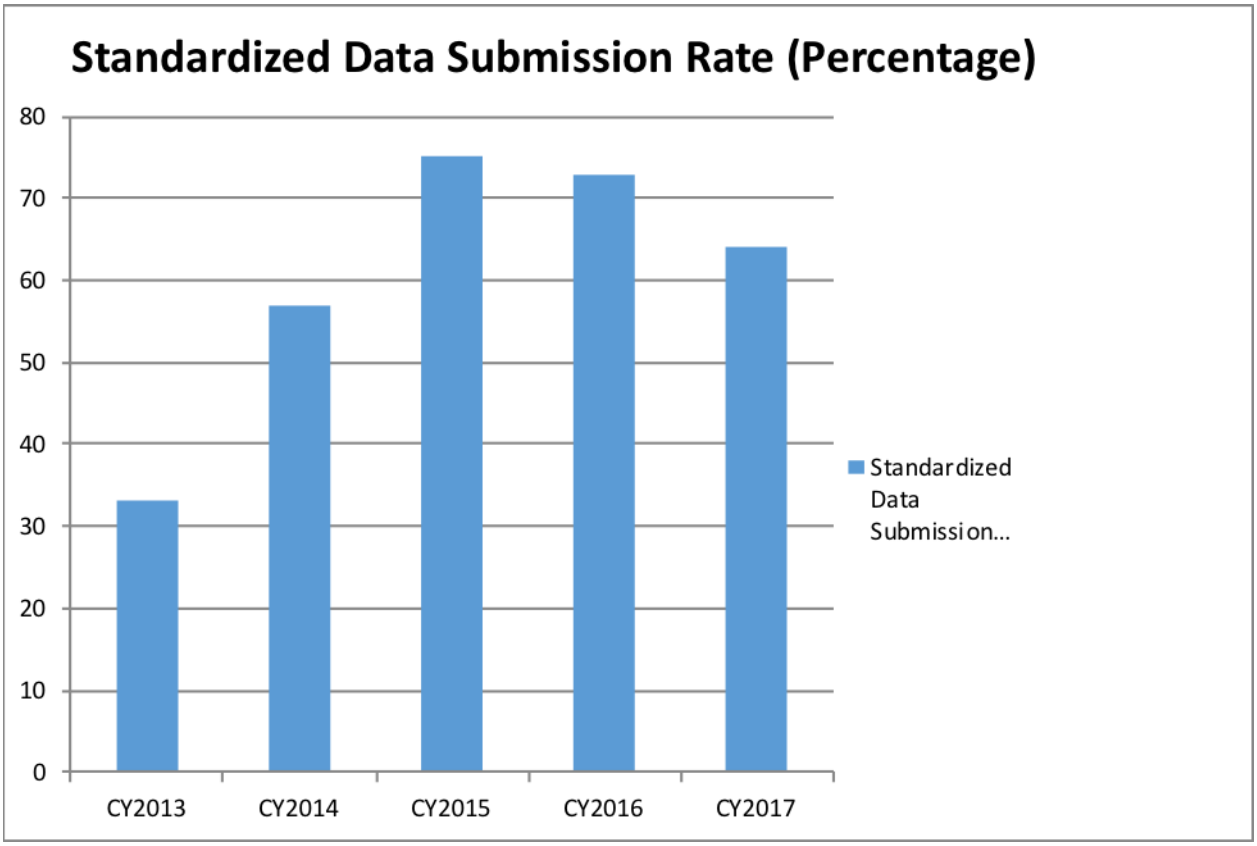
This paper provides an update from the data standards team of CBER (Center for Biologics Evaluation and Research) regarding CBER's current implementation of study data standards. Included in this update are CBER's: standardized data submission metrics, implementation of new standardized study data validation, study data standardization plan, vaccine TAUG & Vaccine Technical Specifications Document, CBER reviewer training program & service, and evaluation and testing of the SEND standards for CBER nonclinical data.

INTRODUCTION

The mission of the Center for Biologics Evaluation and Research (CBER) is to ensure the safety, purity, potency, and efficacy of biological products, which include vaccines, allergenics, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. CBER's data standards team is committed to the development, implementation, and maintenance of a comprehensive data standards program that facilitates the pre- and post-market regulatory review process to make safe and effective medical products available to patients.

STANDARDIZED DATA SUBMISSION METRICS

The graph below shows the percentage of CBER submissions with standardized data for last five years. Other than CY2013, the percentage has been stable around 60-70%.



CBER DATA STANDARDS STAFF

A new CBER data standards team led by Virginia Hussong was established under the Office of Director in CBER in 2017. This team supports all data standards activity of different offices within CBER, including Office of Biostatistics and Epidemiology (OBE), Office of Compliance and Biologics Quality (OCBQ), Office of Blood Research and Review (OBRR), Office of Vaccine Research and Review (OVRR), Office of Tissues and Advanced Therapies (OTAT) and Office of the Center Director (OD).

STUDY DATA VALIDATION

CBER introduced a new validation process at the end of 2017. CBER performs data validation for all BLA submissions and efficacy supplements containing standardized study data. The goal of the validation process is to ensure that submitted study data meets the data standards and is in good quality for review. CBER's data standards team assists CBER's review offices to conduct data walk-throughs, and to issue Information Requests (IR) or Refuse to File (RTF) as needed.

We list below some of the examples of Information Requests:

Issue 1
The xxxx and xxxx studies are missing the AE, CE and CM domains, even though the SUPPAE, SUPPCE and SUPPCM domains have been provided. The reviewer's guides do not explain why these domains are missing. The reviewer's guides and define.xml document the AE, CE and CM domains, explain validation rules, etc.

Issue 2
File names: most supporting documents (e.g. reviewer's guides, protocols, etc.) hyperlinked within the define.xml files have the incorrect filename listed in the hyperlink. All documents appear to be present, however. They can only be manually opened rather than using the hyperlinks in define.xml. Please correct the file names so that the hyperlinks are functional.

Issue 3
In study xxx, 126 (3.6%) events are missing start date/time. Please insert the missing information.

Issue 4
Some of the values in EXSTDTC is not in ISO8601 format, e.g. "-----T19:00", so EXSTDY has missing value. This needs to be fixed.

STUDY DATA STANDARDIZATION PLAN (SDSP)

FDA's Study Data Technical Conformance Guide recommends that sponsors include a study data standardization plan (e.g., in the IND) describing the submission of standardized study data to FDA for clinical and nonclinical studies. The plan assists FDA in identifying potential data standardization issues early in the development program. CBER recommends that sponsors submit the SDSP no later than the end of phase 2 meetings. FDA recommends that sponsors follow the SDSP template developed by PhUSE (Pharmaceutical Users Software Exchange), available on its website[1]. In addition, for clinical studies that will be submitted to CBER, the SDSP appendix should be provided, which should include tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis. The SDSP is a working document, and sponsors can provide revisions whenever they are appropriate. The cover letter accompanying a study data submission should describe the latest version of the SDSP. See screenshot below for the CBER SDSP Appendix:

1 https://www.phuse.eu/css-deliverables

CBER Appendix

1. Introduction

1.1 Purpose

The purpose of this appendix is to document additional study data information. This document should be submitted well in advance of any licensing application (ie, no later than the end of phase 2 meeting) to CBER. Receipt of this document in a timely manner will help to ensure an efficient review process.

1.2 Scope

The scope of this document is to facilitate study data review by CBER reviewers.

2. SDTM Datasets

List all SDTM datasets used/planned for each clinical study in the submission.

SDTM Version:			
STUDY ID:	TITLE:		
DOMAIN	Select Domains to be Submitted X	Variables to be utilized (besides required)	Additional Comments
Trial Design			
TA (Trial Arms)	<X>		
TE (Trial Elements)	<X>		
TI (Trial Inclusion/ Exclusion Criteria)	<X>		

VACCINE TAUG AND VACCINE TECHNICAL SPECIFICATIONS

The Vaccine TAUG was republished by CDISC on April 10, 2018[2]. The Vaccine Technical Specifications Document was published by FDA, CBER on April 19, 2018[3]. A public webinar regarding the Vaccine Technical Specifications Document is scheduled for May 8, 2018. Both documents will be added to the October 2018 release of Technical Conformance Guide.

TRAINING PROGRAM & CONSULTATION SERVICE TO CBER REVIEWERS

CBER has a joint effort with CDER to leverage existing training resources. Training topics include Study Data Standards, JMP, JMP Clinical, and MAED. CBER will develop and provide its own specific study data standards training in October, 2018. CBER's data standards team also provides consultation services to CBER reviewers to facilitate study data review and analysis.

STANDARD FOR EXCHANGE OF NONCLINICAL DATA (SEND) PROJECT

CDER requires SEND for Single Dose Toxicity, Repeat Dose Toxicity and Carcinogenicity studies in NDAs and BLAs for studies initiated after December 17, 2016 and in INDs for studies initiated after December 17, 2017. CBER currently does not require SEND. "Evaluation and Testing of the SEND standard for CBER" is one of the projects listed within CBER & CDER Joint Data Standards Program Action Plan (updated quarterly). The goal is to improve efficiency in the review process for nonclinical toxicology studies. CBER currently is collecting requirements from dedicated nonclinical pharmacology reviewers. CDISC has formed a sub-team to discuss what CBER specific data points and data models should be added in the SEND Implementation Guide (SENDIG). Regular teleconferences are scheduled to determine the scope and construct charter for the SEND project and to create CDISC project requests. Once the SEND project is chartered, a call for participation will be made to the CDISC SEND (and possibly SDTM) team members. CBER will also evaluate tools for analyzing SEND data and conduct pilot studies with sponsor-submitted SEND data.

CONCLUSION

CBER works closely with CDER to leverage combined resources, talent and expertise to maximize stakeholder collaboration, policy development, and project implementation to develop and use data standards for effective and efficient review of submissions of study data.

2 https://www.cdisc.org/standards/therapeutic-areas/vaccines
3https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf

REFERENCES

FDA DATA STANDARDS CATALOG:
HTTPS://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM

STUDY DATA FOR SUBMISSION TO CDER AND CBER:
HTTPS://WWW.FDA.GOV/DRUGS/DEVELOPMENTAPPROVALPROCESS/FORMSSUBMISSIONREQUIREMENTS/ELECTRONICSUBMISSIONS/UCM248635.HTM

STUDY DATA TECHNICAL CONFORMANCE GUIDE:
HTTPS://WWW.FDA.GOV/DOWNLOADS/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/UCM384744.PDF

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CONTACT INFORMATION

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

Lisa Lin
CBER, US FDA
10903 New Hampshire Ave
Silver Spring, MD 20993
Work Phone: 301-796-5059
Email: wei.lin@fda.hhs.gov