Paper SA09

Experiencing the FDA CBER

Angelo Tinazzi and Merve Carrington, Cytel Inc., Geneva, Switzerland

ABSTRACT

Although both FDA CDER (Center for Drug Evaluation and Research) and FDA CBER (Center for Biologics Evaluation and Research) adhere to the same data standards requirements, there is a unique aspect to submitting data to CBER, particularly for vaccine products.

With our upcoming presentation, we will share our recent experiences interacting with and submitting data to the CBER division. Our focus will be on the preparatory work prior to submitting the data packages, specifically in creating the Study Data Standardization Plan (SDSP), and the CBER-specific appendix that details the structure of planned SDTM and ADaM datasets shared with the agency. We will also discuss the agency reviewer feedback and requests following the review of the SDSP and our subsequent interaction with the reviewer, including how we responded to their requests.

INTRODUCTION

OVERVIEW OF FDA STUDY DATA STANDARDS RESOURCES

The FDA requires sponsors to adhere to the guidelines set forth by both CBER and CDER for their respective applications, which entails complying with the established data standards [1] [2]. This enables the FDA to facilitate the review process more efficiently.

The “Study Data Technical Conformance Guide” [3] provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards located in the FDA Data Standards Catalog (Catalog) [4].

The FDA has implemented a set of Technical Rejection Criteria [5] to reinforce its data standard regulations. Although currently limited in scope, these checks scrutinize the submitted data and, if failed, result in the rejection, or hold of the data submission package. This means that the submitted data package will not be evaluated or utilized by the reviewer until it meets the necessary criteria.

The FDA has also established specifications for creating documents using PDF [6], which is the standard for documents as noted in the FDA Data Standards Catalog. It is important to consider these specifications when creating documents such as the SDTM or ADaM reviewer guide. Additionally, familiarity with the Electronic Common Technical Document [7] is necessary, particularly regarding file naming conventions and file locations within data packages. Adherence to these specifications ensures that the submitted documents and data packages meet the necessary requirements for review and approval by the FDA.

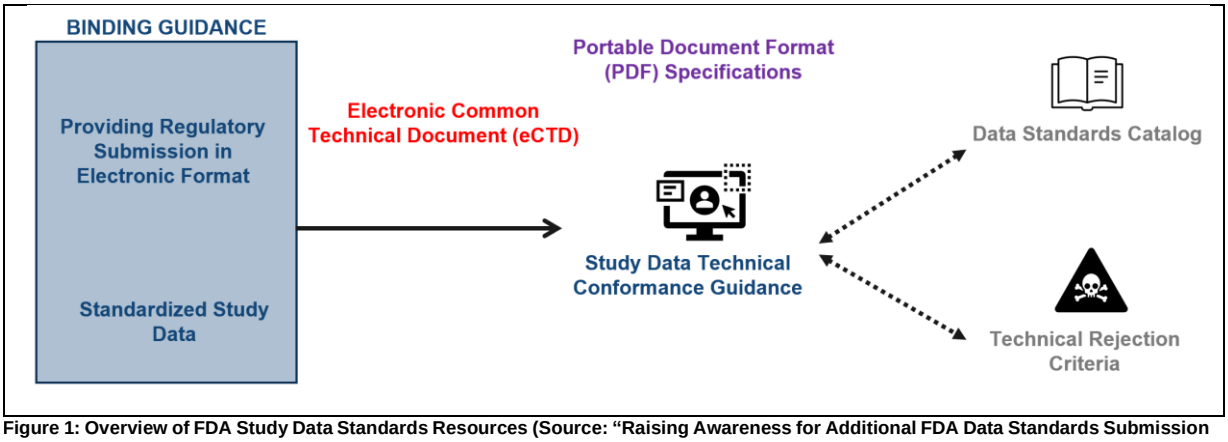


Figure 1: Overview of FDA Study Data Standards Resources (Source: “Raising Awareness for Additional FDA Data Standards Submission Recommendations”, A. Tinazzi, CDISC-EU Interchange, 2023)

In addition to the aforementioned guidance and documents, it is also essential for a data submission expert to be aware

of the existence of other FDA "documents" that may contain additional requirements. Familiarity with these requirements is crucial for ensuring the successful submission and approval of data. For example:

- The “Bioresearch Monitoring Technical Conformance Guide Technical Specifications” [8] or the so called BIMO for the creation of additional outputs to help the FDA inspection process.
- The “Submit an eCTD or Standardized Data Sample to the FDA”, if you aim to make a sample data submission prior to the real one [9]
- If you are also considering and waived to submit clinical study data in non-standard format, the “Providing Regulatory Submissions in Electronic Format - General Considerations” [10] should be considered together with the “Creating Simplified TS.XPT Files” [11] instructions to create a basic TS dataset containing the study start date.
- The FDA webpage for the "Model Data Format for submitting pharmacometrics data and models" [12] outlines additional requirements and recommendations for submitting supplementary material, data, and models in support of pharmacometrics analyses, such as PopPk analysis. These requirements and suggestions should be carefully reviewed and adhered to when submitting such materials to ensure successful review and approval by the FDA.

“ADDITIONAL” FDA DATA STANDARDS SUBMISSION RECCOMENDATIONS

The FDA endorses several CDISC Therapeutic Area User Guides (TAUGs) extensions in its Study Data Technical Conformance Guidance, which are currently integrated into the FDA-supported CDISC standards. Furthermore, the guidance includes a list of additional technical specification documents (see section 5.3. “List of FDA Technical Specification Documents”), which offers comprehensive information on specific topics. The table below contains a table summarizing the contents of these technical documents.

#	References
1	**Vaccines** Technical Specification Guidance v2.1 (Apr 2018 - Dec 2019) https://www.fda.gov/media/112581/download
2	**QT Studies** Technical Specification Document v1.0 (Jun 2019) https://www.fda.gov/media/128187/download
3	Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat **Human Immunodeficiency Virus-1 Infection** v1.0 (Mar 2018) https://www.fda.gov/media/112667/download
4	Technical Specifications—Comparative **Clinical Endpoint Bioequivalence Study Analysis Datasets** for Abbreviated New Drug Applications v1.0 (Sep 2018) https://www.fda.gov/media/116187/download
5	Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of **Noncirrhotic Nonalcoholic Steatohepatitis (NASH)** v1.1 (Aug 2021 – Jan 2022) [20] https://www.fda.gov/media/151864/download

Table 1: FDA Additional Data Standards Guidance

THE CBER “ADDITIONAL” REQUIREMENTS

CDER VS CBER RESPONSIBILITIES

CDER and CBER are the two divisions of the FDA responsible for regulating drugs and biological products, as well as combinations of drugs and biological products. CDER focuses on drug regulation, whereas CBER oversees the regulation of biological products. In some cases, distinguishing between drugs and biological products can be challenging. Typically, CBER is responsible for products such as vaccines, human blood and blood-derived products, gene and cell therapies, in vivo diagnostic tests like allergenic products, and products composed of or intended to contain intact cells or microorganisms, including bacteria, fungi, viruses, or virus pseudo types, as well as viral vectors. Additionally, CBER is responsible for certain drugs used in conjunction with blood banking and transfusion [13]. Below, you'll find examples of recent New Drug Approvals (NDAs) and New Biological Approvals (NBAs) made by these two divisions, which are publicly available at www.accessdata.fda.gov:

- Bendamustine HCl Injection 100 mg / 4 ml for the treatment of patients with chronic lymphocytic leukemia (NDA 215033) – CDER
- Sotyktu (deucravacitinib) tablets for the treatment of adults with moderate-to-severe plaque psoriasis who are

candidates for systemic therapy or phototherapy (NDA 214958) – CDER

- REBYOTA fecal microbiota, live-jslm, for the prevention of recurrence of Clostridioides difficile infection (CDI) following antibiotic treatment for recurrent CDI (BLA 125748) - CBER

Statistics regarding the number of requests processed and approvals granted by these two divisions for various types of approvals can be found on the FDA website (https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-center-drug-evaluation-and-research-pre-approval-safety-review-drugs-and-biologics (CDER) and https://www.fda.gov/about-fda/fda-track-agency-wide-program-performance/fda-track-center-biologics-evaluation-and-research-goal-1.

CDER and CBER share many common principles and processes when evaluating products for market approval. You can find more information in the document "Best Practices for Communication Between IND Sponsors and FDA During Drug Development" available at this link: https://www.fda.gov/media/94850/download. Same applies to data standards requirements at previously discussed; however, there is a unique aspect to submitting data to CBER, particularly for vaccine products; in fact, CBER has specific requirements when submitting data packages to for example the 'Office of Vaccines Research and Review' (OVRR) and when requesting additional details in the Study Data Standardization Plan (SDSP) [14][15], such as the structure of your datasets.

THE SUBMITTING STUDY DATASETS FOR VACCINES TO THE OFFICE OF VACCINES RESEARCH AND REVIEW TECHNICAL SPECIFICATION

The 'Vaccines Technical Specification Guidance,' initially released in April 2018 and followed by a second version in December 2019, was introduced during an FDA webinar [17]. Over the years, several sponsors have shared their experiences and the impact of this guidance on various aspects of their processes, including data governance, medical monitoring, SOPs, data entry guidelines, and CRF (Case Report Form) design [18][19][20].

The focus of this additional FDA CBER guidance is to give some direction on the FDA CBER “preferred usage” of CDISC SDTM domains and variables for vaccine clinical trial data, for example:

- for safety: reactogenicity (CE, FACE, and VS), unsolicited AEs (AE), including medical attended AEs, death (AE, DM, and DD), laboratory safety assessment (LB).
- for efficacy: clinical disease endpoint (CE and MB) and immunogenicity (IS)

The guidance also references the CDISC Vaccine TAUG [21] for the mapping model for Reactogenicity Data.

The guidance, as well as the related CDISC Vaccine TAUG, does not include any ADaM recommendations. While some of the recommendations reiterate what is already suggested in the SDTM IG, such as the expectation of variables like DSDECOD and DSSTDTC in the DS (Disposition) domain, the guidance outlines several specific requirements, which are summarized below.

Mapping Reactogenicity Data

Reactogenicity refers to the expected adverse reactions associated with vaccine administration, encompassing both local and systemic reactions. These reactions are typically solicited for a defined period after vaccination and can include symptoms like fever, myalgia, fatigue, headache, nausea (systemic), and redness/erythema, swelling/induration, and pain/tenderness at the administration site.

The collected findings related to reactogenicity are not confined to a single SDTM domain; they are also used to create corresponding event or findings records in other domains. For instance, if a subject experiences fever, it results in a FA(CE) record, a VS record for temperature, a CE record summarizing the event 'experience,' and potentially an AE record if the event becomes serious, indicated by SUPPAE containing the date when the event became serious (QNAM = SAEDTC). To ensure clear identification and distinction of reactogenicity symptoms assessment from other collected data, VSCAT can be set to 'REACTOGENICITY,' and the relationships can be established through the RELREC dataset.

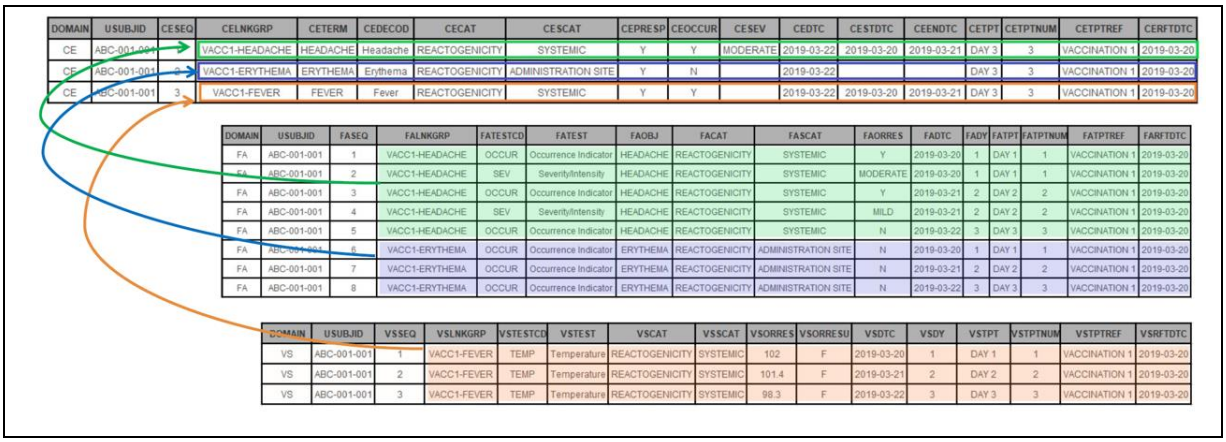
While the CDISC Vaccine TAUG provides examples of two main ways to report reactogenicity data, 'flat' vs. 'nested' models, CBER's preference is for the flat model. In the flat model, FACE is used to store daily records, with an additional record per event per subject in CE summarizing the event 'experience' with details such as the event name (CETERM) and duration (CESTDTC/CEENDTC). This approach may deviate from the SDTM IG, as most collected data is represented only once in SDTM data and is rarely derived.

Additionally, events that continue beyond the assessment interval are mapped to AE. In this case, the event should be clearly identified as 'REACTOGENICITY' using AECAT, and the relationship with CE records should be established through RELREC.

In general, the use of RELREC is recommended when data stored in different domains are related.

Data Traceability

When reactogenicity symptoms are also assessed by the principal investigator in addition to the study subject, such as when the participant reports a potentially severe reaction, “originator” of the assessment should be clearly indicated through the --EVAL variable e.g., CEEVAL = ”INVESTIGATOR”.



DOMAIN	USUBJID	CESEQ	CELNKGRP	CETERM	CEDECOD	CECAT	CESCAT	CEPRESP	CEOCCUR	CESEV	CEDTC	CESTDTC	CEENDTC	CETPT	CETPTNUM	CETPTREF	CERFTDTC
CE	ABC-001-001	1	VACC1-HEADACHE	HEADACHE	Headache	REACTOGENICITY	SYSTEMIC	Y	Y	MODERATE	2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	2	VACC1-ERYTHEMA	ERYTHEMA	Erythema	REACTOGENICITY	ADMINISTRATION SITE	Y	N		2019-03-22			DAY 3	3	VACCINATION 1	2019-03-20
CE	ABC-001-001	3	VACC1-FEVER	FEVER	Fever	REACTOGENICITY	SYSTEMIC	Y	Y		2019-03-22	2019-03-20	2019-03-21	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	FASEQ	FALNKGRP	FATESTCD	FATEST	FAOBJ	FACAT	FASCAT	FAORRES	FADTC	FADY	FATPT	FATPTNUM	FATPTREF	FARFTDTC
FA	ABC-001-001	1	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	2	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MODERATE	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	3	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	Y	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	4	VACC1-HEADACHE	SEV	Severity/Intensity	HEADACHE	REACTOGENICITY	SYSTEMIC	MILD	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	5	VACC1-HEADACHE	OCCUR	Occurrence Indicator	HEADACHE	REACTOGENICITY	SYSTEMIC	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20
FA	ABC-001-001	6	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
FA	ABC-001-001	7	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
FA	ABC-001-001	8	VACC1-ERYTHEMA	OCCUR	Occurrence Indicator	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	N	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

DOMAIN	USUBJID	VSSEQ	VSLNKGRP	VSTESTCD	VSTEST	VSCAT	VSSCAT	VSORRES	VSORRESU	VSDTC	VSDY	VSTPT	VSTPTNUM	VSTPTREF	VSRFTDTC
VS	ABC-001-001	1	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	102	F	2019-03-20	1	DAY 1	1	VACCINATION 1	2019-03-20
VS	ABC-001-001	2	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	101.4	F	2019-03-21	2	DAY 2	2	VACCINATION 1	2019-03-20
VS	ABC-001-001	3	VACC1-FEVER	TEMP	Temperature	REACTOGENICITY	SYSTEMIC	98.3	F	2019-03-22	3	DAY 3	3	VACCINATION 1	2019-03-20

Figure 2: Reactogenicity data mapping using the “flat” model (Source: “Preparing Vaccine Studies for Regulatory Submissions”, M. Bess and K. Kelly, PHUSE US, 2022)

Clinical Disease Endpoint

The Clinical Disease Efficacy Endpoint should be primarily reported in the CE domain with CECAT set to 'efficacy' and CETERM specifying the disease (e.g., 'influenza-like illness'). If more detailed data is collected, consider using the FACE domain. The MB domain can contain test results from various biological assays (e.g., PCR, ELISA, or cell culture). When adjudication is used, include CEEVAL and CEACPTFL as needed.

During the CBER 2018 webinar, it was clarified that text case does not matter, and 'EFFICACY' can be used (in uppercase), following the recommendation in SDTM IG 3.3, section 4.2.4 ('Text Case in Submitted Data').

Confirmation of disease should also be flagged in SUPPDM using CECASE (Clinical Endpoint case flag), indicating 'Y' or 'N.' The method of confirmation should be clearly outlined in the clinical protocol. Additionally, it's advisable to include a checkbox in the CRF to confirm the clinical disease endpoint.

Immunogenicity

Relevant immunogenicity data should be captured in IS domain and not LB as this is used for safety laboratory data only.

Other mapping recommendations and CBER specific requirements

AE Naming Conventions: When distinguishing between different types of adverse events (AE), specific naming conventions are recommended. For example, 'NOCD' is used for new-onset chronic diseases, and 'PIMMC' is used for potential immune-mediated medical conditions. These distinctions are achieved through the AECAT variable. While the primary purpose of --CAT variables in SDTM is to categorize records with known data before collection, these conventions help differentiate specific AE types.

Chronic Diseases: The use of AE and MH domains is recommended for representing chronic diseases exacerbated following vaccination.

Analgesic/Antipyretic Usage: CM with appropriate CMCAT values is suggested for analgesics or antipyretics used for the prevention or treatment of pain and/or fever associated with vaccine administration.

Maternal Immunization: Guidance includes mapping recommendations for maternal immunization, such as establishing the relationship between mother and child. RELSUB is recommended instead of the Associated Person dataset, as the mother is considered a study subject.

aCRF: Alongside the SDSP, CBER recommends submitting an aCRF for at least phase 2 and phase 3 trials.

Traceability: Sponsors are encouraged to provide a clear, traceable pathway from the primary collection documents (e.g., CRF, Diary, ePRO) to the raw datasets (SDTM) and analysis datasets (ADaM).

SPECIFIC SDSP CONTENT FOR CBER

During the FDA webinar in 2018, there was a significant focus on the issues associated with poor-quality data submitted to CBER OVRR in previous years, as also discussed in the July 13, 2017 webinar. This led to CBER frequently requesting additional information and clarity from sponsors, which, in turn, necessitated 2-4 weeks for sponsors to respond. There was even the possibility of a major amendment, causing an extension of the review timeline by up to 3 months. Some of the issues cited included unclear clinical data presentation, such as terminology, definitions, and the timing of events, as well as the absence of follow-up information on subjects with adverse events and datasets that were disorganized and, as a result, difficult to interpret.

As mentioned earlier, the SDSP includes an appendix specific to CBER. In this appendix, sponsors are required to provide comprehensive details, not only regarding the standards used (as is standard practice for other FDA divisions), but also detailed information about the SDTM and ADaM datasets intended for submission for each study, whether planned, ongoing, or closed. This includes a list of non-standard SDTM variables (Supplemental Qualifiers) and their origin in relation to questions on the CRF) or derivation information. The goal is to provide CBER reviewers with the background needed to understand the purpose of the data and, eventually, to offer recommendations. This could involve remapping data to avoid custom domains or unnecessary mapping to supplemental qualifiers. Some companies have even developed internal tools to fully or semi-automatically generate this specific CBER appendix [22].

Figures 3, 4, and 5 from the FDA webinar illustrate how to complete these SDSP sections, including the ISS and ISE sections used to identify potential pooled or integrated analyses.

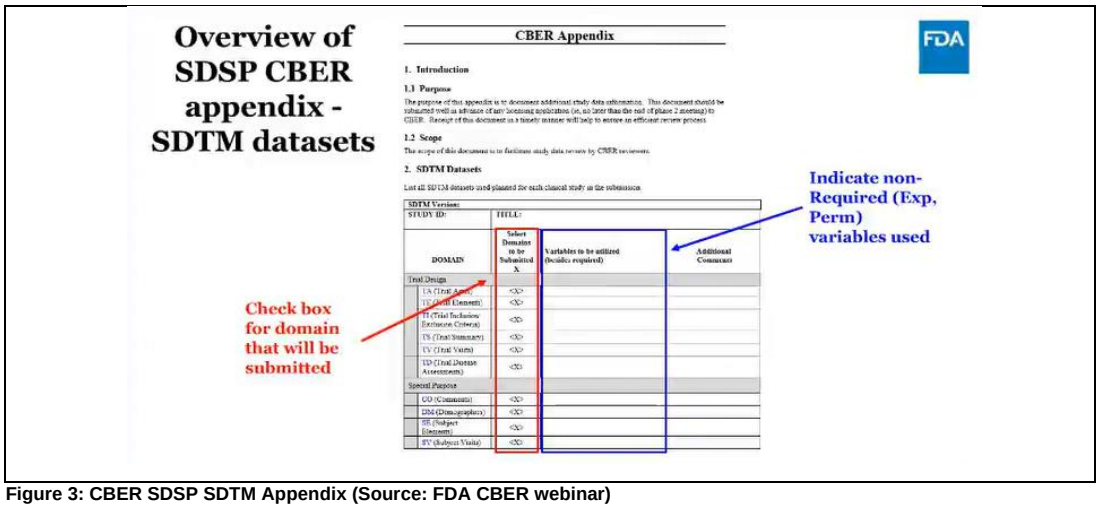
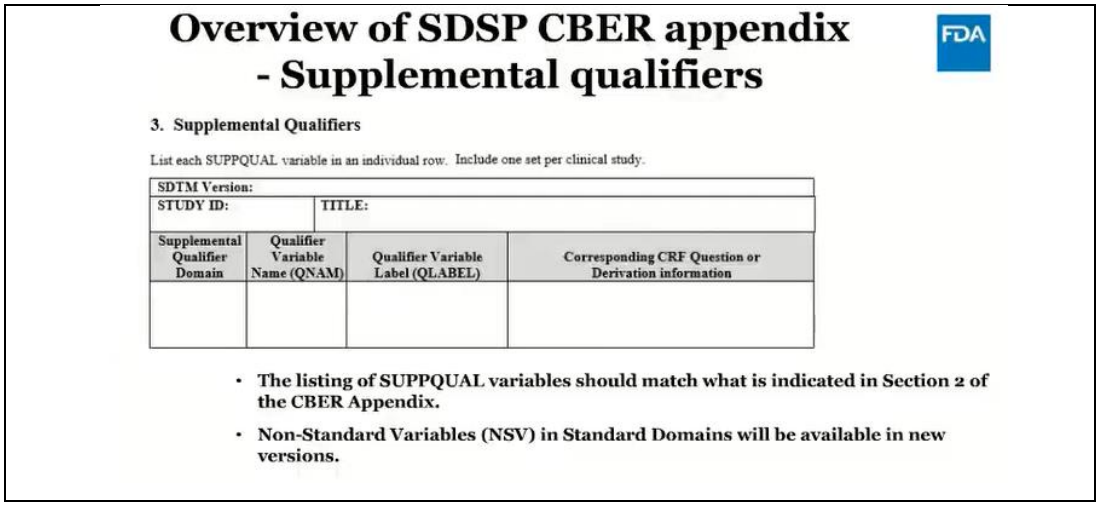


Figure 3: CBER SDSP SDTM Appendix (Source: FDA CBER webinar)



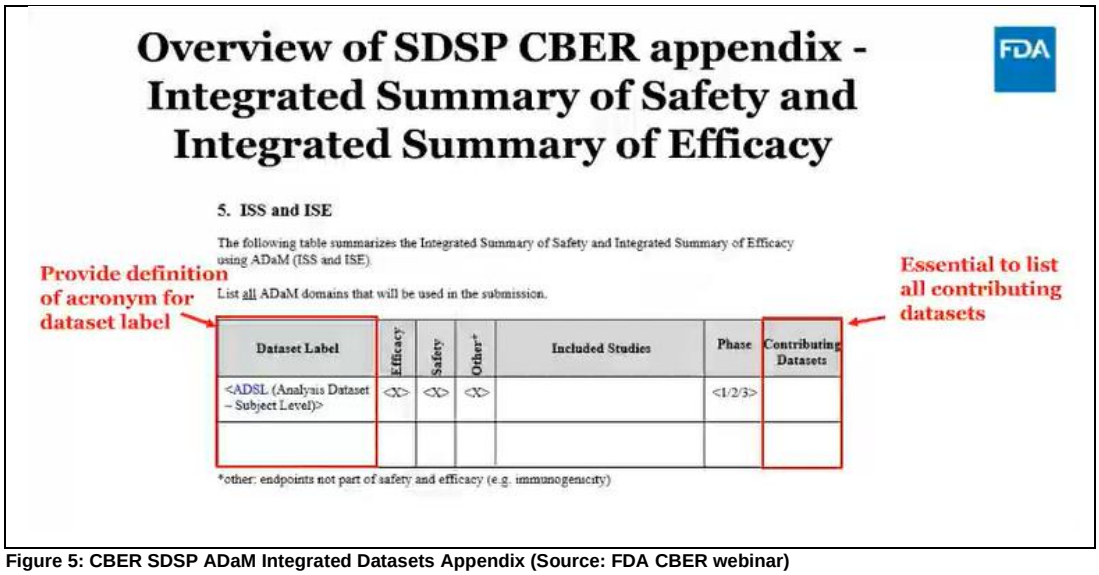


Figure 5: CBER SDSP ADaM Integrated Datasets Appendix (Source: FDA CBER webinar)

Timing of SDSP submission

During the FDA webinar, and following recommendations outlined in the FDA Study Data Conformance Guide, it was emphasized that initiating discussions with the FDA CBER division as early as possible is critical. This can be achieved through a pre-BLA (Biologics License Application) meeting. Waiting too long to engage with the FDA may make it challenging to incorporate CBER's feedback into the design of data collection or to address specific SDTM mapping requirements, which could require retrospective corrections to SDTM data packages. Such delays can impact data traceability, especially if the study has already been analyzed, leading to the production of ADaM, TFLs, and CSR.

The recommended timing for initiating this process is to submit the SDSP by the end of the Phase 2 meeting or earlier, which can be included as an amendment to your Investigational New Drug (IND) application. Furthermore, the SDSP should be regularly amended throughout the course of the study to ensure alignment with CBER's expectations and requirements.

EXPERIENCING THE CBER

At Cytel, our programming and statistical team has accumulated extensive experience in submitting data and interacting with Health Authorities worldwide, notably the FDA. This experience includes working on several Integrated Summaries of Safety (ISS) and Integrated Summaries of Effectiveness (ISE) [24][25][26][27].

As discussed in previous sections, while guidance provided by the FDA, such as the Study Data Technical Conformance Guide, applies to all FDA divisions requiring data submissions using standards, submitting to the CBER division holds a unique position due to its additional requirements compared to other divisions.

Furthermore, CBER places a strong emphasis on early discussions with sponsors during the drug development process. These discussions encompass recommendations not only on how data should be standardized and submitted but also how data should be collected. Therefore, alongside the SDSP, CBER requests the submission of the SDTM aCRF.

It's important to note that when studies have already commenced, and data collection is in progress or even completed, some of CBER's recommendations may not be easily implementable. This is often the case, as most of the studies in our submissions are either ongoing or already completed. For instance, recommendations to include checkboxes for indicating reactogenicity events during a prespecified time frame or checkboxes to indicate daily event collection during the assessment interval may not be feasible if the eCRF has already been designed and validated for deployment.

2019, OUR FIRST EXPERIENCE WITH CBER DATA SUBMISSION REQUIREMENTS

We had our initial experience with CBER submissions in 2019, which involved a non-vaccine biological product—a collection of bacterial spores enriched from fecal donations obtained from healthy, screened donors. This submission included five clinical studies, with two of them under Cytel's responsibility. Four of these studies prompted data mapping suggestions from the appointed CBER reviewer after assessing the SDSP included in the briefing book.

While the indication was different, some similarities existed in reporting, particularly concerning solicited events and vaccines' reactogenicity data. Consequently, the CBER reviewer recommended following the Vaccine CBER guidance. Much of the feedback we received via the CBER SDSP appendix referred to this guidance, such as the use of CECAT = 'EFFICACY' for categorizing or flagging 'special' disease occurrences, or the use of AECAT for classifying and flagging Adverse Events of Special Interest. Other feedback, discussed in the CBER Vaccine guidance and previous

sections of this paper, was also provided, along with various mapping recommendations. The reviewer even referenced other CDISC Therapeutic Area User Guides (TAUGs), such as the Clostridium Difficile Associated Diarrhea (CDAD) TAUG.

In total, we received 19 recommendations, which applied to some or all the five studies. Of these, we disagreed with and could not apply five recommendations. For two other requests, we confirmed that the concerned data were already mapped as per CBER's expectations, indicating that the CBER appendix and the aCRF were insufficient to clarify how the mapping was done.

Our main reasons for not 'accepting' four of their requests were related to the CRF design, making it challenging to clearly link Concomitant Medications and Medical conditions using RELREC. In a couple of instances, we disagreed with their requests, particularly concerning the classification of occurrences collected during the study with CECAT = 'EFFICACY' when considered 'Suspected Recurrences.' This required the use of a complex algorithm described in the Statistical Analysis Plan (SAP), which we deemed inappropriate to derive in SDTM. Additionally, some of their requests were based on the CBER Vaccine Guidance or the CDISC Vaccine Guidance, neither of which existed at the time of the final analysis of some of the concerned studies.

After team discussions, we compiled our responses into a single document and incorporated them into a new version of the SDSP, which we subsequently re-submitted to the FDA CBER. The FDA CBER agreed with our responses, resulting in modifications to eight SDTM domains across different studies, with two of them also necessitating major changes to the ADaM structure and the re-run of linked Tables and Figures

CBER RECENT EXPERIENCE WITH A VACCINE SUBMISSION

Approximately two years after our initial CBER submission experience, we were involved in a new data submission, this time for a Vaccine product. At this point, four studies had already been conducted, and Cytel was appointed to conduct the pivotal study. The experience gained from the previous submission was invaluable, as it allowed the new team to receive relevant training and conduct a gap analysis to align with CBER's requirements. Like the previous experience, the appointed CRO was able to address some of our requests, but not all.

The submission process was akin to the previous experience, involving the provision of a SDSP that included a specific CBER appendix. This time, we also had to anticipate potential non-conformance issues, such as differences in the SV domain structure. The CBER reviewer carefully reviewed the provided information and presented ten requests, half the number compared to the 2019 experience, all related to the SDTM package. Additionally, the reviewer supplied three supplementary documents to illustrate reporting for efficacy, ongoing reactogenicity events, and identifying reactogenicity investigator assessments from subject assessments.

This review process required several meetings and discussions, leading to an official response from the sponsor through a separate document referenced in an amended SDSP. We also recommended that the sponsor apply for a 'Standardized Data Sample' from the FDA, given that this was the company's first-time submitting data packages to the FDA.

Satisfying the requests involved various discussions, and ultimately, all ten requests were met. Four of them did not necessitate changes to our SDTM mapping strategy, as it was equivalent to CBER's recommendations. Notably, one request related to the use of US conventional units in the LB dataset was addressed by adding a new QNAM in SUPPLB. This decision was made before the FDA provided its preferred approach in the latest version of the FDA Study Data Technical Conformance Guidance (June 2023), where they recommended two separate domains for laboratory results, one containing standard results in SI units and an additional custom domain for results in US conventional units. Table 2 provides details of the requests, our responses, and proposals.

CONCLUSIONS

Submitting data packages to CBER introduces distinct challenges, even for sponsors experienced in implementing CDISC standards throughout their product development. CBER's requirements add an additional layer of complexity on top of those already published by CDISC, notably the SDTM Implementation Guidance.

As emphasized in other public sponsor discussions, "*at this time, the CBER guidance itself as well as the Vaccine and COVID-19 CDISC TAUGs are out-of-date. Sponsors must be able to adapt quickly while maintaining quality and integrity of the clinical trial data and make informed decisions for ongoing and completed studies; especially if the changes are not quick or easy to implement*".

#	CBER Request	Cytel / Sponsor Proposal
1	Use PR domain for concomitant non-medications additional non study protocol interventions	We do not have a designated CRF page for Procedures thus we can't indicate which CM records are considered as procedures. However, we can propose to separate procedures and concomitant medications when the raw CM dataset is coded. Concomitant medications will be coded with WHO-DD dictionary and saved in coded CM dataset; the entries that cannot be coded with WHO-DD but can be coded with MedDRA version 24.0 will be separated out and saved in the coded PR dataset. SDTM PR domain will be created based on the coded PR dataset.
2	Efficacy results such as a “Confirmed Diagnosis of XXXXX" should be reported in CE instead of AE or SUPPAE. Please see sample efficacy dataset	“Confirmed Diagnosis of XXXXX" is an efficacy endpoint, collected from XXXXX CRF pages and is mapped to FACE. The efficacy results collected from XXXXX CRF pages are mapped to FACE (FATESTCD = XXXXXX) together with Adjudicated data. AE CRF page also contains "Confirmed XXXXX". But in this case, it is not an efficacy, it's just a qualifier for XXXXX records in AE. The information mapped to the AE/SUPPAE domains is based on the AE CRF pages.
3	Medically attended solicited reactogenicity events flag and details should be reported in CEACNOTH and HO, respectively, instead of SUPPCE	Medically attended solicited reactogenicity events flag is reported as CE.CEACNOTH = 'XXXXX' and details will be reported in HO, instead of SUPPCE
4	Some of the information you intend to report in SUPPSV may be better suited for other domains.	We do agree to update SUPPSV and removed general administrative information.
5	Add STUDYID and SITEID in each dataset.	We do agree to update the SDTM datasets to include SITEID variable in all datasets in addition to STUDYID that is already a required variables for all submitted SDTM domains
6	Include COUNTRY / INVNAM / RFICDTC in DM domain	In addition to COUNTRY and RFICDTC already present in DM domain, the INVNAM / Investigator Name will be added

Table 2: Cytel / Sponsor answer to CBER reviewer feedback / request

REFERENCES

[1] “Providing Regulatory Submission in Electronic Format” (FDA, December 2014) https://www.fda.gov/media/88120/download

[2] “Providing Regulatory Submission in Electronic Format - Standardized Study Data” (FDA, Revision 2 June 2021) https://www.fda.gov/media/82716/download

[3] “FDA Study Data Technical Conformance Guidance » (FDA, March 2023) https://www.fda.gov/media/153632/download

[4] “Data Standards Catalog” (FDA, August 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-catalog-v90

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CONTACT INFORMATION

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

Angelo Tinazzi and Merve Carrington
Cytel Inc.
Geneva, Switzerland
Email: angelo.tinazzi@cytel.com and merve.akram@cytel.com
Web: www.cytel.com
The "Good Data Submission Doctor" Cytel Blog: https://www.cytel.com/blog/author/angelo-tinazzi