PMDA Validation Rules

Preparing for your next submission to Japanese Pharmaceuticals and Medical Devices Agency

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PINNACLE 21

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Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the Pharmaceuticals and Medical Devices Agency and Food and Drug Administration.

Topics

- Rebranding and new releases
- PMDA guidance and validation rules
- Rule structure and content
- Comparison between PMDA and FDA
- Using Pinnacle 21 tools to prepare for PMDA submission
- Recommendations

OpenCDISC has rebranded

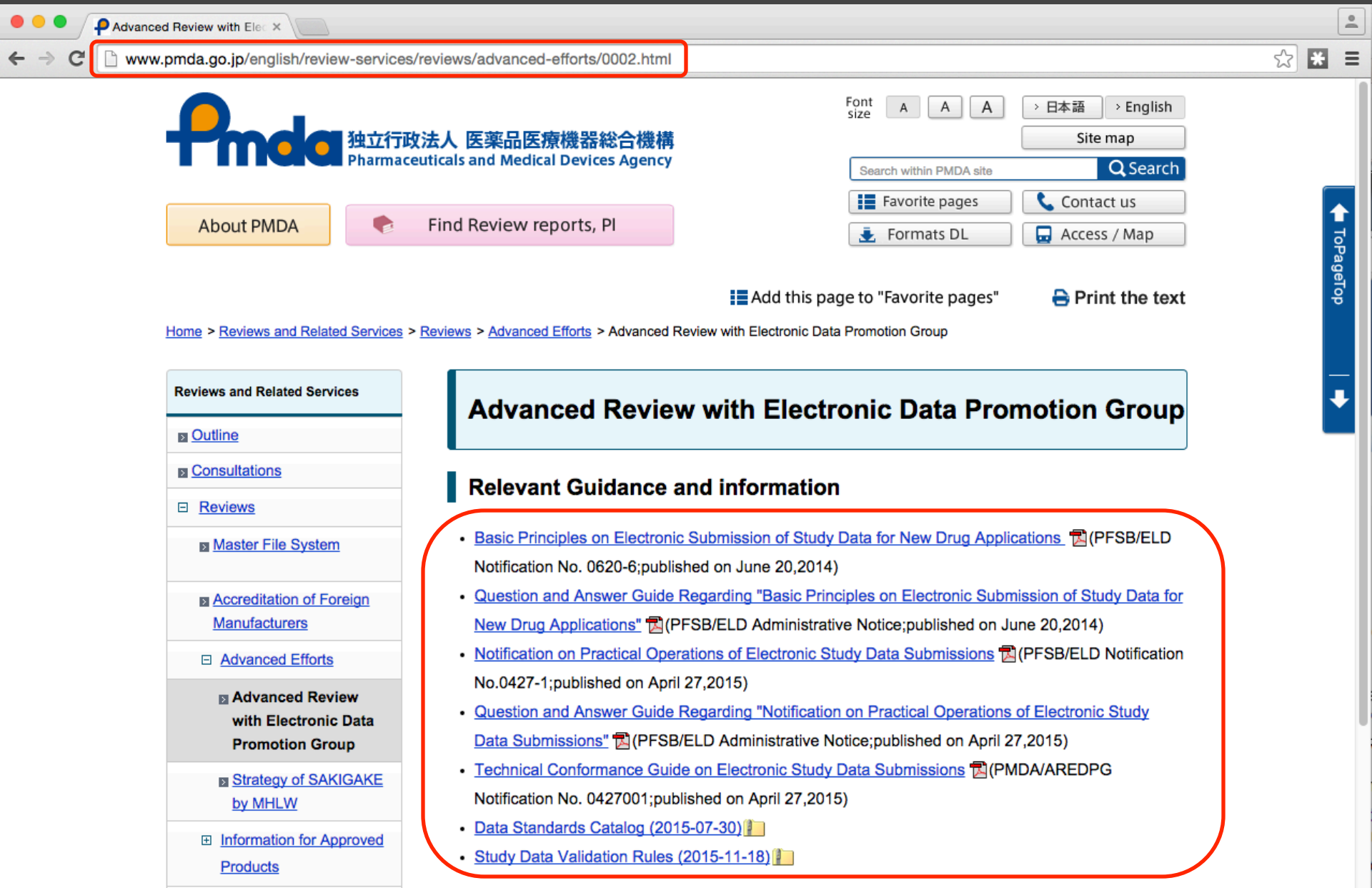
- Why
  - Requested by CDISC
- When
  - Effective November 9th
- What does it mean to you
  - No changes in functionality or business model
  - The only thing that changes is the name
  - OpenCDISC.org content will be migrated under Pinnacle21.net by spring 2016

Pinnacle 21 Releases

with PMDA validation rules support

- Community 2.1.0
  - Released December 7th
  - Open source desktop toolkit for programmers to QC their standardized deliverables
- Enterprise 3.0.0
  - Released November 2nd
  - SaaS collaborative environment for regulatory submission prep, standards management, and continuous compliance
  - Used by PMDA and FDA to validate incoming submissions

PMDA Guidance



Advanced Review with Ele

www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

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Relevant Guidance and information

- Basic Principles on Electronic Submission of Study Data for New Drug Applications (PFSB/ELD Notification No. 0620-6;published on June 20,2014)
- Question and Answer Guide Regarding "Basic Principles on Electronic Submission of Study Data for New Drug Applications" (PFSB/ELD Administrative Notice;published on June 20,2014)
- Notification on Practical Operations of Electronic Study Data Submissions (PFSB/ELD Notification No.0427-1;published on April 27,2015)
- Question and Answer Guide Regarding "Notification on Practical Operations of Electronic Study Data Submissions" (PFSB/ELD Administrative Notice;published on April 27,2015)
- Technical Conformance Guide on Electronic Study Data Submissions (PMDA/AREDPG Notification No. 0427001;published on April 27,2015)
- Data Standards Catalog (2015-07-30)
- Study Data Validation Rules (2015-11-18)

Validation Requirement

"PMDA will perform the validation of all submitted electronic data. Validation of conformance to the CDISC standard will be performed using a tool known as the OpenCDISC Enterprise."

"The applicant should confirm in advance the conformity degree of the data to the CDISC standards prior to the application by referring to the published rules and information on the PMDA validation environment."

"In addition, the error must be explained in the data guide (SDRG and ADRG)."

*Source: Notification on Practical Operations of Electronic Study Data Submissions

The first release of PMDA rules

- Published November 24th
- Based on the latest Pinnacle 21 rules
- Changes in Severity, Message and Description
- Introduces additional PMDA specific validation rules

Covered Standards

- SDTM IG 3.2
- SDTM IG 3.1.3 (3.1.2 Amendment 1)
- SDTM IG 3.1.2
- ADaM IG 1.0
- Define-XML 2.0
- Define-XML 1.0

Rules document structure

- Excel format
  - “machine readable”
  - Most commonly used for metadata
  - Easy to use
- Columns
  - Rule ID (same as Pinnacle 21 Rule ID)
  - Message, Description
  - Domains, PMDA Severity
  - Standards, PMDA Notes

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) --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) TSVAL when TSPARMCD value is RANDOM (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 standard terms.	DS, SC, TS, VS	Warning	X	X	X	
CT2006	<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 within the same value level condition.	QS, TS	Error	X	X	X	
SD0001	No records in data source	Domain table should have at least one record.	ALL	Warning	X	X	X	
SD0002	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL	Reject	X	X	X	Violation of SD0002 will be considered part of Rejection criteria, except for the following variables in DM domain that will be considered Errors. <Variable Name> ARMCD ARM ACTARMCD ACTARM

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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.

Reject Rules

Standard	# of Reject Rules
SDTM	9
ADaM	12
Define-XML	13

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

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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).	ADSL
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).	ADSL
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
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
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
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
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
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
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

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"; 2) CDISC Define xmlns:def="http://www.cdisc.org/ns/def/v2.0"; 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 value	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>	Standard Name must have a value of 'SDTM-IG' or 'ADaM-IG'. Define-XML specification represents Standard Name as def:StandardName attribute on MetaDataVersion element.
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 and '1.0' for ADaM-IG. Define-XML specification represents Standard Version as def:StandardVersion attribute on MetaDataVersion element.
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.
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

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

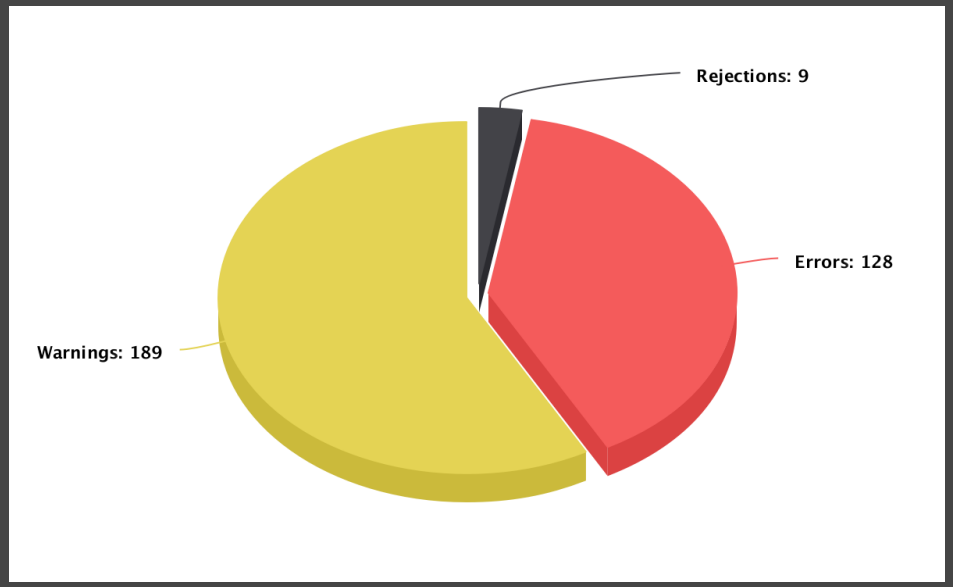
How do PMDA validation rules differ from rules published by FDA?

Difference 1:
Covered standards

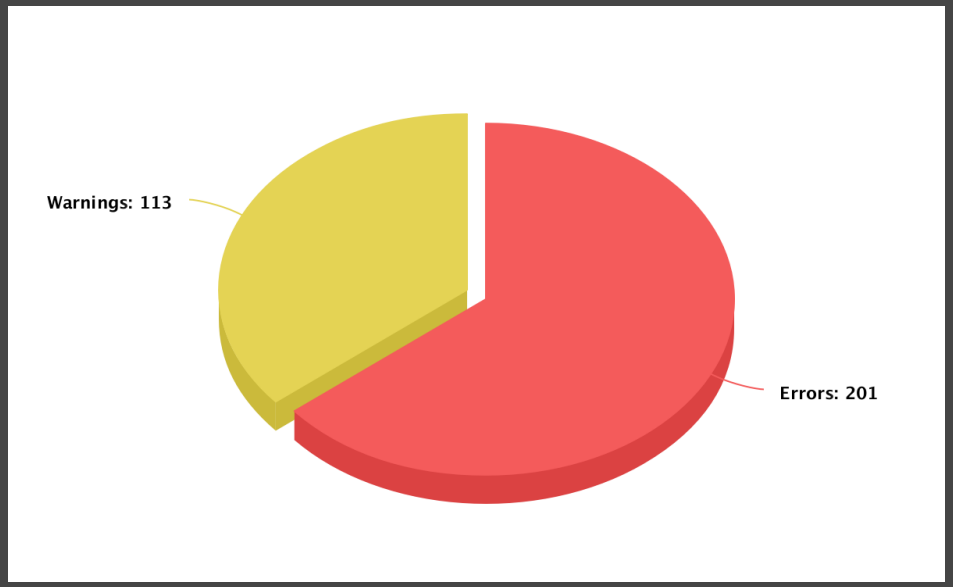
	PMDA	FDA
SDTM 3.2	✔	
SDTM 3.1.3	✔	✔
SDTM 3.1.2	✔	✔
SDTM 3.1.1		✔
SEND 3.0		✔
ADaM 1.0	✔	
Define.xml 2.0	✔	
Define.xml 1.0	✔	

Difference 2:
SDTM rule severity

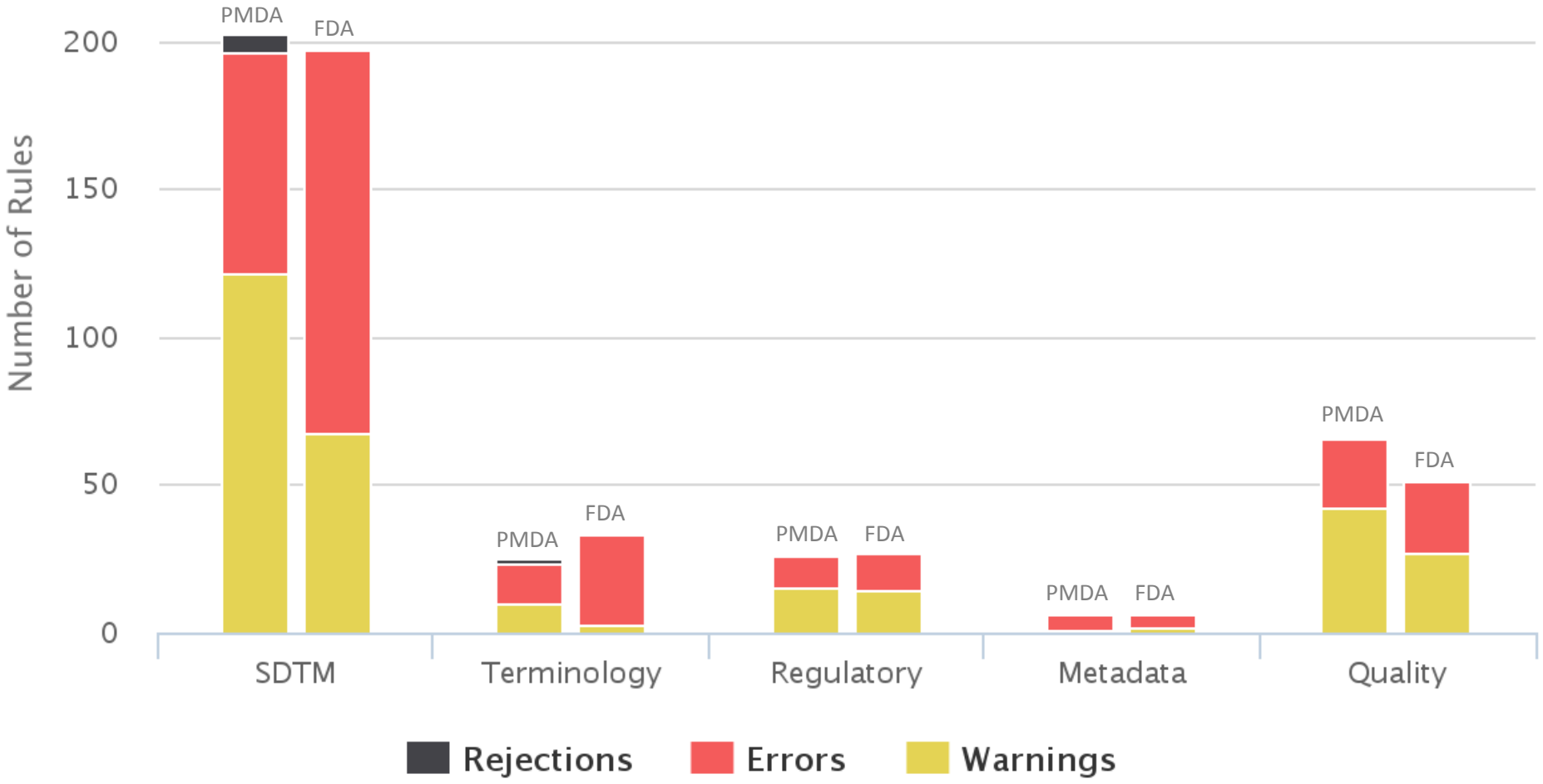
326
PMDA



314
FDA



Difference 3:
SDTM rule severity by dimension



Difference 4:
New rules

- 21 new rules
- Mostly to check data quality
- Examples
  - Observations after End of Participation
  - Treatments before the First Study Treatment or after Last Study Treatment
  - Incorrectly set AE Serious Event flag
  - Negative Study Day in Exposure

Difference 5:
Removed rules

- 9 rules removed
- All deal with Trial Summary parameters controlled by FDA Substance Registration System (SRS)
- PMDA doesn't use FDA SRS dictionary

Difference 6:
Redefined rules

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

Differences Conclusion

- Except for severity, rules are consistent across FDA and PMDA
- Even though PMDA has Reject criteria, FDA rules are still far more strict
  - FDA has more experience and more tools/analysis that depend on standard data
  - It's PMDA's first version, requirements are expected to increase over time
- 77%* of all submission to FDA in 2014-15 failed to load to Clinical Trial Repository (CTR), so don't be surprise to see Reject criteria from FDA too

* Common Errors in Loading SDTM Data to the Clinical Trial Repository, Crystal Allard, FDA OCS

How to use Pinnacle 21 tools to prepare for PMDA submission?

Recommendations

- Always use the latest available validation rules and latest version of Pinnacle 21 tools
- Comply with highest severity across agencies
  - You'll likely need to submit to both
  - Requirements will only get more strict
- Fix all issues that are fixable and explain the rest
- Follow "Continuous Compliance" approach, catch and fix data issues as early as possible

Resources

- PMDA Guidance and information webpage
  http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html
- Basic Principles on Electronic Submission of Study Data for New Drug Applications
  http://www.pmda.go.jp/files/000153708.pdf
- Notification on Practical Operations of Electronic Study Data Submissions
  http://www.pmda.go.jp/files/000206451.pdf
- Technical Conformance Guide on Electronic Study Data Submissions
  http://www.pmda.go.jp/files/000206449.pdf
- Data Standard Catalog
  http://www.pmda.go.jp/files/000206482.zip
- Study Data Validation Rules
  http://www.pmda.go.jp/files/000208341.zip

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Questions

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