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SDSP (Study Data Standardization Plan) Case Studies and Considerations

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ABSTRACT

This poster is intended to cover SDSP case studies focusing on different stages over a drug development lifecycle. Drug development lifecycles and stage gates considered include following 3 phases:

- New Program Phase (pre-IND, IND)
- Retrospective/Ongoing Program Phase (End of phase II/pre-NDA/pre-BLA)
- Already approved /Supplement Program Phase (sNDA/sBLA).

In addition, scenarios where single versus multiple SDSPs for a program will be covered based on IND, population and indication. Additional SDSP topics and considerations will cover:

- Versioning the SDSP covering updates and checks
- Consistency checks between SDSP and other submission documents
- Nuances in CDER and CBER requirements
- CBER Appendix key recommendations for completion
- SDSP Authoring & Reviewing Responsibility Chart

The scope of this poster is to share the data standards information scenarios of SDSP Sections 4 & 5. The PhUSE template and completion guidelines provide clear definition and expectations of other sections of SDSP.

AUTHOR DISCLAIMER

This poster is specific to Merck's SDSP implementation process, including experiences, and scenarios Merck has encountered within their development programs for submission. The experience and scenarios Merck has encountered with the SDSP is being shared with the hope to benefit others within industry but understand other companies implementing SDSP may have additional considerations, and/or constraints to work with. Merck's experience is not thought to be the only experience, but one to learn from and allow industry to benefit from.

BACKGROUND/OVERVIEW

The purpose of the Study Data Standardization Plan (SDSP) is to document and communicate a plan for describing the sponsor's application of data standards in non-clinical and clinical studies across a development program.

The SDSP is an important communication tool between the sponsor and the FDA. The SDSP is a living document that assists the FDA in identifying potential data standardization issues early in the development program, may reduce the number of information requests, and clarify previous sponsor / FDA agreements, to provide clarity and prevent filing delays.

Additionally, improves data traceability when submitting SDSP with CBER appendix to CBER and/or the OVRR (Office of Vaccines Research and Review) early in vaccine development.

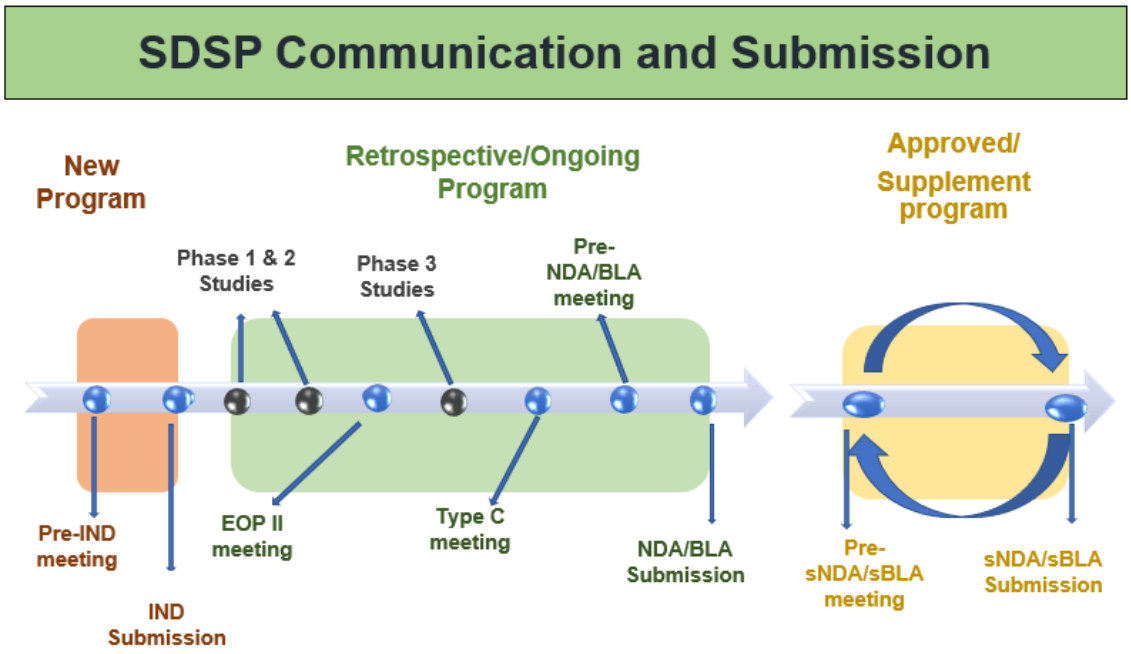
The SDSP has 6 main sections and an appendix (appendix is for CBER submissions only):

- Section 1 - Introduction
- Section 2 - General Sponsor Information
- Section 3 - Product Information
- Section 4 - List of Studies and Standards
- Section 5 - Non-conformance to Supported Standards Justification
- Section 6 - FDA Data Standards Discussions
- Appendix - CBER Appendix

COMMUNICATION OF SDSP WITH FDA AT POTENTIAL STAGE GATES

The diagram shows the SDSP integration into the life cycle of the regulatory IND to NDA submission process including post marketing submission. Timing of the life cycle / flow of drug development is not to the scale.

FIGURE 1. SDSP Communication and Submission



- Recommended initiation at the pre-IND stage of product development.
- Initiation and/ or update of the SDSP needs to take place:
  - If a change to the development plan has occurred as defined critical by team that impact SDSP
  - If a stage gate/meeting/filing is approaching (filing of new IND, meetings: pre-IND, End of Phase [EOP]I/II, Pre-Biological License Application [BLA]/Pre-New Drug Application [NDA]), or
  - If appropriate, review the SDSP annually
- If not given before in any of the stage gates and discussion is needed, communicate SDSP to FDA in the briefing document package at a Type C meeting to ensure agreement.
- The SDSP should be made available to the FDA at critical stage gate meetings. It is not necessary to share updates with FDA for each update to the SDSP.
- SDSP can be submitted outside of a stage gate with agreement or request from FDA

SDSP SCENARIO FOR NEW PROGRAM PHASE (PRE-IND, IND) AND THINGS TO CONSIDER

- The new program phase is when SDSP is prepared to submit at the pre-IND meeting; If there is no pre-IND meeting then submit with original IND or as an amendment if the original IND has already been submitted.
- For CBER submissions, submit the SDSP CBER Appendix within SDSP to the IND. (CBER Appendix could be early to add at this stage)
- **Table 1A** displays nonclinical and **Table 1B** displays planned clinical studies at the time of pre-IND meeting or at IND filing.
- The example (**Table 1B**) does not include sample Study Identifier, Brief Title and Study Design. Refer to PhUSE guidelines for completion instructions.
- List all the appropriate data standard versions planned for the studies from the values provided in PhUSE template. If the versions could change by the time the study starts, then it is acceptable to document as TBD (To Be Determined).
- Since SDSP is a living document, If the exchange and terminology standards version could change over the course, start with initial version and then provide with final version before Pre-NDA/BLA meeting.
- Items recommended to complete SDSP: protocol, FDA standards catalog, DM plan, clinicaltrails.gov, PhUSE SDSP Completion Guidelines, your company's adaptation of PhUSE SDSP Template.

Table 1A. Section 4.1 Nonclinical Section from SDSP Template

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Tox-15-1234	A Single-dose Oral Toxicity Study of MyNewDrug in Rats	SINGLE DOSE TOXICITY	COMPLETED	2014-04-05	SDTM v1.2/ SEND IG 3.0 define.xml 1.0	CDISC SEND Terminology 2013-12-20
Tox-15-1436	A Four-week Oral Toxicity Study with MyNewDrug in Rats Followed by a Four-week Recovery Period	REPEAT DOSE TOXICITY	COMPLETED	2015-10-11	SDTM v1.2/ SEND IG 3.0 define.xml 2.0	CDISC SEND Terminology 2015-03-27

Table 1B Section 4.2 Clinical Studies Section from SDSP Template

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
AA-11	<an abbreviated summary of the protocol title>	<a brief textual description of the protocol design>	PLANNED	2019-03-16	ADaM v2.1 ADaM IG v1.1 ADaM define.xml v2.0 SDTM v1.4 SDTM IG v3.2 SDTM define.xml 2.0	ADaM CT <TBD> SDTM-CT 2018-03-30 MedDRA V21.0 WHO-DDEHDB3Mar18
AA-12	<Same as above >	< Same as above>	PLANNED	2020-03-01	TBD	TBD

SDSP FOR RETROSPECTIVE/ONGOING PROGRAMS (EOP II/PRE-NDA/PRE-BLA)

- A retrospective program phase is where the SDSP is initiated and submitted for any of the stage gates after IND submission (End of Phase [EOP]I/II, Pre-BLA/Pre-ND) and not initiated/submitted during pre-IND/IND stage of development program.
- An ongoing program is where the SDSP was initiated and submitted at the Pre-IND/IND stage gate and updated appropriately for later stage gates after IND.
- **Table 2A** shows a sample of completed, ongoing and planned studies.
- **Table 2B** shows a sample of section 5 of the SDSP for submitting non-conformance data standards.
- This is the phase to consider filling in the pooled studies section (4.3) in SDSP if planning to submit ISS/ISE.
- CBER Appendix if submitting CBER (no later than the EOPII meeting**)**

Table 2A Section 4.2 Clinical Studies Section from SDSP Template

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
ABC-11	<an abbreviated summary of the protocol title>	<a brief textual description of the protocol design>	ONGOING	2018-03-16	ADaM v2.1 ADaM IG v1.0 ADaM define.xml v2.0 SDTM v1.3 SDTM IG v3.1.3 SDTM define.xml 2.0	ADaM CT 2017-09-29 SDTM-CT 2016-03-30 MedDRA V21.0 WHO-DDEHDB3Mar18

ABC-12	< an abbreviated summary of the protocol title >	< a brief textual description of the protocol design >	COMPLETED	2017-03-15	ADaM v2.1 ADaM IG v1.0 ADaM define.xml v2.0 SDTM v1.1 SDTM IG v3.1.1 SDTM define.xml 2.0	ADaM CT 2016-12-16 SDTM-CT 2016-03-30 MedDRA V20.0 Sponsor defined drug dictionary
ABC-13	< same as above>	< same as above>	PLANNED	2020-03-01	TBD	TBD

As per FDA Standard Catalog, SDTM v1.1 and SDTM IG v3.1.1 is not supported by FDA for studies starting on or after 12/17/2016. Therefore, justification should be provided in Section 5 of SDSP.

Table 2B Section 5. Non-Conformance to Supported Standards Justification Section from SDSP Template

Study Identifier	Expected Standard	Provided Standard	Justification for Non-Conformance to Standards (including Exception Information)
ABC-12	SDTM v1.3/ SEND IG v3.1.3	SDTM v1.1 SDTM IG v3.1.1	Submitted waiver on 03JAN2018; waiver granted on 18JAN2018 <Include justification from waiver submission>

SDSP FOR ALREADY APPROVED/SUPPLEMENT PROGRAM (sNDA/sBLA)

- The Supplement program phase is where the SDSP is initiated for an already approved product for sharing at pre-sNDA/sBLA meeting and at the sNDA/sBLA submission.
- Consider including new trials that were not submitted in the original application, status of trials that were still ongoing from the original program, ongoing studies for which the sponsor plans to submit data for sNDA/sBLA and pooled studies for ISS/ISE if applicable.
- If applicable, include nonclinical studies.
- Follow the sample table referred at new program and ongoing program phase scenario for data standards.

SINGLE vs MULTIPLE SDSP

- This excerpt from PhUSE SDSP completion guidelines states: “There will be one SDSP per Investigational New Drug (IND) Application; multiple plans are permissible for a single compound in the event of multiple INDs or per communication with the appropriate regulatory agency”.
- Programs with multiple indications or populations (e.g., Adult vs. Pediatric) under the same IND may want to consider having one SDSP per population. This discussion should be had and agreed upon by SDSP Owners, SDSP Authors, Regulatory Leads in the program and agreement with agency representative.
- If filing under separate INDs, then separate SDSPs are needed
- Studies supporting multiple filings/submissions can be listed in multiple SDSPs
- Sub-indications may also have a separate SDSP within a large indication umbrella
    - SDSPs in Oncology are recommended by indication (e.g., HCC, Melanoma, RCC, Endometrial, NSCLC), to support a supplemental indication submission with agreement of agency representative.
    - Merck's experience has been that the FDA has indicated that the scope of an SDSP within Oncology should include only the study data that will be included in a filing that being submitted to meet the objective (NDA/sNDA/BLA/sBLA). In the case of supplements, it is best to limit the SDSP to include only the study data that is subject of that submission.
- A study could be present in more than one SDSP if the study supports the submission across multiple indications.

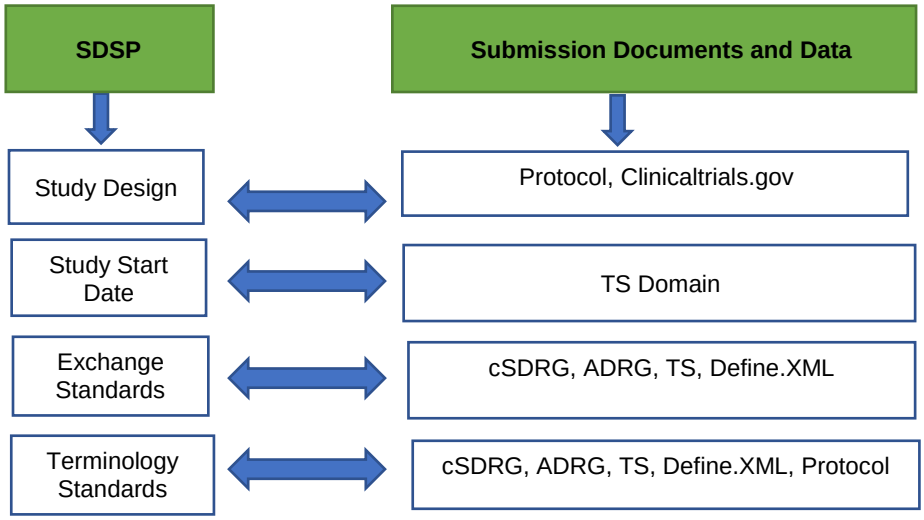
VERSIONING THE SDSP COVERING UPDATES AND CHECKS

- When the SDSP needs to be updated, the current version should be changed back to draft in sponsor's document management tool.
- Best practice is to document the version change history for every update of the SDSP to assist the reviewers, for transparency, and to help with learnings for future programs.
- If a planned study is dropped later in drug development, or a new study is added, the SDSP and version change history should be updated accordingly.

CONSISTENCY CHECKS BETWEEN SDSP AND OTHER SUBMISSION DOCUMENTS

- It is important to ensure the information in SDSP is accurate and consistent among submission documents.
- The following display shows cross checking the data standards information in SDSP with standards data in submission documents.

Figure 2. Consistency Checks Between SDSP and Submission Documents



NUANCES IN CDER AND CBER REQUIREMENTS

Table 3 is a comparison summary of main differences in submission requirements for SDSP when submitting an SDSP to either CDER or CBER.

Table 3. CDER vs CBER Requirements

CDER	CBER
• SDSP without CBER Appendix	• SDSP with CBER Appendix • Annotated CRF recommended after protocol approval
• Recommended SDSP at Pre-IND/IND	• Recommended CBER Appendix at Pre-IND/IND or before EOPII meeting

CBER APPENDIX KEY RECOMMENDATIONS FOR COMPLETION

- The CBER appendix includes tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis to aid CBER reviewers.
- The CBER appendix should be submitted well in advance of any licensing application (no later than the end of phase 2 meeting).
- The PhUSE template and completion guidelines provide detailed instructions for completing the CBER appendix section of SDSP.
- Best practice is to ensure consistency of SDTM/ADaM versions, Study ID and Title description between CBER Appendix and SDSP sections 4.2 and 4.3 (if applicable).

- The Sponsor should pay attention to details in the CBER appendix, especially custom domains, and be prepared for questions/comments from CBER reviewers.

SDSP AUTHORING & REVIEWING RESPONSIBILITY CHART

SDSP is a cross-functional effort. The chart (**Table 4**) may be helpful in identifying authors and reviewers for each section and data standards type from across different functional areas.

Table 4. SDSP Authoring and Reviewing Responsibility Chart

		Roles					
		NC	DM	DSS	SP&S	REG	CS
SDSP Sections	**Sponsor Information (Section 2)**	N/A	R	N/A	N/A	A	R
	Product Information (Section 3)	N/A	C	N/A	N/A	R	C
	Non-Clinical (Section 4.1)	A	N/A	N/A	N/A	R	N/A
	Clinical (Section 4.2)	N/A	C	R	R for all & A for ES	R	C
	Pooled Studies (Section 4.3)	N/A	C	R	R for all & A for ES	R	C
	Non-Conformance with Supported Standards Justification (Section 5)	R (if non-clinical)	C	N/A	C	C	R
	Supported Standards Discussion (Section 6)	R (if non-clinical)	R	N/A	N/A	A	R
	CBER Appendix	N/A	N/A	N/A	A	N/A	N/A

NC: Nonclinical **DM**: Data Management **DSS**: Data Standards Specialist	**SP&S**: Statistical programming & Statisticians **CS**: Clinical Scientist **REG**: Regulatory	**A**: Author; **C**: Co-Author; **R**: Reviewer; **N/A**: Not applicable	**ES**: Exchange Standards

REFERENCES

[1] PhUSE CSS Deliverables - SDSP template and completion guidelines
https://www.phuse.eu/css-deliverables

[2] FDA Technical Conformance Guide
https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf

[3] FDA Standard Catalog
https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[4] Comparing and Contrasting Differences between the PhUSE SDSP and CBER Checklist
https://phusewiki.org/docs/2018_US%20Connect18/DS%20STREAM/ds01%20final%20.pdf

[5] Touchpoints for the Study Data Standardization Plan
https://phusewiki.org/docs/2018_US%20Connect18/PP%20STREAM/pp18%20final.pdf

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