



DS10-FDA & PMDA Validation Rules – What, Why, and How.... but Should You Care?

PHUSE (Virtual) US Connect 2021
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FDA Business Rules

- Help ensure that the study data are compliant, useful and will support meaningful review and analysis
- Applicable to SDTM formatted clinical studies and SEND formatted non-clinical studies
- Human readable
- Reflect current FDA business practice and regulatory review requirements transparently
- Updated regularly
- Aligns with Study Data Technical Conformance
- Used by FDA validator in CDER and CBER

FDA Business Rules Version 1.5, June 2019

<i>Version 1.5 finalized June 2019</i>	
FDA Business Rule ID	FDA Business Rule
Clinical and Nonclinical	
FDAB008	All treatment exposure date/time should be between first and last study treatment date/time.
FDAB009	All paired variables should have a one-to-one relationship. Examples include short name and name of test; parameter name and parameter code or number; variable name and variable label, etc.
FDAB011	All trial design data should be submitted as specified in the FDA Study Data Technical Conformance Guide (TCG).
FDAB012	Deprecated in v1.5.
FDAB013	Deprecated in v1.5.
FDAB015	Character values should not have leading spaces or only have a period character.
FDAB016	Collection study day should be populated when date/time of collection is available.
FDAB017	Controlled terms should use the exact term (case, spelling, and punctuation) used by the terminology maintenance organizations (e.g., MedDRA, CDISC controlled terminology).
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPQUAL).
FDAB019	SUPPQUAL variable length should be no longer than the maximum length of the actual data within the dataset.
FDAB020	Deprecated in v1.5.
FDAB021	Deprecated in v1.5.
FDAB024	Large datasets should be split into smaller datasets no larger than 5 GB in size.
FDAB026	Records with a baseline flag should have a corresponding standard result with a standardized unit where available.
FDAB027	Deprecated in v1.5.
FDAB029	Deprecated in v1.5.
FDAB030	Standard units should be consistent within the same assessment (having the same --TESTCD, --CAT, --SCAT, --SPEC, --METHOD values).

FDA Business Rule ID – This is a unique FDA-assigned code for the FDA Business Rule.

FDA Business Rule – This is a human readable description of the FDA Business Rule.

FDA Validation Rules

- Used by FDA to ensure data are standards compliant & support meaningful review and analysis
- Applicable to SDTM formatted clinical studies and SEND formatted non-clinical studies
- Human readable
- The validator rules accompany the business rules which provide details regarding FDA's assessment of study data for purposes of review and analysis.
- Updated regularly
- Aligns with Study Data Technical Conformance
- Used by FDA validator in CDER and CBER

FDA Validation Rules Version 1.3, October 2018

version 1.3, finalized October 2018

FDA Validator Rule ID	FDA Validator Message	Publisher	Publisher ID	Business or Conformance Rule Validated	FDA Validator Rule	Domains	SDTM 3.1.2	SDTM 3.1.3	SDTM 3.2	SEND 3.0	SEND 3.1
SD1097	No Treatment Emergent info for Adverse Event	FDA	FDAB001	A treatment-emergent flag must be submitted.	A treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3.	SUPPAE	X	X	X		
SD1321	No Treatment Emergent info for Adverse Event (missing SUPPAE)	FDA	FDAB001	A treatment-emergent flag must be submitted.	A treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3.	AE	X	X	X		
SD1037	Missing value for --TOX, when --TOXGR is populated	FDA	FDAB002	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is greater than 0.	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is populated and greater than 0.	AE, MH, CE, EG, LB, PC, PP	X	X	X		
SD0008	Value for --DECOD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for the Dictionary-Derived Term (--DECOD) variable must be populated using a Preferred Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE	X	X	X		
SD1114	Value for --BODSYS not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Body System or Organ Class (--BODSYS) variable must be populated using a System Organ Class of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE	X	X	X		
SD2007	Value for --PTCD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Preferred Term Code (--PTCD) variable must be populated using a Preferred Term Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X		
SD2008	Value for --LLT not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Lowest Level Term (--LLT) variable must be populated using a Lowest Level Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X		
SD2010	Value for --HLT not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for High Level Term (--HLT) variable must be populated using a High Level Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X		
SD2011	Value for --HLTCD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for High Level Term Code (--HLTCD) variable must be populated using a High Level Term Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X		
SD2012	Value for --HLGT not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for High Level Group Term (--HLGT) variable must be populated using a High Level Group Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X		
SD2013	Value for --HLGTC not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for High Level Group Term Code (--HLGTC) variable must be populated using a High Level Group Term Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X		
SD2014	Value for --BDSYCD not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for Body System or Organ Class Code (--BDSYCD) variable should be populated using a System Organ Class Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X		
SD2015	Value for --SOC not found in MedDRA dictionary	FDA	FDAB003	Adverse Events must be coded using MedDRA dictionary.	Value for System Organ Class (--SOC) variable must be populated using a System Organ Class of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X		

Validation Rules Content

- **FDA Validator Rule ID** - This is a unique code assigned to an individual FDA Validator Rule.
- **FDA Validator Message** - This message displayed by the FDA Validator when the data being validated triggers a specific check.
- **Publisher** - Publisher of the content being validated by a specific FDA Validator Rule.
- **Publisher ID** - The unique code assigned to a specific rule (ex. business or conformance) by the publisher.
- **Business of Conformance Rule Validated** - Human readable description of the Publisher's rule being validated by a specific FDA Validator Rule.
- **FDA Validator Rule** - The description of a specific FDA Validator Rule.
- **Domains** – The CDISC SDTM and SEND data domains referenced by the FDA validator rule.
- **SDTM and SEND Versions** – Indicates that the FDA validator rule applies to this version of the standard.

PMDA Rules

- Submission of all clinical trials study data to PMDA (Pharmaceuticals and Medical Devices Agency) before 1st April 2020 should follow PMDA rules v 1.0, anything beyond 1st April 2020 should follow PMDA rules v 2.0
- **PMDA rules versions**
 - Version 1.0 released on 18 November 2015
 - Version 2.0 released on 27 September 2019

PMDA Rules Version 2.0

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.								
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) --PRES (NY) AESER (NY) AESCONG (NY) AESDISAB (NY) AESDTH (NY) AESHOSP (NY) AESLIFE (NY) AECONTRT (NY) AESCAN (NY) AESMIE (NY) AESOD (NY) IECORRES (NY) IESTRESC (NY) --STAT (ND)
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)

PMDA Rules Version 1.0 vs 2.0

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	

FDA vs PMDA

- Except for severity, rules are consistent across FDA and PMDA

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

FDA vs PMDA

- Even though PMDA has Reject criteria, FDA rules are far more stringent

	FDA	PMDA
	Pinnacle 21 Engine 2010.0 uses rules from October 2018	Pinnacle 21 Engine 1810.3 uses rules v 2.0 from September 2019
Number of rules	314	326
Severity		
Reject	4	9
Error	201	128
Warning	113	189

FDA vs PMDA

FDA Rule	PMDA Rule	Change
SD1071: Dataset is greater than 1 GB in size	SD1142: Dataset is greater than 5 GB in size	PMDA can support larger datasets of 5 GB
SD1077: FDA Expected variable not found	SD1140: PMDA Expected variable not found	FDA expects ELEMENT and EPOCH, while PMDA expects --BLFL and EPOCH
SD1097: No Treatment Emergent info for Adverse Event	SD1141: No Treatment Emergent info for Adverse Event	Change in Description
SD0008: Value for --DECOD not found in MedDRA dictionary	Same	PMDA limits this check to AE domain only
SD0008C: Value for --DECOD is in incorrect case	Same	PMDA limits this check to AE domain only

FDA vs PMDA

- Below is a screenshot of Issues Summary from P21 Enterprise for Adverse Events domain

Pinnacle 21 Enterprise Validation Report					
Issue Summary					
Dataset	Rule ID	Publisher ID	Message	FDA	PMDA
AE	SD0002	FDAB027, CG0014, CG0208	NULL value in AEDECOD variable marked as Required	Error	Reject
AE	SD0009	CG0042	No qualifiers set to 'Y', when AE is Serious	Error	Warning
AE	SD0080	FDAB034	AE start date is after the latest Disposition date	Error	Warning
AE	SD0090	FDAB010	AESDTH is not 'Y', when AEOU='FATAL'	Error	Warning
AE	SD2008	FDAB003, CG0377	Value for AELLT not found in MedDRA dictionary	Error	Error
AE	SD1339	FDAB022	Missing EPOCH value, when a start or observation date is provided	Warning	NA
AE	SD1440	FDAB003	Inconsistent value for AEDECOD within AETERM	Warning	NA
AE	SD1441	FDAB003	Inconsistent value for AEHLT within AETERM	Warning	NA
AE	SD1442	FDAB003	Inconsistent value for AEHLGT within AETERM	Warning	NA
AE	SD1443	FDAB003	Inconsistent value for AEBODSYS within AETERM	Warning	NA
AE	SD1444	FDAB003	Inconsistent value for AESOC within AETERM	Warning	NA

FDA vs PMDA

- Even though PMDA has Reject criteria, FDA rules are far more stringent
- More important, the expected handling of findings differs between PMDA and FDA.
- The FDA expects sponsors to either correct any discrepancies between study data and the standard or the business rules or explain meaningful discrepancies in the Reviewer Guide.
- The PMDA has specified the impact of violations according to severity.

For example, if a rule categorized as “Reject” is violated it will cause the review to be suspended until corrections have been made. [2] In consequence, it is recommended to resolve as many violations as possible and to agree in e-data consultation what is acceptable if anything is left

WHY SHOULD WE CARE?

PROS

- Data Integrity & Quality
- Efficiency
- FDA and PMDA expectations
- Significantly reduces the review time for regulatory agencies

WHY SHOULD WE CARE?

CONS

- Significant amount of time and resource investment initially
- Ambiguity of rules at times leading to error in judgement

FDA Business Rule ID	FDA Business Rule
FDAB018	A variable's length across a study should be no longer than the maximum length of the actual data (except for SUPPQUAL).
FDAB019	SUPPQUAL variable length should be no longer than the maximum length of the actual data within the dataset.

WHY SHOULD WE CARE?

CONS

- Not all issues can be fixed
- Frequent updates to the rules

Pinnacle 21 Enterprise Validation Report						
Issue Summary						
Dataset	Rule ID	Publisher ID	Message	FDA	PMDA	
TS	CT2006	FDAB009, CG0021	TSVALCD and TSVAL values do not have the same Code in CDISC CT when TSPARMCD == 'RANDOM'	Error	Error	
TS	SD1278	CG0265	Inconsistent value for TSVALCD within TSVAL	Warning	Error	
TS	SD2273	FDAB011	Missing EXTIND Trial Summary Parameter	Warning	NA	
TS	SD2274	FDAB011	Missing NCOHORT Trial Summary Parameter	Warning	NA	
TS	SD2276	FDAB011	Missing PDPSTIND Trial Summary Parameter	Warning	NA	
TS	SD2277	FDAB011	Missing PDSTIND Trial Summary Parameter	Warning	NA	
TS	SD2278	FDAB011	Missing PIPIND Trial Summary Parameter	Warning	NA	
TS	SD2280	FDAB011	Missing SDTIGVER Trial Summary Parameter	Warning	NA	
TS	SD2281	FDAB011	Missing SDTMVER Trial Summary Parameter	Warning	NA	
TS	SD1076	CG0013	Model permissible variable added into standard domain	Notice	Notice	

Recommendations

- Early planning and strategy is important if the same submission package is submitted to FDA and PMDA.
- Communication with the authorities as early as possible is highly recommended.
- A subject matter expert for submissions supporting the submission teams can be very helpful.
- A high level of harmonization across regulatory agencies is already in place. Further harmonization would be helpful.

Recommendations

- The better understanding of how e-data are processed facilitates a smooth review process.
- Always use the latest available validation rules and latest version of Pinnacle 21 tools
- Fix all issues that are fixable and explain the rest
- Follow “Continuous Compliance” approach, catch and fix data issues as early as possible

References

- <https://www.lexjansen.com/phuse/2018/sa/SA02.pdf>
- <https://www.lexjansen.com/pharmasug/2019/FDA/PharmaSUG-2019-FDA-G003.pdf>
- <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>
- <https://www.pinnacle21.com/sites/default/files/blog/2016/01/P21-PMDA-Validation-Rules.pdf>

CONTACT INFORMATION

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