PMDA's New Validation Rules

Overview of PMDA validation rules version 2.0 and their implementation by Pinnacle 21

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December 4, 2019

PINNACLE 21

P21

Presenter – Sergiy Sirichenko

> Co-founder of OpenCDISC

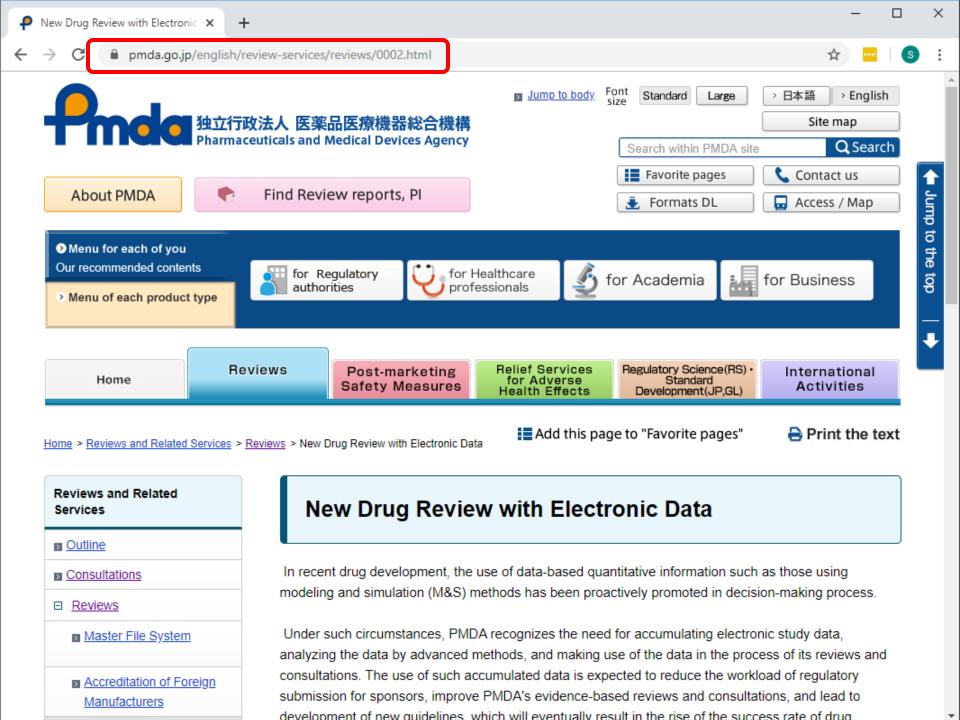> SME on FDA JumpStart, coreDF, and eDATA projects
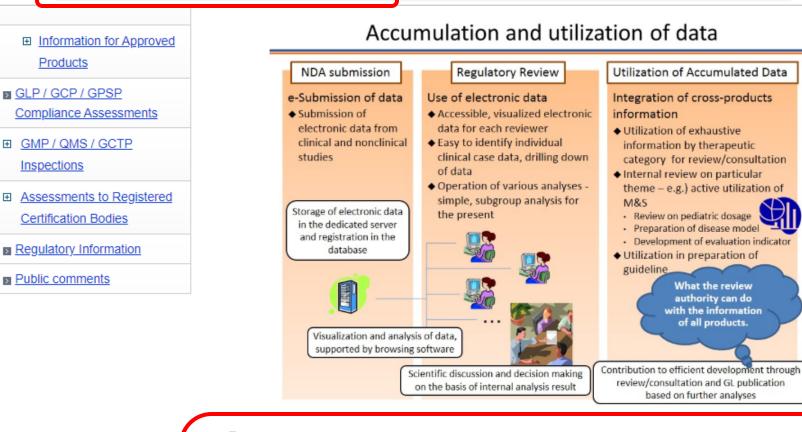
> User advocate

Submitting study data to PMDA

› Optional for now

› Required after April 1ˢᵗ, 2020

  › For all clinical trials in application depending on "Basic Principle Chapter 2.2

› PMDA guidance documents

  › http://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.html
  › https://www.pmda.go.jp/english/review-services/reviews/0002.html

  › https://www.pinnacle21.com/useful-links

    › PMDA guidance documents
    › PMDA presentations
    › Industry experience with PMDA data submissions
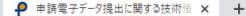
![pmda logo] 独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

▶ Jump to body

Font size | Standard | Large

› 日本語 | › English

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New Drug Review with Electronic Data

Reviews and Related Services

▶ Outline

▶ Consultations

⊟ Reviews

  ▶ Master File System

  ▶ Accreditation of Foreign Manufacturers

In recent drug development, the use of data-based quantitative information such as those using modeling and simulation (M&S) methods has been proactively promoted in decision-making process.

Under such circumstances, PMDA recognizes the need for accumulating electronic study data, analyzing the data by advanced methods, and making use of the data in the process of its reviews and consultations. The use of such accumulated data is expected to reduce the workload of regulatory submission for sponsors, improve PMDA's evidence-based reviews and consultations, and lead to development of new guidelines, which will eventually result in the rise of the success rate of drug

⊞ Information for Approved
   Products

▷ GLP / GCP / GPSP
   Compliance Assessments

⊞ GMP / QMS / GCTP
   Inspections

⊞ Assessments to Registered
   Certification Bodies

▷ Regulatory Information

▷ Public comments

Accumulation and utilization of data

NDA submission

e-Submission of data
◆ Submission of electronic data from clinical and nonclinical studies

Storage of electronic data in the dedicated server and registration in the database

Visualization and analysis of data, supported by browsing software

Regulatory Review

Use of electronic data
◆ Accessible, visualized electronic data for each reviewer
◆ Easy to identify individual clinical case data, drilling down of data
◆ Operation of various analyses - simple, subgroup analysis for the present

Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

Integration of cross-products information
◆ Utilization of exhaustive information by therapeutic category for review/consultation
◆ Internal review on particular theme – e.g.) active utilization of M&S
  · Review on pediatric dosage
  · Preparation of disease model
  · Development of evaluation indicator
◆ Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses

Jump to the top

Relevant Guidance and information

- Notifications and FAQs on Electronic Study Data Submission (2019-04-10)
- Data Standards Catalog (2019-11-01) 📄
- Study 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 (application date)

A pilot plan to confirm the feasibility of the submitted electronic data utilization system

pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0028.html

審査関連業務

⊞ 審査関連業務の概要

⊞ 相談業務

⊞ 治験関連業務

⊟ 承認審査業務（申請、審査等）

　　⊞ 申請等手続き

　　⊟ 審査等について

　　　⊟ 医療用医薬品

　　　⊟ 新医薬品

　　　　⊟ 次世代審査・相
談体制（申請時
電子データ提出）

　　　　　▸関連通知等

　　　　▸ **申請電子デー
タ提出に関す
る技術情報
（FAQ、デー
タ標準カタロ
グ等）**

　　　　　▸説明会・講演
会等

　　　　　▸申請電子デー
タ利用に関す

申請電子データ提出に関する技術情報（FAQ、データ標準カタログ等）

申請電子データ提出に関する技術情報を掲載しております。

- 申請電子データ提出に際して利用可能な規格一覧 📋 （2019年11月1日更新）

- バリデーションルール一覧（2019年9月27日更新）

バリデーションルール	受付期間（申請日）※
バージョン1.0（2015年11月18日）📋	2016年10月1日〜 2021年3月31日
バージョン2.0（2019年9月27日）📋	2020年4月1日〜

※ 申請後に申請電子データを追加提出する場合は、申請時に選択したバージョンのバリデーションルールに基づいて提出してください。

- バリデーション用ソフトウェア（2019年9月27日更新）
PMDAは申請電子データのバリデーションに『Pinnacle 21 Enterprise』を利用します。利用するソフトウェアのバージョン等は下表のとおりです。

ソフトウェアバージョン	バリデーションエンジンバージョン	稼働期間
Pinnacle 21 Enterprise 3.0.5	-	2016年10月1日〜 2020年2月21日
Pinnacle 21 Enterprise 4.0.2	1511.6（バリデーションルールバージョン1.0適用時）	2020年2月22日〜
	1810.3（バリデーションルールバージョン2.0適用時）	

Examination-related work

⊞ Overview of examination

> Please be aware that this is generic Goggle translation which may be not accurate. Do not use it as official PMDA document

⊞ Application procedures

⊟ About examination

⊟ Prescription drugs

⊟ New drug

⊟ Next-generation screening and consultation system (electronic data submission at the time of application)

▸ Related notices, etc.

▸ Technical information on electronic data submission (FAQ, data

Technical information on electronic data submission (FAQ, data standard catalog, etc.)

Technical information on submitting electronic application data is posted.

- List of standards that can be used when submitting electronic application data 📖 (updated on November 1, 2019)

- List of validation rules (updated September 27, 2019)

Validation rules	Application period (application date) *
Version 1.0 (November 18, 2015) 📖	From October 1, 2016 to March 31, 2021
Version 2.0 (September 27, 2019) 📖	From April 1, 2020

* When submitting additional electronic application data after application, please submit it based on the validation rules of the version selected at the time of application.

- Validation software (updated September 27, 2019)
  PMDA uses "Pinnacle 21 Enterprise" for validation of electronic data. The software version to be used is shown in the table below.

Software version	Validation engine version	Operation period
Pinnacle 21 Enterprise 3.0.5	-	From October 1, 2016 to February 21, 2020
Pinnacle 21 Enterprise 4.0.2	1511.6 (when validation rule version 1.0 is applied)	From February 22, 2020
	1810.3 (when validation rule version 2.0 is applied)	

PMDA Data Submissions

PMDA Guidance Documentations

- New Drug Review with Electronic Data
- Data Standards Catalog (2019-11-01)
- FAQs on Electronic Study Data Submission (in Japanese)
- FAQs on Electronic Study Data Submission (Excerpt) (English version, January 2019)
- Technical Conformance Guide (English version, January 2019)
- Study Data Validation Rules Version 1.0 (2015-11-18)
- Study Data Validation Rules Version 2.0 (2019-09-27)
- Attachment 8

PMDA Presentations

- Electronic Data Submission and Utilization in Japan
- CDISC標準準拠データの提出の現状と (Current status of submission of CDISC standard compliant data)

Industry Experience with PMDA Edata Submissions

- Understanding PMDA Engines
- Electronic Data Submission to PMDA : Our experiences and matters of concern
- Lessons Learned for Successful e-Study Data Submission to the PMDA toward the End of Transitional Period
- Challenges of Submitting Electronic Study Data to Two Authorities: the PMDA & FDA
- Process optimization for efficient and smooth e-data submissions to both FDA and PMDA

- Findings About: De-mystifying the When and How
- Considerations and Updates in the Use of Timing Variables in Submitting SDTM-Compliant Datasets
- Implementing CDISC Standards for Device-Drug Studies

ADaM

- Incremental Changes: ADaMIG v1.2 Update
- Timing is Everything: Defining ADaM Period, Subperiod and Phase
- Practical Guidance for ADaM Dataset Specifications and Define.xml

SEND

- The Benefits, Challenges and Myths of SEND

Define-XML

- Using Pinnacle 21 Enterprise for define.xml Creation: Tips and Tricks from a CRO Perspective.
- Do's and Don'ts of Define.xml
- How to use SUPPQUAL for specifying natural key variables in define.xml?

BIMO

- Clinical Development Standards for FDA Bioresearch Monitoring (BIMO) Submissions
- Sponsor Considerations for Building a Reviewer's Guide to Facilitate BIMO (Bioresearch Monitoring) Review

Recent Updates

- **Basic Principles** on Electronic Submission of Study Data for New Drug Applications and Q&A
  - The first official announcement that MHLW/PMDA will require CDISC-standardized study data for NDA.
- **Notification on Practical Operations** of Electronic Study Data Submissions and Q&A
  - Practical issues on e-Study data submission
- **Technical Conformance Guide** on Electronic Study Data Submissions
  - Technical details on e-Study data submission

Latest update on Jan 24, 2019

- **FAQ website**
  - Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and the guide

Latest update on Apr 10, 2019

- **PMDA Data Standards Catalog**
  - List of acceptable versions of Data Exchange Standards and Terminology Standards

Latest update on Mar 3, 2017

under consideration for next update

Updated on Nov 1, 2019

- Information about CDISC **Validation**
  - Validation software version, List of PMDA validation rules

Latest update on Sep 27, 2019

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PMDA data submission process

› Separate from submission of documents

› Several weeks before final submission

› Series of PMDA consultation meetings

    › Preparation

    › Data format

    › Exemption

› Reconciliation of data validation results

Reconciliation of validation results

› PMDA validates with Pinnacle 21 Enterprise

› PMDA compares results with those reported by sponsor

› Focus on *Reject* and *Error* issues

› Missing or extra issues require investigation

  › Version of P21 engine, how it's configured

  › Correct execution of validation

  › False-positive results must be reported

Severity

› *Reject*
  › Rules which, if violated, will cause the review to be suspended until corrections have been made

› *Error*
  › Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made

› *Warning*
  › Rules which, even when violated, will not necessarily require any explanation

Versions of PMDA validation rules

› Version 1.0

  › released in 2015

  › for submissions before April 1, 2020

  › additional 1 year optional "*grace*" period

› Version 2.0

  › published in September 2019

  › for submissions starting April 1, 2020

Rules document structure

› Excel format

› Columns

- › Rule ID (same as Pinnacle 21 Rule ID)
- › Message, Description
- › Domains, PMDA Severity
- › Standards, PMDA Notes

PMDA Study Data Validation Rules
Change History

Date (YYYY/MM/DD)	Sheet Name	Version #	Description
2015/11/18	SDTM Rules	1.0	Initial version.
2015/11/18	ADaM Rules	1.0	Initial version.
2015/11/18	Define-XML Rules	1.0	Initial version.
2019/09/27	SDTM Rules	2.0	Updated with consideration for the conformance rules by CDISC, system update, etc.
2019/09/27	ADaM Rules	2.0	Updated with consideration for the conformance rules by CDISC, system update, etc.
2019/09/27	Define-XML Rules	2.0	Updated with consideration for system update, etc.

Severity:
Reject : Rules which, if violated, will cause the review to be suspended until corrections have been made.
Error : Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made.
Warning : Rules which, even when violated, will not necessarily require any explanation.

SDTM Rules v2.0

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	3.1.2	3.1.3	3.2	PMDA NOTES
CT2001	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL	Reject	X	X	X	Violation of CT2001 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors. <Variable Name (Codelist Name)> AGEU (AGEU) COUNTRY (COUNTRY) IECAT (IECAT) RELTYPE (RELTYPE) SEX (SEX) --BLFL (NY) --DRVFL (NY) --FAST (NY) --OCCUR (NY) --PRESP (NY) AESER (NY) AESCONG (NY) AESDISAB (NY) AESDTH (NY) AESHOSP (NY) AESLIFE (NY) AECONTRT (NY) AESCAN (NY) AESMIE (NY) AESOD (NY) IEORRES (NY) IESTRESC (NY)
CT2002	<Variable Name> value not found in '<Codelist Name>' extensible codelist	Variable should be populated with terms from its CDISC controlled terminology codelist. New terms can be added as long as they are not duplicates, synonyms or subsets of existing standard terms.	ALL	Warning	X	X	X	
CT2003	<Variable Name> and <DecodedVariable Name> values do not have the same Code in CDISC CT	Paired variables such as TEST/TESTCD must be populated using terms with the same Codelist Code value in CDISC control terminology. There is one-to-one relationship between paired variable values defined in CDISC control terminology by Codelist Code value.	ALL	Error	X	X	X	
CT2004	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS	Reject	X	X	X	Violation of CT2004 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors. <Variable Name (Codelist Name)> TSVAL when TSPARMCD value is SEXPOP (SEXPOP) TSVAL when TSPARMCD value is ADDON (NY)
CT2005	<Variable Name> value not found in '<Codelist Name>' extensible codelist	Variable should be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms can be added as long as they are not duplicates, synonyms or subsets of existing	DS, SC, TS, VS	Warning	X	X	X	

SDTM Rules v2.0

Severity:
    Reject   : Rules which, if violated, will cause the review to be suspended until corrections have been made.
    Error   : Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made.
    Warning : Rules which, even when violated, will not necessarily require any explanation.

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	3.1.2	3.1.3	3.2	PMDA NOTES
CT2001	\<Variable Name> value not found in '\<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL	Reject	X	X	X	Violation of CT2001 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors. \<Variable Name (Codelist Name)> AGEU (AGEU) COUNTRY (COUNTRY) IECAT (IECAT) RELTYPE (RELTYPE) SEX (SEX) --BLFL (NY) --DRVFL (NY) --FAST (NY) --OCCUR (NY) --PRESP (NY) AESER (NY) AESCONG (NY) AESDISAB (NY) AESDTH (NY) AESHOSP (NY) AESLIFE (NY) AECONTRT (NY) AESCAN (NY) AESMIE (NY) AESOD (NY) IEORRES (NY) IESTRESC (NY)
CT2002	\<Variable Name> value not found in '\<Codelist Name>' extensible codelist	Variable should be populated with terms from its CDISC controlled terminology codelist. New terms can be added as long as they are not duplicates, synonyms or subsets of existing standard terms.	ALL	Warning	X	X	X	
CT2003	\<Variable Name> and \<DecodedVariable Name> values do not have the same Code in CDISC CT	Paired variables such as TEST/TESTCD must be populated using terms with the same Codelist Code value in CDISC control terminology. There is one-to-one relationship between paired variable values defined in CDISC control terminology by Codelist Code value.	ALL	Error	X	X	X	
CT2004	\<Variable Name> value not found in '\<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS	Reject	X	X	X	Violation of CT2004 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors. \<Variable Name (Codelist Name)> TSVAL when TSPARMCD value is SEXPOP (SEXPOP) TSVAL when TSPARMCD value is ADDON (NY)
CT2005	\<Variable Name> value not found in '\<Codelist Name>' extensible codelist	Variable should be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms can be added as long as they are not duplicates, synonyms or subsets of existing	DS, SC, TS, VS	Warning	X	X	X	

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RULE ID	MESSAGE	PMDA Severity	3.1.2	3.1.3	3.2	PMDA NOTES
CT2001	\<Variable Name\> value not found in '\<Codelist Name\>' non-extensible codelist	Reject	X	X	X	Violation of CT2001 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors. \<Variable Name (Codelist Name)\> AGEU (AGEU) COUNTRY (COUNTRY) IECAT (IECAT) RELTYPE (RELTYPE) SEX (SEX) --BLFL (NY) --DRVFL (NY) --FAST (NY) --OCCUR (NY) --PRESP (NY) AESER (NY)

Pinnacle 21 Japan

› New office in Tokyo

› Managed by Chikaaki Nakao

› Support for Japanese users

Pinnacle 21 support for PMDA rules

› Version 1.0

  › P21 Enterprise v3.0.5 or engine 1511.6 in v4+

  › P21 Community v2.1.3 or engine 1511.6 in v3+

  › *"PMDA Legacy (1511.6)"*

› Version 2.0

  › P21 engine 1810.3 in both Enterprise v4+ and Community v3+

  › *"PMDA (1810.3)"*

PINNACLE 21

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SDTM　　SEND　　ADAM　　DEFINE-XML

Search

[ALL] [FDA] [PMDA 1511.6] [PMDA 1810.3]

Rule ID ▲	Publisher ID	Message	Description	Domains	FDA	PMDA 1511.6	PMDA 1810.3	FDA Severity	PMDA Severity	3.1.2	3.1.3	3.2	Notes
CT2001	CG0020, CG0085, CG0131, CG0232-CG0235, CG0387-CG0396	Variable value not found in non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL	X	X	X	Reject		X	X	X	💬
CT2002	CG0021	Variable value not found in extensible codelist	Variable should be populated with terms from its CDISC controlled terminology codelist. New terms can be added as long as they are not duplicates, synonyms or subsets of existing standard terms.	ALL	X	X	X		Warning	X	X	X	
CT2003	CG0021	Coded and Decoded values do not have the same Code in CDISC CT	Paired variables such as TEST/TESTCD must be populated using terms with the same Codelist Code value in CDISC control terminology. There is one-to-one relationship between paired variable values defined in CDISC control terminology by Codelist Code value.	ALL	X	X	X		Error	X	X	X	
CT2004	CG0021	Variable value not found in non-extensible codelist when value-level condition occurs	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS	X	X	X	Reject		X	X	X	💬
			Variable should be populated with terms from its CDISC										

https://www.pinnacle21.com/validation-rules/sdtm

https://www.pinnacle21.com/validation-rules/sdtm

pinnacle21.com/validation-rules/sdtm

Search | ALL | FDA | PMDA 1511.6 | PMD…

Rule Notes for CT2001

```
PMDA: Violation of CT2001 for the following variable/codelist pairs will be
considered part of Rejection criteria. All others will be considered
Errors.

<Variable Name (Codelist Name)>
AGEU (AGEU)
COUNTRY (COUNTRY)
IECAT (IECAT)
RELTYPE (RELTYPE)
SEX (SEX)
--BLFL (NY)
--DRVFL (NY)
--FAST (NY)
--OCCUR (NY)
--PRESP (NY)
AESER (NY)
AESCONG (NY)
AESDISAB (NY)
AESDTH (NY)
AESHOSP (NY)
AESLIFE (NY)
AECONTRT (NY)
AESCAN (NY)
AESMIE (NY)
AESOD (NY)
IEORRES (NY)
IESTRESC (NY)
--STAT (ND)
```

CLOSE

Rule ID	Publisher ID	Message	D…	…DA everity	PMDA Severity	3.1.2	3.1.3	3.2	Notes
CT2001	CG0020, CG0085, CG0131, CG0232-CG0235, CG0387-CG0396	Variable value not found in non-extensible codelist	Var… term… term… can… ext…		Reject	X	X	X	💬
CT2002	CG0021	Variable value not found in extensible codelist	Var… term… term… can… not… sub… term…		Warning	X	X	X	
CT2003	CG0021	Coded and Decoded values do not have the same Code in CDISC CT	Par… TE:… pop… sar… CD… is … bet… defined in CDISC control terminology by Codelist Code value.		Error	X	X	X	
CT2004	CG0021	Variable value not found in non-extensible codelist when value-level condition occurs	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS		Reject	X	X	X	💬
CT2005	CG0021	Variable value not found in extensible codelist when value-level condition occurs	Variable should be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms can be added as long as	DS, SC, TS, VS		Warning	X	X	X	

pinnacle21.com/validation-rules/sdtm

SDTM   SEND   ADAM   DEFINE-XML

Search | ALL | FDA | PMDA 1511.6 | PMDA 1810.3 |

Rule ID ▲	Publisher ID	Message	Description	Domains	FDA	PMDA 1511.6	PMDA 1810.3	FDA Severity	PMDA Severity	3.1.2	3.1.3	3.2	Notes
SD0004	CG0413	Inconsistent value for DOMAIN	Domain Abbreviation (DOMAIN) variable should be consistent with the name of the dataset.	ALL	X	X	X	Warning		X	X	X	
SD0005	CG0028	Duplicate value for --SEQ variable	The value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within each Unique Subject Identifier (USUBJID), Pool Identifier (POOLID) or Sponsor Device Identifier (SPDEVID) variables value when they are present in the domain.	ALL	X		X	Error		X	X	X	
SD0005	CG0028	Duplicate value for --SEQ variable	The value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within each Unique Subject Identifier (USUBJID) or Pool Identifier (POOLID) variables value when they are present in the domain.	ALL	X	X		Error		X	X	X	
SD0006	FDAB013	No baseline flag record in Domain for subject	All subjects should have at least one baseline observation (--BLFL = 'Y') in EG, LB, MB, MS, PC and VS domains, except for subjects who failed screening (ARMCD = 'SCRNFAIL') or were not fully assigned to an Arm (ARMCD = 'NOTASSGN') or were not treated (ACTARMCD = 'NOTTRT').	EG, LB, MB, MS, PC, VS	X	X	X	Warning		X	X	X	
SD0007	FDAB030	Inconsistent value for Standard Units	Standard Units (--STRESU) must be consistent for all records with the same Short Name of Measurement, Test or Examination (--TESTCD), Category (--CAT), Subcategory (--SCAT), Specimen Type (--SPEC...	FINDINGS	X	X	X	Warning		X	X	X	

Found 471 records

What is new in PMDA rules v2.0?

- › New rules
- › Modified rules
- › Changes in rule assignments
- › No changes in Severity

P²¹

Supported data standards

› No changes in v2.0

› SDTM-IG 3.1.2, 3.1.3, 3.2

› ADaM-IG 1.0

› Define-XML 1.0, 2.0

Summary of rules changes

Rules	SDTM	ADaM	Define-XML
New	115	15	33
Removed	4	2	4
Algorithm change	38	9	
Description/Message	22/7	4/2	10
Rules assignments	+76/-4	+4/-3	
Other	Medical Devices	ADaM OTHER	

ADaM OTHER

› Datasets with name AD*, but not ADSL, BDS or ADAE

   › Now OCCDS is recognized and validated as ADAM OTHER in ADaM-IG 1.0

   › Before OCCDS datasets were incorrectly validated as BDS

› Basic validation for common rules

Examples of new rules

› Value-Level Metadata in define.xml vs. data

› TS domains rules

› New SDTM rules from CDISC

› Analysis Result Metadata (ARM) rules for Define-XML

Bug fixes and enhancements

› ADaM variables which include place holders

   › TRTxxP, TRxxPGy, ANLzzFL, etc.

      › Old: TRT*P – "*" means any value

      › New: TRT#P – "#" means any digits

› Duplicate value for --SEQ variable

   › Added SPDEVID

› Subject is not present in DM domain (Reject)

   › The rule algorithm was tuned to cover cases if the same subject (USUBJID) is enrolled on multiple sites (SITEID)

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Reject Rules

Standard	# of Reject Rules
SDTM	9
ADaM	13 (+1)
Define-XML	14 (+1)

Reject rules (SDTM)

RULE ID	MESSAGE	DESCRIPTION	DOMAINS
CT2001	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL
CT2004	<Variable Name> value not found in '<Codelist Name>' non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist, when its value level condition is met. New terms cannot be added into non-extensible codelists.	QS, TS
SD0002	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL
SD0056	SDTM Required variable not found	Variables described in SDTM IG as Required must be included in the dataset.	ALL
SD0062	Incompatible data source	Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited).	ALL
SD0064	Subject is not present in DM domain	All Subjects (USUBJID) must be present in Demographics (DM) domain.	ALL
SD1020	Missing DM dataset	Demographics (DM) dataset must be included in every submission.	DM
SD1073	Variable prohibited for use in SDTM	Variables described in IG as inappropriate for usage must be not included in the dataset.	ALL
SD1074	Variable which can be used only in SEND	Variables designed only for SEND pre-clinical studies must be not included in the SDTM dataset.	ALL

Reject rules (ADaM)

RULE ID	MESSAGE	DESCRIPTION	DOMAINS
AD0001	Missing ADSL dataset	ADaM Subject level (ADSL) dataset should be included in every submission.	ADSL
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,ITTFL,PPROTFL,SAFFL,RANDFL,ENRLFL cannot be null and at least 1 must be included in ADSL).	ALL
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,ENRLFN cannot be null and at least 1 must be included in ADSL).	ALL
AD0033	*RFL value is not Y or null	A variable with a suffix of RFL must have a value that is Y or null (R = record level flag variable).	BDS, ADAMOTHER
AD0034	*PFL value is not Y or null	A variable with a suffix of PFL must have a value that is Y or null (P = parameter level flag variable).	BDS, ADAMOTHER
AD0035	*RFN value is not 1 or null	A variable with a suffix of RFN must have a value that is 1 or null (R = record level flag variable).	BDS, ADAMOTHER
AD0036	*PFN value is not 1 or null	A variable with a suffix of PFN must have a value that is 1 or null (P = parameter level flag variable).	BDS, ADAMOTHER
AD0176	ABLFL value is not Y or null	ABLFL (Analysis Baseline Flag character) must be Y or null. For parameter-level and record-level character population flag variables: Y = yes (included). Null values are allowed (ADaM IG v1.0 p.13).	BDS
AD0178	ANLzzFL value is not Y or null	A variable of form ANLzzFL (analysis record flag) must be Y or null. Also mentioned in ADAE IG v1.0 p.16.	BDS, ADAE, ADAMOTHER
AD0211	ABLFN value is not 1 or null	ABLFN (Analysis Baseline Flag Numeric) must be 1 or null. For parameter-level and record-level numeric population flag variables: 1 = yes (included). Null values are allowed (ADaM IG v1.0 p.13).	BDS
AD0212	ANLzzFN value is not 1 or null	ANLzzFN (Analyzed Record Flag zz Numeric) must be 1 or null. For parameter-level and record-level numeric population flag variables: 1 = yes (included). Null values are allowed.	BDS, ADAE, ADAMOTHER
CT2001	Variable value not found in non-extensible codelist	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists.	ALL
SD0062	Incompatible data source	Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited).	ALL

Reject rules (Define-XML)

RULE ID	MESSAGE	DESCRIPTION
DD0001	XML schema validation issue within Define.xml	There is an XML schema validation issue with either Define.xml structure or content that is not covered by one of the other rules. It is most likely an issue with element declarations.
DD0002	Missing or invalid <namespace> namespace reference	Define.xml must reference the following namespaces: 1) CDISC ODM xmlns="http://www.cdisc.org/ns/odm/v1.3" for Define-XML v2.0 or xmlns="http://www.cdisc.org/ns/odm/v1.2" for Define-XML v1.0; 2) CDISC Define xmlns:def="http://www.cdisc.org/ns/def/v2.0" for Define-XML v2.0 or xmlns:def="http://www.cdisc.org/ns/def/v1.0 for Define-XML v1.0; 3) XML Schema Instance xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"; and 4) XLink xmlns:xlink="http://www.w3.org/1999/xlink". The XML Schema Instance namespace is only required when a local schema is provided, while the XLink namespace is only required when external documents are provided.
DD0003	Missing required <attribute> value for <object>	Required attributes must be included in Define.xml and cannot be empty.
DD0006	Missing required <element> value	Required elements must be included in Define.xml and cannot be empty.
DD0020	Invalid def:DefineVersion	The def:DefineVersion should have a value of '1.0.0' for Define-XML v1.0 and '2.0.0' for Define-XML v2.0.
DD0021	Invalid Standard Name value <value>	Allowable values of Standard Name are: 'SDTM-IG', 'SEND-IG', or 'ADaM-IG' for Define-XML v2.0 or 'CDISC SDTM', 'CDISC SEND' or 'CDISC ADaM' for Define-XML v1.0. Values must conform to this list of values. Define-XML specification represents Standard Name as def:StandardName attribute on MetaDataVersion element. Note: Refer to the data standards catalog by the relevant Regulatory Agency for acceptance of standards and their versions.
DD0022	Invalid Standard Version value <value> for <standard>	Standard Version must have a valid value for the given Standard Name. Allowed values are '3.1.2', '3.1.3', or '3.2' for SDTM-IG, '3.0' or '3.1' for SEND-IG, and '1.0' or '1.1 for ADaM-IG. Define-XML specification represents Standard Version as def:StandardVersion attribute on MetaDataVersion element. Note: Refer to the data standards catalog by the relevant Regulatory Agency for acceptance of standards and their versions.
DD0025	Invalid MedDRA Version <version>	MedDRA version must be set to decimal value ending with 0 or 1, for example '9.0' or '14.1'. Define-XML specification represents MedDRA version as Version attribute on ExternalCodeList element within CodeList element.
DD0101	Missing define.xml file	Guidance provided by regulatory agencies (FDA and PMDA) states that eCTD submissions must include a define.xml file for each study in Module 4 (nonclinical) and Module 5 (clinical). Note: Refer to the data standards catalog by the relevant Regulatory Agency for acceptance of standards and their versions.
OD0001	XML is not well-formed	Define.xml must contain well-formed XML.
OD0010	Missing XML declaration	Define.xml must start with an XML declaration.
OD0012	Invalid root element	Define.xml must contain a root element called ODM.
OD0022	Duplicate Study OID	The OID attribute for Study element must be unique within a related series of ODM documents.
OD0027	Duplicate MetaDataVersion OID	The OID attribute for MetaDataVersion element must be unique within a single study.

Reject Rules (Exceptions)

› Violation of CT2001 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors.

Variable	Codelist
AGEU	AGEU
COUNTRY	COUNTRY
IECAT	IECAT
RELTYPE	RELTYPE
SEX	SEX
--BLFL	NY
--DRVFL	NY
--FAST	NY

Variable	Codelist
--OCCUR	NY
--PRESP	NY
AESER	NY
AESCONG	NY
AESDISAB	NY
AESDTH	NY
AESHOSP	NY
AESLIFE	NY

Variable	Codelist
AECONTR	NY
AESCAN	NY
AESMIE	NY
AESOD	NY
IEORRES	NY
IESTRESC	NY
--STAT	ND

Reject Rules (Exceptions)

› Violation of CT2004 for the following variable/codelist pairs will be considered part of Rejection criteria. All others will be considered Errors.

Variable	Codelist
TSVAL when TSPARMCD value is SEXPOP	SEXPOP
TSVAL when TSPARMCD value is ADDON	NY
TSVAL when TSPARMCD value is RANDOM	NY

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Reject Rules (Exceptions)

› Violation of SD0002 will be considered part of Rejection criteria, except for the following variables in DM domain that will be considered

Variable
ARMCD
ARM
ACTARMCD
ACTARM

New Reject rules

› ## ADaM

› SD0062: *Incompatible data source*

› Assignments of some Reject rules to other domains

› *AD0005: '*FL value is not Y, N or null* – expended from ADSL to all datasets

› AD0033: *RFL value is not Y or null – extended from BDS to ADAMOTHER

› ENRFL (used as *Enrolment Flag*) – an example of invalid custom variable (instead of *Record Level Flag*) which may create a *Reject* issue

› ## Define-XML

› DD0101: *Missing define.xml file*

New Error rules

› ## SDTM – 47

  › SD1233: *Device is not present in DI domain*

  › SD1254: *DTHFL does not equal 'Y' when AE.AEOUT = 'FATAL'*

  › SD1273: *--TRT equals 'OTHER'*

› ## ADaM – 12

  › AD0253: *Record key from SDTM AE is not traceable to ADaM ADAE (not enough ADAE recs)*

  › AD0011: **FL = N and *FN != 0*

› ## Define-XML – 19

  › DD0012: *Missing MedDRA definition*

  › DD0008: *Element in wrong position within Define.xml*

  › DD0092: *Missing required ParameterOID*

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What engine should I use?

› Select your version of PMDA rules based
on date of your submission

    › Before April 1, 2020

        › Rules v1.0, Engine 1511.6

    › After April 1, 2020

        › Rules v2.0, Engine 1810.3

        › Rules v1.0 is still optional until April 1, 2021

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Community validation

› Use Community version 3.0 or above

› Set up MedDRA

› Stay on-line with your Pinnacle ID during validation

› Look for potential problems on Validation Summary page

› Add AE, DM and EX domains when validating ADaM datasets

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Questions

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