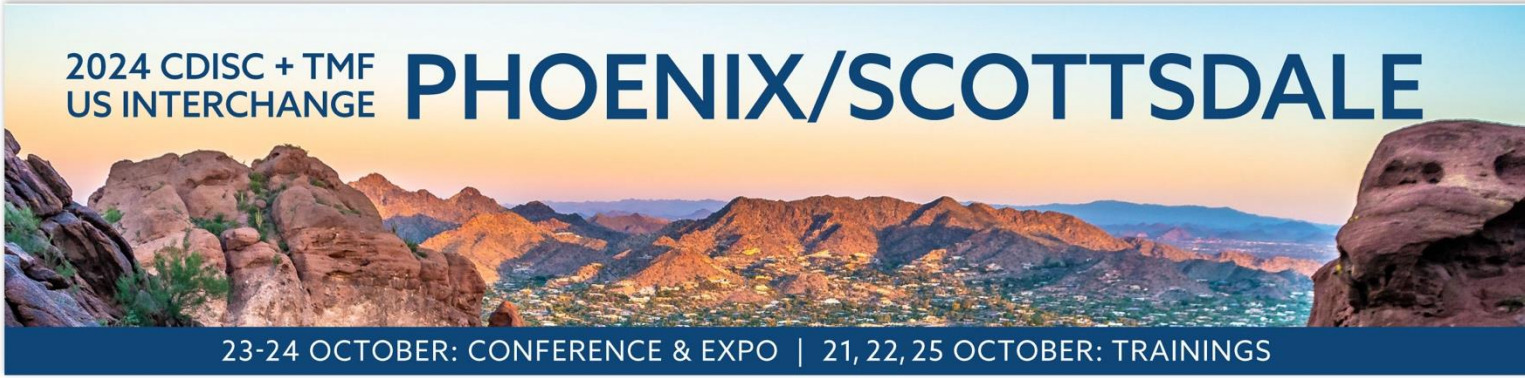
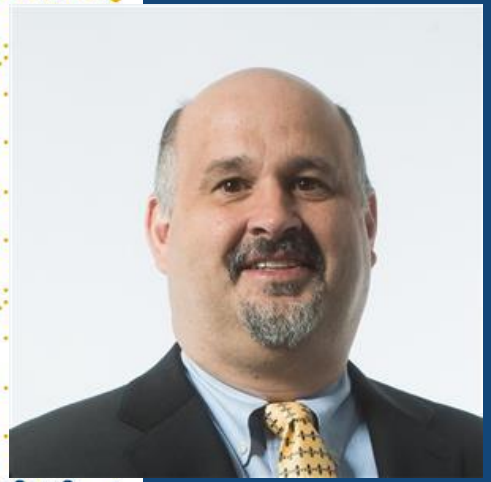



# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

Presented by Kent Letourneau and Sandra Minjoe, ICON



# Meet the Speakers

## Kent Letourneau

Title: Head of Global Data Standards

Organization: ICON

Kent started his career at ICON in 1995 as a statistician. He formed the Global Data Standards team in 2015, with its mission to develop, implement, and enforce industry, ICON, and sponsor specific standards to drive efficiencies and improve quality. Kent is part of the CDISC ADaM team and represents ICON on the CDISC Advisory Council.

## Sandra Minjoe

Title: Senior Principal Clinical Data Standards Consultant

Organization: ICON

Sandra has been in the biotech/pharma industry since 1993, with roles in standards, programming, statistics, data management, and project management. She joined ICON in February, 2018. Sandra has been part of the ADaM team since 2001, is a former ADaM Team Lead,and certified CDISC ADaM trainer, and helps develop ADaM public documents.

# Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Topics Covered

- Content developed by regulatory agencies
- Content developed by industry which are referenced by regulatory agencies
- Best practices for developing a concise set of materials for submissions to both FDA and PMDA

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Content Developed by Regulatory Agencies

Overview

# Content Developed by Regulatory Agencies: High-Level Documents

| Agency | Document | How is it Used? |
|---|---|---|
| **US FDA Binding Guidance Documents** | **FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the FD&C Act.** | This document describes the requirements for submitting electronic data. This is a high-level binding guidance and references multiple technical specifications which provide detail on how to implement this guidance. |
| | **FDA Providing Regulatory Submissions in Electronic Format - Standardized Study Data (June 2021)** | This guidance and the technical specifications documents it incorporates by reference, describe the requirements for an electronic submission of standardized clinical and nonclinical study data under section 745A(a) of the FD&C Act. |
| **Japan PMDA Notification** | **Notification on Handling of Submission of Electronic Study Data for New Drug Applications** | This document describes why the PMDA needs electronic study data and it references their Data Standards Catalog and Technical Conformance Guide. |

# Content Developed by Regulatory Agencies: Overview

## US FDA

- Binding Guidances
- Data Standards Catalog
- Study Data Technical Conformance Guide
- Technical Specifications

## Japan PMDA

- Notification
- Data Standards Catalog
- Technical Conformance Guide

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Content Developed by Regulatory Agencies

Data Standards Catalogs

# US FDA Data Standards Catalog

## Contents

- Shows which standards and versions are and will be accepted
- Often updated several times per year

## Excel spreadsheet

- Allows you to filter to only those appropriate for your study

## Footnote content that is often missed:

- “If a study started before the support ends date, the study can continue to use this specified version of the standard. If a study starts after the support ends date, the study can NO longer use this specified version of the standard. Sponsors cannot use this version of the standard or terminology after this date. Generally, a waiver process may be available. Sponsors and applicants should consult with their review division. An empty field in this column means that a support end date has not been established.”
- When 2 dates are listed in a cell, the first date applies to NDAs, ANDAs, and most BLAs

# US FDA Data Standards Catalog – ADaM Example

- Study start date: 05/01/2021

| Property | FDA Center(s) | Date Support Begins | Date Support Ends | Date Requirement Begins [10] [11] | Date Requirement Ends |
|---|---|---|---|---|---|
| **ADaMv2.1** | **CDER, CBER** | **Ongoing** | | **12/17/2016 [1]<br>12/17/2017 [2]** | |
| ~~ADaMIGv1.0~~ | CDER, CBER | Ongoing | 03/15/2019 [1] [12]<br>03/15/2020 [2] [12] | 12/17/2016 [1]<br>12/17/2017 [2] | 03/15/2019 [1] [12]<br>03/15/2020 [2] [12] |
| ADaMIGv1.1 | CDER, CBER | 10/2/2017 | | 03/15/2019 [1]<br>03/15/2020 [2] | |
| ADaMIGv1.2<br>ADaMIGv1.3 | CDER, CBER | 07/18/2022 | | 03/15/2024 | |

- Meaning:
  - You can submit your study data using either ADaMIG v1.1, 1.2, or 1.3
  - You can NOT submit your study using ADaMIG v1.0

# Catalog-related content from US FDA "Providing Regulatory Submissions in Electronic Format – Standardized Study Data"

"FDA recognizes that standards development organizations may release **version updates** to standards in the interval between the start of a study and the submission of study data to the Agency. The Catalog may list more than one version of a supported standard."

"Sponsors or applicants are encouraged to use the latest version listed in the Catalog. However, when there are **multiple versions** of a standard listed, sponsors or applicants can select the version to use for their study."

"For purposes of this guidance, the study start date for clinical studies is the **earliest date of informed consent** among any subject that enrolled in the study."

# Japan PMDA Data Standards Catalog

## Similar in structure to the US FDA Data Standards Catalog

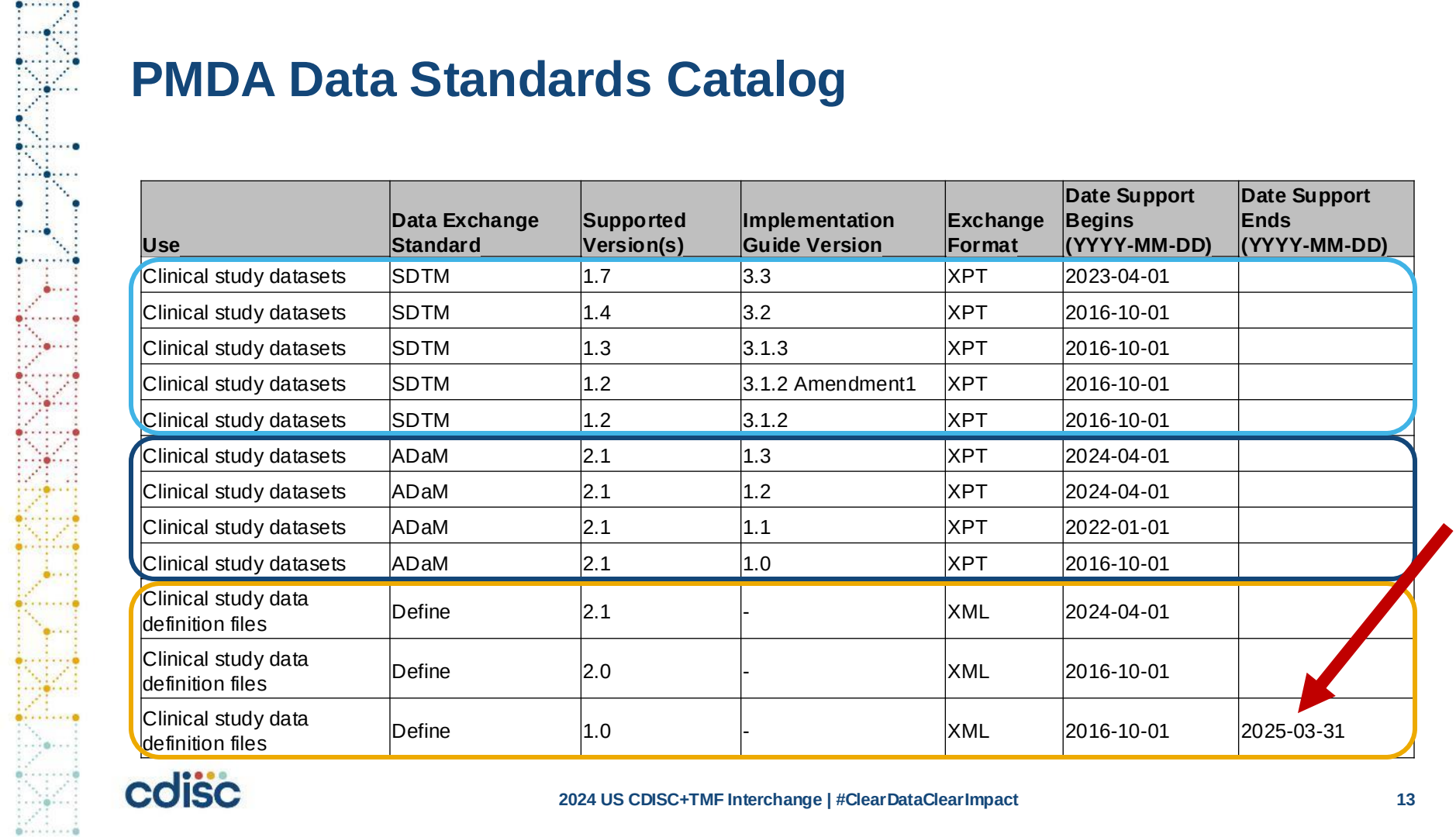
- Excel spreadsheet catalog shows which standards and versions are and will be accepted
- It allows you to filter to only those appropriate for your study
- Updated as soon as a change is instituted, historically every couple years

## Differences from US FDA Data Standards Catalog

- PMDA bases dates Support Begins and Ends on the date of the submission
  - Recall that FDA was based on the date of study start
- Not as many standards and often fewer versions of each standard included

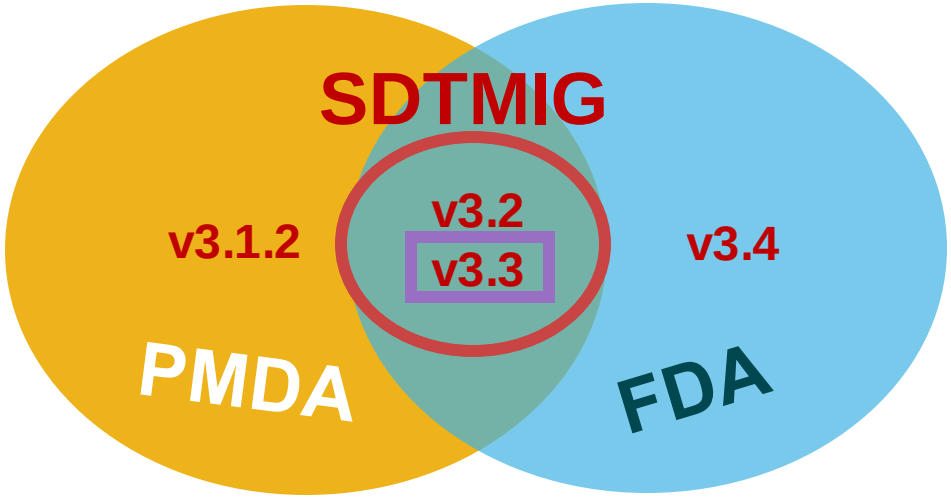
# PMDA Data Standards Catalog

| Use | Data Exchange Standard | Supported Version(s) | Implementation Guide Version | Exchange Format | Date Support Begins (YYYY-MM-DD) | Date Support Ends (YYYY-MM-DD) |
|---|---|---|---|---|---|---|
| Clinical study datasets | SDTM | 1.7 | 3.3 | XPT | 2023-04-01 | |
| Clinical study datasets | SDTM | 1.4 | 3.2 | XPT | 2016-10-01 | |
| Clinical study datasets | SDTM | 1.3 | 3.1.3 | XPT | 2016-10-01 | |
| Clinical study datasets | SDTM | 1.2 | 3.1.2 Amendment1 | XPT | 2016-10-01 | |
| Clinical study datasets | SDTM | 1.2 | 3.1.2 | XPT | 2016-10-01 | |
| Clinical study datasets | ADaM | 2.1 | 1.3 | XPT | 2024-04-01 | |
| Clinical study datasets | ADaM | 2.1 | 1.2 | XPT | 2024-04-01 | |
| Clinical study datasets | ADaM | 2.1 | 1.1 | XPT | 2022-01-01 | |
| Clinical study datasets | ADaM | 2.1 | 1.0 | XPT | 2016-10-01 | |
| Clinical study data definition files | Define | 2.1 | - | XML | 2024-04-01 | |
| Clinical study data definition files | Define | 2.0 | - | XML | 2016-10-01 | |
| Clinical study data definition files | Define | 1.0 | - | XML | 2016-10-01 | 2025-03-31 |



# Developing a concise set of materials for submissions: Catalogs

- Create a single set of content that can be used for both submissions
  - Look at the DS Catalog from both countries to find overlaps
  - Keep in mind that
    - US FDA bases their options on date of study start
    - Japan PMDA bases their options on date of submission
  - When more than one standard will work both countries, consider using the most current




| Example: | Submission date | Study start date |
|---|---|---|
| | 11/01/2024 | 05/01/2021 |

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Content Developed by Regulatory Agencies

(Study Data) Technical Conformance Guides

# US FDA Study Data Technical Conformance Guide

- Supplements the binding guidance "**Providing Regulatory Submissions in Electronic Format — Standardized Study Data (eStudy Data)**"
- Provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards located in the **Data Standards Catalog**
- Language is more readable than regulation documents
- References FDA technical specifications and industry documents
- Modified at least twice per year

# US FDA Study Data Technical Conformance Guide Reference: FDA Technical Specifications

## Includes topics on

- Bioanalytical Methods Templates
- Clinical Endpoint BE Studies
- HIV
- QT Studies
- Next Gen Sequencing
- Rodent Carcinogenicity Studies
- Vaccines
- Noncirrhotic Nonalcoholic Steatohepatitis (NASH)
- M11
- Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

# FDA Technical Specifications Example: Vaccines

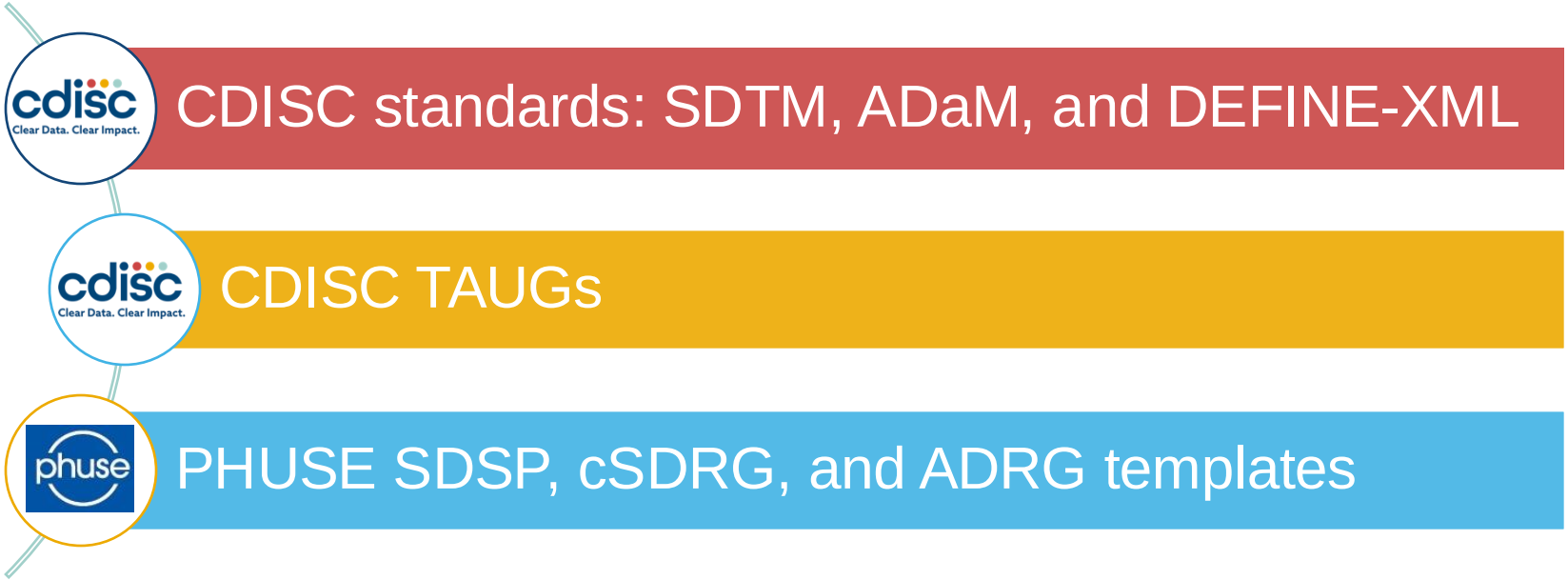
## FDA text box prior to the introduction

*This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

## Notice that it is <u>not</u> binding

- Alternate approach is allowed
- However, this approach is what reviewers are best prepared to review
  - In your best interest to meet this request
- Discuss with your review division if you want to do something different

# US FDA Study Data Technical Conformance Guide References: Industry Documents



# Japan PMDA Technical Conformance Guide

## Similar to the US FDA Study Data Technical Conformance Guide

- References overarching requirement and Data Standards Catalog
- References CDISC standards: SDTM, ADaM, DEFINE
- References PHUSE templates: SDRG and ADRG

## Differences from the US FDA Study Data Technical Conformance Guide

- Doesn't reference FDA Tech Specs or CDISC TAUGs
- Doesn't include content about non-clinical (SEND) data
- Includes a preference to receiving Analysis Results Metadata (ARM)
- Includes content for data in Japanese text

# Developing a concise set of materials for submissions: External references

## Make data consistent across both submissions

- Make use of CDISC standards, plus any appropriate CDISC TAUGs and FDA Tech Specs, when designing datasets

## Create separate define.xml for each agency

- Only PMDA wants ARM content

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Content Developed by Regulatory Agencies

Conformance Rules

# FDA Conformance Rules

## FDA Business Rules

- The Business Rules v1.5 (May 2019) help ensure that the study data are compliant, useful, and will support meaningful review and analysis.
- This applies to SDTM formatted clinical studies and SEND formatted non-clinical studies.
- For more information see Section 8 of the Technical Conformance Guide.

## FDA Validator Rules

- The Validator Rules v1.6 (December 2022) are used by the FDA to ensure data are standards compliant and support meaningful review and analysis.

## FDA Technical Rejection Criteria

- Listed as an appendix in the FDA Study Data Technical Conformance Guide

# PMDA Conformance Rules

- **Different version of rules depending on submission date**

  - Study Data Validation Rules

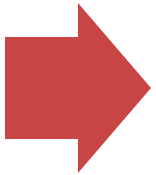
    Please note that when submitting electronic study data to the PMDA via the gateway system, only one version of the validation rules must be selected for a single application, even if it involves multiple studies.

    - Version 1.0 (2015-11-18) Acceptable from Oct 1, 2016 to Mar 31, 2021 (application date)
    - Version 2.0 (2019-09-27) Acceptable from Apr 1, 2020 to Mar 31, 2023 (application date)
    - Version 3.0 (2021-12-15) Acceptable from Jan 1, 2022 to Mar 31, 2025 (application date)
    - Version 4.0 (2023-02-28) Acceptable from Apr 1, 2023 (application date)

- Contains tabs for SDTM Rules, ADaM Rules, Define-XML Rules
- PMDA Severity levels are **Reject**, **Error**, and **Warning**

# Developing a concise set of materials for submissions: Conformance Rules

Different sets of rules means different conformance issues to describe in the Reviewer's Guide



FDA and PMDA each need their own cSDRG and ADRG

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Summary of Best Practices

# Keep Current with References and Links

**US Food & Drug Administration**

- Study Data Standards Resources contains links to
  - Data Standards Catalog
  - Study Data Technical Conformance Guide
  - Many guidance documents, including Tech Specs
  - Business and Validator Rules
- FDA Study Data Technical Rejection Criteria (TRC): What You Need to know!

**Japan PMDA**

New Drug Review with Electronic Data (English) contains links to

- Technical Conformance Guide
- Data Standards catalog
- Study Data Validation Rules

**CDISC**

- Foundational (including SDTM, ADaM)
- Data Exchange (including Define-XML)
- Therapeutic Area User Guides (TAUGs)

**PHUSE**

PHUSE Working Groups

*To find Reviewer's Guides and SDSP, from the search tool select*

- **Working Group**: Optimizing the Use of Data Standards
- **Deliverable Types**: Regulatory Referenced Deliverable

# Develop a concise set of materials when submitting to both US FDA and Japan PMDA: Summary

## Make **data** consistent across both submissions

- Look at the Data Standards Catalog from both countries to find overlaps and choose your IG version
- Make use of CDISC standards, plus any appropriate CDISC TAUGs and FDA Tech Specs, when designing datasets

## Create separate **Reviewer's Guides** and **define.xml** for each agency

- Reviewer's Guides will have differences in Compliance section since different checks are run
- Only PMDA wants ARM content in define.xml

# Practical guidance for successful global regulatory submissions: Understanding FDA and PMDA data standards requirements

## Topics Covered

- Content developed by regulatory agencies
- Content developed by industry which are referenced by regulatory agencies
- Best practices for developing a concise set of materials for submissions to both FDA and PMDA

# Thank You!