



Practical Operations of Electronic Study Data Submissions (SA05)

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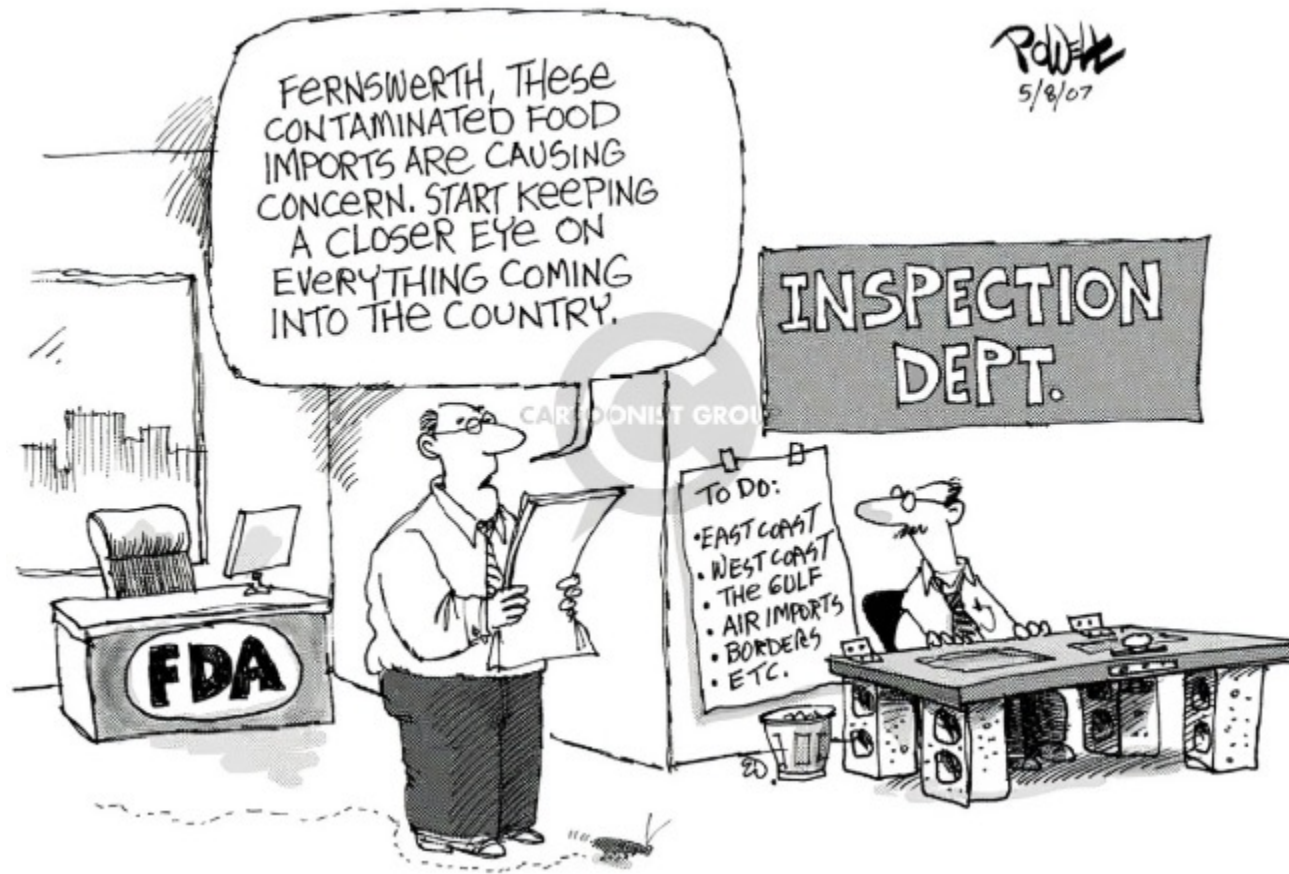
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The story of submissions....



A pivotal factor to ensure successful review and approval for any submission is preparing high-quality study data standard deliverables.

Agenda

- Purpose statement
- Scope
- Situations to consider
- Submission plan & readiness
- Recommended approach
- Pinnacle 21- a final checkpoint
- Final thoughts

Purpose statement

With evolving industry standards and regulatory guidance's, it is vital to have a consistent approach in creating a submission ready package by implementing the requirements from beginning of the data analysis process.

This will ensure quality at every step and enable simultaneous submissions to multiple health authorities in a streamlined manner.

Scope

We'll look from statistical programming perspective and focus on two regulatory authorities, the Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA):

- To compare regulatory requirements and differences in their submissions review process
- Statistical programmer's responsibilities in the submission process for New Drug Application (NDA).
- Discuss best practices & use of various guidance's/validation tools used in submission process.

Situations to consider

Scenario 1: Originally the study was meticulously prepared for FDA submission, adhering to all conformance and validation rules. However, a decision was made to submit the study to PMDA. The study uncovered 'REJECT' issues in P21 report for source data where the sites were closed and could not be fixed.

Scenario 2: A study originally not intended for submission was added to the FDA submission package. This caused the statistical programming team to adapt their deliverables to meet the FDA's requirements with stringent timelines and a stressful environment.

Scenario 3: As the study deliverables were ready for submission, it was realized that the annotated CRF was not created. This resulted in unplanned time and effort being spent by study team to review and map raw data to SDTM with unanticipated findings which lead to SDTM dataset and spec updates.

Better to plan then REPLAN

STEP 1: Planning for submission readiness

- Prepare a submission ready checklist by knowing all the

1. Submission Components

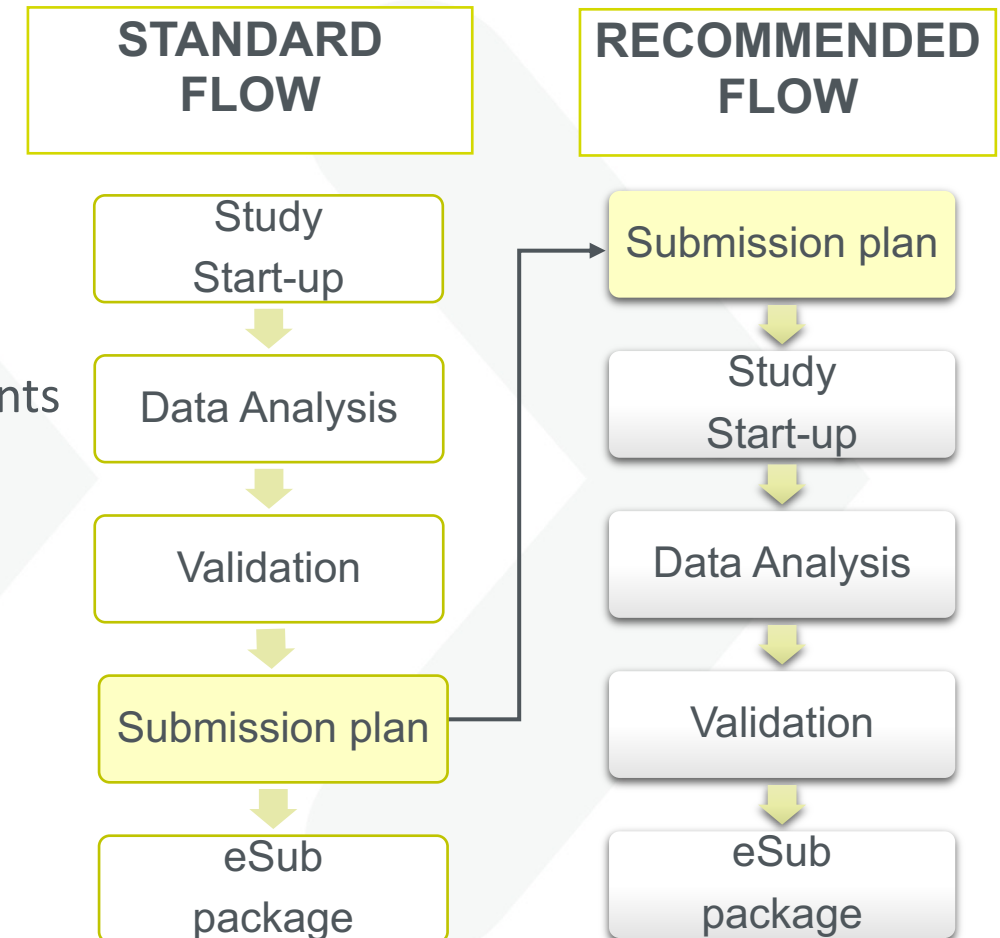
- Gain a thorough comprehension of all the components that comprise a submission package.

2. Regulatory Requirements

- Acquire a deep insight into the specific regulatory requirements.

3. Study Data Traceability

- Traceability permits an understanding of the relationships between the analysis results, analysis datasets, tabulation datasets, and source data.



Submission Components

- Study Data Tabulation Model (SDTM) dataset
- Annotated Case Report Form (aCRF)
- Analysis Data Model (ADaM) dataset
- Define-XML for SDTM and ADaM dataset
- Analysis Results Metadata (ARM) in PDF format*
- Study Data Reviewer's Guide (SDRG)
- Analysis Data Reviewer's Guide (ADRG)
- SAS® programs for creating ADaM dataset and analyses

* ARM was created for PMDA submission purpose only.

Regulatory Requirements

FDA	PMDA
Standards for clinical analysis dataset	
Data Standards Catalog v.9.1 (19-Apr-2023)	Data Standards Catalog (28-Feb-2023)
Study Data Technical Conformance Guide V 4.6 (June-2023)	Technical Conformance Guide on e-Study Data Submissions (01April 2022)
Business Rules v1.5 (May 2019) Validator Rules v1.6 (December 2022)	Study Data Validation Rules Version 4.0 (28-Feb-2023)

PMDA Data Standards Catalog (28-Feb-2023 version)

A	B	C	D	E	F	G
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	
Clinical study datasets	ADaM	2.1	1.1	XPT	2022-01-01	
Clinical study datasets	ADaM	2.1	1.0	XPT	2016-10-01	
Clinical study data definition files	Define	2.0	-	XML	2016-10-01	
▶ Data Exchange Standards Terminology Standards Change History ⊕						

Comprehensive list of Data Standards

Information on supported standard versions & terminologies

Awareness of any change history from previous versions

Uniformity across the team, avoids rework

FDA Technical conformance guide

This guide provides specifications, recommendations, and general considerations on how to submit standardized study data.

Contains Nonbinding Recommendations



Subject Identifier (SUBJID)

The variable SUBJID uniquely identifies each subject that participates in a study. If a single subject is screened and/or enrolled more than once in a study, then the subject's SUBJID should be different for each unique screening or enrollment. For a study with multiple screenings and/or multiple enrollments per subject, SUBJID should be included in other related domains besides DM even though it may cause validation errors. It is recommended to include a table linking each SUBJID for a single subject to that subject's USUBJID with any additional necessary explanation included in the relevant RG.

Unique Subject Identifier (USUBJID)

The variable USUBJID is an identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.²⁵ Each individual subject should be assigned a single unique identifier across the entire application. This is in addition to the subject ID (SUBJID) used to identify subjects in each study and its corresponding study report. An individual subject should have the exact same unique identifier across all datasets, including between SDTM and ADaM datasets. Subjects that participate in more than one study should maintain the same USUBJID across all studies. It is important to follow this convention to enable pooling of a single subject's data across studies (e.g., a randomized control trial and an extension study).

Sponsors should not add leading or trailing spaces to the USUBJID variable in any dataset. For example, applications have been previously submitted in which the USUBJID variable for each individual subject appeared to be the same across datasets; however, in certain datasets, the actual entry had leading zeros added, or zeros added

version 1.6, finalized December 2022					
FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Domains	SDTMIG 3.1.2	SDTMIG 3.1.3
SD0005	Duplicate value for --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	ALL	X	X
SD0006	No baseline flag record in Domain for subject	observation (--BLFL = 'Y') in EG, LB, MB, MS, PC and VS domains, except for subjects who failed screening (ARMCD = 'SCRNFALL') or were not fully assigned to an Arm (ARMCD = 'NOTASSGN')	EG, LB, MB, MS, PC, VS	X	X
SD0007	Inconsistent value for Standard Units	for all records with the same Short Name of Measurement, Test or Examination (--TESTCD), Object of the Observation (--OBJ), Measurement, Test, or Examination Detail (--TSTDTL), Category (--CAT), Subcategory (--	FINDINGS, FINDINGS ABOUT	X	X
SD0008	Value for --DECOD not found in MedDRA dictionary	DECOD) variable must be populated using a Preferred Term of the MedDRA dictionary of a version specified in the define.xml (Case-	AE, CE, MH	X	X
SD0008C	Value for --DECOD is in incorrect case	variable must be sentence case using a Preferred Term of the MedDRA dictionary of a version specified in the define.xml (Case-	AE, CE, MH		
	No qualifiers set to 'Y', when AE is	'Y', then at least one of seriousness criteria variables is expected to have value 'Y' (Involves Cancer (AESCAN), Congenital Anomaly or Birth Defect (AESCONG), Persist or Signif			
FDA Validator Rules Intro FDA Validator Rules v1.6 +					

PMDA

Study Data Validation Rules

Version 3.0 (2021-12-15)

[New Drug Review with Electronic Data | Pharmaceuticals and Medical Devices Agency \(pmda.go.jp\)](#)
[Study Data Standards Resources | FDA](#)

Regulatory validation rules

FDA

Business Rules v1.5 (May 2019)

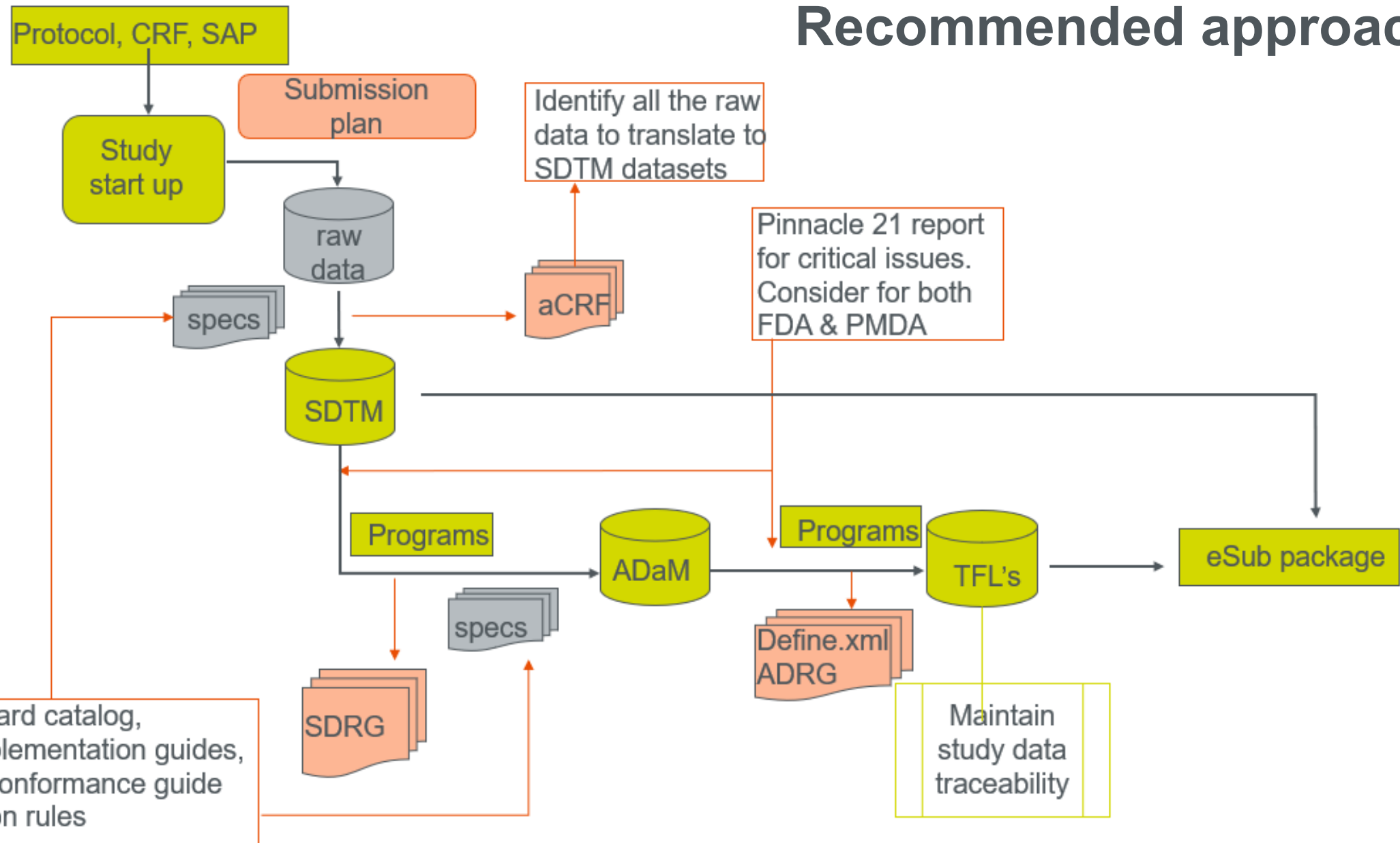
Validator Rules v1.6 (December 2022)

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.

SDTM Rules v3.0

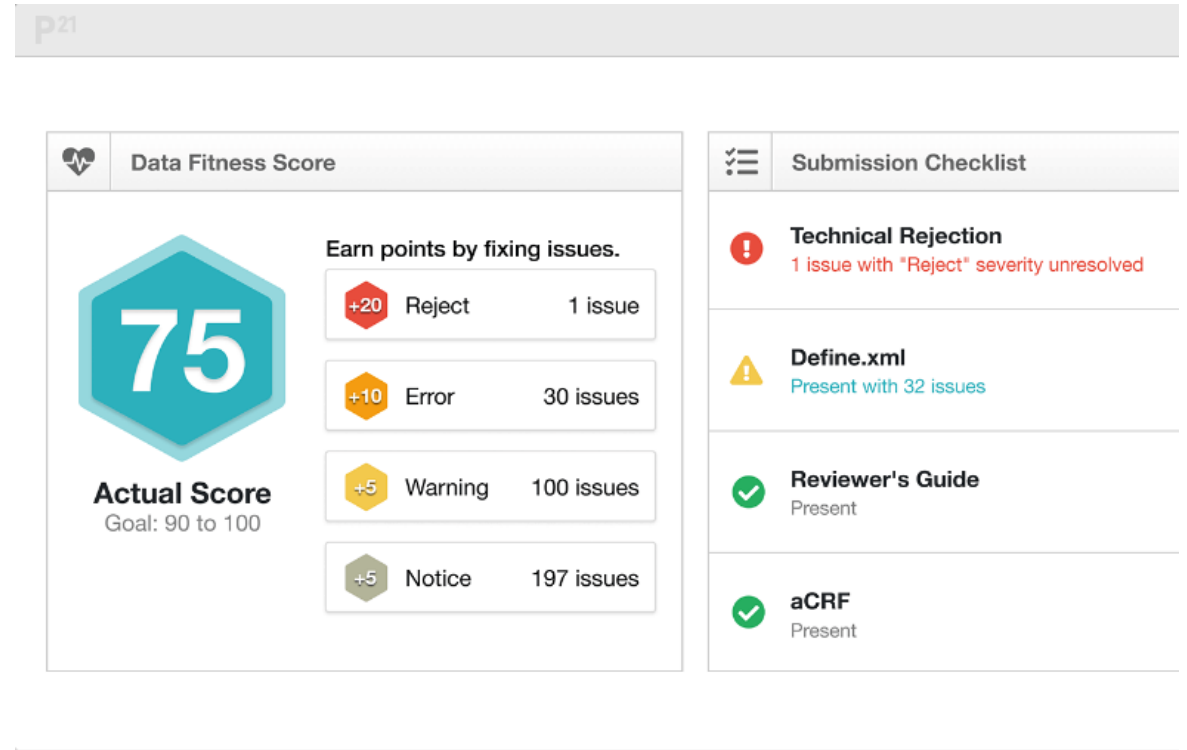
RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	3.1.2	3.1.3
SD0005	Duplicate value for --SEQ variable	The value of Sequence Number (--SEQ) variable must be unique for each record within a domain and within each Unique Subject Identifier (USUBJID), Pool Identifier (POOLID) or Sponsor Device Identifier (SPDEVID)	ALL	Error	X	X
SD0006	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 = 'SCRNFALL') or were not fully assigned to an	EG, LB, MB, MS, PC, VS	Warning	X	X
SD0007	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) and	FINDINGS	Warning	X	X
SD0008	Value for --DECOD not found in 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	AE	Error	X	X
SD0008C	Value for --DECOD is in incorrect case	Case for the Dictionary-Derived Term (--DECOD) variable must be sentence case using a Preferred Term of the MedDRA dictionary of a version specified in the	AE	Warning	X	X
SD0009	No qualifiers set to 'Y', when AE is Serious	When Serious Event (AESER) variable value is 'Y', then at least one of seriousness criteria variables is expected to have value 'Y' (Involves Cancer (AESCAN), Congenital Anomaly or Birth Defect (AESCONG), Persist or Signif	AE	Warning	X	X
Change History SDTM Rules ADaM Rules Define-XML Rules +						

Recommended approach



Pinnacle 21- a final checkpoint

- The last stop before datasets head off for their health authority review.
- It checks the data for compliance with CDISC standards, controlled terminology, and dictionaries like MedDRA and WHODrug.
- Additionally, it evaluates data against each agency's business rules to prevent issues that might delay the submission.
- Excellent validation tool for data quality and is suggested to be used in parallel to data analysis.



Continued...

P21

How to stay compliant with new Validator Rules

If you're an Enterprise user, we recommend that you *always* accept the latest Enterprise deployments and that you **always use the latest available regulatory engines**. For ongoing, in-progress studies in Enterprise, a best practice is to use the latest P21 engine, which will show you the issues for FDA, PMDA, and rules for custom standards and controlled terminology (if your company uses these). Later, when a study is finalized and approaching submission, **switch to the most recent agency engine**.

P21

Which standards are supported by 2211.0?

A major change in PMDA Validator Rules v4.0 is the support of SDTM IG v3.3, as well as the removal of support of Define.xml 1.0. See below:

Rule	Engine	SDTM IG				ADaM IG		Define.xml	
		3.1.2	3.1.3	3.2	3.3	1.0	1.1	1.0	2.0
v1.0	1511.6	✓	✓	✓		✓		✓	✓
v2.0	1810.3	✓	✓	✓		✓		✓	✓
v3.0	2010.2	✓	✓	✓		✓	✓	✓	✓
v4.0	2211.0	✓	✓	✓	✓	✓	✓		✓

Final thoughts



Focus on a consistent approach across the portfolio in creating high quality submission deliverables



Awareness of the chronology of events helps in upfront planning and time management.



Ongoing risk assessment allows stakeholders to evaluate the issues



Provides flexibility and ease as programmers navigate the complex regulatory landscape



Regardless, it's for the FDA or the PMDA the final goal is a quality submission.



Thank you

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