

DS05: Challenges with Implementation of New Standards and Guidance – A Sponsor's Experience with the April 2018 CBER Vaccine Guidance

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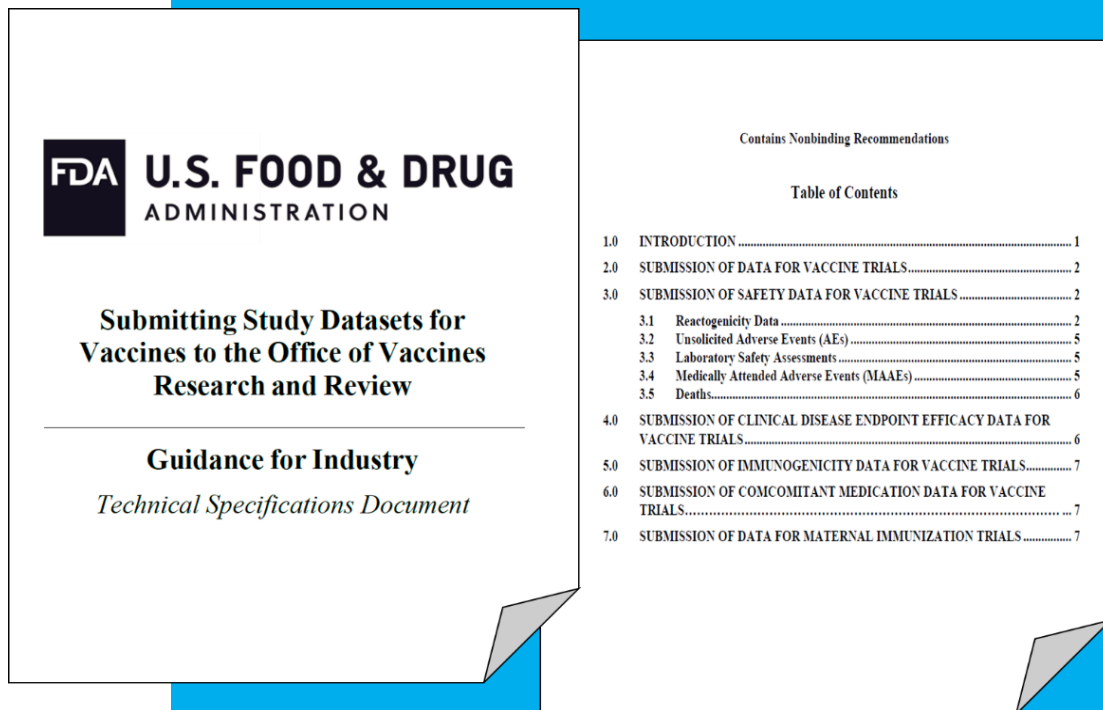


Breakthroughs that
change patients' lives



GLOBAL PRODUCT DEVELOPMENT
Global Biometrics & Data Management

- Original release (v1) in April 2018*
- For immediate implementation
- Contains nonbinding recommendations for certain types of data commonly assessed for vaccine studies and how to represent components of this data within CDISC SDTM datasets



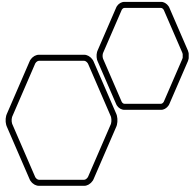
* updated version 2.0 released in October 2019 and version 2.1 (administrative changes) in December 2019

Initial Process

- Document came to Statistical Programming & Analysis group via Regulatory
- Reviewed and identified specific points for implementation
- Assessed each point against current standards
- Identified gaps and differences

The DS domain should always include the Standardized Disposition Name (DECOD), Reported Term (TERM), Category (CAT), and Start Date/Time of Event (STDTC) variables. If relevant (i.e., multiple doses administered over time), the DS domain should include the use of the Order of Element within Arm (TAETORD) timing variable. The TAETORD timing variable should also be included in other domains when the vaccine is multi-dose.

Section #	Topic	Specification	Standards Updates Needed?	Differences - Details
2	Submission of Data for Vaccine Trials	The DS domain should always include the Standardized Disposition Name (DECOD), Reported Term (TERM), Category (CAT), and Start Date/Time of Event (STDTC) variables.	N	
2	Submission of Data for Vaccine Trials	If relevant (i.e., multiple doses administered over time), the DS domain should include the use of the Order of Element within Arm (TAETORD) timing variable.	Y	TAETORD is not currently included in DS domain.
2	Submission of Data for Vaccine Trials	The TAETORD timing variable should also be included in other domains when the vaccine is multi-dose.	Y	TAETORD is not standard variable for most domains.



Next Steps

- Brought together a cross-functional team
- Attempted to communicate the necessary changes to bring datasets in compliance with the specifications



Challenges

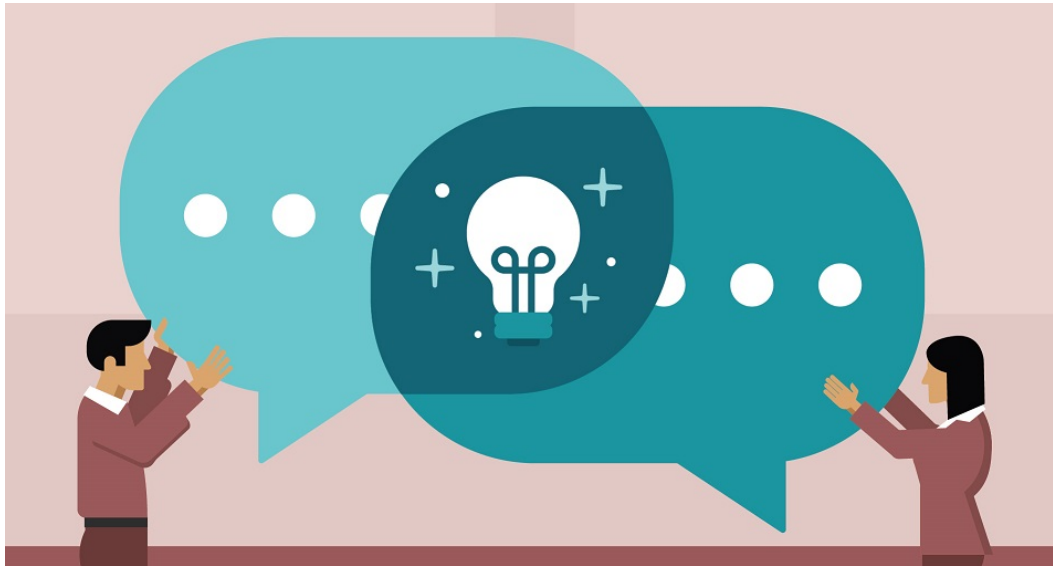


- No established process
- Communication
- Resistance to change
- Cross-functional collaboration
- Prioritizing



2nd Attempt

- Technical team meetings to discuss options
 - Determined most viable options
 - Planned discussion points
 - Assembled examples
- Took options with examples back to broader team



- Identified points needing clarification from agency

Implementation Example

From guidance section 3.1 [Reactogenicity Data]: *If a reactogenicity event should happen to continue beyond the assessment interval, it should also be represented in the AE domain...The start day/date (--STDY/--STDTC) and the end day/date (--ENDY/--ENDTC) of the reactogenicity event should be identical in both the CE and AE domain; whereas the duration (--DUR) should report the time that the event occurred as part of the assessment interval and as part of the continuance separately (e.g., an event that lasted 6 days in the assessment interval and 3 days beyond the assessment would be reported as Clinical Event Duration (CEDUR) = 6 days and Adverse Event Duration (AEDUR) = 3 days).*

In this example, the assessment interval is 6 days. We would inquire whether the subject experienced a particular symptom (e.g. headache) each day for 6 days following the vaccination.

Implementation Example (Cont.)

Vaccination Diary	
Today, have you experienced headache?	
Yes	☐
No	☐
< Back Next >	

Vaccination Diary	
Please indicate whether the headache was:	
Mild	☐
Moderate	☐
Severe	☐
< Back Next >	

Subject diary

Symptom present on last day Subject Diary was completed?
[Were Symptoms Present Last Day of Diary]

CRF

[A:Y] ☐ [cmpVSDSONGO] ☐
 YES
 [VSDSONGO]
 Ongoing?
 [A:Y] ☐ YES
 [A:N] ☐ [cmpVSDSSDAT] ☐
 NO
 [VSDSSDAT] (MM/DD/YYYY)
 Stop Date
 Req / Req / Req (2018-2025)
 [A:N] ☐ NO

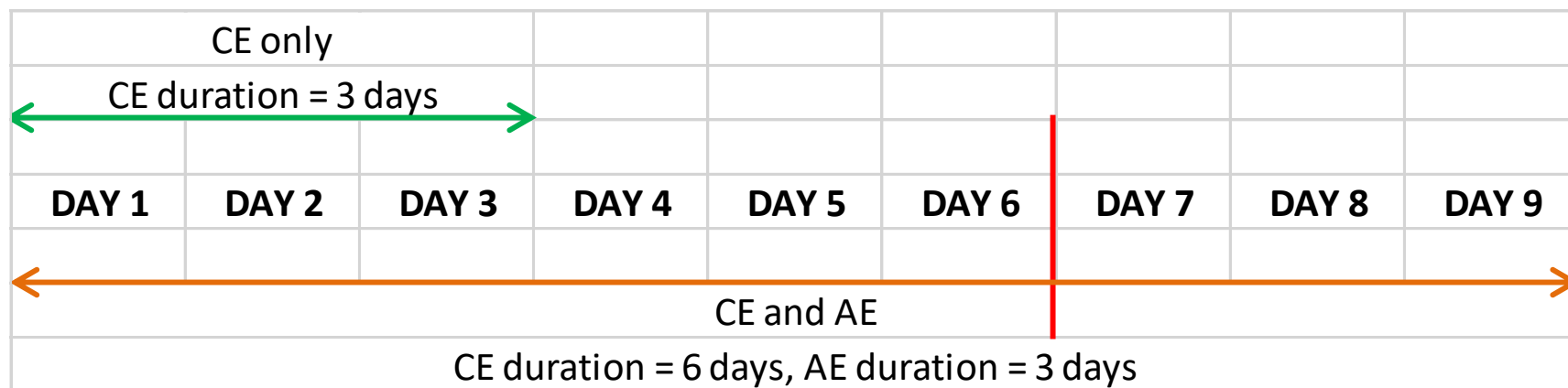
Implementation Example (Cont.)

Two scenarios:

Green: headache lasts 3 days

Orange: headache lasts 9 days

Assessment interval = 6 days



	xxTERM	xxSTDTC	xxENDTC	xxDUR
CE	HEADACHE	2020-01-01	2020-01-09	6
AE	HEADACHE	2020-01-01	2020-01-09	3

Implementation Example (Cont.)

Challenges/Issues

- Requested usage of the --DUR variables contradicts the SDTM IG*.
- Challenging for sites to accurately determine the duration values to enter for CEDUR/AEDUR.
- Data reconciliation.
- Standard duration derivations applied generically across all studies/domains.

Questions

- Does this impact AE analysis?
- How to analyze and interpret duration for reactogenicity?
- Will it impact the safety profile for the vaccine?
- Affect of diary entry errors?

*Section 4.1.4.3.1

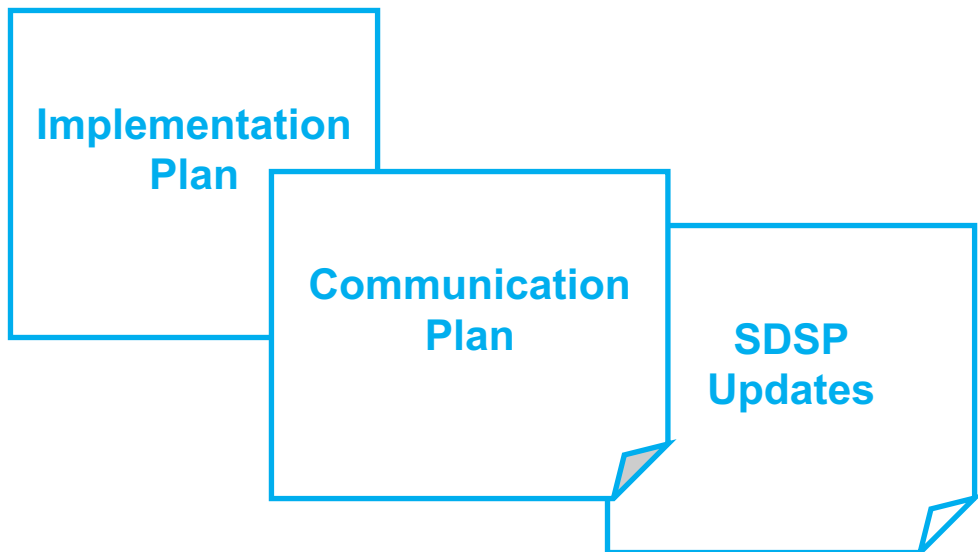
Taking it Forward

- Initiated dialogue with CBER
- External collaboration



Implementation Considerations

- Roll out each change individually as finalized or all together?
- Where/when to implement?
 - Completed/ongoing/future studies
 - Timing of study close-out and reporting
- Impact to CSR?
- Data integration



Current Status

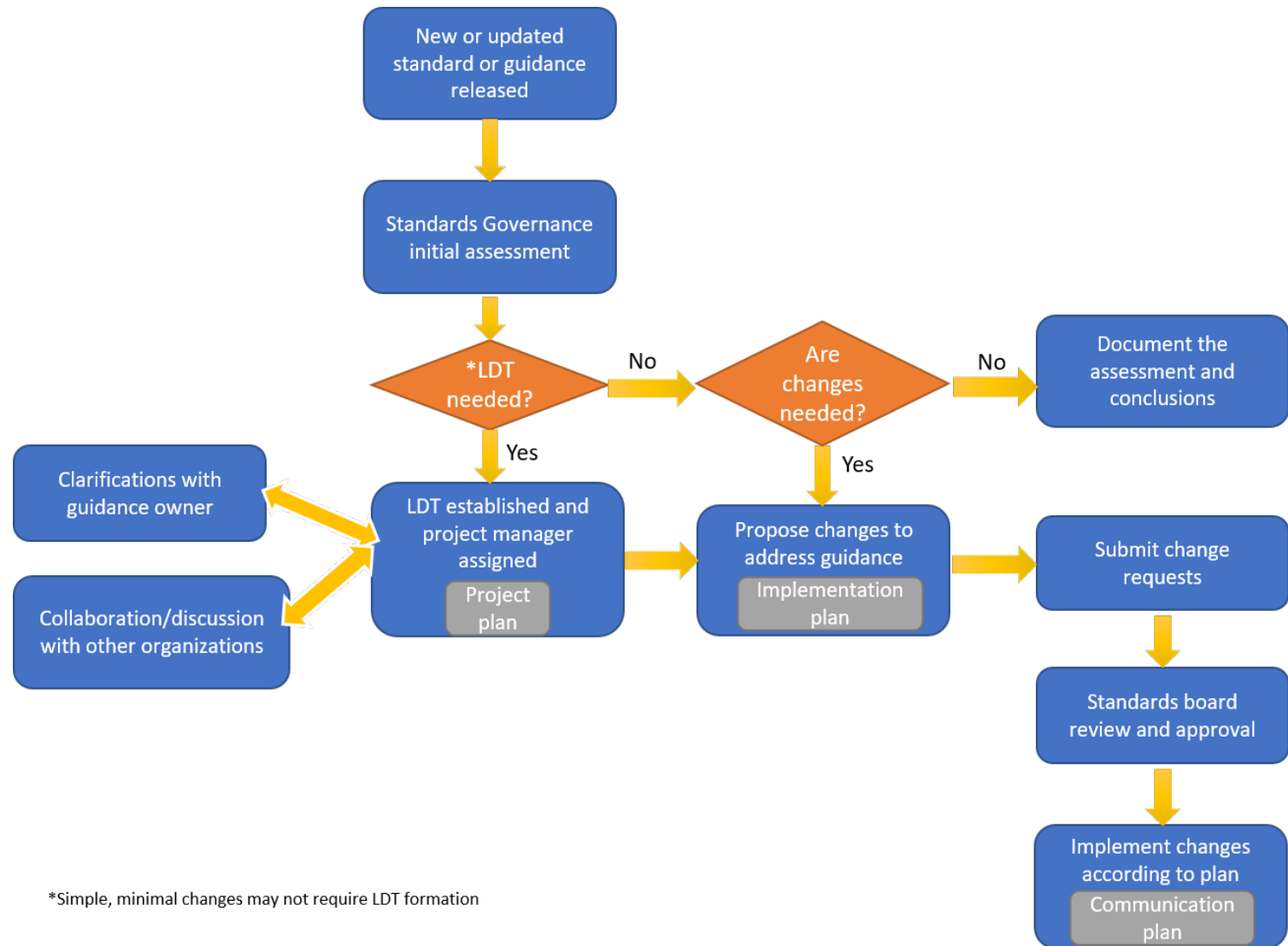
- Cross-industry discussions underway
- Awaiting agency feedback
- Preparing standards change requests
- Contemplating implementation plans

Lessons Learned/Recommendations

Need:

1. “Big picture” approach
2. Defined process
3. Leadership & project management
4. Two-way, effective communication
5. Flexibility and collaboration

Limited Duration Team



*Simple, minimal changes may not require LDT formation

How Could This Apply to You?

- Ongoing releases of new standards and updates
- FDA Technical Conformance Guide
- TA-specific guidance/technical specifications
- Regulatory feedback

Questions?

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