Paper SA14

Industry Experiences Submitting Standardized Study Data to Regulatory Authorities

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ABSTRACT

Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) require standardized study data for certain regulatory submissions. Industry approaches to meeting these requirements vary across companies and depend on regulatory review divisions. PHUSE's Optimizing the Use of Data Standards established Industry Experiences Submitting Standardized Study Data to Regulatory Authorities project to share industry experiences and recommend best submission strategy and planning practices. The paper starts with an overview of submission activities that outlines the scope of the submission work; discusses regulatory requirements and differences between FDA and PMDA submissions; discusses legacy data conversion; and explores the ways to incorporate and optimize the use of the Study Data Standardization Plan (SDSP). The paper also presents communication strategy and methods between sponsors and regulatory authorities that can facilitate an effective exchange of the standardized study data and the submission related information. In addition, the paper includes Frequently Asked Questions sections to discuss the commonly asked questions to ensure that the contents of the paper are practical and relevant to the audience in the industry. The working group believes that by taking these steps and referring to the factors and considerations discussed in the paper, it could help the readers to develop the best strategy and planning and make the best decisions for their own study data standardization and submission.

INTRODUCTION

BACKGROUND

PHUSE's Optimizing the Use of Data Standards - Industry Experiences Submitting Standardized Study Data to Regulatory Authorities is a collaborative, non-competitive PHUSE forum for industry to share submission experiences and develop best practices including submission strategy and planning, regulatory requirements and interactions with the regulatory authorities. The project was formed to:

(1) Investigate and recommend best strategy and planning practices for preparing data for a regulatory submission;
(2) Suggest communication practices within sponsors and between sponsors and regulators that can facilitate an effective exchange of the standardized study data and the submission related information.

PROBLEM STATEMENT

FDA and PMDA have provided the industry with guidance documents and technical guides for submitting standardized study data. Over the course of implementation, the industry has recognized that the requirements differ between FDA review divisions and between regulatory authorities across the globe. The evolution of standards during the regulatory submission life cycle further compounds the challenges. Industry approaches to meeting these requirements and challenges vary across companies. The submission activities involve different groups and organizations, both within and outside of the sponsor company, which makes the process more complicated.

SCOPE

The paper starts with an overview of submission activities that outlines the scope of the submission work; discusses regulatory requirements and differences between FDA and PMDA submissions and legacy data conversion; and explores the ways to incorporate and optimize the use of Study Data Standardization Plan (SDSP). The paper also presents communication strategy and methods within sponsors and between sponsors and regulatory authorities that can facilitate an effective exchange of the standardized study data and the submission related information.

ABBREVIATIONS, ACRONYMS AND DEFINITIONS

Term	Description
ADaM	Analysis Data Model
ARM	Analysis Results Metadata
ANDA	Abbreviated New Drug Application
BLA	Biologic License Agreement
DBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
eCTD	Electronic Common Technical Document
FDA	Food and Drug Administration
IND	Investigational New Drug
Legacy Data	Study data that does not conform to the standards by the date of requirement specified in the published Data Standards Catalog. Unless specified, Legacy Data can refer to either tabulation or analysis data.
NDA	New Drug Application
PMDA	Pharmaceutical and Medical Devices Agency
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model

OVERVIEW OF SUBMISSION ACTIVITIES

TIME COURSE AND DESCRIPTION OF ACTIVITIES

The key to a successful acceptance of standardized study data for New Drug Application (NDA) or Biologic License Agreement (BLA) is to have a clear path to follow through the submission process. Submission team needs to identify the requirements, scope of work, when and what resources are required throughout the submission workflow. This section aims to provide a high-level overview of the type of activities along with potential functional areas involved in the activity.

Figure 1 depicts a standard submission time course. The figure starts at Phase 1, first in human studies, through the NDA filing. There are activities prior to the first in human studies such as the submission of the Investigational New Drug (IND) and pre-clinical studies but for purposes of this paper the time course will begin with the first in human studies.

Figure 1: Time Course of Standard Clinical Submission Cycle

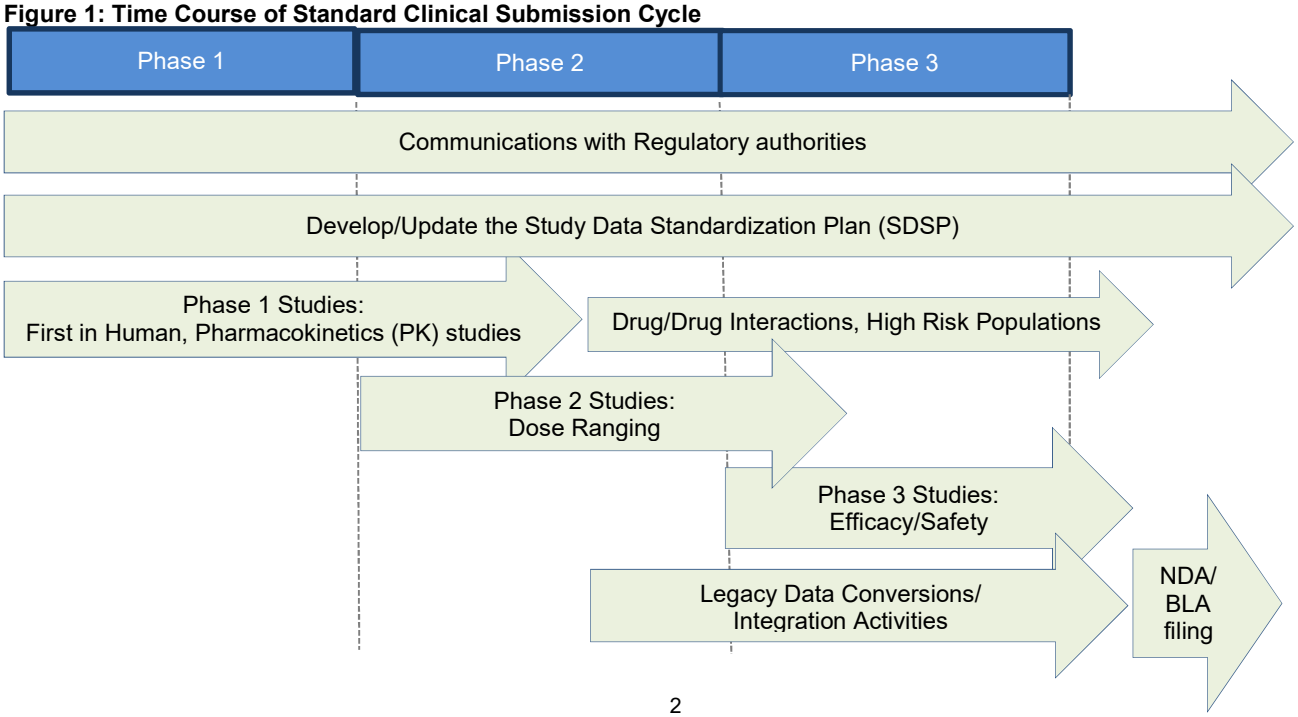

Table 1 lists the activities required throughout the submission life cycle encompassing all the clinical development phases. Often these activities will not be done in parallel in order to expedite the timeline for the filing of the submission. Suggested functional areas involved are also included in the table below.

Table 1: List of Submission Activities and Functional Area Involvement

Submission Activity	Suggested Functional Area Involvement
Develop/Update the Study Data Standardization Plan (SDSP) (includes all studies completed, active or planned)	Biostatistics/Statistical Programming, Data Management, Clinical, Regulatory Affairs
Prepare topline results from completed studies for briefing materials in preparation of a regulatory meeting	Biostatistics/Statistical Programming, Clinical, Medical Writing
Draft protocol and statistical analysis plan for studies planned in next phase of the clinical development	Biostatistics, Clinical
Draft proposal/questions for regulatory meeting	Regulatory, Biostatistics/Statistical Programming, Clinical
Prepare standardized data packages (i.e. Clinical Data Interchange Standards Consortium (CDISC) or Legacy) for all studies being submitted to regulatory	Biostatistics/Statistical Programming
For studies that have been converted into a different format, perform reconciliation on key analysis results using the new data format	Biostatistics/Statistical Programming, Data Management
Submit Bioresearch Monitoring (BIMO) deliverables to Center for Drug Evaluation and Research (CDER)	Biostatistics/Statistical Programming, Regulatory Affairs, Clinical
Submit packages to regulatory authorities	Regulatory Affairs

EXCEPTIONS TO THE STANDARD SUBMISSION

Figure 1 and Table 1 depicted a time course and a list of activities for a standard submission but below are other types of submissions that have different regulatory requirements:

(1) orphan submission for rare disease
(2) breakthrough and fast track therapies
(3) abbreviated new drug application for generics

In an orphan submission, only one pivotal phase 3 study is required for an NDA filing. The overall length of clinical development could be simplified and compressed.

Breakthrough or fast track therapy designations can have priority reviews and an accelerated approval. These are granted by FDA to speed the development and/or the review process leading to a potentially shorter clinical development. An applicant who receives breakthrough or fast track designation has an opportunity for more frequent FDA communications during the drug development period. In addition, these types of accelerated reviews can obtain a rolling submission allowing reviewers to review segments of the application resulting in a shorter overall review cycle.

In an abbreviated new drug application for generics, preclinical and clinical data are typically not included. The application includes scientific data showing that the generic is bioequivalent to an existing marketed product. There are different regulatory requirements for the application; differences also exist depending on which regulatory authority is reviewing it.

In addition to the different type of submissions, there is also a joint submission where two pharmaceutical companies develop a compound and submit to the regulatory authorities. Generally, it follows the same submission strategy flow and folder structure as the standard submission.

TIMING OF SUBMITTING DATA SUBMISSION PACKAGES

There are no requirements to submit data to FDA prior to the planned filing date. From a data delivery perspective, you can submit your data submission packages to FDA at the time of the planned submission together with the rest of the filing dossier.

On the other hand, for PMDA the data submission package is filed separately ahead of dossier. Prior to the delivery of the package, there is a requirement to have consultation meetings regarding study data submission.

The next section discusses the requirements and differences between FDA and PMDA.

STUDY DATA SUBMISSION REQUIREMENTS

It is essential to understand the regulatory requirements to plan, develop, and submit study data package.

For NDAs, BLAs, Abbreviated New Drug Applications (ANDAs), and supplemental applications, FDA mandates studies starting after December 17, 2016 to submit study data according to the FDA Data Standards Catalog. For INDs, the requirement applies for studies that start (first informed consent date) after December 17, 2017. The FDA Data Standards Catalog lists all data standards supported and retired by FDA. Legacy studies that started after December 17, 2016 must be converted prior to submission. If a study used an earlier version of a CDISC standard after the support date ended in the Data Standards Catalog, the study will require up-versioning.

According to the PMDA Guidance, they mandate submissions that occur after April 01, 2020 must be done in electronic submission in standard format regardless of study start. PMDA also has a Data Standards Catalog that list their supported standards.

While sponsors may have complied with the supported standards, experiences have shown that the agency may have strong preferences to follow a later standard that is ahead of the mandatory schedule.

While both agencies require CDISC standards, there are differences in the validation rules, other requirements and documentations that sponsors are expected to address. A complimenting PHUSE publication “FDA and PMDA Study Data Submission Distinctions” will contain a comprehensive FDA and PMDA requirements to address similarities and differences between these two agencies. The details of the differences between both agencies is not part of this paper due to the comprehensive content.

The next section shares a case study and frequently asked questions to help plan and prepare study data submission.

CASE STUDY: FDA AND PMDA SUBMISSION EXPERIENCE FROM A SPONSOR

Project Description: Two studies were submitted to FDA using a hybrid submission package given that the studies had started prior to the FDA mandatory date for submitting standardized study data. The hybrid submission package contained a compliant Study Data Tabulation Model (SDTM) submission package and Analysis Data Model (ADaM) Subject Level Analysis Dataset (ADSL) with other legacy analysis datasets.

Target Goal: Use a single data submission package to support FDA and PMDA

Sponsor Experience:

- FDA agreed to the hybrid submission package. The sponsor followed the conformance validation rules applied to all SDTM datasets and ADaM ADSL. Conformance issues found were explained in the clinical Study Data Reviewer’s Guide (cSDRG). The packages for both studies were accepted by FDA.
- The same hybrid submission package was delivered to PMDA. One study that only contained “ERROR” issues was accepted with the ‘ERROR’ issues being properly explained in cSDRG; however, the second study was rejected because it contained “REJECT” issues.

Lessons Learned:
Although both agencies accepted CDISC standards, the regulatory validation rules, including severity categories, are different. What is acceptable to FDA may not be acceptable to the PMDA. Therefore, it is essential to execute Pinnacle 21 using the PMDA validation rules; resolve reject issues; and share the error issues with the PMDA at data consultation meeting ahead of the submission.

FREQUENTLY ASKED QUESTIONS (FAQ): PLANNING FOR FDA AND PMDA SUBMISSIONS

Can we create a single study data package and submit it to both FDA and PMDA?
Both agencies use the same CDISC standards; however, there are still differences in requirements and recommendations. This limits sponsor’s ability to create a single study data package that satisfies both FDA and PMDA. Differences include:

- Severity of the validation rules
- Substance Registration System
- File naming conventions
- Software programs format
- Analysis Results Metadata (ARM) (strongly recommended by PMDA)
- Potential update to the cSDRG due to PMDA officer’s recommendation during the e-Data consultation meeting

What would you recommend if a study is submitted to both FDA and PMDA?

- Plan the trial using the latest CDISC versions of SDTM, ADaM and controlled terminologies supported by both agencies
- Ensure checks are performed against the CDISC conformance rules and regulatory authorities' business and validation rules
- Resolve rejection issues and address (resolve or justify) remaining issues
- Open the dialog with the authorities as early as possible
- Use the ARM, as this might give a huge benefit to the review process in providing executable and easy to use code to the reviewers

What if I do not know if we submit to PMDA?

The implications could be severe and could require significant re-work. Hence, plan ahead and be prepared. Regardless which regulatory authority, sponsors should run the CDISC conformance rules and agency validation rules to ensure there are no 'REJECT' issues.

LEGACY DATA CONVERSION

As the industry is transitioning into the era of standardized study data, it is common that a sponsor may have some studies that used legacy data format or early version of standardized data format. The sponsor must assess the situation and be prepared for legacy data conversion (including up-versioning) in order to meet regulatory requirements discussed in the previous section. Legacy data conversion (including up-versioning) is complex and resource consuming. It is crucial for a successful submission to have a comprehensive strategy and implementation plan at an early stage of the product life cycle.

ASSESS THE SCOPE OF CONVERSION AND UP-VERSIONING

Types and Categories of Legacy Studies That May Need Conversion or Up-versioning

There are two types of studies that may need conversion or up-versioning:

- Legacy studies whose data is not of CDISC standard
- Studies that followed earlier version of standard that is not supported by regulatory authorities anymore according to Data Standard Catalog

Based on study start date and data standard used, studies that may need to be converted or up-versioned can be classified in three categories:

- Legacy studies that started after December 17, 2016 for NDAs, BLAs, ANDAs (December 17, 2017 for INDs). These studies must be converted unless a waiver is granted.
- Studies that followed earlier version of standard that is not supported anymore according to FDA Data Standard Catalog. These studies must be up-versioned unless a waiver is granted.
- Legacy studies that started before December 17, 2016 for NDAs, BLAs, ANDAs (December 17, 2017 for INDs). Whether or not to convert these studies is not mandatory; but detailed discussions about how to decide on the strategy will be provided later in the paper.

The Study Data Standardization Plan (SDSP) is a powerful tool that can be utilized to track the data standard that was used when each study was set up and the data standard that will be used for the submission.

Conversion/Up-versioning Methodologies

There are multiple approaches for conversion/up-versioning

- Legacy source -> SDTM, legacy analysis -> ADaM, independently

  With this approach, while the traceability and consistency from legacy source data to SDTM and from legacy analysis data to ADaM can be more easily handled and maintained it lacks data point traceability between converted SDTM and converted ADaM. Because Clinical Study Report (CSR) outputs were produced using legacy data, steps need to be taken to verify that at least key outputs could be reproduced using converted SDTM and ADaM. Potential issues need to be addressed in the legacy data conversion plan and report.

- Legacy source -> SDTM -> ADaM
    - **CSR using legacy as source.** This approach could best maintain the traceability from SDTM to ADaM. However, because CSR outputs were produced using legacy data, steps need to be taken to verify that at least key outputs could be reproduced using converted SDTM and ADaM. Potential issues need to be explained in the legacy data conversion plan and report. This approach has higher cost due to almost a full scale of re-derivation in ADaM and has higher possibility of discrepancies between original CSR outputs and new ADaM datasets.
    - **CSR using ADaM as source.** This approach could best maintain the traceability. An early anticipation on potential legacy data conversion allows action to be taken earlier to take advantage of this route.

Every approach has limitation and issues requiring evaluation. In the FDA Study Data Technical Conformance Guide, FDA does not recommend an approach but emphasizes that the issues associated with a certain approach must be properly addressed. Regardless of which approach is taken, traceability must be maintained and data flow must be represented clearly. For traceability reasons, FDA may still request legacy data.

Additional Cost for Conversion

Significant cost occurs during the conversion process that requires resources to:

- Convert the datasets
- Run compliance checks and address the issues
- Create cSDRG/Analysis Data Reviewer's Guide (ADRG)
- Produce more detailed metadata files to create the define.xml
- Verify that the converted data reproduces the key results created using legacy data

DECIDE ON THE LEGACY DATA CONVERSION STRATEGY AND PLANNING

There are factors that need to be considered:

- Ensure to meet the regulatory requirements (mandatory timelines for electronic submission by FDA and PMDA as specified in Data Standards Catalog)
- Refer to previous discussions with regulatory authorities
- Evaluate cost and benefits, including the impact on resources and timelines
- Consider the key objectives of the study and the role the study will play in the submission, such as Pharmacokinetics (PK), safety, efficacy, etc.
    - Pivotal studies may carry more weight on converting; and in most cases, pivotal studies will be converted
    - Supporting studies including earlier phase studies, including healthy volunteer studies, PK studies, Clinical Pharmacology (CP) studies, may have some flexibility within boundary of mandatory requirements by conducting partial conversion on selected important domains
- Consider the stage of the study analysis and reporting activities
- Review pooling needs

During the process, it is recommended to engage internal cross-functional teams, such as regulatory affairs.

For FDA submissions, sponsors have the option to request a waiver for studies that do not conform to the FDA Data Standards Catalog. See later section for details on the waiver.

It is recommended that harmonizing various versions of standardized data be done at pooled level rather than at study level.

If a sponsor chooses to conduct limited conversion for supporting studies, some examples of legacy data conversion strategy and planning could be considered:

- Submission of only legacy Case Report Tabulations (CRT) package for supporting studies that started before the mandatory date where legacy data format was used in CSR output production
- Submission of legacy CRT package for supporting studies that started before the mandatory date where legacy data format was used in CSR output production plus selected converted SDTM domains based on the key objectives of the study
- Submission of legacy CRT package for supporting studies that started before the mandatory date where legacy data format was used in CSR output production plus a full set of converted SDTM domains plus ADSL

- Submission of legacy CRT package for supporting studies that started before the mandatory date where legacy data format was used in CSR output production plus a full set of converted SDTM domains plus ADSL plus ADaM datasets that are related to key analyses

For all these examples, on one hand, it provides the legacy source data and analysis data that were used in CSR reporting; on the other hand, SDTM datasets submitted would allow FDA to run their automated tools, such as data fitness check, and to load the source data into their data repository.

Once the strategy, including what studies will be converted and how to convert them, is identified, an action plan needs to be created. The plan should include: resource allocation (both quantity and experience) and timelines for the overall the conversion objective and for each deliverable.

In addition, the strategy needs to be communicated properly with regulatory authorities. Refer to *Section COMMUNICATIONS WITH REGULATORY AUTHOURITIES* for more details.

INCORPORATE AND OPTIMIZE USE OF STUDY DATA STANDARDIZATION PLAN (SDSP) IN SUBMISSION STRATEGY AND PLANNING

In 2014 FDA recommended the pharmaceutical industry to include a submission plan to summarize the adoption of data standards for completed, ongoing and planned studies. This proposed document would help identify the use of legacy data formats that would enable regulatory authorities to make decisions that support a meaningful review. Planning and communication with regulatory authorities would help set expectations and alignment on the use of data prior to an application. In 2015, FDA recognized the PHUSE SDSP template in the FDA Study Data Technical Conformance Guide. The release of the PHUSE SDSP template (v1.0) and SDSP Sponsor Implementation Guide gave sponsors a format and direction for outlining the studies; summarizing the exchange standards that would help raise awareness to the reviewer; and providing a section documenting non-conformance and concurrence on data plans prior to a submission. Similarly, Center for Biologics Evaluation and Research (CBER) released an appendix that would provide supplemental information to the PHUSE SDSP.

DEVELOPMENT OF SDSP

Gathering study-level information is the first step to authoring the SDSP. It requires cross-functional support from both non-clinical and clinical teams. Identifying a team with the history and knowledge of the product and individual trials is key to retrieving accurate information. Obtaining the inventory of trials and their data standards require orchestration between functional areas that may not typically have regular interactions. The collection of historical information is an investment in time and resources.

Initiating the SDSP and Content Assembly

Best practice is to implement the SDSP at the start of non-clinical development. Assembling an SDSP is a time-consuming task. During the preparation, sponsors must identify the studies and data standards and determine how those trials will be pooled for analysis.

Individuals with oversight to the filing strategy and touchpoints with functional areas during the product development life cycle would have a main role to coordinate the authoring of the SDSP. There is no single approach to implementing the SDSP in an organization and various experiences have yielded successful process outcomes in sharing the SDSP. Below are collected examples of how various organizations coordinated the SDSP assembly:

Example #1: Statisticians and programmers initiate and facilitated the content ownership and collection on the use of data standards. Once the document is ready, the SDSP would be handed to regulatory affairs team for FDA sharing.

Benefits:

- Programming team has study knowledge of SDTM and ADaM implementation while statisticians have study level and integrated analysis knowledge.
- Cross-functional areas (e.g. data management, clinical, non-clinical) would be supportive content providers.

Example #2: Regulatory liaisons own and initiate the SDSP while data management in clinical and non-clinical facilitate the collection of content

Benefits:

- Assigns content ownership to the team with the study standard implementation knowledge. Data Management identifies Controlled Terminology, dictionary versions and collects exchange standards from the team.
- Leverages the project management skills from data management to maintain the document through the product life cycle.
- Cross-functional areas (e.g. statistics, programmers, clinical, non-clinical) would be supportive content providers.

Example #3: Standards team initiates the document and distributes the SDSP to the study level, cross-functional teams to review, confirm and complete an accurate SDSP. Once the document is ready, the SDSP would be handed to regulatory affairs team for FDA sharing.

Benefits:

- A single point of contact oversees defining study data standards as early as possible, including:
    - organizing data standards up-versioning
    - ensuring a successful and timely assembly of the content
    - implementing consistency
    - reducing duplicated efforts
    - promoting the study data standards awareness
- While each function has study level knowledge, it is still efficient to have a single point of contact who would coordinate the activities.
- Centralizing the creation of the document enables consistency across all submissions within the company.

Risk: The Standards Team representative heavily relies on other functional areas to provide their respective information.

In-life SDSP Implementation Considerations

Since PHUSE released the SDSP template (March 2018), sponsors are implementing the SDSP for in-life products, in other words, a retrospective application. Industry has been challenged with recovering data and dictionary versions that supported earlier studies.

Scenario #1: Implementing SDSP in-life for the first time in a program that has a long product development.

Recommendations:

- Leverage the knowledge of a cross-functional team to coordinate and communicate the history of standards implemented for the study.
- Be flexible working within the team. Although a company procedure may assign a specific role to complete the information, it is important to find the historians who have access to archived supportive documents and can correctly reflect the data standards applied in earlier product development.

Scenario #2: Products that are ready for submission and the SDSP has not been previously shared.

Recommendation:

- When possible, submit the SDSP in the application based on the exchange and dictionary standards implemented in the submission. If timelines are sensitive, the alternative is to apply the SDSP towards supplemental applications or post-marketing commitments.

As trials are added to the life cycle, sponsors can update and maintain the SDSP. Sponsors should share the SDSP at a stage gate interaction or at submission inside Electronic Common Technical Document (eCTD) Module 1.13.9.

Frequently Asked Questions (FAQ): Development of SDSP

How do you establish support and structure in your organization to commit to completing the SDSP?

- Identify the leaders in your organization who have the current information and background to support the reporting of accurate information.
- Since information can come from multiple sources, identify a primary owner of the information and consider supportive roles.

- In situations where the activity does not exist, ask who has the skill set who could help facilitate or bridge the exchange of information. Be clear when establishing the roles and do not assume that the individual facilitating the activities is the content owner.
- Define a common location where two teams can edit the SDSP and coordinate parallel authoring and publishing of the SDSP.

During the development of the SDSP, who knows when a product transitions from non-clinical to the first clinical study?

The owner of the SDSP as described in *Section Initiating the SDSP and Content Assembly* has oversight to the product development life cycle and can assist in bridging the information from non-clinical to clinical development.

How frequently should sponsors update and review the SDSP internally?

Ideally, when new information is available the SDSP, sponsors should review and update the SDSP. However, it is recommended that the SDSP content be revisited at least annually to obtain the status of trials and the supportive standards.

What are the expectations for identifying the pooled analysis when there is not a clear plan to integrate data so early in the product life cycle?

- Authoring the SDSP early in the product development life cycle can bring challenges for sponsors when the plans for pooled analysis or the use of data to support analysis have not been developed. Early in the product development life cycle, the plans for integrated data may not exist in early releases of the SDSP. As the product reaches End of Phase II meeting or 12-15 months prior to a submission, sponsors are encouraged to discuss the plans for pooling safety and efficacy data.
- As studies approach submission, authors will be expected to adjust the studies in the pooled analysis during stage gate milestones and finalize the document at the time of the submitted application.

When is the optimal time to share the SDSP?

The PHUSE SDSP Completion Guidelines contains recommendations for sharing the SDSP at stage gate meetings. If sharing the SDSP too late, sponsors may not have the opportunity to vet the request and gain alignment on the approach to submitting data; thereby, jeopardizing the submission. Example:

- Missed opportunity for legacy conversion at earlier stage or waiver request
- Implemented a standard that is no longer supported in the Data Standards Catalog
- Miscommunicating expectations (e.g. pooling analysis strategy)

If you have plans to convert legacy data to a data standard, how do you document it in the SDSP?

The PHUSE SDSP Completion Guidelines contains recommendations. When study data is up-versioned from legacy data standards to standardized data (i.e. SDTM, ADaM) it is encouraged to list the legacy format and then add the additional information below the 'Up-version<ed>' text in the template. Refer to the example documents in which this is included.

What to do when indications are designated as rare disease, orphan, break-through or unmet medical need?

Still applies but the scope/volume of protocols may be smaller. The structure and practice to implement the SDSP remains the same.

Do we include all studies that we run or just the ones that we submit?

Sponsors should include all studies that were opened under the IND regardless if it is planned for the original or supplemental application. Possible exception may be oncological use, which may have multiple indications under the same IND. In these cases, sponsors can have separate SDSP for each indication.

USE OF SDSP AS A STRATEGY AND PLANNING TOOL

Once the SDSP is drafted, the next step is to identify any gap from trials that were not developed in accordance to the FDA Data Standards Catalog. Studies that do not conform to standards will require an assessment on the submission strategy.

Option 1: Plan activities to conform to the expected data standards.

- Refer to *Section Decide on the Legacy Data Conversion Strategy and Planning* as a guide for possible considerations to the decision-making process.
- Action: Ensure you revisit the SDSP to reflect the data standard implement at time of submission.

Option 2: Apply for a waiver to seek alignment on expectations for submitting data. Refer to *Section Waiver under FDA COMMUNICATION STRATEGY* for further details.

NOTE: Sponsors may implement multiple options within the submission

If regulatory input is required to determine the study data submission strategy, the sponsor should interact with the regulatory authorities on their position and rationale by utilizing SDSP. The next section will discuss the practices of regulatory interactions.

COMMUNICATIONS WITH REGULATORY AUTHORTITIES

Decisions and strategies must be organized and communicated internally before presenting the situation for regulatory agreement. When sponsors are ready for regulatory engagement, pre-work is needed to prepare the briefing materials in advance of the meeting. Sponsors should consider the following practices that pertain to submitting standardized study data:

- Share the SDSP at each stage gate interactions with FDA to align on the strategy and planning through the submission life cycle and process (SDSP can be attached to the briefing document for each interaction, and discussions and agreements reached can be added to SDSP for further actions and future communications)
- Summarize the plan (e.g. using tables, or diagrams)
- Justify the plan, for instance,
    - How mandatory requirements have been met
    - How the plan serves the purpose of the submission
    - How the plan facilitates the review

FDA COMUNICATION STRATEGY

In 2017 FDA released a draft Guidance for Industry that describes the Formal meetings between FDA and Sponsors or Applicants of Prescription Drug User Fee Act (PDUFA) Products. These interactions are identified as:

- **Type A** – used to help stalled product development program proceed or to address safety concerns
- **Type B** – occurs at pre-defined endpoints before or after the submission of clinical data or new filing
- **Type B End of Phase (EOP)** – used for products seeking marketing approval
- **Type C** – any other meetings that fall outside A & B and can be technical in nature

If meeting is granted, FDA will identify the meeting in the following format:

- Face to face
- Teleconference/ Videoconference
- Written response only where a response is sent to requesters in lieu of the earlier options

When addressing submitting study data to regulatory authorities, sponsors should communicate the following:

- Deviation from the deliverables outlined in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format- Standardized Study Data
- Up-versioning that may include a Legacy Conversion Plan
- Studies or approaches that require regulatory agreement prior to submission
- Review of the pooled analysis plan

Study Data Standardization Plan (SDSP)

The SDSP is a living document that should be shared with CDER or CBER at stage gate meetings and at the time of submission. To make best use of the regulatory interaction, it is recommended to identify trials that require reviewer's agreement on the use of data standards to support the submission. It is also recommended to submit the SDSP no later than the End of Phase 2 meeting.

While CDER wants to be informed on the development and adoption of data standards shared at stage gate meetings, CBER seeks additional information in a CBER Appendix. The content contains metadata details that facilitate CBER review and could

affect sponsor's mappings. For CBER submissions, sponsors should allow enough time to gain concurrence on the information presented in the CBER Appendix.

Waiver

Waiver request applies to studies that no longer have a version of the data standards supported in the FDA Data Standards Catalog. To apply for a waiver, sponsors must e-mail the FDA technical staff when planning to submit study data that is no longer supported in the FDA Data Standards Catalog.

- For CDER submissions, waiver requests should be addressed to: cder-edata@fda.hhs.gov
- For CBER submissions, waiver requests should be addressed to: cber.cdisc@fda.hhs.gov

The waiver process should be the first line of communication to share the rationale for non-conformance of legacy data or retired standards. Once agreed upon, sponsor should document the outcome in SDSP Section 6: FDA Data Standards Discussions.

FDA encourages the sponsor to submit the waiver request to the FDA technical staff as early as possible during product development life cycle. They intend to notify the requestor within 30 days from the date the waiver request is received. FDA will notify the sponsor or applicant in a written email as to whether the waiver request is denied or granted.

General Correspondence

Sponsors have additional options to communicate with FDA:

- Contact the project manager via e-mail or phone with applicant specific questions
- Raise non applicant specific inquiries directly to CDER or CBER edata mailbox

PMDA COMMUNICATION STRATEGY

Consultation on study data submission can be requested multiple times during product life cycle. Attachment 8 and Attachment 8-2 should be prepared prior to the consultation. Refer to the complimenting PHUSE publication *"FDA and PMDA Study Data Submission Distinctions"* for details.

Sponsors can request the following meetings with PMDA:

- **Clinical Trial Consultation** (normally, End of Phase 2) – Identify the study data and/or analysis data planned for electronic submission necessary for a new drug application
- **e-Data Consultation Meetings** include discussions on:
    - **Consultation on Exemption** - Discuss and reach agreement on the exemption to submit electronic study data submission or conduct legacy data conversion
    - **Consultation on Preparation**- Discuss and review the following:
        - methods for storing data (e.g. custom domains) and handling variables
        - approaches for legacy data conversion
        - submission method to send study data
    - **Consultation on Data Format** – Discuss validation results
- **Pre-NDA Meeting** - Occurs approximately two months prior to the planned filing date for final confirmation on the submission package

If meeting is granted, the PMDA will identify the meeting in the following format:

- Face to face
- Teleconference (at PMDA discretion)

CONCLUSION

Submitting standardized study data to regulatory authorities is a critical and complex process and it requires strategy, planning and communication. Sponsors need to proactively identify and prepare for challenges throughout the submission life cycle. In summary, this paper discussed the following recommendations:

- Understand which regulatory authority the submission goes to and its regulations

- Convert legacy study data from studies that require conversion based on the agreement between the sponsor and regulatory authority
- Utilize the SDSP/Attachment 8 (8-2) to aide in internal planning, development, and submission of standardized study data
- Communicate strategy and implementation plans for submitting standardized study data at regulatory meetings
- Implement the standards as referenced in the FDA/PMDA Data Standards Catalog
- Ensure checks are performed against the CDISC conformance rules and regulatory authorities' business and validation rules; resolve rejection issues and address (resolve or justify) remaining issues

It is essential to start the process early and revisit it by taking steps above in order to deliver a high quality and compliant submission package in a lean, resourceful, and cost-effective way.

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