Cytel

phuse·connect
connect·share·advance

5-8 November
ICC Birmingham

EU 2023
The Clinical Data Science Conference

Experiencing the FDA CBER

Angelo Tinazzi and Merve Carrington, Cytel Inc.

PHUSE EU Connect 2023

5h -8th November 2023

Paper SA09 – Submission and Agency (SA)

Disclaimer and Disclosures

The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of Cytel.

I have no real or apparent conflicts of interest to report.

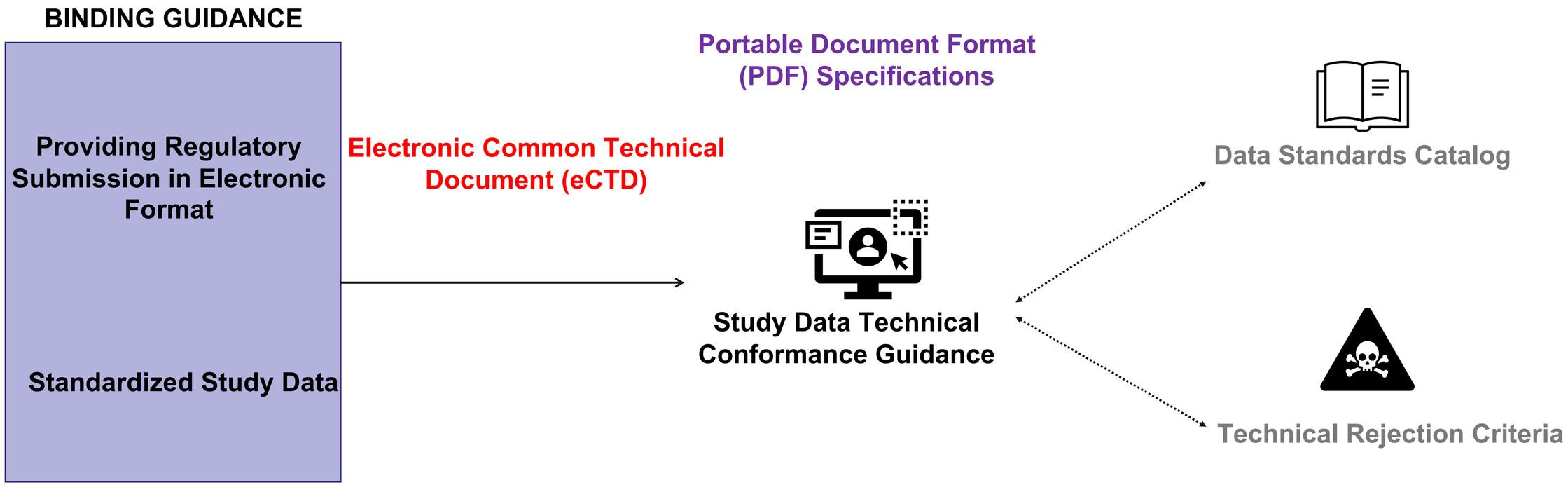
Agenda

- Overview of FDA Data Submission Requirements
- Experiencing the CBER
- Conclusions

Overview of FDA Data Submission Requirements

- Data Technical Specifications Guidance(s)
- CDER vs CBER
- CBER Vaccines Technical Specification Guidance
- CBER SDSP Specific Appendix

Overview of FDA Data Submission Requirements
Data Technical Specifications Guidance(s)



Unlocking the Potential: Exploring Overlooked FDA Guidance for CDISC Implementers, A. Tinazzi, CDISC Japan / EU Interchange 2023

Overview of FDA Data Submission Requirements
Data Technical Specifications Guidance(s)

- Referenced **CDISC TAUGs** in the FDA SDTCG
- Providing Regulatory Submissions in Electronic Format - General **Considerations, 1999 (Legacy Submission)**
- **Bioresearch Monitoring** Technical Conformance Guide Technical Specifications
- Creating **Simplified TS.XPT** Files
- Submit an eCTD or Standardized Data **Sample** to the FDA (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda)
- Model Data Format for submitting **pharmacometric data and models** (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format)

#	FDA Additional Data Standards Guidance References	SDTM	ADaM	Other
1	**Vaccines** Technical Specification Guidance v2.1 (Apr 2018 / Dec 2019) 10 Pages	√		CRF design recommendations
2	**QT Studies** Technical Specification Document v1.0 (Jun 2019) 24 Pages		√	Good examples
3	Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat **Human Immunodeficiency Virus-1 Infection** v1.0 29 Pages (Mar 2018)		√	Big Summary SL dataset
4	Technical Specifications—**Comparative Clinical Endpoint Bioequivalence Study** Analysis Datasets for Abbreviated New Drug Applications v.1.0 (Sep 2018) 46 Pages		√	
5	Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of **Noncirrhotic Nonalcoholic Steatohepatitis (NASH)** v1.1 44 Pages (Aug 2021 / Jan 2022)	√	√	Controlled Terminology NSV Good examples

Unlocking the Potential: Exploring Overlooked FDA Guidance for CDISC Implementers, A. Tinazzi, CDISC Japan / EU Interchange 2023

Overview of FDA Data Submission Requirements
CDER vs CBER

CDER	CBER
Center for Drug Evaluation and Research	Center for Biologics Evaluation and Research
Drug Regulation	Biological Product Regulation
• Naturally occurring substances purified from mineral or plant source materials (excluding vaccines or allergenics) • Products that are produced from nonhuman animal or solid human tissue sources • Antibiotics • Chemically synthesized molecules (excluding vaccines and allergenics) • Hormone products, regardless of method of manufacturing, e.g., insulin, human growth hormone, pituitary hormones • Certain agreed upon classes of substances constitutively produced by fungi or bacteria	• Vaccine • Human blood or blood derived product • Gene and cell therapies • In vivo diagnostic test such as allergenic • Products composed of or intended to contain intact cells or intact microorganisms including bacteria, fungi, viruses or virus pseudo types, or viral vectors • certain drugs used in conjunction with blood banking and/or transfusion [continue]
Adhere to a lot of similar principles and process in assessing product for market approval	

"Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research", from www.fda.gov

Overview of FDA Data Submission Requirements
CDER vs CBER (Example of Recent Approvals)

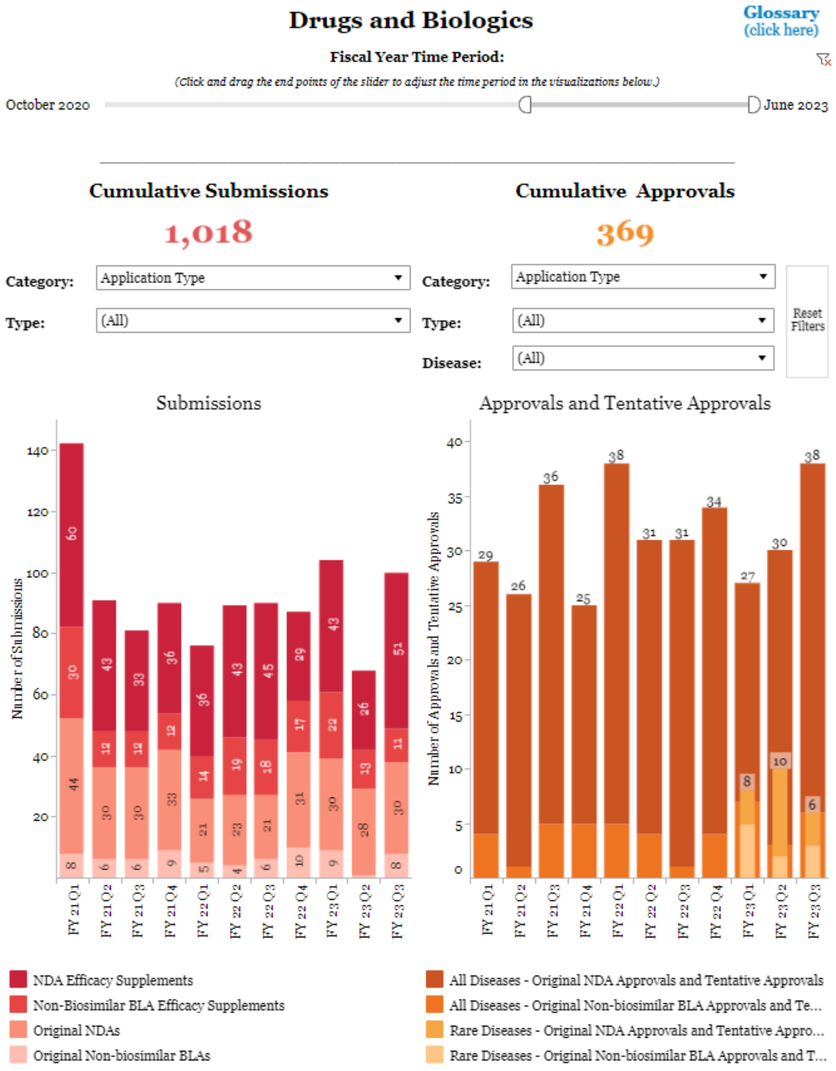
- **Bendamustine HCl** Injection 100 mg / 4 ml for the treatment of patients with **chronic lymphocytic leukemia** (NDA 215033) – CDER
- **Sotyktu (deucravacitinib)** tablets for the treatment of **adults with moderate-to-severe plaque psoriasis** who are candidates for systemic therapy or phototherapy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

www.accessdata.fda.gov

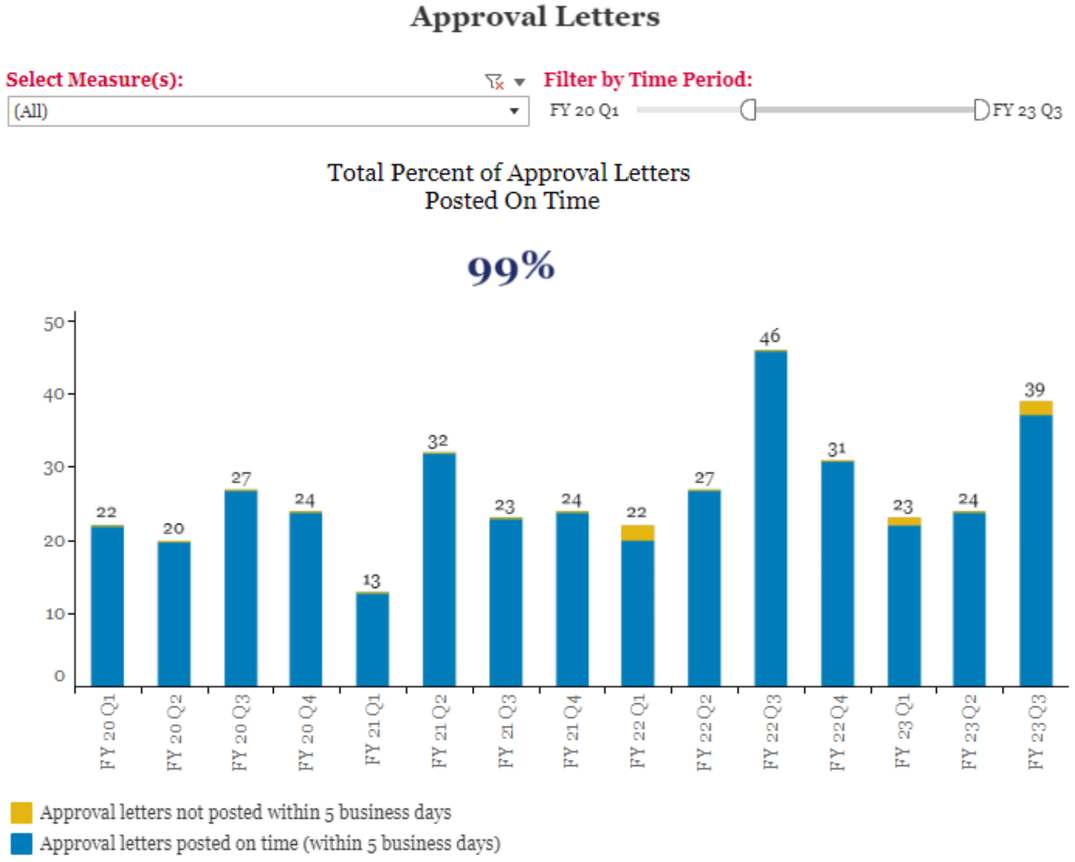
Overview of FDA Data Submission Requirements

CDER vs CBER (Statistics Publicly Available)

CDER



CBER



Overview of FDA Data Submission Requirements
CBER Vaccines Technical Specification Guidance

Office of Vaccines Research and Review Technical Specifications (OVRR)

SDTM Only

Overview of FDA Data Submission Requirements
CBER Vaccines Technical Specification Guidance (Reactogenicity)

U.S. FOOD & DRUG ADMINISTRATION

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

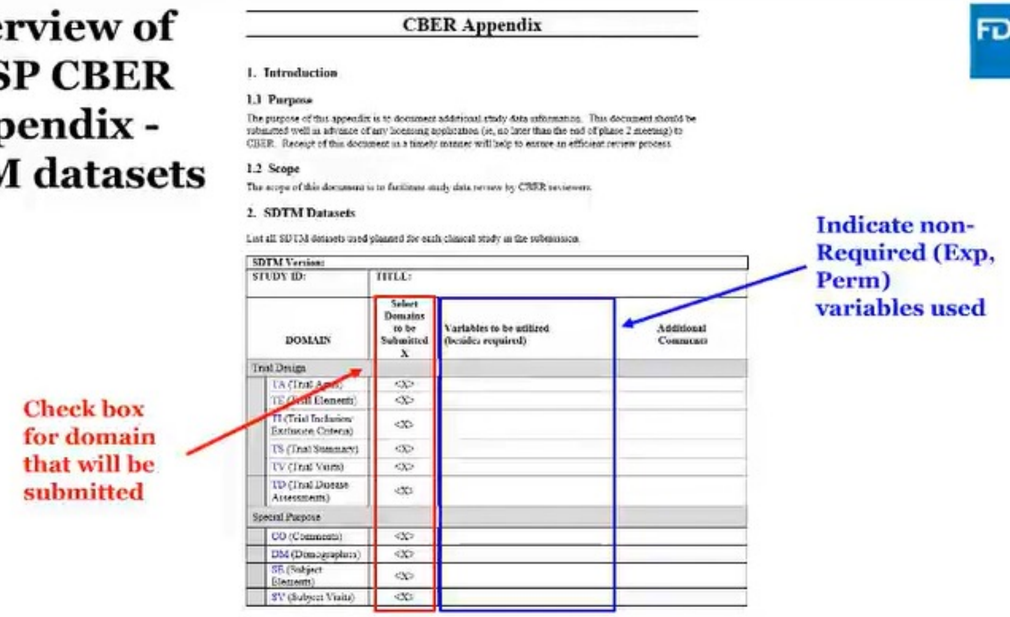
Source: "Preparing Vaccine Studies for Regulatory Submissions", M. Bess and K. Kelly, PHUSE US, 2022

- Reactogenicity is the **set expected adverse reactions related to vaccine**
  - **local** or **systemic**
  - **solicited** for a **certain period** after the administration;
  - typical reactions are fever, myalgia, fatigue, headache, nausea (Systemic) and redness/erythema, swelling/induration, pain/tenderness (Administration-site)
- **Solicited event** (daily), e.g., fever, that **results in FA(CE)** record, **results in VS record for temperature**, **results in a CE** record, **potentially results in an AE** record

Overview of FDA Data Submission Requirements
CBER SDSP Specific Appendix

U.S. FOOD & DRUG ADMINISTRATION

Overview of SDSP CBER appendix - SDTM datasets



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 applications (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 (Includes required)	Additional Comments
Trial Design			
TA (Trial Arms)	<X>		
TE (Trial Element)	<X>		
TI (Trial Inclusion/ Exclusion Criteria)	<X>		
TS (Trial Summary)	<X>		
TV (Trial Visits)	<X>		
TD (Trial Disease Assessment)	<X>		
Special Purpose			
CO (Comments)	<X>		
DM (Demographics)	<X>		
SE (Subject Elements)	<X>		
SV (Subject Visits)	<X>		

Check box for domain that will be submitted

Indicate non-Required (Exp, Perm) variables used

Overview of SDSP CBER appendix - Supplemental qualifiers

3. Supplemental Qualifiers

List each SUPPQUAL variable in an individual row. Include one set per clinical study.

SDTM Version:			
STUDY ID:	TITLE:		
Supplemental Qualifier Domain	Qualifier Variable Name (QNAM)	Qualifier Variable Label (QLABEL)	Corresponding CRF Question or Derivation information

- The listing of SUPPQUAL variables should match what is indicated in Section 2 of the CBER Appendix.
- Non-Standard Variables (NSV) in Standard Domains will be available in new versions.

Source: Optimizing Your Study Data Submissions to FDA: Office of Vaccines Research and Review (OVRR) Data Submission

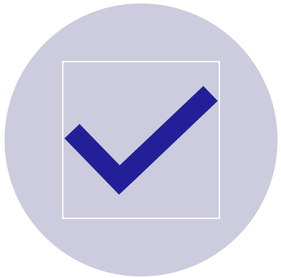
The objective is to **provide background to the CBER reviewers** so that they **understand the purpose of the data**, and eventually provide **recommendations**, including but not limited to remapping data to **avoid custom domains** or **unnecessary mapping to supplemental qualifiers**

Experiencing the CBER

- Our Experience in a Nutshell
- Submission 1: Non Vaccine Product 2019
- Submission 2: Vaccine Product 2022

Experiencing the CBER
Our Experience in a Nutshell

MAINLY FOR **VACCINE** SUBMISSION **BUT NOT ONLY**

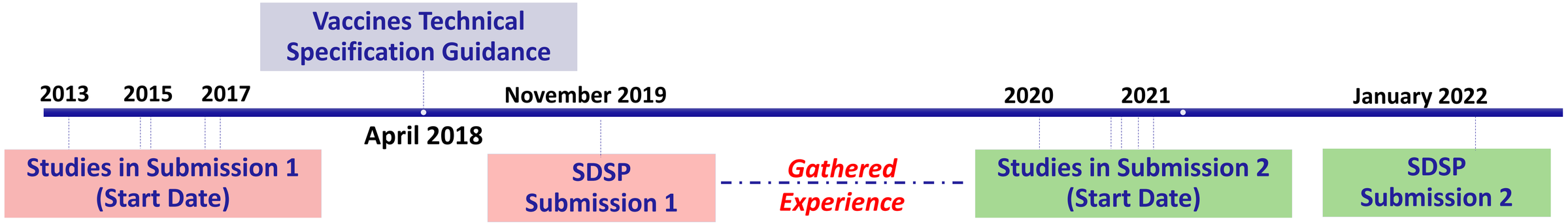


VERY **DETAILED ASSESSMENT OF OUR SDSP** AND **SAMPLE CRF**

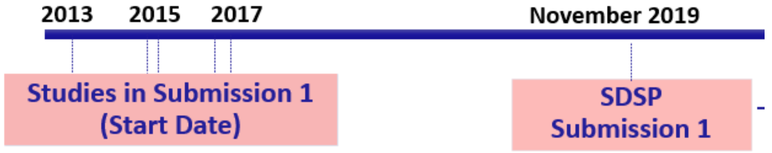
ADHERENCE TO VACCINE TAUGS, VACCINES TECHNICAL SPECIFICATION GUIDANCE AND OTHER RELEVANT CDISC TAUGS

SOME **REQUESTS COULDN'T BE SATISFIED** E.G., IMPACTING CRF DESIGN (DOCUMENTED DISCUSSION / AGREEMENT IN THE SDSP)

Experiencing the CBER
Our Experience in a Nutshell



Experiencing the CBER
Submission 1: Biological Non-Vaccine Product



Background

- “Similarities” with Vaccine e.g., way of reporting solicited events
- 2 out 5 studies under Cytel responsibilities
- SDSP (pre-BLA)

Rejected Request (s)

Classify recurrences with CECAT = “EFFICACY” requires complex algorithm we do think more appropriate for ADaM

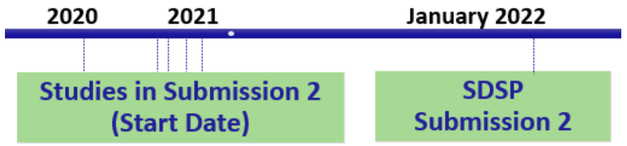
CBER Feedback

- 19 requests for change
- 5 “rejected” in agreement with sponsor
- Examples from other TAUGs

Implementation

- Cytel / Sponsor feedback → SDSP Amendment
- 8 SDTM domains impacted
- 2 SDTM updated implied a major modification on ADaM → TFLs

Experiencing the CBER
Submission 2: Vaccine Product



Background

- “Shared” previous experience with Cytel team / sponsor
- 1 out 6 studies under Cytel responsibilities + ISS
- Gap-Analysis
- SDSP (pre-BLA)

Examples of Requests

- US LB conventional unit in addition to SI added in SUPPLB (“use custom domain” official statement in FDA SDTCG June 2023)
- “Separate” concomitant medications (CM) vs non medications (PR). CRF unproper design, requests handled through medical coding

CBER Feedback

- 10 requests for change
- 3 Specific mapping instructions with examples
- 4 requests did not require any change

Implementation

- Lengthy discussion with sponsor
- Cytel / Sponsor feedback → Document referenced in an updated SDSP
- 5 SDTM domains impacted
- Minor Update on ADaM, no traceability issue (ongoing analysis)

Conclusions

Conclusions

Submitting data packages to CBER presented **unique challenges**

Additional requirements on top of the existing ones published by CDISC

Early Discussion with CBER, **submit the SDSP**

Raise awareness with the DM/BS/Prog teams

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.

Source: Challenges with Implementation of New Standards and Guidance – A Sponsor's Experience with the April 2018 CBER Vaccine Guidance", S. VanPelt Nguyen and L. Zhang, PHUSE US, 2023 https://www.lexjansen.com/phuse-us/2020/ds/DS05.pdf

References

FDA Guidance(S)

"Providing Regulatory Submission in Electronic Format" (FDA, December 2014)
https://www.fda.gov/media/88120/download

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

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

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

"Technical Rejection Criteria for Study Data" (FDA, May 2018)
https://www.fda.gov/files/drugs/published/Technical-Rejection-Criteria-for-Study-Data.pdf

"Portable Document Format (PDF) Specifications" (FDA, September 2016)
https://www.fda.gov/media/76797/download

"Electronic Common Technical Document (eCTD)" (FDA, March 2023)
https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd

"Bioresearch Monitoring Technical Conformance Guide Technical Specifications" (FDA, August 2022)
https://www.fda.gov/media/85061/download

References

FDA Guidance(S) – Cont.

"Submit an eCTD or Standardized Data Sample to the FDA" (FDA, January 2022) https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda

"Providing Regulatory Submissions in Electronic Format - General Considerations" (FDA, January 1999) https://www.fda.gov/media/71200/download

"Creating Simplified TS.XPT Files" (FDA, November 2019) https://www.fda.gov/media/132457/download

"Model Data Format for submitting pharmacometrics data and models" (FDA, August 2021) https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

"FDA Overview – CDER vs. CBER", T. White http://www.expedient-solutions.com/workshop/files/01_FDA_Overview_Presentation_Tacey.pdf

"Study Data Standardization Plan", v1, PHUSE, 2018 https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/SDSP.zip

"From Before to After: Preparing and Concluding your FDA Data Submission", Cytel Blog, https://www.cytel.com/blog/preparing-and-concluding-your-fda-data-submission

"Vaccines Technical Specification Guidance" v2.1, FDA CBER, Dec 2019 https://www.fda.gov/media/112581/download

References

CBER / Vaccine Other Sponsor Experiences

"Challenges Addressing CBER Guidance on Reactogenicity, from Collection to Analysis", S. VanPelt Nguyen, E. Bernstein-Hanlon, L. Houterloot, R. Li, PHUSE US, 2023 https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/US/Florida/PAP_VX02.pdf

"Challenges with Implementation of New Standards and Guidance – A Sponsor's Experience with the April 2018 CBER Vaccine Guidance", S. VanPelt Nguyen and L. Zhang, PHUSE US, 2023 https://www.lexjansen.com/phuse-us/2020/ds/DS05.pdf

"Adapting and Evolving with OVRR Requirements", J. Mastri and S. McLaughlin, CDISC-EU, 2023

Vaccine TAUG v1.1, CDISC, 2018 https://www.cdisc.org/standards/therapeutic-areas/vaccines/vaccines-therapeutic-area-user-guide-v1-1

"Automation of the SDSP CBER Appendix for Vaccine Studies", N. Jones, P. Solanki and J. Patel, PharmaSUG, 2023 https://www.pharmasug.org/proceedings/2023/DS/PharmaSUG-2023-DS-148.pdf

Other Recommended Readings

"An FDA Submission Experience Using the CDISC Standards", A. Tinazzi, PHUSE EU, 2018 https://www.lexjansen.com/phuse/2017/rg/RG04.pdf

"Presenting Clinical Data for Regulatory Submission: A Stats Perspective", Cytel Blog, https://www.cytel.com/blog/presenting-clinical-data-for-regulatory-submission-a-stats-perspective

"Introduction to ISS/ISE", F. Le Maulf, IX Italian CDISC User Network, 2023, https://wiki.cdisc.org/display/ITAUG/9th+CDISC+Italian+User+Network+Day

"The Integration Dilemma",A. Tinazzi, PHUSE-EU, 2022, https://phuse.s3.eu-central-1.amazonaws.com/Archive/2022/Connect/EU/Belfast/PAP_SI09.pdf

"The Good Data Doctor on Data Submission and Data Integration", Cytel ebook, 2023, https://www.cytel.com/cdisc-ebook-2023?hsCtaTracking=226ee8ce-f409-49bd-8c01-c76eff2d3fed%7C9c92ff7a-1fe0-4dfb-92cd-be67459c36ad

"Submit an eCTD or Standardized Data Sample to the FDA", FDA, 2022 https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda

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.

Thank you.

Angelo Tinazzi, Senior Director
Cytel Inc.
Standards, Systems, CDISC Consulting, Statistical Programming
Clinical Research Services
Route de Pré-Bois 20
C.P 1839, 1215 Geneva, SWITZERLAND
email: angelo.tinazzi@cytel.com

Subscribe to Cytel Blog to receive update on my
Good Data Submission Doctor Blog Series
https://www.cytel.com/blog/topic/cdisc

Cytel