An Expeditious Approach for Handling Pinnacle 21 Messages
Meet the Speaker

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- Lyubov Sushchenko
- Anthony Coulange
- Sai Krishna Gopi
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**

**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
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.

**Issue Summary Tab View**
Lists all issues found in each dataset and provides a count of each issue.

**Dataset Summary Tab View**
Provides list of datasets available in a study with information about each dataset in a snapshot view.

**Details Tab View**
Lists all issues in an expanded format and is presented on the record level.

**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.
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**
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

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

- SDTM Datasets
- What is this issue
- SDTM Datasets
- Our tool
  - Who can solve the issue
  - How to document remaining issues in cSDRG
- Pinnacle 21 Report
- Reports ready for review
- Reports reviewed
- How to track previous review
- cSDRG
## Who Can Solve the Issue?

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

<table>
<thead>
<tr>
<th>Source</th>
<th>Pinnacle 21 ID</th>
<th>Message</th>
<th>Severity</th>
<th>Found</th>
<th>Role</th>
<th>Reviewer Comments</th>
<th>Old Reviewer Comments</th>
<th>Old found</th>
<th>Message csDRG</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>CT2001</td>
<td>AEACN value not found in Action Taken with Study Treatment 'non-extensible co-codlist'</td>
<td>83</td>
<td>SDTM_FULL [03/18/22]: AE action was collected individually for each of the three drugs. Per SDTM 3.2, the value of AEACN should be MULTIPLE, where individual action should be stored in the SUPROQUAL variables. The term &quot;MULTIPLE&quot; follows CDISC guidelines.</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD0002</td>
<td>NULL value in AEEDCOD variable marked as Required</td>
<td>3</td>
<td>DATA_ISSUE [03/18/22]: data issue</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD0080</td>
<td>AE start date is after the latest Disposition date</td>
<td>65</td>
<td>ONGOING [03/18/22]: ongoing study</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD1001</td>
<td>AECN value not found in Action Taken with Study Treatment 'non-extensible co-codlist'</td>
<td>276</td>
<td>SDTM_FULL_ISSUE [03/18/22]: AE action was collected individually for each of the three drugs. Per SDTM 3.2, the value of AECN should be MULTIPLE, where individual action should be stored in the SUPROQUAL variables. The term &quot;MULTIPLE&quot; follows CDISC guidelines.</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD0080</td>
<td>AE start date is after the latest Disposition date</td>
<td>197</td>
<td>ONGOING [03/18/22]: ongoing study</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD1001</td>
<td>AECN value is redundant with other variable value</td>
<td>6</td>
<td>SDTM_HYBRID_ISSUE [03/18/22]: ongoing study</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD2010</td>
<td>Value for AEHLT not found in MedDRA</td>
<td>14</td>
<td>DATA_ISSUE [03/18/22]: ongoing study</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE</td>
<td>SD2011</td>
<td>Value for AEHLTCD not found in MedDRA dictionary</td>
<td>14</td>
<td>DATA_ISSUE [03/18/22]: ongoing study</td>
<td>Click here for more details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## SDTM Validation Message Action Plan

<table>
<thead>
<tr>
<th>Rule ID</th>
<th>Message</th>
<th>Description</th>
<th>Issue category</th>
<th>Action Details</th>
<th>Examples / Notes for Action Details</th>
<th>Template for cSDRG explanation</th>
</tr>
</thead>
</table>
| SD0058  | Variable appears in dataset, but is not in SDTM model | Only variables listed in SDTM model should appear in a dataset. New variables should not be added, and existing variables must not be renamed or modified. | Spec issue / Known issue | (1) If possible, re-map the variable to an appropriate SDTM variable.  
(2) Else if it is a CRF captured variable and is non-standard, then move it to SUPP-- domain.  
(3) Else if it is a derived variable that the study team wants in, then move it to SUPP-- domain.  
(4) Else if this error belongs to SV domain, explain this in cSDRG. Check the cSDRG explanation.  
(5) Else if this error belongs to SUBID variable in domains for Multiple Subject participation instances, explain this in cSDRG. Check the cSDRG explanation.  
(6) Otherwise, if a non-standard variable was kept by mistake, then drop it. | (1) For SV domain, non-standard variables.  
SVRESP, SVOCCUR, SVREASOC, SVREPOGOCI 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.  
(2) As per the FDA TCG recommendations, for a study with multiple screenings and/or multiple enrollments per subject, SUBID 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. | “This check fired for the non-standard variables SVRESP, SVOCCUR, SVREASOC, SVREPOGOCI. 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 <<SDTM Model 1.4>>”  
Note: Text within the << >> can be adjusted based on the necessity/occurrence within the respective study.  
(2) cSDRG rationale for SUBID variable in domains (except DM) for Multiple Screenings/enrollments of a subject in a clinical trial.  
“This check fired for the non-standard variable SUBID. To comply with the recent FDA guidance, SUBID was added in a given dataset which act as key identifier to distinctly represent multiple participations of a subject within a trial.” |
| SD0999  | 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. | (1) cSDRG rationale for AP domains:  
“Pinnacle 21 limitation: AP domain class is not yet supported by Pinnacle 21 version <<xxx>>”  
(2) cSDRG rationale for custom domain: XD for Multiple Screenings/enrollments of a subject in a clinical trial.  
“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/or enrollments within the submission. Additional details regarding this domain could be found in the cdrig section: 3.3 SDTM Subject Domains.” |
| 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 | (1) Identify the errored records and notify Data Management with necessary information to fix the issue.  
(2) Check for any programmatic mistakes or spec issues and fix it. | (1) If the CRF has fields for --STAT and --REASND then inform the issue to DM.  
(2) If the CRF or eDR 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. | --- |

**Note:** The table provides a sample of the actions for specific SDTM validation messages, focusing on the action details and the template for cSDRG explanations. Each message is categorized and detailed, following the guidelines outlined in SDTM standards and FDA TCG recommendations.
Reviewer’s Guide

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

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**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:
  - Pinnacle 21 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:
  - LDMP 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**

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Diagnostic Message</th>
<th>Severity</th>
<th>Count</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LB</td>
<td>Missing Units on Value</td>
<td>Error</td>
<td>22</td>
<td>Not an error: Lab results for pH and Specific Gravity have no units</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Dataset(s)</th>
<th>Diagnostic Message</th>
<th>Severity</th>
<th>Count</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAE</td>
<td>Neither AVAL nor AVALC are present in dataset</td>
<td>Error</td>
<td>1</td>
<td>The dataset is a hierarchical occurrence structure, the message is not relevant to this structure.</td>
</tr>
</tbody>
</table>
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