

# An Expeditious Approach for Handling Pinnacle 21 Messages

## Meet the Speaker

Malini Narreddy

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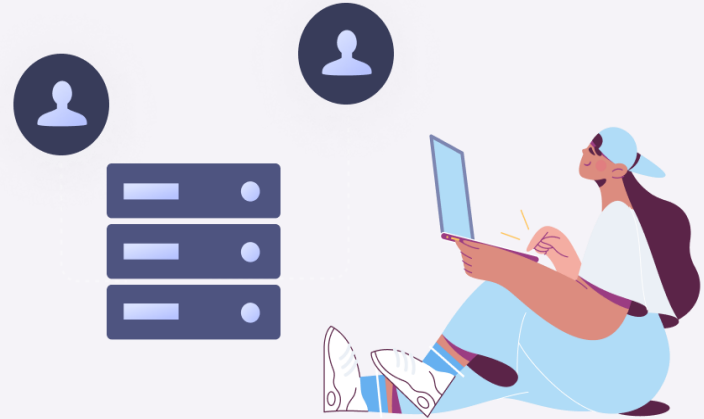
## Acknowledgements

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# Agenda

- Standards Overview
- Study Data Validation & its Scope
- Pinnacle 21 Overview
- Sample P21 Community Validator Report
- Directory for Pinnacle 21 Validation Rules
- Severity of Violations
- Issue Categorization
- Sanofi Tools
- Point of Contact
- Validation Message Action Plan
- Conclusion



# Standards Overview in Clinical Research Process

- Study data standards provide a consistent framework for organizing data, which includes templates for datasets and standard names for variables, identifying appropriate controlled terminology and conducting calculations with common variables.



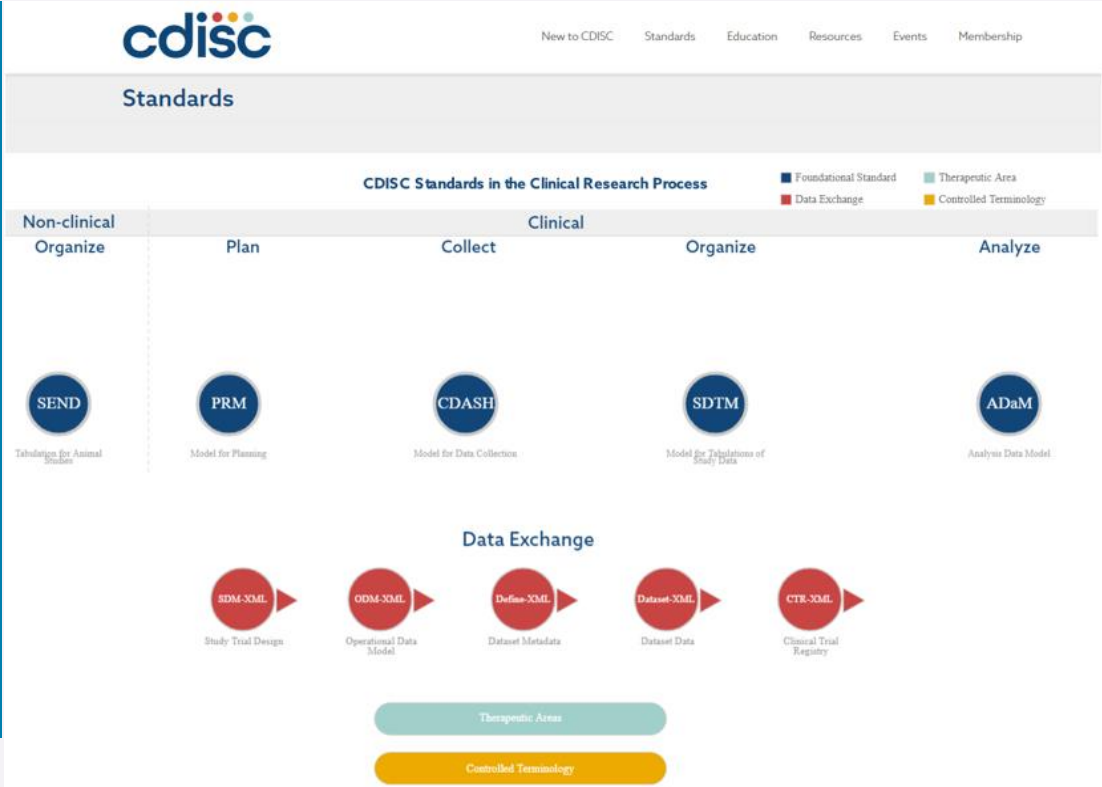
**FDA Required CDISC standards**

**Controlled Terminology**

- SEND
- SDTM
- ADaM

**Define-XML**


**Supported CDISC TAUGs in the FDA Study Data Technical Conformance Guide**



The diagram illustrates the CDISC Standards in the Clinical Research Process, categorized into Non-clinical and Clinical phases. The Clinical phase is further divided into Plan, Collect, Organize, and Analyze. Standards are represented by colored circles: blue for Foundational Standards, red for Data Exchange, light blue for Therapeutic Areas, and yellow for Controlled Terminology.


Phase	Sub-Phase	Standard	Category
Non-clinical	Organize	SEND	Foundational Standard
Clinical	Plan	PRM	Foundational Standard
	Collect	CDASH	Foundational Standard
	Organize	SDTM	Foundational Standard
	Analyze	ADaM	Foundational Standard
Data Exchange	Study Trial Design	SDM-XML	Data Exchange
	Operational Data Model	ODM-XML	Data Exchange
	Dataset Metadata	Define-XML	Data Exchange
	Dataset Data	Dataset-XML	Data Exchange
	Clinical Trial Registry	CTR-XML	Data Exchange

Legend: Foundational Standard (Blue), Data Exchange (Red), Therapeutic Area (Light Blue), Controlled Terminology (Yellow)



**PMDA Required CDISC standards**

- SDTM
- ADaM
- Define-XML
- Analysis Results Metadata (ARM for Define-XML)



**CDISC standards are preferred for China submissions**

# Study Data Validation & Its Scope

- FDA TCG states that “**Study data validation helps to ensure that the study data are compliant, useful, and will support meaningful review and analysis**”.
- Validation comprises of different kinds of checklists:
  - ✓ Data Quality Checks
  - ✓ CDISC Conformance Checks
    - ✓ SDTM Conformance Rules
    - ✓ ADaM Conformance Rules
    - ✓ Define.xml Conformance Rules
  - ✓ Regulatory Conformance Checks
    - ✓ FDA Business Rules
    - ✓ FDA Validator Rules
    - ✓ PMDA Validation Rules
  - ✓ FDA Study Data Technical Conformance Guide Guidelines
  - ✓ FDA eCTD Technical Rejection Criteria Conformance Rules





### ➤ What is Pinnacle 21?

- Software used to prepare clinical trial data for regulatory submission
  - Checks for data compliance on even non-regulatory submissions
- Former name – OpenCDISC

### ➤ Why Use Pinnacle 21?

- Checks to see if the study data is compliant with CDISC Standards
- Covers all the FDA Business rules
- FDA & PMDA utilize Pinnacle 21 to validate the submission data
- All findings must be documented in the Reviewer's Guide
- Recurring, auto updates that enhance checks on a regular basis



Free, Open-Source Project



Commercial, Enterprise-Wide Software

# Sample P21 Community Validator Report - SDTM

## Validation Summary Tab View

The header section shows select validation options, such as the version of dictionaries, configuration, and validation version

Pinnacle 21 Validator Report	
Configuration: C:\Users\le0370637\OneDrive - Sanofi\Documents\Pinnacle 21 Community\configs\2010.1\SDTM-IG 3.2 (FDA).xml	
Define.xml: F:\define.xml	
Generated: 2022-07-05T22:10:53+02:00	
CDISC SDTM CT Version: 2015-03-27	
CDISC QRS CT Version: 2015-03-27	
MedDRA: 24.1	
SNOMED: 2022-03-01	
UNE: 2022-02-13	
MED-RT: 2022-03-07	
Validation Engine Name: FDA 2010.1	
Software Version: 4.0.1	

Navigation: Validation Summary | Dataset Summary | Issue Summary | Details | Rules

## Dataset Summary Tab View

Provides list of datasets available in a study with information about each dataset in a snapshot view

Processed Sources								
Domain	Label	Class	Source	Records	Rejects	Errors	Warnings	Notices
GLOBAL	Global Metadata	--	--	0	1	0	0	0
AE	Adverse Events	EVENTS	ae.xpt	11643	20	11640	20485	0
		SPECIAL						
DM	Demographics	PURPOSE	dm.xpt	558	0	0	579	0
DS	Disposition	EVENTS	ds.xpt	2665	0	1	793	0
		SPECIAL						
SV	Subject Visits	PURPOSE	sv.xpt	53598	0	5	47617	0
Total				68464	21	11646	69474	0

Navigation: Validation Summary | Dataset Summary | Issue Summary | Details

## Issue Summary Tab View

Lists all issues found in each dataset and provides a count of each issue

Issue Summary				
Source	Pinnacle 21 ID	Message	Severity	Found
GLOBAL				
	DD0101	Missing define.xml file	Reject	1
AE				
	SD0002	NULL value in AEDECOD variable marked as Required	Reject	20
	CT2001	AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist	Error	11639
	SD0058	Variable appears in dataset, but is not in SDTM model	Error	1

Navigation: Validation Summary | Dataset Summary | Issue Summary | Details | Rules ...

## Details Tab View

Lists all issues in an expanded format and is presented on the record level

		Pinnacle						
Domain	Record Count	Variables	Values	Pinnacle 21 ID	Message	Category	Severity	
GLOBAL				DD0101	Missing define.xml file	Presence	Reject	
AE		11639 AEACN	MULTIPLE	CT2001	AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist	Terminology	Error	
AE	840	AEDECOD	null	SD0002	NULL value in AEDECOD variable marked as Required	Presence	Reject	

Navigation: Validation Summary | Dataset Summary | Issue Summary | Details | Rules ...

## Rules Tab View

Lists each Rule ID with the detailed description. The links to each rule ID in the Issue Summary and Details worksheets take you to this worksheet

Pinnacle 21 ID	Publis her ID	Message	Description	Category	Severity
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.	Terminology	Error

Navigation: Dataset Summary | Issue Summary | Details | Rules



# Directory for Pinnacle 21 Validation Rules

➤ Complete list of validation Rules can be accessed on the Pinnacle 21 website using the link below:

➤ [VALIDATION RULES](#)

RESOURCES | **VALIDATION RULES** | BLOG | DOWNLOADS | DOCUMENTATION | COMMUNITY FORUM

Standard: **SDTM** Engine: ALL | FDA | PMDA 1511.6 | PMDA 1810.3 | NMPA Search

Rule ID	Name	Description	Domains	FDA	PMDA 1511.6	PMDA 1810.3	NMPA	FDA Severity	PMDA Severity	3.1.2	3.1.3
SD0001	CG0408, 278	No records in data source	Domain table should have at least one record.	ALL	X	X	X	X	Warning	X	X
SD0002	CG0014, CG0208, 12, 257	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL	X	X	X	X	Reject	X	X

Found 515 records

# Severity of Violations

## Two levels

### Reject:

If Rules are violated → Review will be suspended until corrections are made.  
Fix all Reject issues

### Other:

Must be resolved or documented



## Three levels

### Reject:

If Rules are violated → Review will be suspended until corrections are made. Fix all Reject issues

### Error:

If Rules are violated without prior explanation/authorization from PMDA → Review will be suspended until corrections are made

### Warning:

If Rules are violated → Explanation is optional

Violation of the PMDA Validator Rules results in:

- **Suspension of Approval Review**
- **Impact on Approval Timeline**



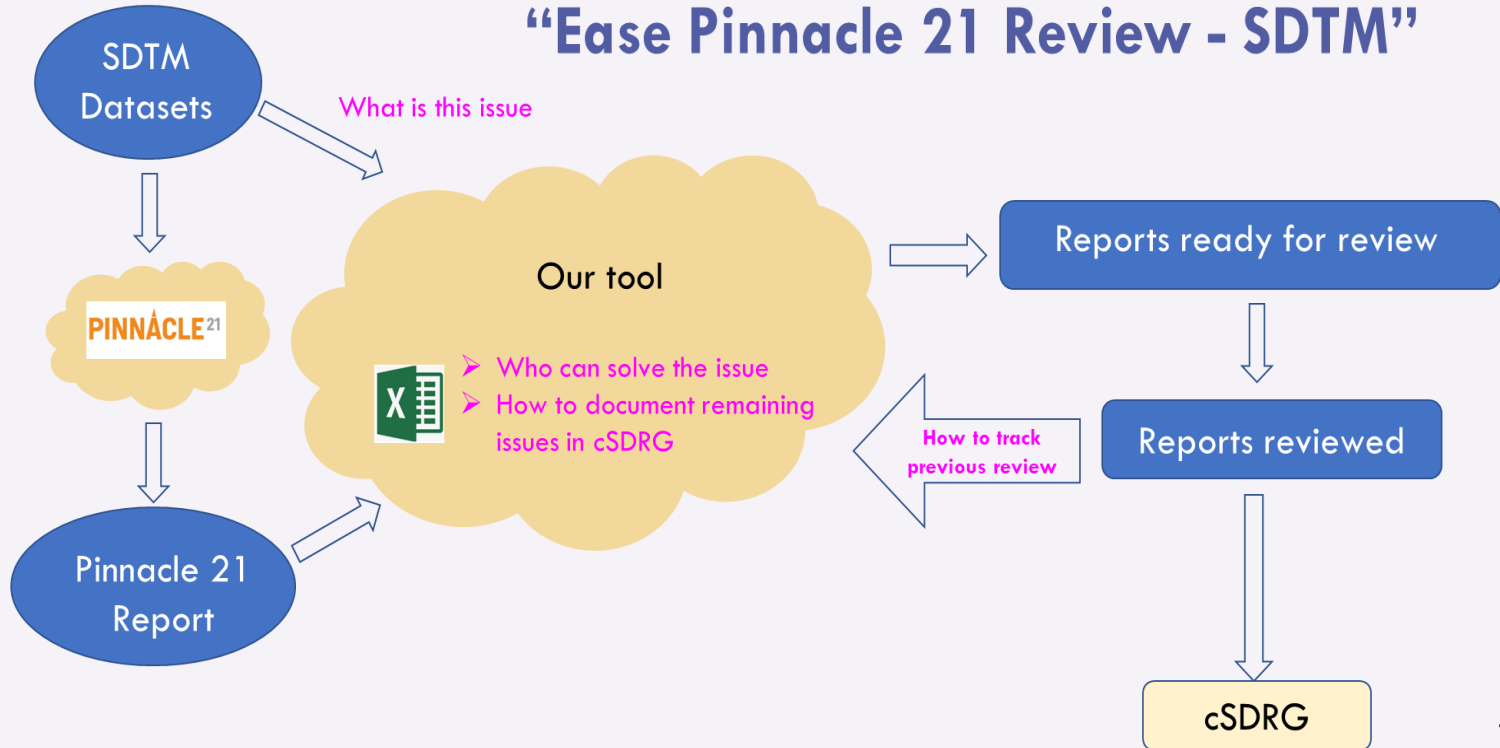
# SDTM Issue Categorization From Programmer's Viewpoint

P21 category	Sanofi Issue Categorization	Description
Metadata	Spec issue	Discrepant variable attributes like name, label, type, core (Req/Exp must exist), additional variables compared to SDTM attributes  Discrepant dataset, variable or variable attributes compared to define.xml
Terminology	CT issue	Discrepant with CDISC CT, MedDRA code, WHO Drug, LOINC code or define.xml term
Cross-reference	Data issue/Spec issue/Programming issue	Value in one dataset miss-match with another
Presence	Data issue/Spec issue/Programming issue	Missing a dataset, subject record, required variable, value or define.xml
Limit	Data issue/Spec issue/Programming issue	Negative values, start after end, low greater than high, study day = 0
Format	Spec issue/Programming issue	Not ISO 8601, value length too long, contains invalid characters, truncated values, not uppercase, etc.,
Consistency	Data issue/Spec issue/Programming issue	Duplicates, inconsistent units, value in one variable inconsistent with value in another variable
Structure	Spec issue	Discrepant with the list of variables mentioned in SDTMIG metadata
	Known issue	P21 bugs, SDTMIG guidance vs FDA guidance, label discrepancy, PMDA validation engine issues

# Sanofi Tool for Pinnacle 21 Report Follow-up

- Post processing Macros for Pinnacle 21 report
  - Identifies Data issue or Compliance issue
  - Tracks changes from previous report

## “Ease Pinnacle 21 Review - SDTM”



# Who Can Solve the Issue?

Type of Issue	Point of Contact
Metadata (Structure)	Subject Matter Expert / Study Programmer
Controlled Terminology	Standards Governance Team / Data Manager
Data	Data Manager
Dictionary (MedDRA, WHO Drug, LOINC)	Data Manager / Coding Experts
Derivation	Statistician / Study Programmer

# How to Track the Previous Review?

➤ **Initial** Pinnacle 21 report with review comments



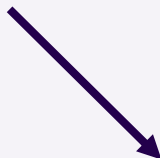
➤ To ensure **follow-up** from one report to another:

- ✓ **Orange** - Previous comments are retrieved
- ✓ **Purple** - New issues

Source	Pinnacle 21 ID	Message	Severity	Found	Role	Reviewer Comments	Message_cSDRG
AE	CT2001	AEACN value not found in 'Action Taken with Study Treatment' non-extendible codelist		83	SDTM_FULL	[03/18/22]: AE action was collected individually for each of the three drugs. Per SDTM IG 3.2, the value of AEACN should be MULTIPLE, where individual action should be stored in the SUPPQUAL variables. The term "MULTIPLE" follows CDISC guidelines.	<a href="#">Click here for more details</a>
AE	SD0002	NULL value in AEDECOD variable marked as Required		3	DATA_ISSU	[03/18/22]:data issue	<a href="#">Click here for more details</a>
AE	SD0080	AE start date is after the latest Disposition date		65	ONGOING	[03/18/22]: ongoing study	<a href="#">Click here for more details</a>



Source	Pinnacle 21 ID	Message	Severity	Found	Role	Reviewer Comments	Old Reviewer Comments	Old found	Message_cSDRG
AE	CT2001	AEACN value not found in 'Action Taken with Study Treatment' non-extendible codelist		276	SDTM_FULL_ISSUE	[03/18/22]: AE action was collected individually for each of the three drugs. Per SDTM IG 3.2, the value of AEACN should be MULTIPLE, where individual action should be stored in the SUPPQUAL variables. The term "MULTIPLE" follows CDISC guidelines.	[03/18/22]: AE action was collected individually for each of the three drugs. Per SDTM IG 3.2, the value of AEACN should be MULTIPLE, where individual action should be stored in the SUPPQUAL variables. The term "MULTIPLE" follows CDISC guidelines.	83	<a href="#">Click here for more details</a>
AE	SD0080	AE start date is after the latest Disposition date		197	ONGOING_STUDY	[03/18/22]: ongoing study	[03/18/22]: ongoing study	65	<a href="#">Click here for more details</a>
AE	SD1039	AECAT value is redundant with other variable values		6	SDTM_HYBRID_ISSUE				<a href="#">Click here for more details</a>
AE	SD2010	Value for AEHLT not found in MedDRA		14	DATA_ISSUE				<a href="#">Click here for more details</a>
AE	SD2011	Value for AEHLTCD not found in MedDRA dictionary		14	DATA_ISSUE				<a href="#">Click here for more details</a>



# SDTM Validation Message Action Plan

Rule ID	Message	Description	Issue category	Action Details	Examples / Notes for Action Details	Template for cSDRG explanation
SD0058	Variable appears in dataset, but is not in SDTM model	Only variables listed in SDTM model should appear in a dataset. New sponsor defined variables must not be added, and existing variables must not be renamed or modified.	Spec issue / Known issue	<p>(1) If possible, re-map the variable to an appropriate SDTM variable.</p> <p>(2) Else if it is a CRF captured variable and is non-standard, then move it to SUPP-- domain.</p> <p>(3) Else if it is a derived variable that the study team wants in, then move it to SUPP-- domain.</p> <p>(4) Else if this error belongs to SV domain, explain this in cSDRG. Check the cSDRG explanation.</p> <p>(5) Else if this error belongs to SUBJID variable in domains for Multiple Subject participation instances, explain this in cSDRG. Check the cSDRG explanation.</p> <p>(6) Otherwise, if a non-standard variable was kept by mistake, then drop it.</p>	<p>(1) For SV domain, non-standard variables: SVPRESP, SVOCCUR, SVREASOC, SVEPCHGI are added to the SDTM global metadata as per the guidance from the FDA TCG. So, no action needed to fix this error in SDTM for these variables. Instead provide a proper justification in the Reviewer's guide.</p> <p>(2) As per the FDA TCG recommendations, for a study with multiple screenings and/or multiple enrollments per subject, SUBJID should be included in other related domains besides DM. So, no action needed to fix this error in SDTM. Instead provide a proper justification in the Reviewer's guide.</p>	<p>(1) cSDRG rationale for SV domain:</p> <p>"This check fired for the non-standard variables SVPRESP, SVOCCUR, SVREASOC, SVEPCHGI. To comply with the recent FDA guidance, SV structure was adjusted to include these NSV's to SV even though these variables are not in &lt;&lt;SDTM Model 1.4&gt;&gt;"</p> <p>Note: Text within the &lt;&lt;&gt;&gt; can be adjusted based on the necessity/occurrence within the respective study.</p> <p>(2) cSDRG rationale for SUBJID variable in domains (except DM) for Multiple Screenings/enrollments of a subject in a clinical trial.</p> <p>"This check fired for the non-standard variable SUBJID. To comply with the recent FDA guidance, SUBJID was added in a given dataset which act as a key identifier to distinctly represent multiple participations of a subject within a trial."</p>
SD9999	Dataset class not recognized	The structure for custom dataset should be based on one of the general observation classes (EVENTS, FINDINGS, INTERVENTIONS) defined by the SDTM model.	Known issue	If this check fired for AP, XD domains, explain in cSDRG		<p>(1) cSDRG rationale for AP domains:</p> <p>"Pinnacle 21 limitation: AP domain class is not yet supported by Pinnacle 21 version &lt;x.x.x.&gt;"</p> <p>(2) cSDRG rationale for custom domain: XD for Multiple Screenings/enrollments of a subject in a clinical trial.</p> <p>"Followed regulatory agency's guidance on multiple participations of a subject and created a custom domain (XD) with a similar structure to DM to represent subject's multiple screenings and/or enrollments within the submission. Additional details regarding this domain could be found in the csdrg section: 3.3 SDTM Subject Domains."</p>
SD0023	Missing value for --STAT, when --REASND is provided	Completion Status (--STAT) should be set to 'NOT DONE', when Reason Not Done (--REASND) is populated.	Data issue / Spec issue / Programming issue	<p>(1) Identify the erred records and notify Data Management with necessary information to fix the issue.</p> <p>(2) Check for any programmatic mistakes or spec issues and fix it.</p>	<p>(1) If the CRF has fields for --STAT and --REASND, then inform the issue to DM.</p> <p>(2) If the CRF or eDL data has the provision to capture only Reason for Not Done, then assign the value of --STAT = "NOT DONE" in SDTM based on the non-missing value of --REASND variable.</p>	

# Reviewer's Guide

➤ Data Conformance Summary section is the place to document all Pinnacle 21 validator issues

Study LDCP-888-035

Study Data Reviewer's Guide

## 4. Data Conformance Summary

### 4.1 Conformance Inputs

Was a validator used to evaluate conformance? Yes

If yes, specify the version(s) of the validation rules:

Pinnacle21 Community v2.2.0, SDTM 3.2

Were sponsor-defined validation rules used to evaluate conformance? Yes

If yes, describe any significant sponsor-defined validation rules:

LDCP Inc. executes a sponsor-defined conformance rule to confirm variable values that are 200 characters have not been truncated.

Were the SDTM datasets evaluated in relation to define.xml? Yes

Was define.xml evaluated? Yes

Provide any additional compliance evaluation information:

### 4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	Missing Units on Value	Error	22	Not an error: Lab results for pH and Specific Gravity have no units

Study SAMPLE-9999

Analysis Data Reviewer's Guide

## 6. Data Conformance Summary

### 6.1 Conformance Inputs

Specify the software name and version for the analysis datasets

Pinnacle 21 version 2.2.0

Specify the version of the validation rules (i.e. CDISC, FDA) for the analysis datasets

CDISC

Specify the software name and version for the define.xml

config-adam-1.0.xml

Specify the version of the validation rules (i.e. CDISC, FDA) for the define.xml

CDISC

### 6.2 Issues Summary

Pinnacle 21 Notices were evaluated for potential problems but are not listed here. The following is a summary of Error level messages. There were no Warning level messages.

Dataset(s)	Diagnostic Message	Severity	Count	Explanation
ADAE	Neither AVAL nor AVALC are present in dataset	Error	1	The dataset is a hierarchical occurrence structure, the message is not relevant to this structure.



# Key Takeaways

Pinnacle 21 Report Review → Less Burden → More Effective → Time Efficient

Validation Message Action Plan → User Guide for Stakeholders

Model Guide → Continuous Updates Allow for Better Reference

Reviewer's Guide → Enhanced Documentation of Unresolved Issues

Thank  
you

