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What Good Looks Like in Study Data Standardization Plan (SDSP) and CBER Appendix

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ABSTRACT

What should the SDSP include to make a good usable document to support the regulatory reviewer and sponsor? After all, the SDSP is used by various reviewers extracting different information from the document to assess compliance with data standards. For sponsors, the SDSP can facilitate internal discussions that are considered necessary to build a submission strategy.

The focus of this paper is to highlight and share Merck's experience while implementing and assembling the SDSP prepared for CDER and CBER. This topic will consider common themes learned and gained from recent SDSP circulation to health authorities. In addition, this paper will cover how the SDSP has been a communication tool used internally by Merck to plan future trial development and how it has cross-functionally aligned key stakeholders to support future product milestones.

INTRODUCTION

FDA has made strides to become more open in conveying their regulatory reviewing needs to support marketing applications. An example of their transparency is the FDA Study Data Technical Conformance Guide (TCG), which is released bi-annually to clarify needs for a better review experience. Through the movement to modernize review, FDA has strongly recommended sponsors to communicate and interact with the agency during key milestones in the product lifecycle and to submit questions to a CDER or CBER electronic data mailbox for technical data inquiries. Positive collaboration has been encouraged and early interaction with FDA to gain alignment on the expectations has resulted in clear understanding of the submission plan. One tool that has enabled the industry to have a proactive engagement is the Study Data Standardization Plan (SDSP).

In 2014 FDA announced their recommendation to include a submission plan, which stressed the importance of summarizing data standard implementation. This plan would support a meaningful review and an alignment on data expectations in advance of a marketing application. By 2015, FDA recognized the PhUSE template in their Study Data Technical Conformance Guide. The addition of the PhUSE SDSP Completion Guidelines also helped clarify suggested timepoints and stage gates where sponsors could gain agreement on the planned use of data. The latest PhUSE SDSP template contains a table for sponsors to identify studies; a summary of exchange standard adoption that would help raise awareness to the reviewer; and a section documenting non-conformance and concurrence on data plans prior to a submission. As trials are added to the lifecycle, sponsors can update and maintain the SDSP until it is shared at a stage gate or shared in eCTD Module 1.13.9.

The objective of the paper is to share lessons gained in authoring a high quality SDSP and CBER Appendix; to use the document as a framework to guiding internal discussions related to use of electronic data; and to raise awareness of differences so that sponsors seek concurrence with FDA reviewers. In addition, the paper will share SDSP implementation challenges and offer an approach for addressing the challenges.

LESSONS LEARNED

Since the SDSP was first introduced in the FDA Study Data TCG, Merck has implemented a range of SDSPs covering multiple therapeutic areas in drugs, vaccines, special populations, single product with multiple indications, and post-marketing commitments both at the start of product development and retrospective application. While drawing from experiences assembling the SDSP and working with numerous teams, there was a common set of themes and questions raised by teammates on how to best approach the creation of a quality SDSP that should be further examined.



RETAIN ALL SECTIONS IN SDSP TEMPLATE

When authoring the SDSP for the first time, authors may find that not all sections apply in the initial document, especially when only the pre-clinical data is available. The recommendation is to retain all sections and tables in the template and indicate "Not Applicable". As the product develops, information to populate the other sections will be needed and it will be easier to insert the information, rather than re-create sections of the template.

IDENTIFY ACCURATE CONTENT

Every SDSP must contain the correct studies prepared for the specific indication and study population. Retrieval of the trial information opened under the IND, require teams to recover study documentation and recall historical knowledge, especially for products with a long program. The change in study team personnel can cause the collection of this simple task to become a challenging activity to recover; however, sponsors are responsible for identifying all supported trials and cross-functional orchestration is required.

In addition, sponsors should also include trials conducted for specific countries if it will be supported in the submission. In other words, sponsors who conduct clinical trials outside the US market to meet country-specific requirements should still include those studies in the SDSP if it is supporting the label, pooled analysis, or opened under the IND.

CONSIDER PER POPULATION ANALYSIS

As the product expands after initial approval, sponsors may decide to pursue further analysis on special populations to extend the license or product exclusivity. A common example is when a product has sufficient safety data for an adult population and wishes to pursue a pediatric population. During these opportunities, author should ask whether the original data will be resubmitted or referenced to support the newly specified population and analysis. In these cases, authors have the option to reference a prior IND rather than duplicating all the original information that may or may not submit data. Any new studies targeted for the specific population would be added.

For studies pursuing a new indication, Merck has chosen not to duplicate the same trials from a prior submission or IND even if it is identified as supportive. Unless the data is being resubmitted for the new indication, Merck has used the IND reference identifier in lieu of duplicating information. Efforts to avoid repeating study standards across multiple SDSPs help to manage the status of the trial and the adoption of standards consistently that could differ between and across supplements.

ORGANIZE TRIAL PHASES BASED ON EARLIEST STUDY START DATE

Some protocols are divided into a base study and extension, where the initial study begins in an earlier phase and due to amendments, the extension is designed in a latter phase. When a single trial straddles two different phases of a lifecycle, authors should identify the study start date based on clinicaltrials.gov. In these situations, the trial is recognized only once on clinicaltrials.gov and does not need to be listed twice on the SDSP. When this happens, authors should use the study start date from the earlier phase as the driver for determining the standard adoption. Documenting the study start of the latter phase may result in adopting later standards or the need to provide additional documentation.

INCLUDE COMPLIMENTING EXCHANGE STANDARDS

Experienced reviewers will know that the model and the implementation guide are a pair of complimenting standards. Authors should take into consideration the pair when documenting the SDTM and ADaM standard versions in the SDSP. For non-CDISC or sponsor proprietary data that has never been supported in the FDA data standards catalog, the Exchange standard is expected to be listed as Legacy data.

DOCUMENT PLANNED AND ONGOING TRIALS

When the study status is indicated as PLANNED or ONGOING, the supported data standards may not be known, or sponsors may defer to adopt a later standard rather than the standard driven by the study start date. If the exchange standard is not yet known, it has been Merck's experience to share the standard that is currently used during in-life reporting. This could change to help aide in the pooled analysis or future analysis. An alternative option is for sponsors to provide what is known to date and update the SDSP when collective changes are applied and ready for a stage gate meeting.



RECORD DATES USING ISO FORMAT

When working with the SDSP template, authors are expected to use the ISO date format whenever indicated as: ccyy-mm-dd. When multiple authors are involved in consolidating the document, various dates can be introduced based on preferences by the individual author. As a result, the inconsistent format makes it an unnecessary challenge for both internal reviewers and regulatory reviewers to understand whether the date or month is reversed. If partial date is still unknown for the version of controlled terminology, the recommendation is to assign it: *to be determined, TBD*.

CBER APPENDIX LESSONS LEARNED

The CBER Appendix was first introduced in the January 2018 PhUSE version 1.0 release. It is additional supplemental information that is prepared specifically for CBER reviewers to highlight additional contents of interest. When assembling the information supported in this section, there are recent lessons learned should be planned.

CONTENTS IN CBER APPENDIX

Merck supports various SDTM standards and some implementation domains were built into older versions of SDTM as custom domains. Unless users understand the domain, mappings and history, the movement to adopt domains presented in later standards may not be so obvious or transparent.

- Refer to the valid domains in the SDTM section for the version been submitted. If you used a domain from a later version of SDTM you can add it to the Custom domain section and identify the domain as a prototype
- Add the variables that are helpful for reviewers except required variables in SDTM
- Ensure that the SUPP section includes all SUPP domains
- Provide an explanation of the SUPPQUAL variables
- Indicate the domains that have a relationship in the RELREC section

COMMUNICATION TOOL

Assembling an SDSP is a time intensive task that requires careful identification of the trials that contribute to the submission. During the preparation, sponsors must first identify the trials, determine how it will support submission (e.g. pivotal v. supportive), and how it will be pooled for a larger analysis. Authoring the SDSP can facilitate discussions needed for a team to identify any gaps and prepare a submission strategy. Let's examine both the internal and external use of the SDSP.

INTERNAL

Gathering a team with the right history and knowledge of the trials is key to retrieving accurate information about the trial and supported exchange standards. Coordinating and capturing the inventory of trials should take the most time. You may have studies that were done for country specific purposes that were/were not opened under the IND that needs to be considered. Once the inventory of trials is documented, the next step is to determine which trials were developed in accordance with the FDA data standards catalog. Studies that do not conform to standards will require a waiver to seek alignment on expectations for submitting data. Internally, the team must determine the impact one standard has against the pivotal trials and whether it makes sense to provide justification for complying with an earlier standard over a later standard. This planning may not be available early in the product development, but it can be updated as stage gate meetings approach.

EXTERNAL

Based on lessons learned, Merck now understands that the SDSP should not be introduced as the first communication to seek concurrence on the use of legacy or retired standards. Experience has shown that the waiver process should be the first line of communication to share the rationale for non-conformance. Once agreed upon, the SDSP *Section 6: FDA Data Standards Discussions* is the appropriate location to consolidate all the communications exchanged and agreed upon by the FDA on the use of data (i.e. waiver date, general correspondence, pre-NDA/pre-BLA meeting, Type C).



IMPLEMENTATION CHALLENGES

Authors can easily identify data standards in the SDSPs when it is initiated at the beginning of the pre-clinical and clinical development. The maintenance needed to update the Exchange Standards is generally known and straightforward to document. However, since the PhUSE SDSP template was released only a year ago, many sponsors are still having to retrospectively author an SDSP in the middle of a product lifecycle. Therefore, retrieval of the information from studies that have already completed or have transitioned with teams from pre-clinical to clinical, can make this simple task even more challenging. Obtaining exchange standards from someone with product and study development knowledge is essential.

If a submission is planned to CBER, Merck's experience is to include the PhUSE SDSP with CBER Appendix for studies that will be in the submission as part of the End of Phase 2 meeting. In accordance to FDA Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review (OVR), sponsors also include the annotated case report form (acr.pdf) from all studies. The annotated CRF is accompanied to support and complement the review. From experience, the omission of the acr.pdf could result in communication exchanges for clarifications.

In the CBER Appendix, the information sought is more detailed for each trial in the planned submission. In the appendix, sponsors should include domains borrowed or adopted in newer SDTM implementation guide as a prototype. These adoptions that are not recognized in the identified exchange standard would need to be identified as a custom domain. Sponsors should include the later version adopted in the comments section of the appendix.

CONCLUSION

Leveraging lessons learned across studies and collecting feedback offered by health authorities have enabled Merck to share the experience with new authoring teams. By publishing a high quality SDSP and having early interaction at recommended milestones, Merck gained concurrence on the use of the expected exchange standards that better prepared submission teams.

The SDSP can provide a framework to guide internal and external discussions related to use of electronic data and raise awareness of differences needing FDA agreement. When used as a communication tool, the SDSP and CBER Appendix can help manage the status of the trial and the adoption of standards.

When working on submissions to CBER, remember to include the CBER Appendix when developing the SDSP. Sponsors are expected to identify valid domains developed in accordance to multiple implementation guides. It is important for authors to identify the domain(s) used from a later version as a prototype; provide explanations on how supplemental qualifier variables are used in the analysis; and include the acr.pdf for all studies.

Planning requires careful identification of the trials that contribute to the submission and aid in the identification of the pooled analysis. Since the SDSP is not a replacement for a waiver, it is a recommended practice for sponsors to engage with health authorities as early in the product development and record agreements in the SDSP. Advance sharing of the SDSP sets expectations for an efficient and meaningful review.

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>

FDA Guidance for Industry: Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf>

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