PINNACLE 21 BY CERTARA

PMDA'S NEW VALIDATION RULES 4.0 EXPLAINED

Overview of PMDA Validation and its ENGINE “PMDA 2211.0”

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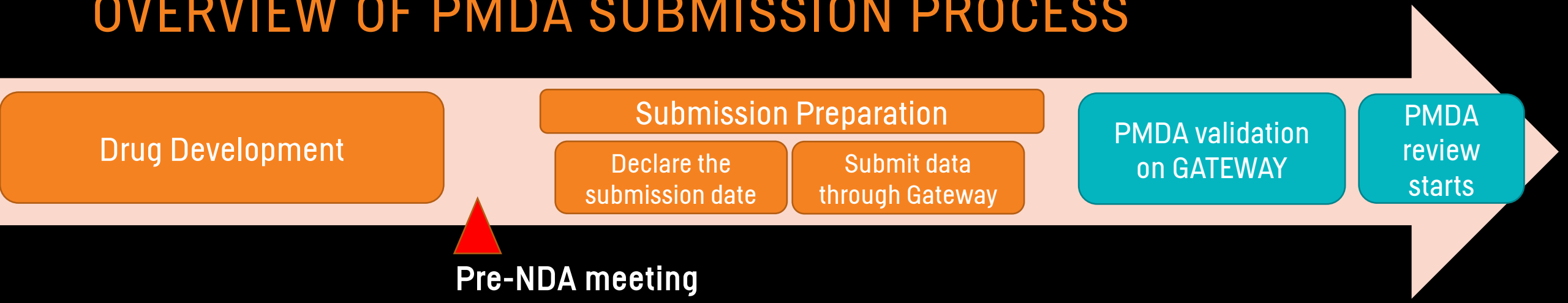
DISCLAIMER

The views and opinions presented here represent those of the speaker and should not be considered to present advice or guidance on behalf of the regulatory agencies or standards development organization.

AGENDA

- Overview of PMDA submission process
- List of PMDA Validation Rule and Engine
- What is in PMDA 2211.0 engine?
  - Changes in SDTM
  - Changes in Define.xml
  - Changes in ADaM
- Summary

OVERVIEW OF PMDA SUBMISSION PROCESS



Please choose one validation engine for one submission.

Pre-NDA Meeting - Confirm finalized submission package and submission date.

PMDA Review will not begin or continue when:

- A “Reject” issue is found
- P21 Validation fails due to submitted file problem
- No validation report
- Validation rule is not consistent between Form A and GATEWAY

PMDA PUBLICATIONS

Notifications

- Notification on Electronic Study Data

Notification on Handling of Submission of Electronic Study Data for New Drug Applications (PSEHB/PED Notification No. 0401-10, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022)

- Q&A Regarding Notification on Electronic Study Data

Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022)

- Notification on Gateway Application

New Drug Applications Using the Gateway System (PSEHB/PED Notification No. 0401-7, by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022)

- Technical Conformance Guide

Technical Conformance Guide on Electronic Study Data Submissions (PMDA/CPE Notification No. 0401003 and PMDA/CRS Notification No. 0401001, by the Director of Center for Product Evaluation and the Director of Center for Regulatory Science, Pharmace Google Chrome l Devices Agency, dated April

https://www.pmda.go.jp/english/review-services/reviews/0002.html

PMDA VALIDATION RULES & ENGINE

				SDTM IG				ADaM IG		define.xml	
RULE	ENGINE	START	END	3.1.2	3.1.3	3.2	3.3	1.0	1.1	1.0	2.0
V1	PMDA 1511.6	2016-10-01	2021-03-31	Y	Y	Y		Y		Y	Y
V2	PMDA 1810.3	2020-04-01	2023-03-31	Y	Y	Y		Y		Y	Y
V3	PMDA 2010.2	2022-01-01	2025-03-31	Y	Y	Y		Y	Y	Y	Y
V4	PMDA 2211.0	2023-04-01		Y	Y	Y	Y	Y	Y		Y
Note: PMDA uses P21 Enterprise Version 5.1.2.											

https://www.pmda.go.jp/english/review-services/reviews/0002.html

PMDA VALIDATION RULE

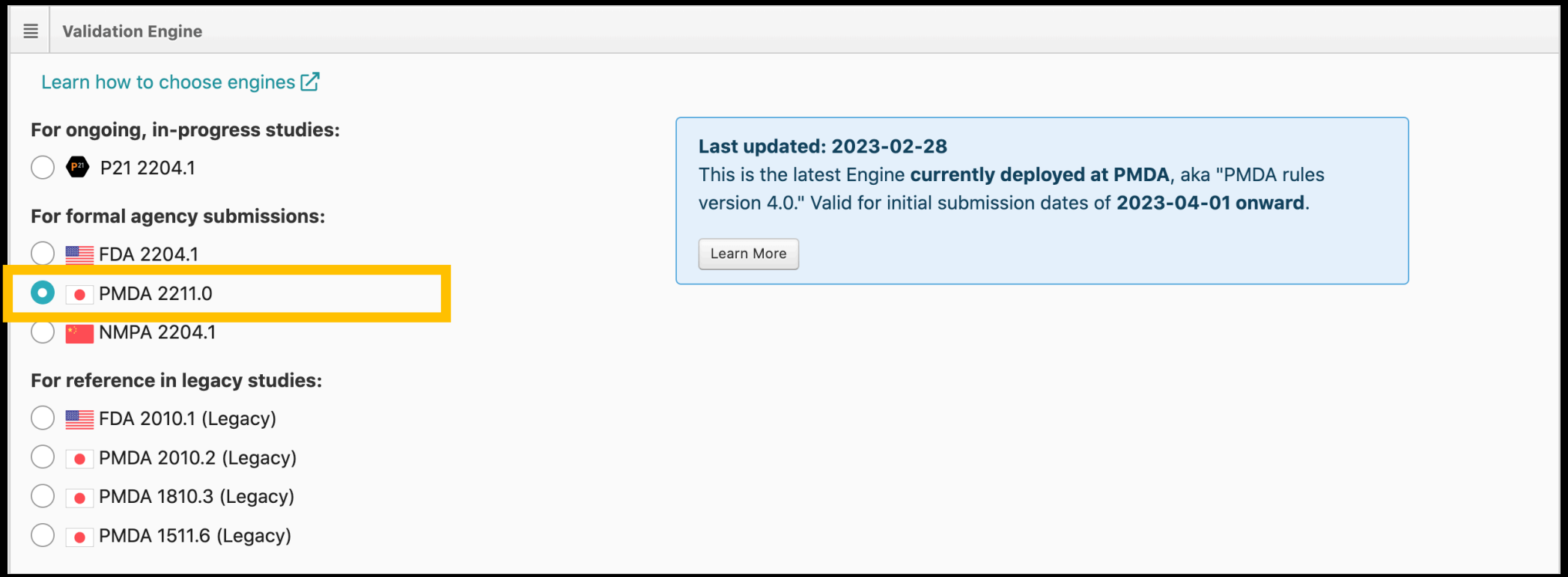
The PMDA severity of the rules (“Reject”, “Error”, and “Warning”) correspond to the three levels of importance of the validation rules for CDISC-conformant data as described in the PMDA Technical Conformance Guide.

Define-XML Rules v4.0

RULE ID	MESSAGE	DESCRIPTION	PMDA Severity	2.0	PMDA NOTES
		represents Documents as def:leaf elements within MetaDataVersion element.			
DD0016	Referenced Method is missing	Referenced Method must first be defined on Methods tab. Define-XML specification represents Methods as MethodDef elements within MetaDataVersion element.	Error	X	
DD0017	Referenced Value Level metadata is missing	Referenced ValueListOID value must match OID attribute of def:ValueListDef element within MetaDataVersion element.	Error	X	
DD0018	def:ArchiveLocationID/def:leaf mismatch	The ItemGroupDef def:ArchiveLocationID should match the ID of the child def:leaf.	Error	X	
DD0019	Invalid FileType value	The FileType must have a value of 'Snapshot'.	Error	X	
DD0020A	Invalid def:DefineVersion value	The def:DefineVersion should have a value of '2.0.0' for Define-XML v2.0.	Reject	X	PMDA does accept the define.xml version 2.0.0 only under this validation rule.

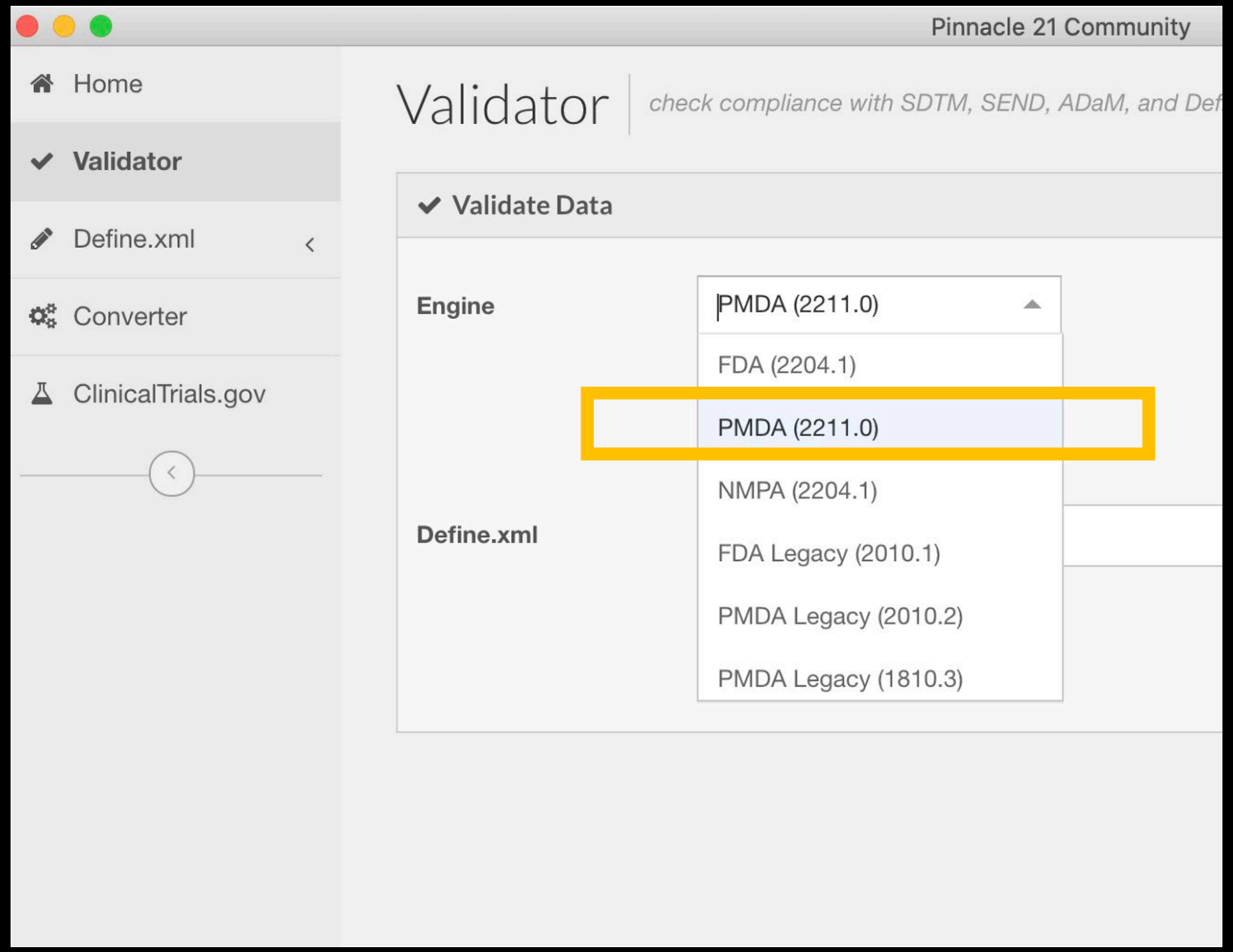
https://www.pmda.go.jp/english/review-services/reviews/0002.html

ENGINE CONFIGURATION IN P21 ENTERPRISE



- Only one version of the validation rule can be selected for all stuies in the same application

ENGINE CONFIGURATION IN P21 COMMUNITY



CHANGES IN SDTM

SDTM & PMDA STANDARD CATALOG

PMDA Data Standards Catalog (2023-02-28) - Data Exchange Standards						
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 - Transport	SAS Transport (XPORT)	5	-	XPT	2016-10-01	
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	

https://www.pmda.go.jp/english/review-services/reviews/0002.html

- PMDA accepts SDTM IG v3.1.2, v3.1.3, v3.2, and v3.3.

NEW RULES IN SDTM IG 3.3

465 Rules have been added, including CDISC conformance rules and data quality checks.

P21 Community Users:

Please post questions about any rules that are unclear in the Community Forum: https://www.pinnacle21.com/forums

UPDATE FOR SDTM IG 3.2 OR LOWER

- **11** algorithm updates for optimizing results
- **2** messages
- **12** descriptions
- **14** assignments
- No new rule, No deleted rule, No severity change

Note:
These updates apply to the lower versions “3.1.2” and ”3.1.3” when there are same standard variables.

ALGORITHM AND ASSIGNMENT CHANGE

- **Algorithm Change**

SD0005, SD0007, SD0026, SD0029, SD0095, SD1117, SD1201, SD1230, SD1234, SD2003, SD22442

- Assignment Change

SD0002, SD0040, SD0051, SD0083, SD1029, SD1043, SD1098, SD1099, SD1142, SD1272, SD1275, SD1283, SD1299, SD1300

Note:
These two type may have the impact on validation result.

CHANGES IN DEFINE.XML

"DEFINE.XML" & PMDA STANDARD CATALOG

PMDA Data Standards Catalog (2023-02-28) - Data Exchange Standards

Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
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	

https://www.pmda.go.jp/english/review-services/reviews/0002.html

- PMDA will not accept Define.xml V1.0 in new applications after April 2025

NEW/REMOVED RULES

- NEW

  DD0020A (Invalid def:DefineVersion value)

  Severity: Reject
  Description: The def:DefineVersion should have a value of '2.0.0' for Define-XML v2.0

- REMOVED

  DD0020 (Invalid def:DefineVersion value)

MODIFIED RULES

- Modified Algorithm

  DD0050 (Domain/SASDatasetName mismatch for split dataset)
  It recognizes split domains and split SUPPQUAL domains in define.xml and helps reduce false positive issues.

- Modified Descriptions

  DD0037, DD0072, DD0079, DD0099, DD0100

  Note: Changes about single and double quotation are excluded.

SEVERITY CHANGE

- Upgrade (“Warning” to “Error”)

  DD0102 (Invalid Annotated CRF document name)
  PMDA would like to recognize the file name of Annotated CRF. It is not mandatory to change the file name to “acrf.pdf”

Note: If the file name is updated, it must be updated in define.xml and revalidated. We recommend explaining it in the Reviewer’s Guide instead of updating the file name.

CHANGES IN ADAM

ANY CHANGE?

- No Change.

SUMMARY OF CHANGES

SUMMARY OF PMDA 2211.0

	ADaM IG 1.0	ADaM IG 1.1	SDTM IG 3.1.2	SDTM IG 3.1.3	SDTM IG 3.2	SDTM IG 3.3	define.xml V2.0
New Rule	0	0	0	0	0	465	1
Removed Rule	0	0	0	0	0	0	1
Algorithm Change	0	0	9	9	11	0	1
Severity Change	0	0	0	0	0	0	1
Message Change	0	0	1	1	2	0	0
Description Change	0	0	11	11	12	0	5
Assignment Change	0	0	8	9	14	0	0

RECOMMENDATION IN PROCESS

- Use PMDA guidance as primary source of information
- Fix ALL Reject issues
- Keep the same version of validation rules for one application if submission date is scheduled
- Utilize the latest version of standard in new engine “2211.0” if submission date is unknown.

TECHNICAL RECOMMENDATIONS

- SAS CPORT Procedure doesn't create “xport” v5 format
- Give same file name and dataset name for “xport” files
- Use unicode as SAS session encoding
- Update “Standard Version” in dedfine.xml to the one selected in validation
- Revalidate all files with P21 when file/filename are updated.

Note: File name and relative path expression should be case sensitive depending on the platform.

SUMMARY

- PMDA validation rule v4.0 can be used for PMDA submissions from April 1, 2023 and onward
- Engine “PMDA 2211.0” implements the PMDA validation rule v4.0
- SDTM IG v3.3 is supported by PMDA 2211.0.
- Minimal changes in SDTM IG v3.1.2, v3.1.3, and v3.2
- Define.xml v1.0 is not supported by PMDA 2211.0
- No changes in ADaM

REFERENCE

- PMDA Documents (Japanese)
  - Data Standard Catalog, Data Validation Rule

    URL:https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.htm
  - Notification on Electronic Study Data
  - Q&A Regarding Notification on Electronic Study Data
  - Notification on Gateway Application
  - Technical Conformance Guide

    URL:https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0026.html
- PMDA Documents (English)
  - Notification on Electronic Study Data
  - Q&A Regarding Notification on Electronic Study Data
  - Notification on Gateway Application
  - Technical Conformance Guide
  - Data Standards Catalog and Study Data Validation Rules
    https://www.pmda.go.jp/english/review-services/reviews/0002.html
- WORKSHOP for the persons who submitting e-data to PMDA (Title: About electric data submission, Current Status and Point to Consider, etc) Japanese Only

  https://www.jpma.or.jp/information/evaluation/symposium/2023_03_02.html
- Technical Paper Record Layout of a SAS Version 5 or 6 Data Set in SAS Transport (Xport) Format (SAS TS-140)
  URL:https://support.sas.com/techsup/technote/ts140.pdf

P21

THANK YOU ;)

KEEP IN TOUCH!

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