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Authoring Considerations for Creating PhUSE Study Data Standardization Plan (SDSP) and CBER Appendix

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ABSTRACT

FDA supported the PhUSE Study Data Standardization Plan (SDSP) as a mechanism for early communication of exchange data standards. The SDSP captures an inventory of trials and the versions of data standards throughout the life of the product development. Similarly, Center for Biologics Evaluation and Research (CBER) released an appendix that provides supplemental information to the PhUSE SDSP. While orchestrating the assembly of the SDSP, sponsors should consider the needs of Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) to have a meaningful review.

The focus is to highlight and share Merck's experience while implementing and assembling the SDSP prepared for CDER and CBER. The paper will address:

- Authoring considerations for creating the SDSP and CBER Appendix
- CBER Appendix implementation challenges
- Advantages of SDSP and CBER Appendix adoption
- Timing of regulatory interaction

INTRODUCTION

The use of a Study Data Standardization Plan (SDSP) was first introduced in the July 2016 FDA Study Data Technical Conformance Guide (TCG) v3.1. The inclusion of the SDSP was identified as a non-binding recommendation that sought sponsors to plan, prepare and share their company position on the use of data standards prior to a regulatory submission. The early interaction promoted a two-way communication for setting expectations implemented during product development.

Prior to the TCG announcement, pre-submission meetings, technical Type C meetings, general correspondences, submission of waivers, were all examples of early opportunities for sponsors to share and gain consensus on the data formats. Although these meetings and interactions are still communication outlets, these strategies are considered late in a product lifecycle. If concurrence with the FDA could not be reached, sponsors had to quickly align on an agreement, which led to increased cost, rework and resources to address changes.

With the SDSP template available from PhUSE and the FDA welcoming earlier interaction, sponsors now have an opportunity to present the use of data standards throughout product development life-cycle beginning with non-clinical data in the IND stages and through the NDA\BLA and post-marketing commitments. Advance sharing of the SDSP, enables sponsors to drive decisions on legacy data conversions or plan for up-versioning of data that would allow for data integration across multiple studies.

Years prior to the availability of the PhUSE SDSP template, CBER created a CBER SDSP Checklist that obtained additional information from sponsors in advance of a submission. Through the PhUSE and FDA collaboration, the SDSP template was streamlined to support both CDER and CBER. In March 2018, PhUSE released the SDSP (v1) template that incorporated a CBER Appendix that included additional background on the planned data. This paper will highlight the SDSP and CBER Appendix authoring considerations while addressing challenges, advantages and timing of regulatory interaction to support a CDER or CBER SDSP review.

SDSP AUTHORING CONSIDERATIONS

Sponsors should allow sufficient time to identify the content owners and SDSP owners to orchestrate the SDSP assembly. The amount of work contributing to the SDSP is directly related to: when you begin SDSP implementation; volume of trials; CROs or external partnerships who contribute to the SDSP sections; and the complexity of the

program. The next five sections will examine the steps needed to identify a team to implement SDSP and the considerations of authoring the SDSP body.

IDENTIFYING ROLES CONTRIBUTING TO THE SDSP

Although the FDA Study Data TCG was clear that the SDSP would be the vehicle for sharing data standards prepared for electronic submissions, Merck spent several months raising awareness, obtaining agreement from senior leaders and identifying a team of subject matter experts (SME) who would support defining and maintaining a company process to adopt the SDSP. The dedicated SME team was comprised of experienced Regulatory, Non-Clinical and Clinical Data Management, Data Standard Specialists, Statistician, Statistical Programming and other supporting submission roles to address the FDA expectations.

Once the dedicated team of SMEs gained traction, it was not long before the team had to educate each other on the availability of information and the triggers that prompted authoring of the SDSP sections to begin. During the SDSP process development, the team was challenged to identify the existing meetings and documents that would enable content owners to gather information while exploring new tools to address the gaps. Tasks and topics that required cross-functional hand-off and transitions required more discussions. For example, simple tasks like identifying a common location for sharing the SDSP, publishing and sharing the SDSP with FDA, and maintenance were far more complex when multiple authors were involved.

Defining roles of an SDSP owner and content owner and identifying the functional area to support the role eventually took shape as skill sets and tasks became clearer. Although the SDSP owner had responsibilities for seeing that the SDSP was maintained and published for FDA sharing, the owner had to rely on the actual study team to provide the trial details and data standards needed to support the SDSP sections. The Merck internal collaboration resulted in developing a lean process model.

After Merck's Standard Operating Procedure (SOP) release, SMEs still continue to provide oversight of the process and advise operational teams adopting the SDSP at a product level. Since the Study Data TCG first introduced the SDSP in July 2016, it has taken Merck a year to raise awareness, educate users, and stand-up a process.

Cross departmental collaboration must be considered to orchestrate a lean and efficient SDSP assembly.

RETROSPECTIVE SDSP IMPLEMENTATION

Since PhUSE released the SDSP template (March 2018), sponsors have to implement the SDSP for in-life products. For programs that are in Phase 2 or later, sponsors may find it challenging to recover data and dictionary versions that supported the program in the early IND. The retrieval of historical information requires cross-functional coordination and communication between teams that contribute to the clinical and non-clinical sections of the SDSP.

Drawing from Merck's experience, it was extremely challenging to find the original study teams who had background to the data standards implemented at study start and study end. In multiple cases, gathering information greater than ten-years and gaining access to legacy systems had to be considered while planning the timelines for SDSP assembly.

The initial task for starting an SDSP in-life is a large undertaking requiring authors to assemble and reconcile pieces of information that collectively forms the SDSP. Authoring teams need to plan ahead and buffer time before committing to a SDSP release to CDER or CBER.

VOLUME OF TRIALS

Products with a high number of trials spanning across a long product life-cycle will have more challenges in documenting legacy studies in comparison to new INDs. As the program expands and new trials are added or terminated, authors should update the SDSP to keep the status of trials current and aligned with reviewing expectations. Proactive management will ensure accuracy and efficient SDSP publishing.

CLINICAL RESEARCH ORGANIZATIONS (CRO) AND EXTERNAL PARTNERSHIPS

Programs that have trials contracted to a CRO or vendor may find that additional effort is needed to retrieve information to support the SDSP. A project liaison serving as a CRO contact may not have same understanding or awareness of information needed to create the SDSP sections. SDSP authors cannot assume that the same role used internally to obtain information corresponds to the same roles in the CRO. Therefore, it may take multiple interactions to obtain detailed information about dictionary versions and controlled terminology.

If a program involves an external partnership such as in-licensed compound, co-developed program or acquisition, additional time is required to collaborate and validate the information. Agreements on content owners should be defined early and arrangements to retrieve the information should be dealt with jointly.

COMPLEXITY OF THE PROGRAM

For submissions involving a combination therapy with additional populations (e.g. adults, pediatrics), sponsors should allow more the lead time to develop the SDSP. Not only will there be a need to create an SDSP supporting each monotherapy, but the SDSP for the combination therapy must also be carefully assembled to ensure the trials are consistently cross referenced.

Authoring of the SDSP grows increasingly difficult to maintain when pediatric studies in a combination therapy need to be cross-referenced back to the monotherapy or vice versa. In this situation where trial(s) are supporting multiple SDSP, the data standards and dictionary versions may require synchronization and organization prior to sharing to FDA.

CBER APPENDIX AUTHORING CONSIDERATIONS

For an SDSP prepared for CBER, authors should allocate more time to address CBER Appendix.

In the initial PhUSE template (released March 2018), the SDSP template included a CBER Appendix that contained five additional sections to facilitate CBER review. Sections include: Introduction, SDTM Datasets, Supplemental Qualifiers, ADaM Datasets, and Integrated Summary of Safety and Efficacy (ISS and ISE).

Unlike the SDSP body, which contains an inventory of all non-clinical and clinical trials and the trial status (completed, ongoing, planned), the CBER Appendix contains the additional information from clinical trials that are planned for the actual submission. In other words, the CBER Appendix is a smaller subset of the trials listed in the SDSP body. The next five sub-sections describe the authoring considerations for creating the CBER Appendix.

INTRODUCTION

While the SDSP body is authored in the early stages of the IND, CBER recommends that the CBER Appendix be created no later than an End of Phase 2 meeting.

It has been Merck's practice to identify a meeting opportunity to actively seek agency feedback on both the SDSP body and CBER appendix. This engagement has led to fruitful discussions and establishment of clear expectations of data standards ahead of the submission.

SDTM DATASETS

For each trial supported in the IND, CBER requests a table that lists all planned SDTM datasets. The table is similar to the SDTM Datasets section found in the tabulations Clinical Study Data Reviewer's Guide (CSDRG). However, unlike the CSDRG that is shared at the time of the Biologic License Agreement (BLA), the CBER Appendix - SDTM Datasets section is intended to be shared during the trial development phase.

The section identifies a list of planned domains, regardless if actual data is present. Organized by domain class (trial design, special purpose, interventions, events, findings, findings about, Relationships and custom), the SDTM Datasets table includes information about the SDTM domains, variables used for analysis that are not required by the SDTM model and sponsor custom domains. This section provides background to the CBER reviewers so that they understand the purpose of the data. Information presented in the SDTM Datasets section could result in CBER making recommendations to remap data to avoid custom domains.

SUPPLEMENTAL QUALIFIERS

In comparison to the SDSP submitted to CDER, CBER is seeking a list of supplemental qualifiers planned for each clinical trial. The Supplemental Qualifier section includes a comprehensive list of supplemental domains (SUPPXX), qualifier variable name and label (QNAM, QLABEL) and origin as it relates to a corresponding question on the CRF or derivation information.

Data mapped to supplemental qualifiers is often overused. CBER has expressed that supplemental variables are difficult to mine given a sponsor's approach to placement of data that does not fit the SDTM model. During the review, sponsors may find CBER offering suggestions to remap data that would display data in supplemental qualifiers.

When developing the CBER Appendix, sponsors should identify the supplemental qualifiers contributing to the key analysis. Relevant information identifying the variable's purpose will help avoid additional feedback.

ADAM DATASETS

The ADaM Datasets section is only included for each clinical trial with a planned analysis. Therefore, this section may be a smaller subset of clinical trials taken from the SDTM Datasets section.

Organized by domain structure (subject level analysis dataset, basic data structure, occurrence data structure), the ADaM Datasets table identifies the name of the analysis dataset and its labels.

Although the template title implies that datasets must be ADaM, sponsors should include any legacy analysis dataset name and label. Authors should include background and purpose for creating the legacy analysis dataset to ensure a more efficient reviewing experience.

ISS AND ISE

In comparison to an SDSP body which lists the trials included in the pooled analysis, CBER recommends sponsors to identify the pooled datasets and share the purpose (efficacy, safety, other). The additional information found in the CBER Appendix should also identify the clinical trial phase and contributing datasets used to support the analysis.

Although the information would eventually be shared in the Analysis Data Reviewer's Guide (ADRG), the early identification promotes early planning and collaboration for the expected analysis.

CBER APPENDIX IMPLEMENTATION CHALLENGES

Given the details supplied in the appendix, CBER may recommend remapping data to meet reviewing needs. The feedback is easier to address before collector deployment and before the volume of impacted studies increase. However, before it becomes a challenge, it is advantageous for sponsors to share the SDSP and CBER Appendix early and gain concurrence on the data structure to avoid rework.

For authors creating the Supplemental Qualifiers section, it may be challenging to identify the QNAM and QLABELs from clinical trials where the efficacy or immunogenicity analysis is not yet well-defined. As a result, it has been Merck's practice to disclose a full list of all supplemental qualifiers. As the product gains maturity and the analysis are further developed, Merck has identified opportunities to share the SDSP and CBER Appendix as a living document in advance of the submission.

ADVANTAGES OF SDSP AND CBER APPENDIX ADOPTION

The SDSP, which is an inventory of all trials operating under the IND, not only aides internal teams to focus on the submission and planned pooled analysis, but it also serves as a communication tool for sharing data standards implemented during product development. In a single document, the SDSP and CBER Appendix gives FDA reviewers and sponsors a summary of trials supporting the submission and background of data standards to determine if data structures could support an efficient review.

Information contained within the CBER Appendix offers reviewers a level of granularity that is not available in the SDSP body. The information contained in the Appendix identifies the standard and custom domains and variables used to support the primary and key analysis datasets. This information in the CBER Appendix is helpful to drive study and pooled analysis discussions that benefit the both the sponsor and CBER.

TIMING OF REGULATORY INTERACTIONS

The SDSP is a living document that should be shared with CDER or CBER, at major stage gates such as: Pre-IND, IND, End of Phase or Type C Meeting, Pre-Submission Meeting and at submission. To make best use of the regulatory interaction, it has been Merck's practice to identify trials that require reviewer's agreement on the use of data standards to support the submission. The early sharing and concurrence gained from the regulatory interaction could be foreseen to replace the process for submitting waivers.

While CDER wants to be informed on the development and adoption of data standards shared at major stage gates, CBER seeks additional information that could have sponsors reconsider mappings to help facilitate a more meaningful review. Sponsors should allow enough time to gain concurrence on the information presented in the CBER Appendix. Although CBER recommends sponsors to share the CBER Appendix no later than an End of Phase 2 meeting, there is a benefit to having an earlier regulatory interaction.

CONCLUSION

The information presented in this paper offer authors suggestions and considerations while creating the SDSP body and CBER Appendix. Drawing from Merck experience while implementing the SDSP, it required cross functional collaboration to identify key roles to contribute details to the SDSP process. Even with defined roles and responsibilities, authors need to reserve ample time to compile the content and avoid underestimating the work ahead when addressing products with a large volume of trials, CROs and partnerships and complex programs. Accurate and timely sharing of information presented in the SDSP helps drive data standard decisions to support the product development.

In addition, sufficient details in the CBER Appendix that describe the purpose and content of custom datasets and supplemental qualifiers will provide CBER reviewers an early understanding of a sponsor's use of data. The advance sharing of the SDSP and CBER Appendix at the recommended prior to End of Phase 2 promotes early regulatory interactions that set expectations for an efficient and meaningful review.

Although the SDSP template only became available in March 2018, authors of this paper plan to share lessons gained on the use of SDSP and CBER Appendix back to the Optimizing Data Standards Working Group. The next step is to offer suggestions to the PhUSE Working Group so that the SDSP Completion Guideline and SDSP Sponsor Implementation Guide will incorporate additional considerations for authoring the SDSP and CBER Appendix.

REFERENCES

PhUSE Study Data Standardization Plan Template (v1)
https://www.phuse.eu/documents//sop/wp/phuse-tp001-study-data-standardization-plan-v1-8409.docx

PhUSE Study Data Standardization Plan Completion Guideline (v1)
https://www.phuse.eu/documents//sop/wp/phuse-wp001-sdsp-completion-guideline-v1-8407.pdf

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