

FDA SEND Submissions: Does the Pinnacle 21 Open Source Validator Predict Findings from the FDA's SEND Validators

Michael Wasko, August 4, 2016





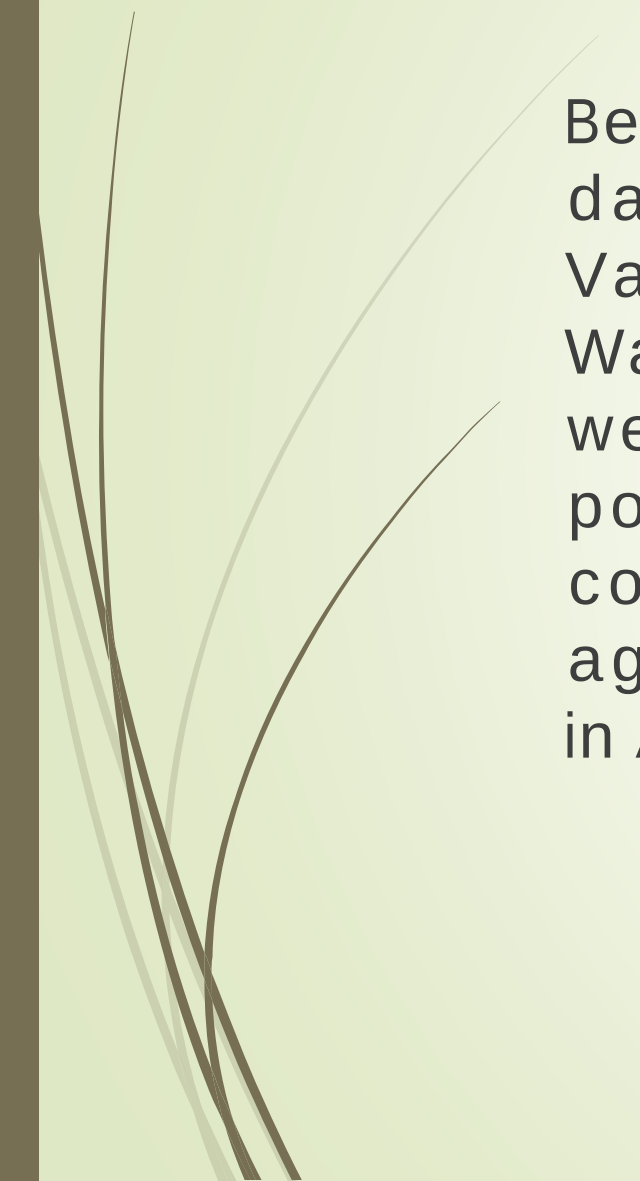
Introduction



The Pinnacle 21 Community SEND validator is an open source tool used by many sponsors and software vendors, alike, to evaluate SEND datasets for compliance to CDISC's SEND standard. An appreciation of how well it predicts results from the different SEND validators used by FDA SEND at this point in time is important. This presentation summarizes and compares FDA SEND validator findings to Pinnacle 21 SEND validator findings (prior version 2.1.0 and current version, 2.1.1) for several recent FDA SEND repeat-dose toxicology submissions.



Methods



Before submission to FDA in early January 2016, the SEND datasets were validated using the Pinnacle 21 Community Validator (formerly OpenCDISC)., Version 2.1.0. All Errors, Warnings, and Notices in the Pinnacle 21 validation report were addressed before FDA submission until only false positive Warnings and Notices remained. No submissions contained Errors. The same or similar datasets were tested against the Pinnacle 21 Community Validator Version 2.1.1 in April 2016.



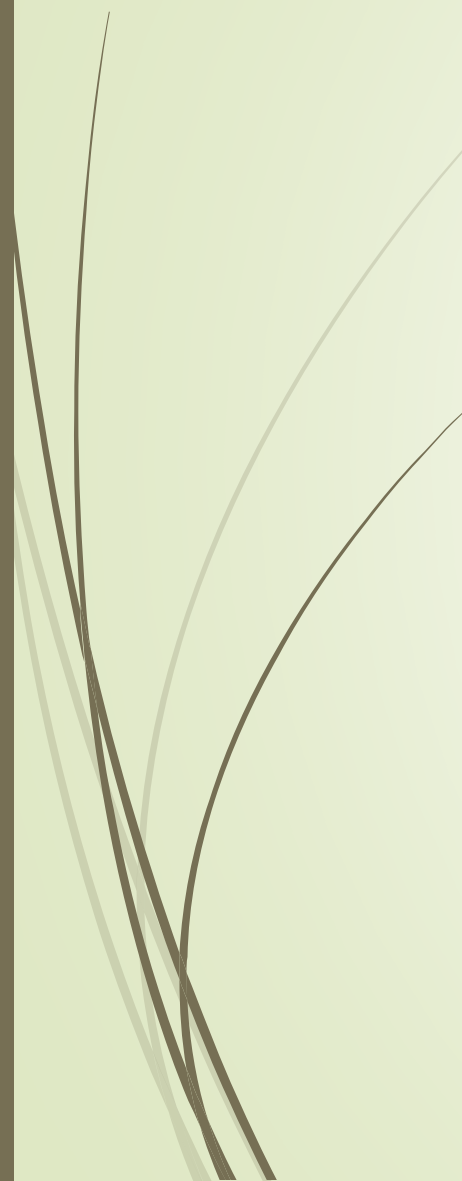
Comparison of SEND Validator Rules For FDA and Pinnacle 21 version 2.1.0

The Pinnacle 21 Community SEND Validator, Version 2.1.0, includes all of the published FDA Specific SEND Validation Rules, Version 2.1 (most recent version). Out of more than 200 SEND validation rules, we found 4 differences in version 2.1.0 of Pinnacle 21 Community SEND Validator:





FDA SEND Validation Rule	Message	Difference
FDAN014	Domain table should have at least one record	An Error for FDA; a Warning for Pinnacle 21. FDA rule pertains to TX, TS, and DM.
FDAN019	Null value in variable marked as Required.	An error for FDA; a Warning for Pinnacle 21. FDA rule pertains to TS.

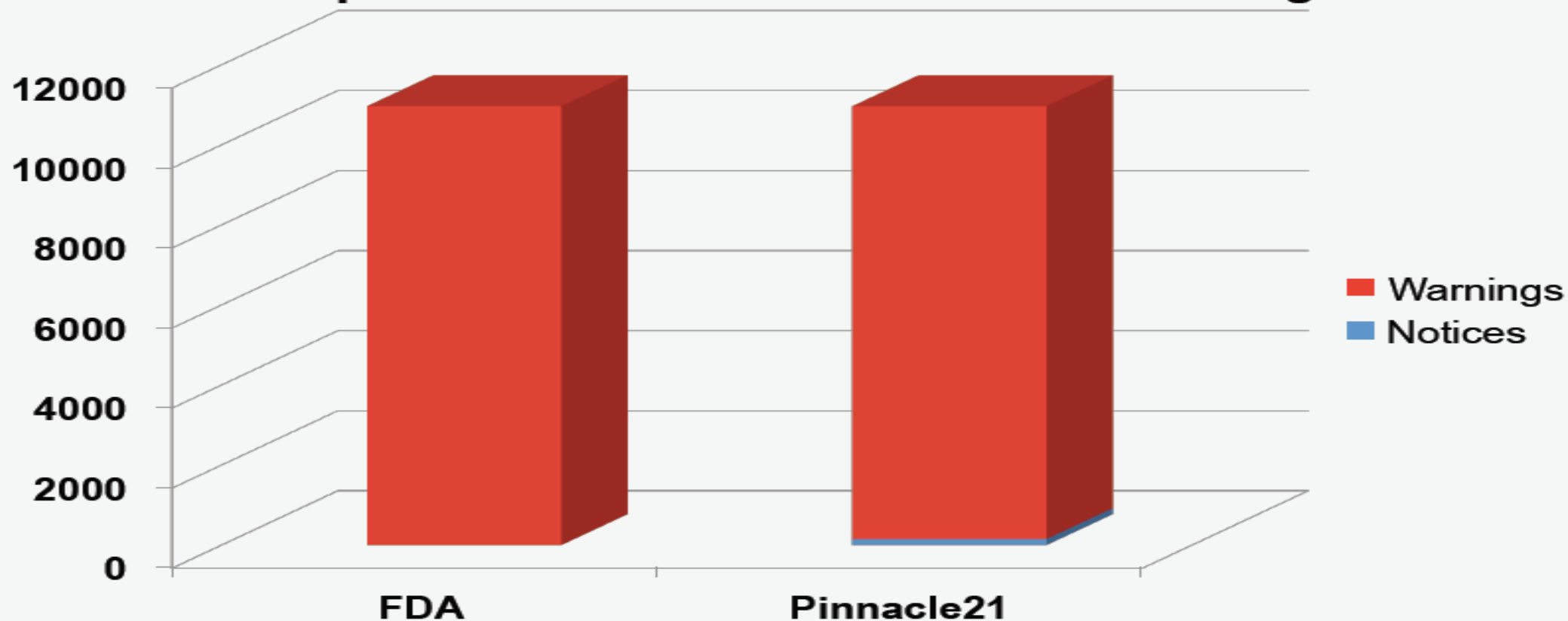


FDA SEND Validation Rule	Message	Difference
FDAN031	Model permissible variable added into standard domain.	A Warning for FDA; a Notice for Pinnacle 21.
FDAN055	Permissible variable with missing value for all records.	A Warning for FDA; a Notice for Pinnacle 21.

Comparison 1

Study Type: 13-week GLP Cynomolgus Monkey Study with a 13-week Recovery Period
No. Records: 44,201
No. Domains: 19 plus Define xml & pdf
No. Errors: 0 (both validators)

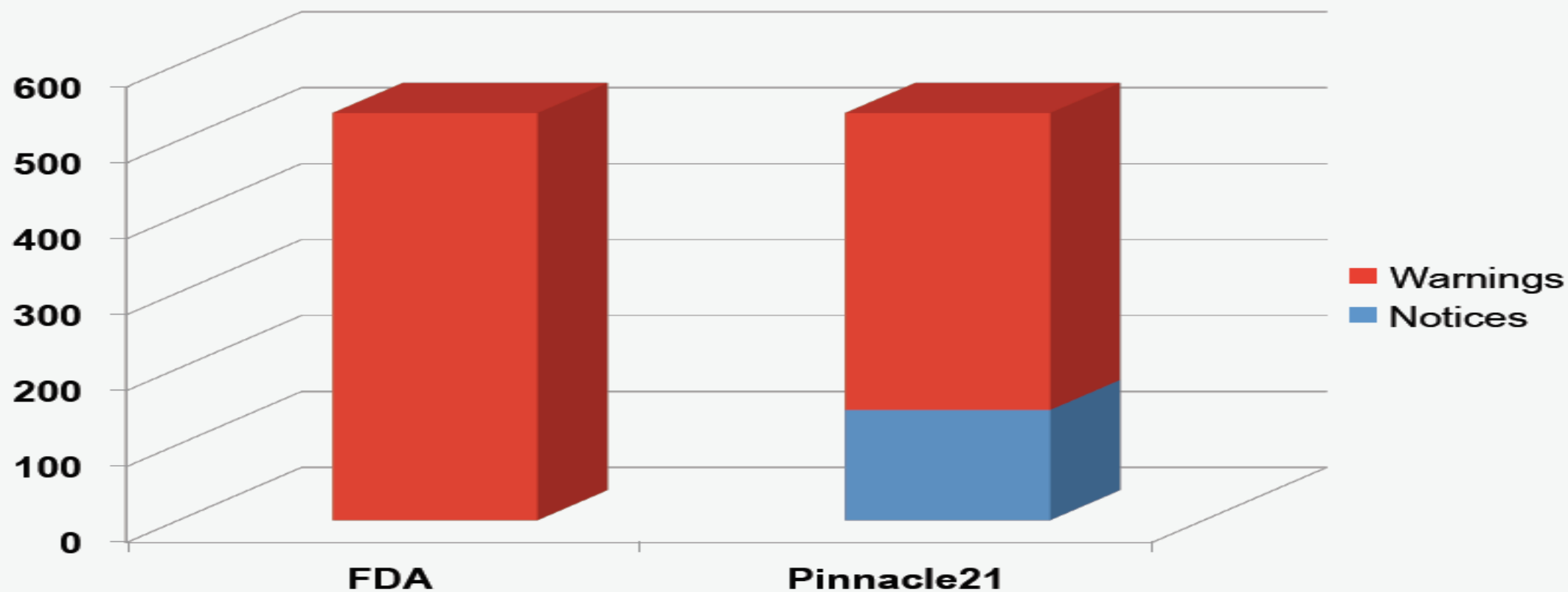
Comparison of Numbers of Validator Findings



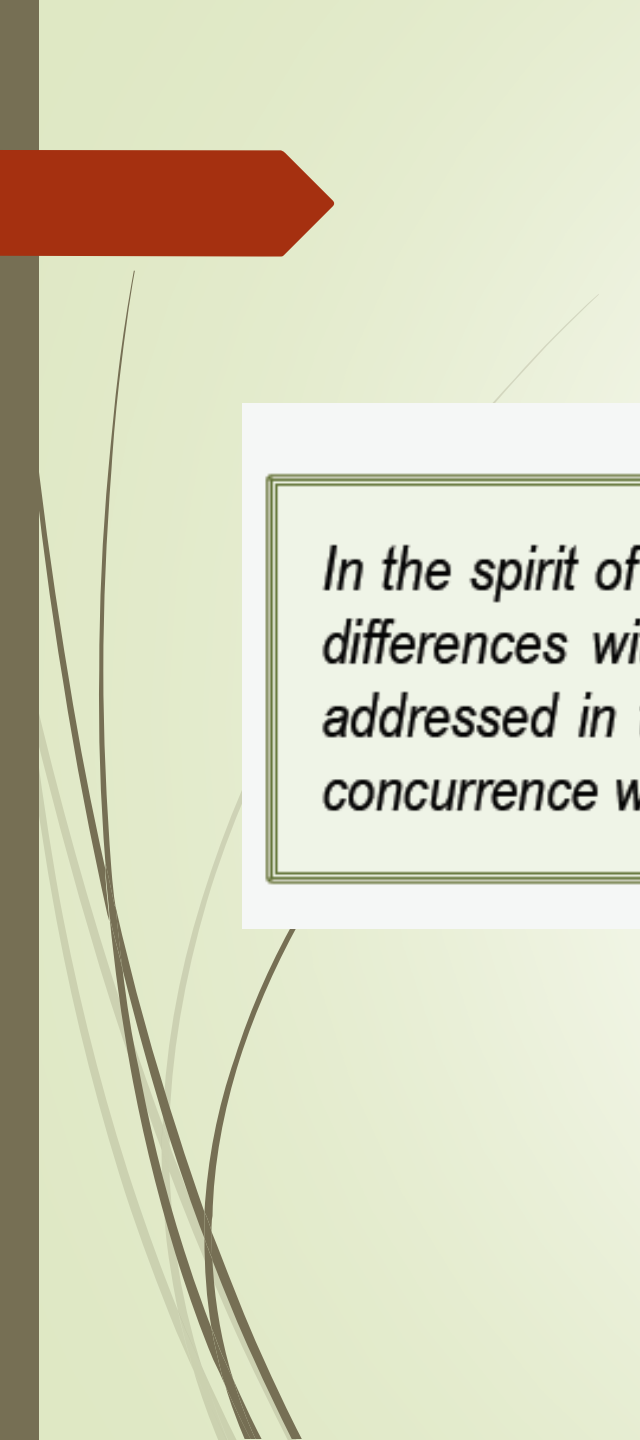
Comparison 2

Study Type:	Three-month repeat-dose rodent toxicology study with a one-month sacrifice
No. Records:	17,547
No. Domains:	19 plus Define xml & pdf
No. Errors:	0 (both validators)

Comparison of Numbers of Validator Findings



For both comparisons., the only difference in validation findings from FDA and Pinnacle 21 validation reports is that FDAN055 is considered a Warning by FDA and a Notice by Pinnacle 21.



In the spirit of collaborative Open-source software development, we discussed these differences with Pinnacle 21 and were informed that these four differences will be addressed in the next release of the Community SEND validator, resulting in 100% concurrence with published FDA validation rules.



Comparison of SEND Validator Rules For FDA and Pinnacle 21 version 2.1.1

The Pinnacle 21 Community SEND Validator, Version 2.1.1, includes all of the published FDA Specific SEND Validation Rules, Version 2.1 (most recent version). Out of more than 200 SEND validation rules, we found 0 differences in version 2.1.1 of Pinnacle 21 Community SEND Validator



Open Source Community Feedback Result

- Pinnacle 21 released an updated validator on 25-MAR-2016
- Improvements in regards to SEND validation for FDA are as follows:
 - Downgrade FINDINGS --STDTC to "Not Recommended" (bug fix)
 - Change severity from "Notice" to "Warning" for FDAN031 and FDAN055 in SEND (FDA) config (bug fix)
 - Change SD0001 in SEND (FDA) config so that issues with TS, TX, DM are reported as "Error" (bug fix) for FDAN014 and FDAN015
 - Change SD0002 in SEND (FDA) config so that issues with TS are reported as "Error" (bug fix) for FDAN018 and FDAN019
 - Added rule SD9999 to catch unrecognized datasets (enhancement)
 - Validation of Define.xml



Open Source Community Feedback Result

New Feature in regards to SEND validation for FDA as follows:

- Validation of Define.xml
 - Capability to validate define.xml versions 1.0 and 2.0
 - Version 2.1.0 could only validate define.xml version 2.0 which up until the recent Define.xml Errata from CDISC could not be used for SEND datasets
- NOTE: Pinnacle21 created and maintains the validation rules for Define.XML
 - Currently validation rules for define.xml have not been published by FDA or CDISC



What Validator is the FDA Using?

- At the CDISC Face to Face with FDA in April it was confirmed that FDA is utilizing the Pinnacle 21 version 2.1.1 Community Validator
- Confirmed by numerous Trial/Sample submissions in March through June by multiple vendors and sponsors



How to Use Validation Reports to Identify Issues Which Require Attention?

- Verify the dataset contains all the correct files
- Verify the integrity/quality of the Define.xml is acceptable
 - Utilize Pinnacle21 Validator Define.xml Validation function
- Filter through rules and investigate each XPT file to assess validity of Warning
- All Errors should be addressed/rectified
 - Some exceptions do exist and require FDA notification
- Reduce all warnings until confident remaining warnings that exist are false positive warnings

FDA Validation Rules Cited by Both Validators in 2 FDA Submissions - All were False Positives

FDAN031	Model permissible variable added into standard domain
FDAN035	Variable is in wrong order in domain
FDAN055	Permissible variable with missing value for all records
FDAN148	Missing values for both MADTC and MADY variables
FDAN154	Missing value for LBORRESU, when LBORRES is provided
FDAN169	Missing value for LBORRES, when LBORRESU is provided
FDAN212	Duplicate records
FDAN232	No result modifier (--RESMOD) qualifier for -- domain
FDAN341	Value not found in SEND Trial Summary Parameter Test Code Extensible code list

Example of Warnings/Errors to Assess

EG			
	CT2002	FDAN341	EGSTRESC value not found in 'ECG Result' extensible codelist
	SD1078	FDAN055	Permissible variable with missing value for all records
	SD1079	FDAN035	Variable is in wrong order within domain
EX			
	SD1078	FDAN055	Permissible variable with missing value for all records
	SD1079	FDAN035	Variable is in wrong order within domain
FW			
	SD1078	FDAN055	Permissible variable with missing value for all records
LB			
	CT2002	FDAN341	LBTEST value not found in 'Laboratory Test Name' extensible codelist
	CT2002	FDAN341	LBTESTCD value not found in 'Laboratory Test Code' extensible codelist
	SD1078	FDAN055	Permissible variable with missing value for all records
	SD1117	FDAN212	Duplicate records

Example of Warnings/Errors to Assess

LB					
CT2003	FDAN342	LBTESTCD and LBTEST values do not have the same Code in CDISC CT			Error
CT2002	FDAN341	LBORRESU value not found in 'Unit' extensible codelist			Warning
CT2002	FDAN341	LBSTRESU value not found in 'Unit' extensible codelist			Warning
CT2002	FDAN341	LBTEST value not found in 'Laboratory Test Name' extensible codelist			Warning
CT2002	FDAN341	LBTESTCD value not found in 'Laboratory Test Code' extensible codelist			Warning
SD0018	FDAN058	Invalid value for LBTESTCD variable			Warning
SD1078	FDAN055	Permissible variable with missing value for all records			Warning
SD1117	FDAN212	Duplicate records			Warning
SE2306	FDAN151	Missing values for all required set(s) of timing variables [DM.RFSTDTC with LBDTC] , LBDY and VISITDY,			Warning



Conclusion

- ▶ Comparison of validation findings for two SEND FDA submissions supports the conclusion that the Pinnacle 21 Community Validator predicts FDA validator findings for both the number of findings and validation rules cited.
- ▶ We also conclude that both validators produced the same findings on a domain-by-domain basis. Severity levels differed in version 2.1.0 and were resolved with release of version 2.1.1.
- ▶ It is recommended to address all Errors and Warnings from the Pinnacle 21 validation report until only false positive Warnings remain in advance of submitting SEND datasets to FDA.
- ▶ While use of a good SEND validator is critical, it does not obviate the need to visually examine each domain for SEND compliance by knowledgeable individuals



New News and FDA updates on SEND datasets and submissions as of August 2016

- CDISC has published SENDIG (Standard for Exchange of Nonclinical Data Implementation Guide) version 3.1 on 07JULY
 - FDA has not yet published SENDIG V3.1 in the Data Standards 2016Catalog and has not given indication as to when it will be published
 - Major changes include:
 - Introduction of –NOMDY and –NOMLBL
 - Introduction of Cardiovascular and Respiratory Domains



New News and FDA updates on SEND datasets and submissions as of August 2016

- FDA published an updated Data Standards catalog on 18JULY2016
 - DEFINE.XML version 1.0 will no longer be supported after March 2017
- CDISC released an Errata to Define.xml standards making Define.xml version 2.0 compatible with SEND



Questions