Paper DS07

Collaborating on Standards: An Approach to Harmonizing Vaccine Regulatory Submissions

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ABSTRACT

In a significant collaboration, seven leading vaccine organizations—AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck, Moderna, Pfizer, and Sanofi—have formed the Vaccines Industry Standards Group (VISG). Over the past two years, this initiative has focused on harmonizing interpretations of regulatory submission guidance and CDISC data standards. The group recognizes that aligning on processes—such as participant diary data collection and submission of reactogenicity and efficacy data—accelerates time to market and benefits global health. This unified approach enables proactive alignment on standards in preparation for engagement with health authorities and standards organizations, in addition to promoting clarity and consistency in submission standards. Our collaborative model serves as a blueprint for other niche groups within the pharmaceutical industry, demonstrating how organizations can work together to streamline regulatory processes while maintaining a competitive edge in product innovation.

INTRODUCTION

Vaccine clinical trials are conducted to evaluate the safety, immunogenicity, and efficacy of a vaccine.

Reactogenicity assessment is an important part of vaccine safety evaluation and is defined as a set of reactions or adverse events that can occur shortly after vaccination and are generally considered to be a response to the vaccine. This data is solicited over a pre-defined period post vaccination with participants reporting whether each solicited event was present or absent for each day in a reactogenicity diary.

Efficacy is determined by evaluating how many participants who were vaccinated developed the disease of interest compared with those who received a placebo or comparator vaccine. Participants are monitored post-vaccination for specific disease-related signs and symptoms, with diagnoses typically confirmed through laboratory testing.

Immunogenicity testing assesses the body's immune response to a vaccine.

The United States Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) has outlined specifications for how organizations should submit reactogenicity and efficacy datasets for vaccine licensure. The Guidance for Industry "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review"[1] (hereafter known as the "OVRR guidance"), originally published in April 2018 (v1.0), is a technical specifications document "designed to aid clinical and statistical reviewers in the review of vaccine applications". It is referenced in FDA's Study Technical Conformance Guide[2] as of October 2018 (v4.2) and was updated in October (v2.0) and December 2019 (v2.1) with v2.1 being the current version as of the time of this paper. The OVRR guidance primarily addresses how to represent reactogenicity and efficacy datasets in SDTM, providing instruction for the usage of specific domains and variables. To comply with this guidance, organizations needed to reconsider how safety and efficacy data were collected and reported.

As organizations were independently working through the guidance, it became apparent that some elements were open to interpretation, presented various challenges with how data has historically been collected/reported, and/or did not align with CDISC[3] standards. As a result, in January 2020, members from six organizations met for a one-day in-person forum to discuss common challenges with implementing the guidance.

The group had an engaging and collaborative day of discussion, and through the Biotech Innovation Organization (BIO) Group[4], submitted feedback to CBER that resulted from the interorganizational collaboration. The COVID-19 pandemic was declared in the midst of this exchange, hence CBER did not issue a response, and organizations returned to their individual assessments and implementation of the OVRR guidance.

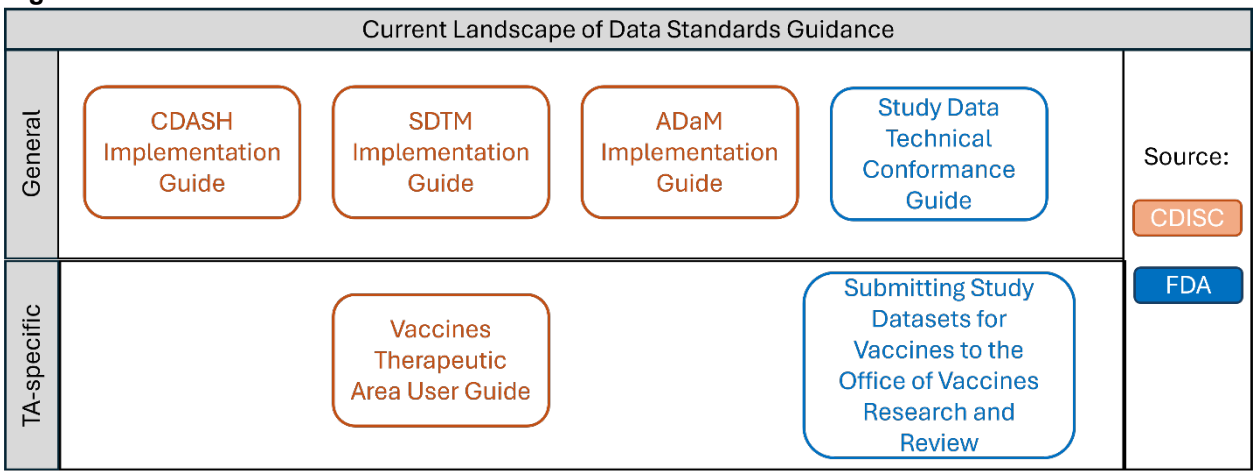
BACKGROUND

Health authorities each have their own set of requirements and guidelines for data submission and regulatory review, which can create challenges in the submission process for organizations operating in multiple regions. Organizations must navigate and comply with each health authority's unique criteria, which can lead to increased complexity and extended timelines.

Where health authorities expect submission of individual trial datasets, CDISC standards are largely expected for submission, to ensure consistency, transparency, and efficiency during the review process. Utilizing CDISC standards also enables a streamlined approach to data collection, analysis, and submission.

In addition to the foundational standard CDISC Implementation Guides like CDASH IG, SDTM IG, and ADaM IG, there is a dedicated therapeutic area user guide (TAUG)[5] for vaccines (Figure 1). This guide outlines how to apply CDISC standards to represent data specific to vaccine trials, with a particular emphasis on safety data related to reactogenicity events collected during these trials. The TAUG, while beneficial, pre-dates the OVRR guidance which provides more specific recommendations, resulting in some contradictory information.

Figure 1:



While CBER has published the OVRR guidance, detailing their preferences for vaccine data submissions, there is no similar guidance from other health authorities at this time. Thus, organizations must decide whether to apply the OVRR guidance to all submissions or only for submissions to US FDA. Since some components of the OVRR guidance contradict published CDISC standards, additional explanation may be needed when submitting OVRR-compliant data to other health authorities outside of the US who may not be familiar with the guidance. If organizations instead choose the approach of using different standards for different submissions, this requires more resources and could result in differences across submissions.

Harmonizing data standards and submission formats to meet the diverse requirements of multiple health authorities is a resource-intensive process that often requires extensive cross-functional collaboration and

adaptation. By addressing these divergent regulatory requirements and aligning interpretations of the requirements, organizations can streamline their submission processes, reduce errors, and improve the efficiency and effectiveness of their regulatory interactions.

FORMATION OF THE VACCINES INDUSTRY STANDARDS GROUP (VISG)

In early 2023, the Sanofi Vaccines group faced challenges related to feedback from CBER about their SDTM and ADaM datasets as well as the statistical analysis. In a similar spirit of the January 2020 engagement, Sanofi contacted counterparts from other organizations asking if they were facing similar challenges. These organizations recognized the value of a collaboration and set forth with a goal to achieve the following:

- Share regulatory challenges faced by all organizations.
- Discuss the understanding of regulatory feedback/ guidance and how to comply.
- Be an open forum to share and discuss implementation plans, including the pros and cons of each option.
- Strive for efficiency to support regulatory reviews in the spirit of vaccine development and public health.

This collaboration has been named the Vaccines Industry Standards Group (VISG). The VISG is composed by seven organizations: AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck, Moderna, Pfizer, and Sanofi.

Regular meetings facilitate open and in-depth discussions among member organizations, which include sharing experiences, insights, and challenges related to interpreting the OVRR guidance and relevant regulatory feedback.

A chairperson leads the monthly meetings and drives the agenda topics. Most topics are introduced and discussed via email before each meeting, allowing for mature discussion and summarization during live meetings. All meetings are recorded, and meeting notes are taken in a shared application by a rotating volunteer. A shared workspace dedicated to VISG exists for all other kinds of communications (for example, document sharing). VISG participants freely raise new topics or questions, typically receiving input from other members within 1-3 days.

The group engages in in-depth discussions surrounding data collection and mapping guidelines, acknowledging that examples, guidance, or feedback may be subject to varied interpretations. The group also shares examples provided by and responses from CBER to questions submitted through the CBER eData[6] mailbox. Feedback from these discussions has provided valuable insights, allowing organizations to anticipate and address potential issues proactively, thereby minimizing the need for rework and clarification requests from health authorities.

VISG is also used as a sounding board for different implementations and facilitates valuable discussions among member organizations. For example, there is variability in how organizations collect the investigator's assessment of participant-reported data. Some organizations apply the investigator's assessment to daily records, while others apply it to the summarized event level records. By exploring these differing methodologies, organizations gain insights into alternative strategies and pros and cons of each, stimulating innovative thinking and prompting introspection about the data collection processes.

This collaboration has yielded significant practical benefits for member organizations, such as reducing discrepancies and inconsistencies in submission packages and allowing organizations to be proactive when considering feedback received by others. By sharing knowledge, discussing diverse practices, aligning interpretations, and evaluating outcomes, member organizations can critically evaluate their methodologies and explore innovative solutions to enhance operational processes more effectively.

By fostering a collaborative environment, the VISG can identify common challenges and work towards a consensus on best practices. This collaborative effort ensures that all member organizations have a clear and unified interpretation of the regulatory requirements, reducing inconsistencies and improving overall compliance.

CHALLENGES

The current published guidance materials are sometimes contradictory and often insufficient to address all possible scenarios, resulting in significant challenges to produce the desired data format.

Examples include:

1) CBER has an expectation for certain derived (and potentially complex) information to be included in SDTM while SDTM is intended to tabulate collected data with only minimal derivations, such as reference dates and study days. This creates a paradox for organizations striving to comply with the submission guidelines while adhering to the core principles of SDTM. The inclusion of derived data in SDTM not only deviates from its intended purpose but also introduces complexities in the data collection and downstream processes.
   For example, the OVRR guidance expects the --DUR variable to be derived in SDTM whereas according to CDISC, the --DUR variable should only be used if the duration was collected and only when start and end dates/times are not collected. For reactogenicity events, dates are captured for all events rather than durations, so --DUR is not expected in SDTM.

OVRR guidance v2.1:

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).

SDTMIG v3.3:

4.4.3.1 Intervals of Time and Use of Duration

As defined by ISO 8601, an interval of time is the part of a time axis, limited by two time "instants" such as the times represented in SDTM by the variables --STDTC and --ENDTC. These variables represent the two instants that bound an interval of time, while the duration is the quantity of time that is equal to the difference between these time points.

ISO 8601 allows an interval to be represented in multiple ways. One representation, shown below, uses two dates in the format:

YYYY-MM-DDThh:mm:ss/YYYY-MM-DDThh:mm:ss

While the above would represent the interval (by providing the start date/time and end date/time to bound the interval of time), it does not provide the value of the duration (the quantity of time).

Duration is frequently used during a review; however, the duration timing variable (--DUR) should generally be used in a domain if it was collected in lieu of a start date/time (--STDTC) and end date/time (--ENDTC). If both --STDTC and --ENDTC are collected, durations can be calculated by the difference in these two values, and need not be in the submission dataset.

SDTM v1.7:

--DUR	Duration	Char	ISO 8601	Collected duration of an event, intervention, or finding. Used only if collected on the CRF and not derived.

CE dataset

STUDYID	DOMAIN	USUBJID	CESEQ	CETERM	CECAT	CESCAT	CEPRESP	CEOCCUR	CESTAT	CEREASND	EPOCH	CESTDTC	CEENDTC	CESTDY	CEENDY	CEDUR	CETPTREF	CERFTDTC
999999	CE	999999-101-101001	1	ERYTHEMA	REACTOGENICITY	ADMINISTRATION SITE	Y	Y			TREATMENT 1	2023-07-01	2023-07-04	1	4	P4D	VACCINATION AT VISIT 1	2023-07-01T09:15
999999	CE	999999-101-101001	2	FEVER	REACTOGENICITY	SYSTEMIC	Y	N			TREATMENT 1						VACCINATION AT VISIT 1	2023-07-01T09:15
999999	CE	999999-101-101001	3	HEADACHE	REACTOGENICITY	SYSTEMIC	Y		NOT DONE	INCOMPLETE DIARY	TREATMENT 1						VACCINATION AT VISIT 1	2023-07-01T09:15

2) The current CDISC Vaccines TAUG (last revised April 2018) does not align with current regulatory requirements, namely the OVRR guidance.

   For example, the TAUG illustrates three possible models for reactogenicity data (flat, nested, or highly nested), however CBER expects the flat model to be used for submitting reactogenicity data. Organizations must invest additional effort to reconcile these differences and ensure compliance with the most current regulatory standards.

3) The OVRR guidance does not provide detailed instructions on certain points, which leaves them open to interpretation and makes implementation challenging.

   For example, the guidance offers limited details on handling efficacy data, presenting only a basic scenario and no detailed examples of common industry situations, like:

   a. No clear guidance on generating the CDECASE "clinical disease endpoint case" flag in SUPPDM for a trial with multiple primary efficacy endpoints. Only after consulting CBER was guidance provided to a member organization to create CDECASE1 and CDECASE2 in SUPPDM.
   b. No clear guidance on how to report confirmed and suspected cases. After contacting CBER, an example file was provided by the agency (Figure 2), which specified that confirmed cases and suspected illnesses should be reported as separate records in the CE domain. Including examples like the one below as an appendix in the OVRR guidance would be beneficial.

Figure 2:

ROW	USUBJID	CETERM	CECAT	CEOCCUR	CESTDTC	CEENDTC	CESEV	CESTDY	CEENDY
1	ABC-1001	COVID-19 like illness	Efficacy	Y	2020-07-10	2020-07-20		40	50
2	ABC-1001	COVID-19 confirmed	Efficacy	Y	2020-07-10	2020-07-20		40	50
3	ABC-1001	Chills	Efficacy	N					
4	ABC-1001	Cough	Efficacy	Y	2020-07-10	2020-07-19	Moderate	40	49
5	ABC-1001	Shortness of breath	Efficacy	N					
6	ABC-1001	Fever	Efficacy	Y	2020-07-10	2020-07-20	Mild	40	50
7	ABC-1002	COVID-19 like illness	Efficacy	Y	2020-08-01	2020-08--06		35	40
8	ABC-1002	COVID-19 confirmed	Efficacy	N	2020-08-01	2020-08-06		35	40

4) Some CBER expectations evolve over time but are not reflected in the OVRR guidance.

   For example, while the OVRR guidance indicates that reactogenicity events continuing beyond the protocol-defined assessment period be reported in both the CE and AE domains in SDTM, more recent feedback from CBER instructed that reactogenicity events should only be reported in the SDTM CE domain. The OVRR guidance has not been updated to reflect this newer recommendation.

5) Some requests from CBER do not align with CDISC requirements.

   For example, CBER prefers the variable ARMNRS (Reason Arm and/or Actual Arm is Null) to be included in trials following SDTM IG version 3.2, while this variable was not introduced by CDISC until SDTM IG version 3.3. Implementing this request in studies using v3.2 introduces compliance issues, creates challenges populating the standard treatment arm variables for that version, and duplicates information that is already available in the Demographics domain.

6) Organizations often receive feedback from CBER at the project level, making it difficult to track and ensure implementation across trials within an individual company. Sponsors must also determine whether the feedback applies only to the trial/submission for which it was received or should be applied universally across all vaccine trials.

   For example, concerns with eDiary compliance have been communicated through regulatory interactions for individual trials. Participant-reported reactogenicity data is collected daily via a diary during the protocol-defined period and participants are generally given until midnight each day to enter their data. Data may be missing for a day due to technical issues, forgetfulness, or other reasons. When receiving feedback in this manner, it can be challenging to determine whether

their concerns are solely for the one trial or applies across vaccine submissions in general. This impacts an organization's approach to addressing the feedback. Compliance concerns for an individual trial may cause an organization to reassess communications such as alerts and diary review responsibilities within the trial. On the other hand, if determined to be general feedback, it may result in broader changes, such as expanding diary entry windows or providing back-up entry methods, which has much greater impact to sponsors, vendors, and sites.

The lack of synchronization between different guidance documents and the actual regulatory expectations may lead to confusion and misinterpretation, further complicating the submission process. This misalignment forces organizations to interpret requirements and adjust, leading to potential inconsistencies and delays. Organizations must stay vigilant and proactive to ensure compliance with regulatory guidelines and expectations.

FUTURE GOALS AND AREAS FOR COLLABORATION

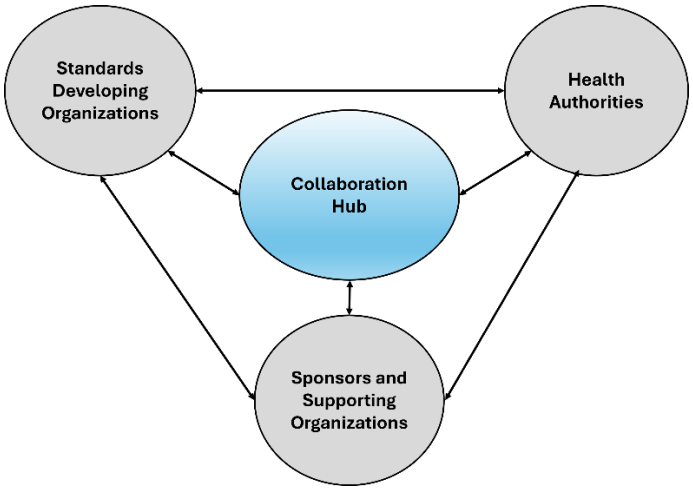
Our collaborative efforts are focused on topics encompassing data collection, SDTM, ADaM, and statistical analysis, with the goal to enhance the overall quality and reliability of vaccine data submitted for regulatory review. The VISG has targeted critical areas where organizations encounter significant challenges, like mapping and reporting participant-reported diary data, reactogenicity data, and efficacy data.

Formation of the VISG demonstrates how collaboration within the industry can address regulatory challenges and improve efficiency. By promoting shared learning and aligning on regulatory expectations through routine discussions, VISG has helped member organizations navigate complex regulatory requirements, streamline submissions and address feedback from health authorities more effectively. This approach has supported vaccine development and offers a model that could be applied in other therapeutic areas. These activities highlight how collaboration can lead to practical improvements, ensuring that new products reach the market efficiently and support public health goals. We hope that by sharing our story, it can serve as a blueprint for other cross-industry collaborative efforts.

In the future, the VISG would also like to work in closer collaboration with health authorities and CDISC to help refine and clarify submission standards and associated guidance documents. The aim would be to create a win-win collaboration for all parties.

Such collaboration could be facilitated through a channel for open communication between sponsor organizations, health authorities and other standard organizations (e.g., CDISC), independent of the sponsor projects (Figure 3). Communication could be at a standard level rather than at sponsor company/project/trial level. This would help all organizations to have the same baseline information and the same understanding of health authorities' expectations. Furthermore, it would allow health authorities and CDISC to answer questions only once, simultaneously alerting other organizations about new information.

Figure 3:



This type of collaboration would allow for:

- Harmonization of the standards across all sponsor organizations and health authorities.
- Discussion between sponsor organizations, health authorities and CDISC before implementation of new requirements to allow for feedback and correct interpretation.
- Communication between sponsor organizations and health authorities, to share challenges and complexities involved with implementing certain requirements.
- Efficient implementation of new requirements for all sponsor organizations, i.e., quicker and with an aligned interpretation of these new requirements.
- Reduction of back-and-forth at sponsor project level on standards questions.
- Discovery of potential concerns sooner during the development of the new standard.
- Update of Vaccines TAUG and other CDISC and regulatory guidance to keep them current and aligned.

Interaction involving any proprietary information of sponsor organizations' projects and specific trials would be out of the scope of this type of collaboration.

CONCLUSION

In summary, the VISG exemplifies how collaboration within a competitive industry can lead to significant advancements in submission processes to support regulatory reviews. By prioritizing open sharing and alignment on common regulatory challenges, VISG has created a robust model for a proactive engagement across industry, particularly the FDA, while also setting the foundation for improved standards across the vaccine industry. The group's success in harmonizing regulatory guidance interpretations, sharing data collection approaches, and fostering a mutual understanding of health authority expectations showcase the value of transparency and shared learning.

Through such collaboration, participating organizations enrich the collective knowledge base of the industry. This transparency fosters an environment of continuous improvement, encouraging others to learn from both successes and challenges faced during implementation. Ultimately, this iterative process enhances the overall effectiveness of practices across the industry.

This collaborative spirit not only accelerates the regulatory submission process but also ensures that new vaccine products reach the market more efficiently, potentially benefiting public health. Looking to the future, VISG aims to deepen its impact by engaging in structured dialogues with health authorities and contributing to updated guidance materials that will streamline the way for all organizations. VISG's model provides a blueprint for industry-wide collaboration that could be adapted to other therapeutic areas, where regulatory complexities may similarly hinder progress. By setting aside competition to work toward a common good, VISG member organizations underscore the potential of industry collaboration to drive meaningful and lasting improvements across the pharmaceutical landscape, aligning with the global commitment to advancing healthcare.

REFERENCES

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2 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Study Data Technical Conformance Guide. Version 5.9, October 2024. https://www.fda.gov/media/153632/download.

3 Clinical Data Interchange Standards Consortium (CDISC). https://www.cdisc.org/standards/foundational.

4 Biotechnology Innovation Organization (BIO). https://www.bio.org/

5 Clinical Data Interchange Standards Consortium (CDISC). Therapeutic Area Data Standards User Guide for Vaccines. Version 1.1 (Provisional), April 2018. https://www.cdisc.org/standards/therapeutic-areas/vaccines/vaccines-therapeutic-area-user-guide-v11/html.

6 CBER eData mailbox. cber.cdisc@fda.hhs.gov

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RECOMMENDED READING

Challenges Addressing CBER Guidance on Reactogenicity, from Collection to Analysis.
https://phuse.s3.eu-central-1.amazonaws.com/Archive/2023/Connect/US/Florida/PAP_VX02.pdf

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