cdisc®

2026 Europe Interchange

THE FUTURE IS CONNECTED: STANDARDS AND AI POWERING DIGITAL TRANSFORMATION

MILAN, ITALY | MAIN CONFERENCE: 20-21 MAY | TRAININGS & WORKSHOPS: 18, 19, & 22 MAY

It Got Worse Than Expected: Three Years of Retrospective CBER Requests on SDTM, ADaM, and TFLs

Mark Malayas / Angelo Tinazzi, Cytel Inc.

Speakers

Mark Malayas
Principal Statistical Programmer
Cytel Inc.

Angelo Tinazzi
Senior Director - Statistical Programming
Cytel Inc.

Agenda

1. Overview of FDA CBER

2. Specific Requirements for CBER submission

3. Summary of our experience working with CBER submission

Overview of FDA CBER

CBER vs CDER

The FDA's CDER and CBER are the two primary divisions regulating human medical products.

CDER Center for Drug Evaluation and Research	CBER Center for Biologics Evaluation and Research
Role: Regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.	**Role:** Protects and advances the public health by ensuring that biological products are safe and effective.
Primary scope: Prescription drugs, generic drugs, biosimilars and over-the-counter drugs.	**Primary scope:** Complex biological products like vaccine, gene therapies, blood products.
Approval Type: New Drug Application (NDA)	**Approval Type:** Biologics License Application (BLA)

Specific Requirements for CBER submission

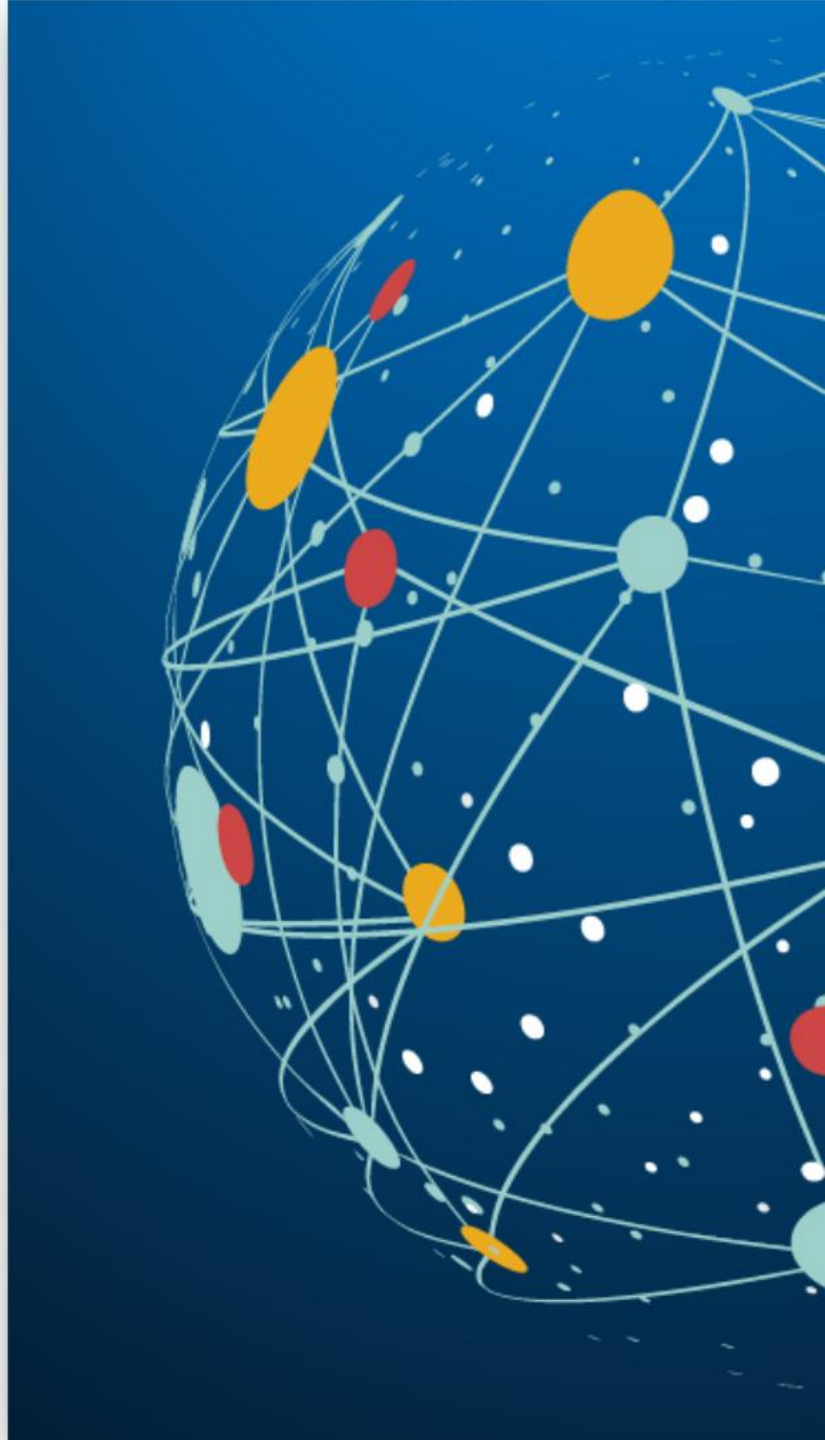
Vaccine Data

Guidance for Submission to FDA CBER (Vaccine)

Study Data Technical Conformance Guide
(March 2026)

Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review
(December 2019)

Vaccines Therapeutic Area User Guide v1.1 (TAUG-Vax)
(April 2018)



Specific Requirements for CBER Submissions

- **The CBER SDSP Appendix**

  The CBER SDSP appendix should include tables of proposed SDTM domain/variable usage, Supplemental Qualifiers variables and proposed ADaM datasets and data structures.

- **SDTM annotated CRF**

  It is recommended to provide aCRF ahead of the trial start or at the time the protocol is submitted.

- **Safety Data and Preferred SDTM Domains**

  Safety data must include reactogenicity data (solicited adverse events), unsolicited AEs, medically attended adverse events (MAAEs), and mortality data.

  Usage of specific domains for vaccine safety (CE, FACE, VS), efficacy (CE, MB), and immunogenicity (IS) is highly recommended.

Known Challenges on CBER Submissions

- **Outdated Guidance Documents**

While the CDISC standards and FDA Technical Conformance Guide document is updated, the Vaccine TAUG and Guidance for Submitting Study Datasets to OVRR are quite outdated.

- **Misalignment of CBER and CDISC guidance**

Following CBER requests on SDTM datasets can lead to compliance issues on CDISC validation.

Some requests require complex mapping or derivations that is inconsistent with SDTM principles.

Formation of Vaccines Industry Standards Group (VISG)

Several organizations formed a group to collaborate and share experience regarding these challenges and feedback from CBER.

(*As presented in CDISC EU 2025 "Collaborating on Standards: An Approach to Harmonizing Vaccine Regulatory Submissions" – Sanofi/GSK)*

Summary of our experience working with CBER submission on Vaccine Data

What got worse?

- **Our initial assessment of the FDA requests underestimated the total scope of the required updates**

We tried to challenge some of the requests but ended up implementing all of them.

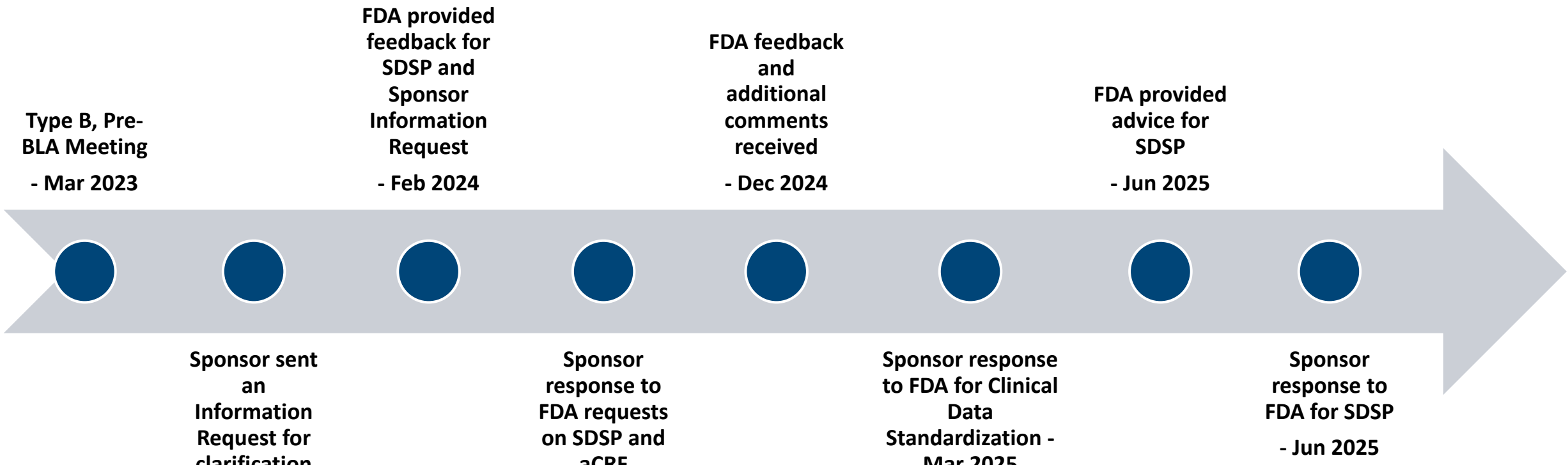
- **Multiple rounds of comments/feedback**

The series of comments and requests from FDA leads to updates that would later on lead to another update. The initial request is just the “tip of the iceberg”.

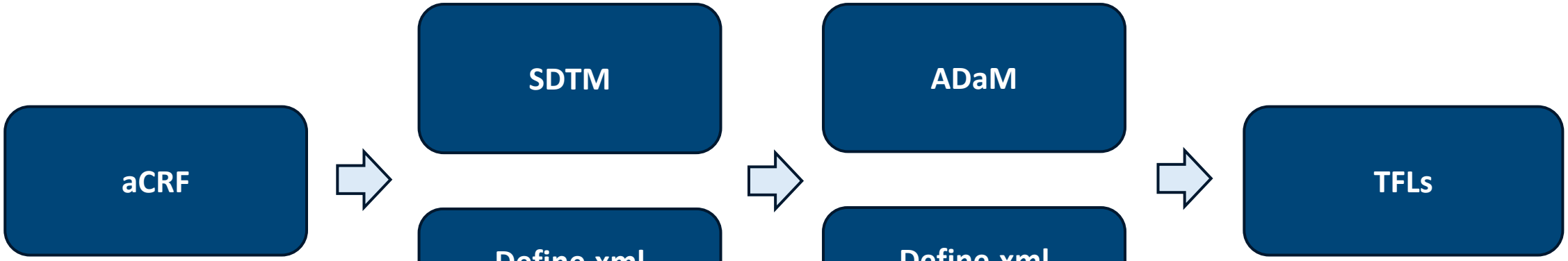
- **Different reviewers / regulations throughout the years**

Because of the duration of the submission process, we have interacted with different reviewers from FDA. The regulations on vaccine data within the FDA has also changed.

Case Study: Timeline of Interaction with FDA CBER



Updates Requested by CBER and downstream impact



- aCRF need to be updated to reflect SDTM mapping.

- Updated mapping of data in CE, FA, AE, VS.
- Additional variables to aid in review.
- Additional variables in all domains.
- Update documentation.

- Update ADaM datasets affected by SDTM.
- Separate ADaM dataset for clinical disease efficacy endpoint.
- Update documentation.

- Re-create outputs impacted by the updated datasets.
- Provide additional outputs.

Summary of Updates Requested by CBER

SDTM – Some Expected Requests

- Report **clinical disease efficacy endpoints in CE** instead of AE/SUPPAE.
- Recommended use of **AECAT='Immediate Adverse Event'** for immediate events that are not solicited. Solicited events should be reported in CE with **CECAT='Immediate Reaction'**.
- Temperatures taken to assess/support an unsolicited adverse event should be reported in VS with VSCAT "Adverse Event."
- **Create LC domain** (LB dataset in US conventional units). Include LBTOXGR and LBRIND. LBTOXGR should be derived when not provided by central lab.

Summary of Updates Requested by CBER

SDTM – Some Unexpected Requests

- Solicited reactogenicity data should be mapped to CE and FACE. Split FA to FACE (for solicited events) and FAEF (for efficacy endpoints). But unsolicited events that are also **clinical endpoints** should be mapped in both **CE** and **AE**.

- Add **RFSTDTC** and **SITEID** from DM in all events domain. Add **RFTDTC** and **TPTREF** in all domains. Add **EPOCH** variable in all datasets to aid in analysis.
  Derive the duration (**--DUR**) in the CE dataset for the solicited events.

- Use **SV** dataset for all subject visit data (scheduled or unscheduled) and not use VE domain. Use **SVOCCUR** to indicate occurrence. (Even for datasets using older SDTMIG)

- Use **--EVAL** in FA and VS to indicate who recorded the event. Derive the --EVAL based on the source data.

Summary of Updates Requested by CBER

ADaM

- Remove the **clinical disease efficacy endpoint** records in ADAE.
- Create a separate **ADEFF** (efficacy) dataset from the **ADREACT** (reactogenicity).
- Additional variables (**timepoint** and **timepoint reference**) in ADaM datasets to aid in review.
- Update ADaM datasets impacted by changes to SDTM domains.

Impact on TFLs and other submission outputs

TFLs

- Re-generate impacted TFLs by updated analysis datasets.
- Generate additional set of TFLs (Post-hoc analysis) to support the CSR addendum to complement FDA requests.

Packages

- Submitted different packages (one package for the original completed CSR, one package with the updated datasets based on CBER requests).

Update on SDSP

SDPS needs to be updated on the following sections:

- List of Studies (Clinical) - to reflect the changes in the submission packages
- CBER Appendix - to reflect updates on the datasets
- Non-Conformance to Supported Standards - to document, provide justification, and outline strategies for any deviation from standards

Update Define.xml, Reviewer Guides

- Documentation needs to be updated accordingly
- Needed to explain the issues in the compliance section that is because of CBER request

Lessons Learned

- Initial preparation is key. Early interaction with FDA is beneficial for successful submission. Incorporate the CBER/OVRR guidance from data collection.
- Be aware that there is a gap with the current standards vs what FDA CBER requests, and that specific mapping of datasets are not covered in the current guidance.
- Document everything.

"It takes less time to do a thing right than to explain why you did it wrong." — *Henry Wadsworth Longfellow*

References

Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (December 2019)

CDISC Vaccines Therapeutic Area User Guide v1.1 (TAUG-Vax) (April 2018)

Guidance for Industry Providing Regulatory Submissions in Electronic Format – Standardized Study Data (March 2026)

Experiencing the FDA CBER - PHUSE EU Connect 2023 - Angelo Tinazzi and Merve Carrington, Cytel Inc.

Collaborating on Standards: An Approach to Harmonizing Vaccine Regulatory Submissions – CDISC Europe Interchange 2025 - Médéric Celle (Sanofi) and Estella Sani (GSK)

Study Data Submissions: Office of Vaccines Research and Review (OVRR) Data Submission - May 2018

Optimizing Your Study Data Submissions to FDA: OVRR Data Submission - May 2018

Thank You!

Questions?