PharmaSUG 2018 - Paper DS-11

# Avoid chasing one's Tail - Challenges and Solutions for managing changes in SDTM Standards Development

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## ABSTRACT

Change is the way of life that applies to data standards. Internal organizational changes such as acquisitions may lead to the support of a new Therapeutic area (TA). External factors such as changes in regulatory requirements, new or revised standards released by Standards Development Organizations such as CDISC also need to be taken into account when building companies standards.

This presentation discusses our experience, various challenges encountered and solutions taken at Shire on SDTM standards, with regards to the harmonization of legacy company standards and the development processes to ensure a faster, more reliable and more consistent implementation of SDTM standards.

## INTRODUCTION

Shire has an established a Standards Governance model with a Clinical Standards Board and a Governance Team for each standard. The Shire SDTM Governance Team developed its own interpretation of the SDTM Data Standards concepts that are aligned to the CDISC SDTM Implementation Guide (SDTMIG). These SDTM Data Standards concepts take into account how the collected data is being mapped or derived, its representation as a SDTM domain and the generation of the corresponding aCRF and Define xml. Shire SDTM Toolkit is the name of the SDTM Standards Library created within Shire. This ensures that the SDTM Data Standards are applied consistently in a uniform way across all studies.

## DEVELOPMENT OF COMPANY-SPECIFIC SDTM STANDARDS

When starting to establish SDTM standards within a company, the following factors should be considered:

- Determine the specific CDISC SDTMIG version and associated materials that should be used as the basis of the library, factoring in the date the regulatory support date ends for that version.
- Define the metadata that aligns to the specific CDISC SDTM Model and SDTMIG.
- When determining the mapping of a particular topic to a specific domain in SDTM, evaluate the information being captured, as that can impact mapping decisions.
- Identify different use cases and think about metadata versioning and management within the workflow.

### SDTM METADATA LIBRARY DEVELOPMENT PROCESS

The SDTM Governance Team is responsible for interpreting the CDISC SDTM concepts and representing the standards metadata as specifications. Shire SDTM toolkit is the name of the SDTM Standards Library created within Shire. This SDTM Toolkit is part of the end-to-end implementation of standards. It maps the collected information and is the source for ADaM datasets.

Once the SDTM Library is defined, it is shared with the strategic CRO partners. The CROs can then evaluate how best to incorporate this metadata content into their own tools and processes. The CROs adhere to Shire standards while using their tools and processes to maintain efficiencies.

This SDTM Library was developed using an iterative process. In that process, requirements that aligned to business needs were identified through cross functional collaboration. These principles are based on an agile development methodology. We chose this approach because agile methods and processes

generally encourage teamwork, accountability and frequent inspection and adaptation of the work, allowing for the rapid delivery of a high-quality end product.

It is important to determine how and when to best release the SDTM Library for use within the organization. Initially at Shire, we released standards as they were developed, which made adoption challenging. Now we have a yearly release schedule for updates to the SDTM Library. Any study that starts after the release date would use the latest updated SDTM Library.

## CHANGE CATEGORIES AND FACTORS

*"Change is inevitable. Change is constant." -Benjamin Disraeli*

As the saying goes, everyone should embrace change to succeed. Organizational changes within a company can impact processes, tools and/or technology. Careful consideration on how to handle the change can make the difference between progress and hindrance. A Standard SDTM Library is no different, and this section discusses the details of change categories. The following are categories of changes that impact a company:

- External Change
- Internal Change

### EXTERNAL CHANGE

Change can be driven by factors external to the company such as changes in regulations and rules by regulatory agencies such as the Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA). Other sources of change could be when a standard development organization, such as CDISC, releases a new or updated standard, or when tools and technology used by strategic CRO partners change. For a Standards SDTM Library, all these external factors have the potential to impact development, and must be taken into account concurrently.

### External Change - Regulatory Authorities:

The regulatory authorities are constantly finding ways to make the approval process more consistent, predictable and efficient, increasing patients' access to state-of-the-art treatments. Currently, FDA and PMDA are the primary agencies with roadmaps to streamline their processes and develop internal tools to help in this effort. When study data submitted to the agency is in a standard structure, it improves the agency's ability to review the submission. These requirements and expectations are communicated by FDA and PMDA as various documents and regulations or Federal Registries (FR).

The following are examples of documents updated at different times that each company needs to pay attention to:

- Study Data Technical Conformance Guide
- Data Standards Catalog
- Providing Regulatory Submissions in Electronic Format for submissions under 745A(a) of the Federal Food, Drug and Cosmetic Act for FDA
- The Basic Principles on Electronic Submission of Study Data for New Drug Applications for PMDA

Below are examples of changes to the requirements and expectations that are communicated by each regulatory agency to the industry.

#### ***FDA***

FDA has developed some guidance on what to expect:

1. The agency updates the Study Data Technical Conformance Guide (TCG) and Data Standards Catalog at regular intervals as needed. The information in the TCG must be carefully reviewed and considered to be followed as much as possible. When not

possible, this must be communicated to the reviewer through Study Data Reviewers Guide (SDRG).

2. Studies starting after Dec16, 2016 must be submitted using a CDISC SDTM version listed in the Data Standards Catalog. There are two types of dates identified in the Data Standards Catalog. One is the Support Begin and End Dates and the other the Requirement Begin and End Dates. When a new version of a standard is updated in the Data Standards Catalog, with the Requirement Begin Date then studies can be submitted in that new version. When a particular standard has the Requirement End Date, all studies submitted to the agency that start after this date must not use that version of the standard. Refer to FDA documentation for further details.
3. For submission, FDA also has released business and validator rules. The business rules identify high-level requirements, which are then implemented as one or more validator rules. Validator rules are intended for implementation in checking tools such as FDA's DataFit service, and must be considered to ensure conformance. These may be updated by the agency as needed.
4. For clinical and nonclinical studies that start after December 17, 2016, FDA plans to add Technical Rejection Criteria as part of the existing eCTD validation criteria to enforce the use of Study Data Standards. FDA will give the industry 30 days' notice on the eCTD website prior to the criteria becoming effective.
5. In addition to Technical Rejection, FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs. RTF and RTR represent a broader range of concerns that go beyond the scope of this paper.

***PMDA***

PMDA has developed some guidance on what to expect:

1. The agency updates the Technical Conformance Guide (TCG) and Data Standards Catalog, in both Japanese and English. The information in the TCG must be carefully reviewed and considered to be followed as much as possible. When not possible, this must be communicated to the reviewer through Study Data Reviewers Guide (SDRG).
2. Studies starting after Apr 1, 2020 must use a CDISC SDTM version listed in the Data Standards Catalog. The Data Standards Catalog has Support Begin and End Dates. When a new version of a standard is updated in the Data Standards Catalog, the Support Begin Date identifies when studies can be submitted in that new version.
3. For submission, PMDA also has released Validation Checks with additional status "Reject". Validation Checks can be checked using tools and must be considered to ensure conformance. These will be updated regularly.

## External Change - Standards Development Organizations:

The aim of CDISC, as a Standards Development Organization, is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare.

1. CDISC updates the SDTM standard and releases it either as provisional or final depending on their established criteria. Starting in 2018, CDISC has announced an annual release schedule of the standards. This date, the first Friday in November, is when a standard may have a release, although each standard is not required to do so each year. This provides the industry with a predictable schedule for reviewing the released documents.
2. It can be helpful when personnel within a company volunteer in the CDISC working groups, so that the organization is aware of upcoming changes and planning. Additionally, it allows organizations to review proposed changes earlier in the process, and provide their input.

### External Change - Strategic CRO Partners:

Sponsor companies use strategic CRO partner's processes, tools and technology in the conduct of their studies. When the tools and/or technology change, there could be a possible impact on sponsor deliverables such as Define-XML, Pinnacle 21 Validation Report. For example, Shire found that different CRO Partners had varying timelines for when they would be able to provide Define-XML in version 2.0, and so developed an approach to support both short- and long-term needs.

### INTERNAL CHANGE

Change can be driven by internal factors within the company. For example, merging with another company, or developing content for new Therapeutic Area (TA) standards.

### Internal Change - Mergers and Acquisitions (M&A):

Mergers and Acquisitions can be common within a company, and can be for a variety of reasons, such as when executives identify the opportunity to fill a strategic gap in the product portfolio. M&A activity may impact the organizational structure, affect operating models, or initiate changes to processes, tools and technologies. Every effort should be made to learn about the data standards that were implemented within the distinct organizations, to aid in determining the best process for harmonization.

The harmonization process includes assessing the implementations for compliance and conformance to CDISC, regulatory requirements and company-specific standards. The next steps forward may include providing guidance on how to bridge gaps in interim processes, and providing a framework on deciding when to migrate a given study to updated standards. It is also important to perform an impact assessment of any internally maintained metadata or materials, processes, or tools across the organizations.

### Internal Change - New Therapeutic Area (TA):

Companies may sometimes consider expanding into new disease areas or novel therapies. In order for standards teams or standards SMEs to best represent this data, they need to learn about the disease area by discussing with the medical monitor or clinician. The data that needs to be mapped to support analysis may result in creating new standards based on these additional use cases.

It is vital that any relevant CDISC Therapeutic Area User Guides (TAUGs) are reviewed, and any applicable concepts and mapping decisions are incorporated. When considering solutions identified in a TAUG, it is important to note that some options (e.g., new variables) are forward-looking, and may need to be adjusted to work within a given version of SDTM.

## WHAT ARE THE CHALLENGES AND SOLUTIONS?

### CHALLENGE #1

| Category | Challenge |
|---|---|
| External Change – Regulatory Agency | Landscape of agency changing requirements and guidances.<br><br>For example, FDA Guidances include the release of Business checks, Validation checks and Study Data Technical Conformance Guide. |

### SOLUTIONS:

- Keep track of the commonly released agency documents. This includes understanding what constitutes a requirement versus what is guidance.
- Volunteer in CDISC and/or PhUSE groups to learn and collaborate on how to handle such changes.

- At Shire, we established a Data Standards Governance Model to provide a cross-functional forum for discussing some of the specific needs and how this can be handled.
- The standards development process followed agile methods to adjust to the changing needs. For example, the FDA Study Data Technical Conformance Guide describes that ARM and ARMCD for non-treated subjects are to be blank when represented. This is in conflict of how ARM and ARMCD are described in the SDTM Implementation Guide version 3.2 or earlier. To address this, Shire SDTM Governance team proposed an interim solution and passed it through Data Standards Governance to ensure there is a consistent approach in how studies within Shire align to this guidance.

## CHALLENGE #2

| Category | Challenge |
|---|---|
| External Change – Standards Development Organization such as CDISC | Updates to the foundational standards or the release of a new Therapeutic Area standard (TAUG) may result in changes to SDTM concepts, model or controlled terminology. This can include the addition of new standard domains. |

## SOLUTIONS:

- Keep track of the commonly released CDISC Implementation Guides (IGs) and related documents. This includes understanding the disease metadata and domains associated with it.
- Volunteer in CDISC groups and attend webinars to learn about the changes which are not always clear from an end-user's perspective. For example, the IGs for the CDISC SDTM (clinical) and SEND (non-clinical) standards are based on a common model, SDTM. The different IG documents are linked to distinct SDTM model documents as follows:
    - Both the SDTMIG v3.2 and the CDISC non-clinical standard SENDIG v3.0 are associated with the SDTM Model, version 1.4.
    - When the next version of non-clinical Standards SEND was developed (SENDIG v3.1), the SDTM model was extended, and released as version 1.5.
    - Subsequently, the CDISC SEND DART was released, further extending the SDTM Model, and was released as version 1.6.
    - The industry is waiting for the release of next version of SDTMIG 3.3, which will be anchored in the SDTM Model, version 1.7.
- We have found that having a Data Standards Governance Model helps to propagate throughout the organization some of the challenges discussed in industry forums (e.g., CDISC and PhUSE).

## CHALLENGE #3

| Category | Challenge |
|---|---|
| External Change – Strategic Partners | Updates to the process, tools and technology may result impacting Sponsor deliverables. For example, at Shire not all CRO Partners were immediately able to provide Define-XML in version 2.0. |

## SOLUTIONS:

- Including CROs in the Governance Model helps to share some of the challenges and discuss solutions that would align to the Sponsor Company's needs.

- As an example, Shire's SDTM Governance team established an approach to support both versions of Define-XML 1.0 and 2.0. In addition, Shire encouraged the CROs to develop a more concrete roadmap for adopting the most recent version of Define-XML as appropriate. We also evaluated the capability of the CRO tools and reviewed the generated Define-XML. Reference materials were developed and guidance was provided to support the quality review of Define-XML documents.
- We also found that training CRO teams on Shire's established standards helped to streamline the adoption of our standards within their tools and processes.

**CHALLENGE #4**

| Category | Challenge |
|---|---|
| Internal Change – Merger and Acquisition | During merger and acquisitions, each company has their own established company-specific standards. |

**SOLUTIONS:**

- Have each company share their methodology and process for creating SDTM datasets. Provide guidance on the next steps, such as using company-standards as-is, bridging any gaps to the current requirements or creating a new version compliant to CDISC and agency needs.
- The Standards development process should leverage concepts from agile development methodology, where standards are continuously evaluated and adjusted to the changing needs. For example, this includes reviewing the SDTM concepts across merging organizations, and identifying harmonization techniques to make sure that one standard is followed moving forward.
- Having a Shire Data Standards Governance Model helped us in discussing different implementations of SDTM. For example, we found that CROs can have divergent processes and interpretations in support of for implementing SDTM. Discussing the specific processes helped us to understand the differences and provide guidance that supported all consumers while allowing us to receive deliverables with consistent expectations.

**CHALLENGE #5**

| Category | Challenge |
|---|---|
| Internal Change – New Therapeutic Area | When studies in rare diseases are being developed it is hard to understand the disease. |

**SOLUTIONS:**

- Learn about the new disease, population by collaborating with study team and company medical staff.
- Review and contribute when developing a protocol to understand study design concepts such as primary and secondary end points or rating scales.
- Understand what data are captured and how they can be mapped based on the CDISC Therapeutic Area Standards and modelling the information to better align to analysis needs.
- Discuss these in the Shire Data Standards Governance Model and understand how the concepts can be built towards the development of the Shire SDTM standards.

## CONCLUSION

This paper discussed the considerations when creating company specific standards and overall standards development process. In addition the paper discusses different agents of change that lead to challenges and possible solutions associated with the standards development. Although the examples are more specific to Shire and SDTM development, these solutions can be applied to data standards development in general.

When personnel are engaged in understanding the external change factors, it helps a company be more equipped to embrace the changing landscape. Similarly when a company's strategic priorities are to accelerate new therapies for new disease areas, the personnel need to build expertise in support of any new concepts or domains.

Understanding the changing landscape of CDISC, agency requirements, and internal company needs along with a robust Data Standards Governance process supports overall standards development, keeps us from chasing our tail!

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## ACKNOWLEDGMENTS

I would like to acknowledge Diane Piper who provided a framework to establish data standards within Shire and SDTM Governance Team for their continued support.

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