

# PINNACLE<sup>21</sup> BY CERTARA

## WHAT IS IN PMDA ENGINE 2010.2?

Overview of PMDA Validation Rule v3.0 and its  
implementation by Pinnacle 21

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- ▶ Working in the pharma industry since 2012
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# ASKING QUESTIONS

Click this icon to ask a question  
any time during the webinar

Your questions will be  
answered at the end

A screenshot of a chat interface. On the left side, there is a vertical menu with four icons: a blue asterisk, an information 'i' icon, a question mark icon, and a back arrow icon. The question mark icon is highlighted with an orange arrow. The main area of the chat is titled 'CHAT' and contains a large text input field and a 'SEND' button at the bottom right.

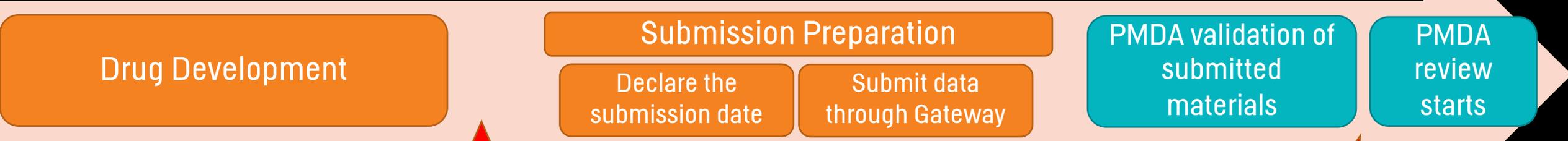
# AGENDA

- ▶ Overview of PMDA submission process
- ▶ PMDA validation rules and related P21 engines
- ▶ What is in PMDA 2010.2 engine?
  - ▶ Changes in ADaM
  - ▶ Changes in SDTM
  - ▶ Changes in Define.xml
  - ▶ Algorithm change in config file how P21 finds target variables in ADaM



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# OVERVIEW OF PMDA SUBMISSION PROCESS



## Pre-NDA meeting

To confirm finalized submission package and submission date

PMDA confirms the validation results (e.g., "Error results w explanations")

If Reject issues are found, PMDA review will not begin until it is corrected.

Keep the same version of PMDA validation rules for the same application

# PMDA NOTIFICATIONS

## Notification of Basic Principles

- First Notification published on 6/20/2014
- Announcement that the electric data submission is required for NDA

## Notification on Practical Operations

### Practical issues

- Handling of clinical study data subject to electronic submission
- Method of e-data submission, etc.

## Technical Conformance Guide

### Technical detailed information

- System requirements
- Folder structure
- Validation of e-data, etc.

# PMDA VALIDATION RULES

- ▶ PMDA performs validation of CDISC-conformant data using Pinnacle 21 Enterprise
- ▶ The applicant needs to check the data conformity to CDISC rules using PMDA validation rules prior to the application

## Data Standards Catalog and CDISC Data Validation

- [Data Standards Catalog \(2021-12-15\)](#) 📄
- CDISC Data Validation Rules
  - [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 (application date)

# 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.

## ADaM Rules v3.0

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	1.0	1.1	PMDA NOTES
AD0001	Missing ADSL dataset	ADaM Subject level (ADSL) dataset should be included in every submission.	GLOBAL	Reject	X	X	
AD0005	*FL value is not Y, N or null	A variable with a suffix of FL must have value that is Y, N or null (exception 1: RFL, PFL, ABLFL, ANLzzFL. Exception 2: Population flags COMPLFL,FASFL,ITTF,PPROTFL,SAFFL,RANDFL,ENRFL cannot be null and at least 1 must be included in ADSL).	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Reject	X	X	
AD0006	*FN value is not 0, 1 or null	A variable with a suffix of FN has a value that is not 0, 1 or null (exception: RFN, PFN, ABLFN, ANLzzFN and population flags Numeric COMPLFN,FASFN,ITTFN,PPROTFN,SAFFN,RANDFN,ENRFLFN cannot be null and at least 1 must be included in ADSL).	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Reject	X	X	
AD0007	Secondary variable *FN is present but its primary variable *FL is not present	If a Flag Numeric (*FN) variable is present, its corresponding Flag Character (*FL) variable must be present.	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Error	X	X	
AD0010	*FL = Y and *FN != 1	When a Flag variable (FL) is Y, its corresponding Flag numeric variable (FN) must be 1.	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Error	X	X	
AD0011	*FL = N and *FN != 0	When a Flag variable (FL) is N, its corresponding Flag numeric variable (FN) must be 0.	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Error	X	X	
AD0012	Secondary variable *FN is populated but its primary variable *FL is not populated	When a numeric Flag variable (*FN) is populated, its corresponding character Flag variable (*FL) must be populated.	ADAMOTHER, BDS, ADAE, OCCDS, ADSL	Error	X	X	

# VERSIONS OF PMDA VALIDATION RULES & P21 SUPPORTED ENGINES (P21 ENTERPRISE)

Validation Engine

Start with P21 Engine. When a study is near submission, use Configure to switch its Data Package to an agency-specific Engine.

**For ongoing, in-progress studies:**

P21 2111.0

**For formal agency submissions:**

FDA 2010.1 

PMDA 2010.2 

NMPA 2010.1 

**For reference in legacy studies:**

FDA 1907.2 (Legacy) 

PMDA 1810.3 (Legacy) 

PMDA 1511.6 (Legacy) 

## Version 3.0

Published in December 2021

For submissions starting 1/1/2022 (application date)

## Version 2.0

Published in September 2019

Acceptable from 4/1/2020 to 3/31/2023 (application date)

## Version 1.0

Published in 2015

Acceptable from 10/1/2016 to 3/31/2021 (application date)

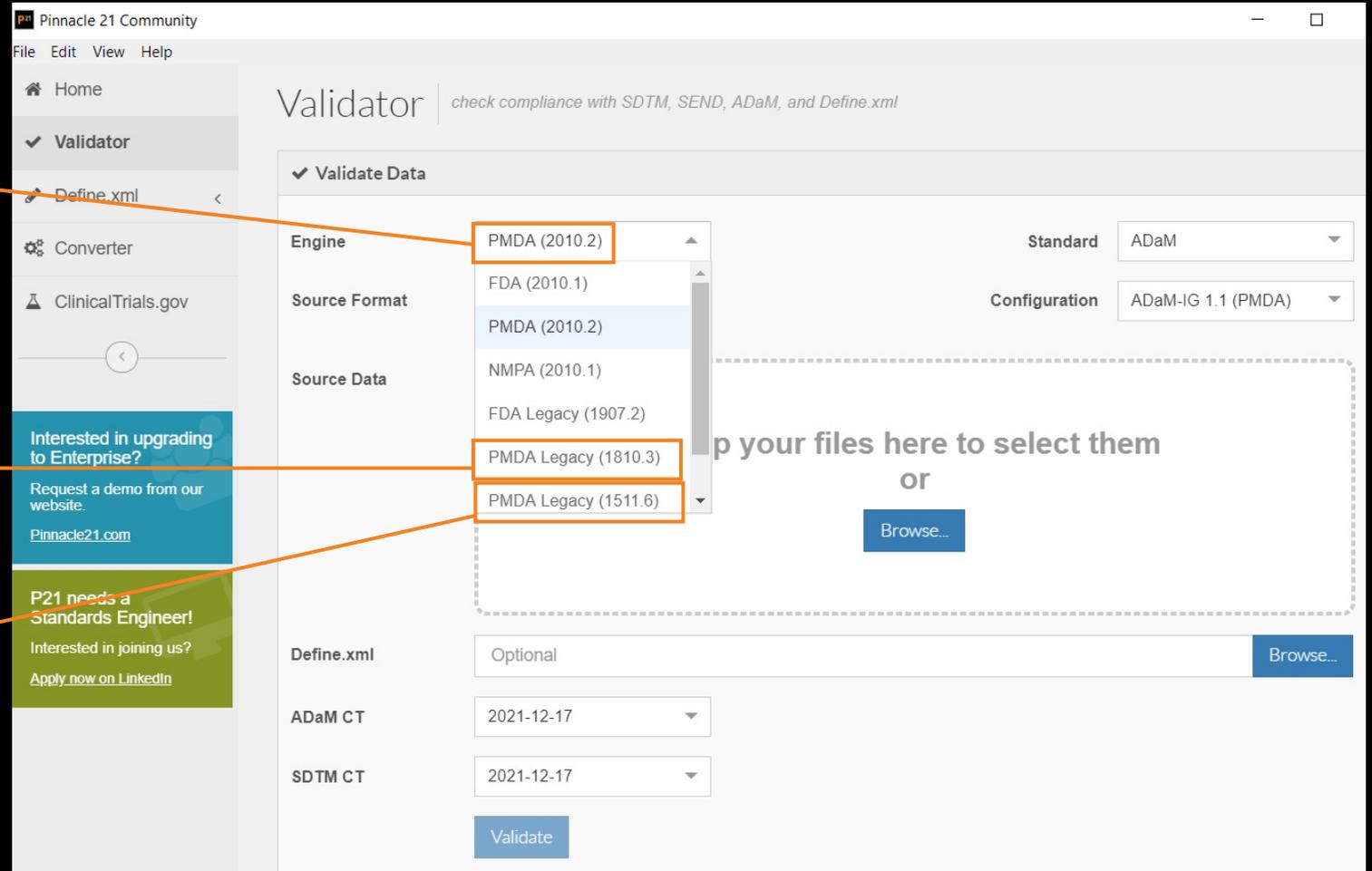
- ▶ Only one version of the validation rule can be selected in the same application.

# VERSIONS OF PMDA VALIDATION RULES & P21 SUPPORTED ENGINES (P21 COMMUNITY)

**Version 3.0**  
Published in December 2021  
For submissions starting 1/1/2022 (application date)

**Version 2.0**  
Published in September 2019  
Acceptable from 4/1/2020 to 3/31/2023 (application date)

**Version 1.0**  
Published in 2015  
Acceptable from 10/1/2016 to 3/31/2021 (application date)



# WHAT IS IN PMDA 2010.2 (PMDA VALIDATION RULE V3.0)?

- ▶ Implementation of ADaM IG v1.1 and changes in existing rules

	ADaM 1.0	ADaM 1.1	SDTM3.1.2	SDTM3.1.3	SDTM3.2	Define.xml
New	8	253	0	0	0	0
Removed	34	-	6	10	10	0
Severity change	4	-	0	0	0	0
Algorithm change	8	-	10	19	24	3
Description/ Message	36	-	29	42	45	3
Rule assignments	38	-	1	1	6	0
Metadata	1	-	2	2	2	-
# of total rules	226	253	348	409	426	135

- ▶ Algorithm change in config file how P21 finds target variables in ADaM



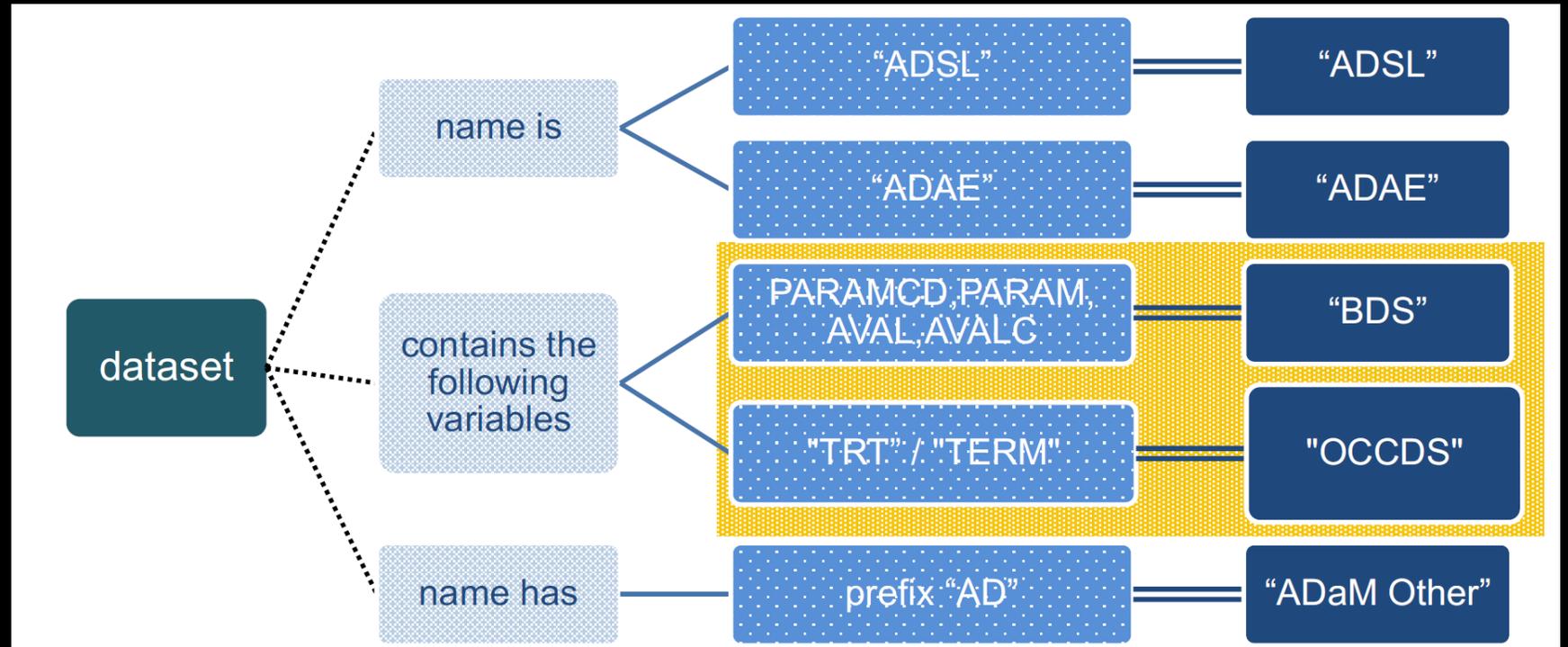
# CHANGES IN ADAM

# NEW ADDITION OF ADAM IG V1.1 (253 RULES)

- ▶ 234 rules are implemented out of 271 rules in CDISC conformance rule v2.0.
- ▶ Some operational checks

# HOW 2010.2 ENGINE IDENTIFIES DATA STRUCTURES

- ▶ OCCDS is a defined structure in ADaM IG v1.1.
- ▶ P21 identifies data structures as follows:





## CHANGES IN ADAM IG V1.0

## 8 NEW RULES IN ADAM IG V1.0

Rule ID		Reason
AD0041A	(*DT variable has missing SAS Date Format)	To check for missing SAS format for date/time variables
AD0042A	(*TM variable has missing SAS Time Format)	
AD0043A	(*DTM variable has missing SAS Datetime Format)	
AD0251	(CNSDTDSC is present but CNSR is not present)	CG251 was removed from CDISC ADaM conformance rule 2.0 but add AD0251 for PMDA validation
AD0320	(Non-standard dataset label)	The CDISC ADaM Conformance Rules v2.0 has a new rule:320 ->AD0320 added
AD1024	(Traceability rules not executed due to missing DM dataset)	To remind users that DM, AE, and EX should be included in validations for traceability purposes.
AD1025	(Traceability rules not executed due to missing AE dataset)	
AD1026	(Traceability rules not executed due to missing EX dataset)	

## 34 REMOVED RULES IN ADAM IG V1.0

- ▶ 34 rules are deleted from the CDISC ADaM Conformance Rule V2.0; therefore, those are also deleted from 2010.2 engine.

AD0062,AD0063,AD0065,AD0068,AD0073,AD0074,AD0094,AD0100  
AD0101,AD0107,AD0108,AD0115,AD0153,AD0158,AD0161,AD0162  
AD0171,AD0172,AD0173,AD0174,AD0175,AD0179,AD0185,AD0186  
AD0187,AD0188,AD0189 AD0190,AD0191,AD0192,AD0193,AD0202  
AD0203,AD0213

## 4 RULES IN SEVERITY CHANGE IN ADAM IG V1.0

Rule ID	
AD0033	(*RFL value is not Y or null)
AD0034	(*PFL value is not Y or null)
AD0035	(*RFN value is not 1 or null)
AD0036	(*PFN value is not Y or null)

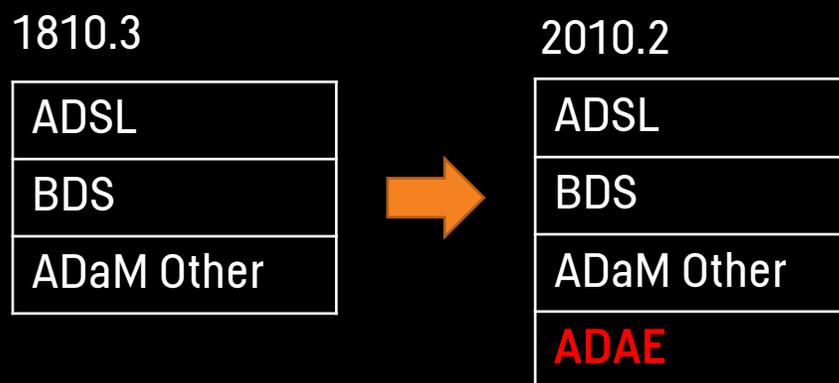
- ▶ For those variables defined in ADaM IG (ITT, SAF, FAS, PPROT(\*RFL/\*PFL/\*RFN/\*PFN)) variables, the severity remains the same.
- ▶ Other custom variables end with (\*RFL, \*PFL, \*RFN, \*PFN) are downgraded from Reject to Error

# ALGORITHMS OF 8 RULES WERE MODIFIED IN ADAM IG V1.0

Rule ID		Changes
AD0059	(*TM is not a numeric variable)	ARELTM variable was added to rule algorithm.
AD0127	(BASE or BASEC is populated for a unique USUBJID, PARAMCD but no baseline record exists)	Fixed a bug when rule was not firing if only one variable BASE or BASEC is present in a dataset.
AD0221	(Inconsistent value for %Variable.1%CAT%Variable.2%)	Additional Character variable %Variable.1%C was added for uniqueness.
AD0269	(%Variable% flag value is not Y or null)	ONTRTFL and LVOTFL variables were added to rule algorithm.
AD1011	(Secondary variable %Variable% is populated but its primary variable %Variable.1% is not populated)	*DTC variables were added to rule exceptions.
AD1012	(Secondary custom variable is present but its primary variable is not present)	Added exceptions for variables introduced in ADaM 1.2 BTOXGRN, ATOXGRLN, ATOXGRHN, BTOXGRHN, BTOXGRLN, STRATARN, STRAT#RN, STRATAVN, and STRAT#VN.
AD1012A	(Secondary variable is present but its primary variable is not present)	Added exceptions for introduced in ADaM 1.2 BTOXGRN, ATOXGRLN, ATOXGRHN, BTOXGRHN, BTOXGRLN, STRATARN, STRAT#RN, STRATAVN, STRAT#VN.
SD1230	(Variable datatype is not the same as DataType in define.xml when value-level condition occurs)	Rule algorithm was modified to ignore records with a missing value to avoid false-positive messages for Integer data type.

# 38 RULES HAVE CHANGES IN ASSIGNMENTS IN ADAM IG V1.0

EX., AD0005 (*%Variable.1%FL value is not Y, N or null*)



- ▶ Mainly ADAE, ADaM Other are added to rules or ADaM Other is removed from rules



# CHANGES IN SDTM

# SDTM FOR PMDA E-DATA SUBMISSION

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	1.4	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	

- ▶ PMDA accepts SDTM that is based on SDTM IG v3.1.2, v3.1.3 and v3.2

# 10 REMOVED RULES IN SDTM

3.1.2, 3.1.3, 3.2		Reasons
SD1145	(MHENDTC date is after RFSTDTC)	Was not a valid rule.
SD1259	(Invalid value for SETCD)	SETCD variable is for SEND.
SD2240	(Invalid TSVCDREF value for INDIC)	SNOMED related rules are deleted.
SD2257	(Invalid TSVAl value for INDIC)	
SD2258	(Invalid TSVAlCD value for INDIC)	
SD2259	(TSVAl/TSVAlCD value mismatch for INDIC)	

3.1.3, 3.2		Reasons
SD2266	(Invalid TSVCDREF value for TDIGRP)	SNOMED related rules are deleted.
SD2267	(Invalid TSVAl value for TDIGRP)	
SD2268	(Invalid TSVAlCD value for TDIGRP)	
SD2269	(TSVAl/TSVAlCD value mismatch for TDIGRP)	

# ALGORITHMS OF 24 RULES WERE MODIFIED IN SDTM

- ▶ Minor modification that could reduce false-positives

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# 6 RULES HAVE CHANGES IN ASSIGNMENTS IN SDTM

3.1.2		3.1.3		Changes	3.2		Changes
SD0012	<i>(--STDY is after --ENDY)</i>	SD0012	<i>(--STDY is after --ENDY)</i>	Added to SE	SD0012	<i>(--STDY is after --ENDY)</i>	Added to APAE, APMH, SE
					SD0005	<i>(Duplicate value for -SEQ variable)</i>	Removed from DE, DX
					SD0058	<i>(Variable appears in dataset, but is not in SDTM model)</i>	Added to RELSUB
					SD1005	<i>(Invalid STUDYID)</i>	Added to RELSUB
					SD1236	<i>(Duplicate value for -SEQ variable)</i>	Added to DX
					SD1299	<i>(No timing variables are present in dataset)</i>	Added to DE, DI, DO, DR, DT, DU, DX, RP, SR, SS, SU, TR, TU, VS

# CHANGE IN P21 SDTM METADATA

- ▶ Removed CL.COUNTRY from IT.DM.COUNTRY and ISO 3166 is chosen as codelist for COUNTRY
- ▶ Removed assigned CDISC CT codelist from TSVALNF variable and ISO 21090 is chosen



- ▶ Check for codelists (DD0033,Unknown NCI Code value for Codelist) are removed for COUNTRY and TSVALNF but the checks for the values remain.
  - ▶ SD1322 (Value for COUNTRY not found in ISO 3166)
  - ▶ SD1297 (TSVAL is populated with a value from the ISO 21090 null flavor codelist)



# CHANGES IN DEFINE.XML

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# DEFINE.XML FOR PMDA E-DATA SUBMISSION

PMDA Data Standards Catalog (2021-12-15) - 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 data definition files	Define	2.0	-	XML	2016-10-01	
Clinical study data definition files	Define	1.0	-	XML	2016-10-01	

- ▶ PMDA accepts Define.xml that is based on Define IG V1.0 and 2.0

# ALGORITHMS OF 3 RULES WERE MODIFIED IN DEFINE.XML

Rule ID		Changes
DD0021	(Invalid Standard Name value)	Added 'SEND-IG-AR' and "BIMO" standards <b>*No expected impact to PMDA submissions</b>
DD0022	(Invalid Standard Version value for standard)	Added versions: <ul style="list-style-type: none"><li>• '3.3' for SDTM-IG standard</li><li>• '1.2' for ADaM-IG standard</li><li>• '1.0' for new SEND-IG-AR standard</li><li>• '1.0' for new BIMO standard</li></ul> <b>*No expected impact to PMDA submissions</b>
DD0049	(Name/Domain/SASDatasetName mismatch)	Updated to support SQAP domains (Suppquals for associated persons)



ALGORITHM CHANGE IN CONFIG FILE HOW P21  
FINDS TARGET VARIABLES IN ADAM

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# GENERAL CONCEPT OF HOW P21 FINDS TARGET VARIABLES

## CASE 1: PMDA 1511.6

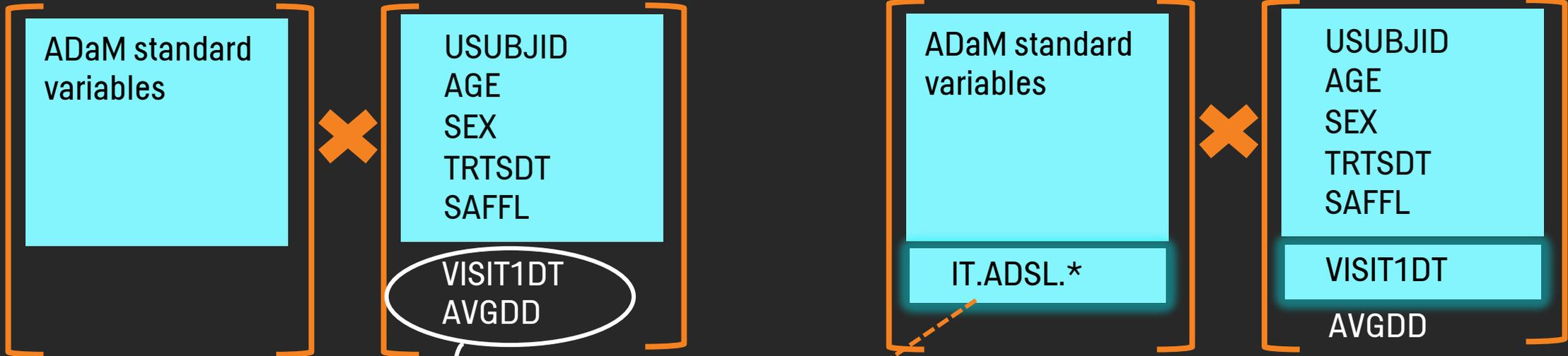
## CASE 2: PMDA 2010.2

### P21 Metadata

### ADSL (User data)

### P21 Metadata

### ADSL (User data)



Variables not in P21 Metadata were not checked

```
<ItemRef ItemOID="IT.ADSL.DTHCAUS" OrderNumber="138" Mandatory="No" Role="ADSL Subject-Level Trial Experience Variables" val:Core="Permissible"/>  
<ItemRef ItemOID="IT.ADSL.DTHCAUSN" OrderNumber="139" Mandatory="No" Role="ADSL Subject-Level Trial Experience Variables" val:Core="Permissible"/>  
<ItemRef ItemOID="IT.ADSL.DTHCGR#" OrderNumber="140" Mandatory="No" Role="ADSL Subject-Level Trial Experience Variables" val:Core="Permissible"/>  
<ItemRef ItemOID="IT.ADSL.DTHCGR#N" OrderNumber="141" Mandatory="No" Role="ADSL Subject-Level Trial Experience Variables" val:Core="Permissible"/>  
<ItemRef ItemOID="IT.ADSL.*" OrderNumber="142" Mandatory="No" Role="Representor of any additional variable" val:Core="Permissible"/>
```

<https://www.sas.com/content/dam/SAS/documents/event-collateral/2021/ja/sas-users-group-2021/slides/I3-3-nakao.pdf>

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Config file

## WHERE \* IS IMPLEMENTED

	1511.6 (IG v1.0)	1810.3 (IG v1.0)	2010.2 (IG v1.1)
ADSL	-	-	Y
ADAE	-	-	Y
BDS	-	-	Y
OCCDS	-	-	Y
ADaM Other	-	Y	Y

## P21 RECOMMENDATION

- ▶ Use PMDA guidance as major source of info
- ▶ Fix all Reject issues
- ▶ Keep the same version of validation rules for an application
- ▶ Utilize the latest version of engine
- ▶ Use the latest engine for ongoing, in-progress studies



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## IN CONCLUSION

- ▶ PMDA validation rule v3.0 is acceptable for PMDA submissions from January 1, 2022 and onward
- ▶ PMDA engine 2010.2 implements the PMDA validation rule v3.0
- ▶ With the modification and refinement of rules, the new engine runs more checks
- ▶ ADaM validation for IG v1.1 is now supported

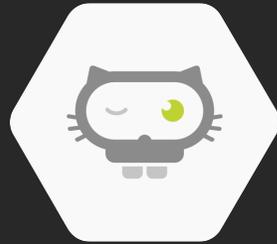
QUESTIONS?

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THANK YOU ;)

# KEEP IN TOUCH!



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