CDISC Italian User Network 2020

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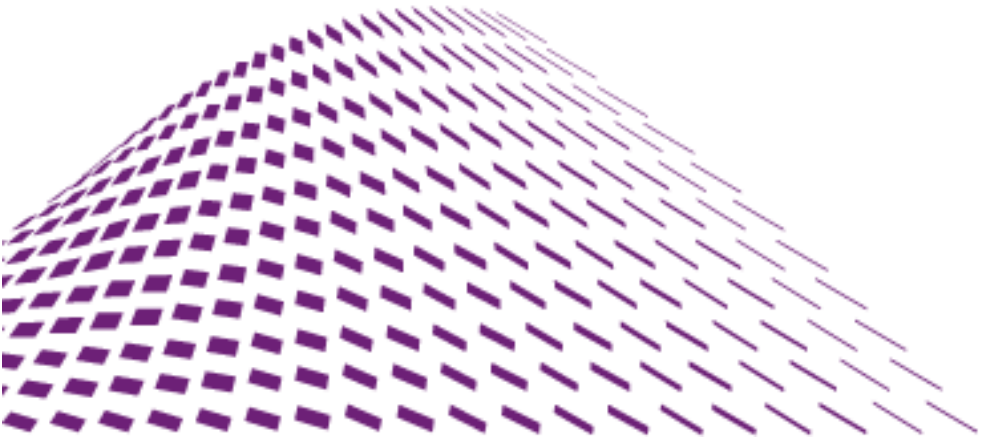
Health innovation that matters

Validation Rules and Validation Tools

Presented by Silvia Faini
Principal Statistical Programmer, LivaNova
7th October 2020

Agenda

1. Validation Rules
    1. CDISC Conformance Rules
    2. FDA Rules
    3. PMDA Rules
2. Validation Tools
    1. Pinnacle 21 Community
    2. PointCross eDataValidator
    3. Report comparison



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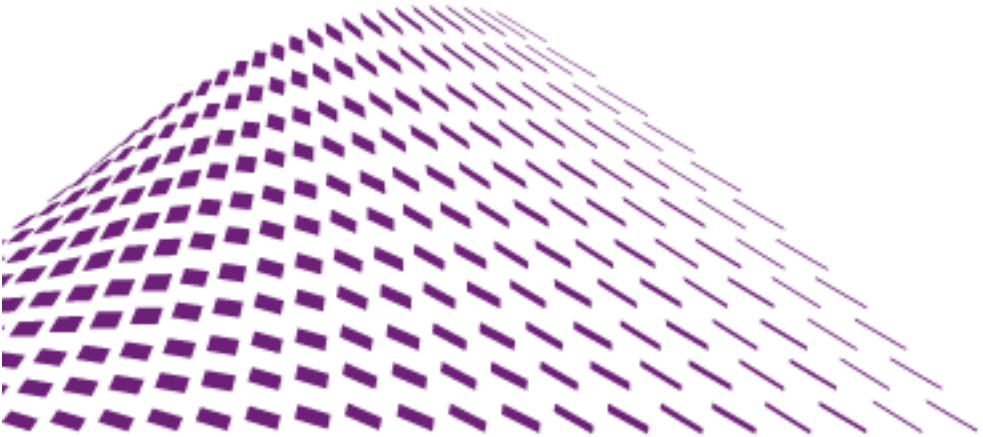
Validation Rules



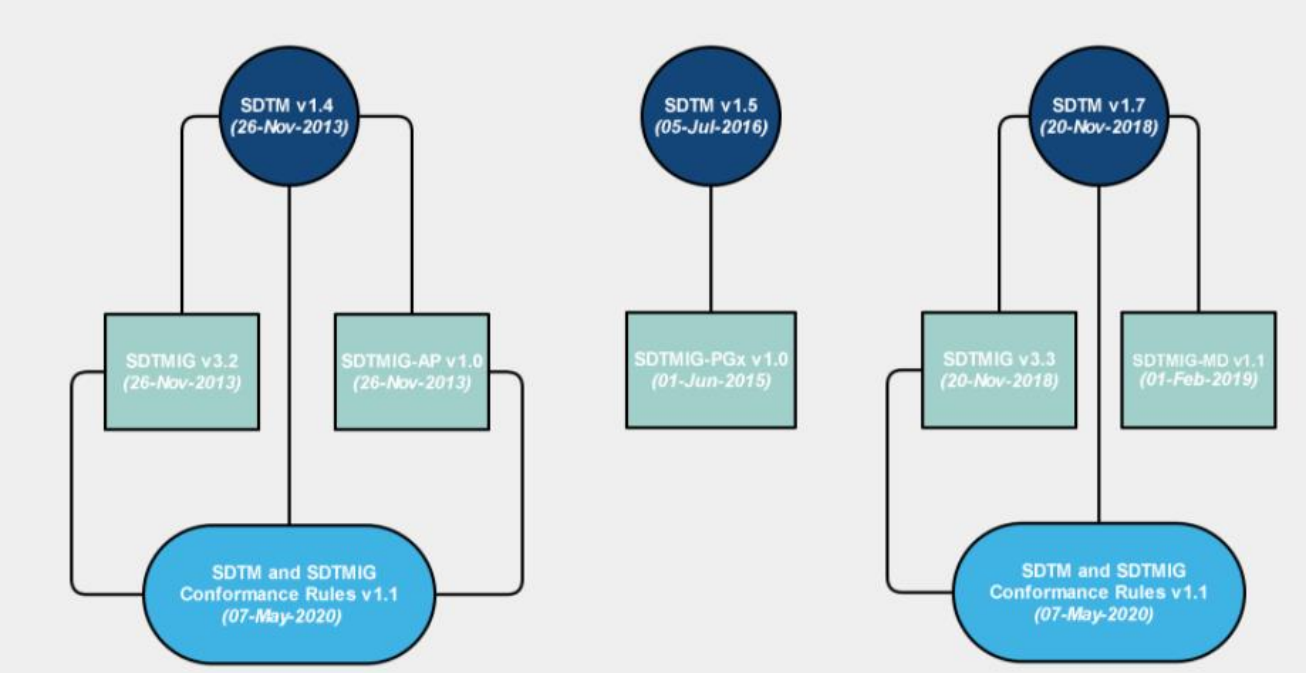
Definitions of Rule Sets

- Conformance Rules are created and maintained by CDISC, describe the criteria that must be met to be in compliance with the CDISC standard.
- Business Rules are created by a specific organization to describe the criteria that should be met to allow for the deliverable to be useful in the conduct of normal business practice.
- Technical Rejection Criteria for Study Data: the minimum requirements for eCTD submissions to be accepted by the agency at the gateway.
- Validator Rules are rule sets utilized by validation tools. Each validator can have its own set of validation rules, validation tools implement the check of different set of validation rules.

From Development and Documentation Guide of "Conformance Rules v1.1 for SDTM and SDTMIG v3.2 & v3.3"

CDISC Conformance Rules – SDTM 1/6

- Reference CDISC Guidelines and Conformance Rules



https://www.cdisc.org/standards/foundational/sdtmig

CDISC Conformance Rules – SDTM 2/6

SDTM Conformance Rules

- Scope: to provide a logic statement which consists of scoping attributes (i.e. applicable class, domains, variables), the rule itself, and, if applicable, a conditional statement.
- Info provided: Rule ID (CGxxxx), SDTM IG Version, Rule Version, Class, Domain, Variable, Rule, Condition, Document, Section, Item, Cited Guidance, Release Notes.

Rule ID	SDTM IG Version	Rule Version	Class	Domain	Variable	Rule	Condition	Document	Section	Item
CG0001	3.2	1	ALL	ALL	DOMAIN	DOMAIN = valid Domain Code published by CDISC	Not custom domain	IG v3.2	2.6	3.d
CG0001	3.3	1	ALL	ALL	DOMAIN	DOMAIN = valid Domain Code published by CDISC	Not custom domain	IG v3.3	2.6	3.e
CG0002	3.2	1	ALL	ALL	--DUR	--DUR collected and not derived	--DUR ^= null	Model v1.4	2.2.5	
CG0002	3.3	1	ALL	ALL	--DUR	--DUR collected and not derived	--DUR ^= null	Model v1.7	2.2.5	
CG0006	3.2	2	ALL	ALL	--DY	--DY calculated as per the study day algorithm as a non-zero interger value	Date portion of --DTC is complete and date portion of RFSTDTC is a complete date AND --DY is ^= null	IG v3.2	4.1.4.4	

https://www.cdisc.org/standards/foundational/sdtmig

CDISC Conformance Rules – SDTM 3/6

SDTM Conformance Rules (continue)

- >410 conformance rules:
  - Into the new version no more present the definition of programmable or conditionally programmable (depending on the availability of other documentation)
  - No more explicit reference to correspondent FDA rules
- Observation class or rule category scope for the rule using an abbreviation of 3-characters or less:
  - ALL – All observation classes, SPC – Special-Purpose Class, FND – Findings Class, EVT – Events Class, INT – Interventions Class, TDM – Trial Design Domains, AP – Associated Persons Domains
- Domain scope for the rule using standard CDISC domain abbreviations, if it applies to multiple domains list separated by commas, keyword ALL if applies to all domains.
- Variable contains variable name, variable name with dashes as prefix, keyword GEN for rules which apply to all variables.

CDISC Conformance Rules – SDTM 4/6

SDTM Conformance Rules (continue)

- A rule should be a concise and unambiguous statement of the conformance principle to be applied. Only 1 principle is stated per rule.
- Guidelines for composing rule statement:
  - Any reference to a variable in a domain is in the form "Domain.Variable" (e.g., DM.ARM).
  - a selection from a discrete list described in guidance (but not in CDISC CT), then the syntax should be "Variable in (value1, value2…)".
  - a selection from a discrete list described in CDISC CT, then the syntax should be "Variable in {CT List Name}". Note the use of braces instead of parentheses.
  - keyword "null" rather than phrases such as *is missing, equals blank, or should not be populated*.
  - Logical operators *(<,=,>,in,not,^)* should be used in place of phrases such as *less than or equal to, not greater than, should equal*, and so on.
  - The term one-to-one is used to identify that an object has an isomorphic relationship with another object (i.e., value pair is unique).

CDISC Conformance Rules – SDTM 5/6

SDTM Conformance Rules (continue)

- If the rule is applied only when a specific condition is met, then the condition is specified in the Condition column.
- Guidelines for composing condition statement:
  - It is not necessary to preface the condition with "If ..." this is implicit.
  - Multiple parts of the condition should be separated by standard logical operators (e.g., AND, OR, AND NOT). Parentheses are allowed to help clarify when multiple logical operators are used in a single condition.
  - Controlled terminology or terminology taken from SDTMIG should be used to describe conditions or requirements in a standard way.
  - *First, Last, Unique, Exists, Null, One-to-one* are terms with a specific definition to be used in condition statements.

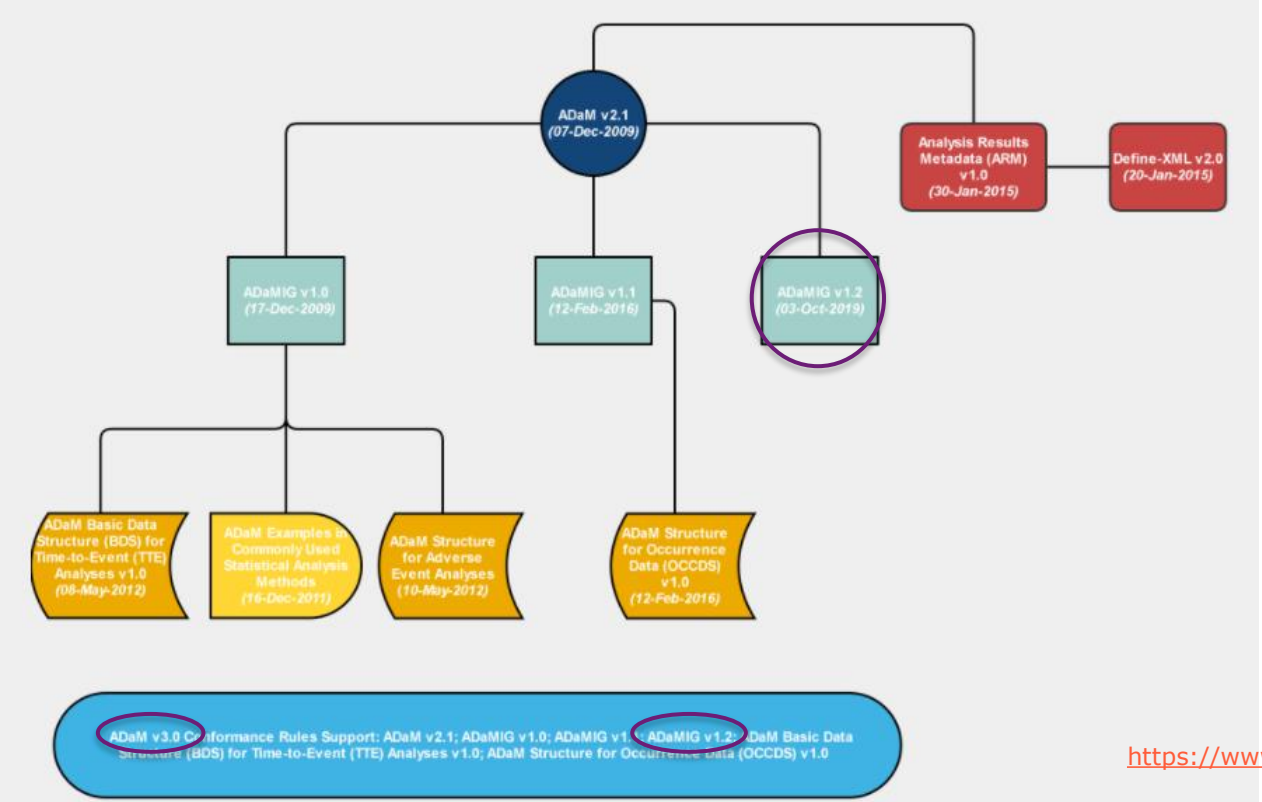
CDISC Conformance Rules – SDTM 6/6

SDTM Conformance Rules (continue)

- In these assumptions there is the effort to set standard rules to create automated controls, but this can be more or less possible depending on several factors:
  - System in which they are implemented
  - Characteristics of the rule

  ... also a part of manual checks is essential to assess adherence to the SDTM guidelines.

CDISC Conformance Rules – ADaM 1/3



https://www.cdisc.org/standards/foundational/adam

CDISC Conformance Rules – ADaM 2/3

ADaM Conformance Rules

- ADaM Conformance Rules v2.0 released in Q1 2019
- Based on ADaMIG v1.0, ADaMIG v1.1, OCCDS v1.0
- Scope:
  - To enable development of software to perform ADaM dataset checks.
  - To test ADaM datasets structure and certain standardized variable values.
- Not meant to define the whole spectrum of ADaM compliance, e.g.:
  - principle of harmonization (ADaMIG 3.1.1), the best to control this is during ADaM programming.
  - variable name and variable content, ADaMIG 3.1.5 suggests fragments to be used in naming ADaM variables, overall when the position of the fragment is dependent on variable purpose.
- These rules are intended to be used for single studies.
- Info provided: Check Number, IG Version, ADaM Structure Group, Machine-Testable Failure Criteria, Message Type, Guide, Section, Item, Cited Guidance.
- Rules are duplicated for ADaMIG v1.0 and ADaMIG v1.1 (ID is Check Number + IG Version)

https://www.cdisc.org/standards/foundational/adam

CDISC Conformance Rules – ADaM 3/3

ADaM Conformance Rules (continue)

- >350 conformance rules.
- ADaM Structure Group: key words to identify the ADaM structure
- Machine-Testable Failure Criteria: text use as requirement specification which could be implemented in a variety of programming languages.
- Message Type: Error, Warning, Note

Check Number	IG Versic	ADaM Structure Group	Machine-Testable Failure Criteria	Message Type	Guide	Section	Item	Cited Guidance
1	1.0	ADSL	ADSL dataset does not exist	Error	Model v2.1; ADaM IG v1.0	6; 2.3.1		Model v2.1, Section 6: ADSL a a clinical trial even if no oth ADaM IG v1.0, Section 2.3.1: data from a clinical trial eve
1	1.1	ADSL	ADSL dataset does not exist	Error	Model v2.1; ADaM IG v1.1	6; 2.3.1		Model v2.1, Section 6: ADSL a a clinical trial even if no oth ADaM IG v1.1, Section 2.3.1: data from a clinical trial eve
2	1.0	ALL:SDTM	A variable is present in ADaM with the same name as a variable present in SDTM but the variables do not have identical labels	Error	Model v2.1; ADaM IG v1.0	4.1.2; 3	4 (General Variable Naming Conventions)	Model v2.1, Section 4.1.2: An copy of the SDTM variable, a principle of harmonization k

CDISC Conformance Rules – SDTM and ADaM

CDISC Conformance Rules

- Different approach/structure/content of the excel files, e.g.:
  - In SDTM Rule ID (CGxxxxx) vs in ADaM Check Number (xx).
  - In ADaM Message Type (Error, Warning, Note), this info is not included in SDTM.
  - In ADaM Programmable info is not provided.
  - In SDTM FDA Rule ID is provided, it is not provided in ADaM as FDA.
  - In both ADaM and SDTM rules are duplicated for IG versions → no more difference

- Conformance rules are not always aligned with the most recent versions of CDISC guidelines, but new releases are foreseen in 2020:
  - Conformance Rules v1.2 for SDTM v2.0 and SDTMIG v3.4 (Batch 1 Resolving Public Comments, Batch 2 in development)
  - Conformance Rules v2.0 for SENDIG v3.1 (In Public Review)
  - ADaMIG Conformance Rules v3.0 (Resolving Public Comments)
  - Define-XML v2.1 Conformance Rules (In Development)

FDA Business Rules

- **FDA Business Rules** describe the business requirements for regulatory review to help ensure that study data is compliant and useful and supports meaningful review and analysis.
  - the list grow and change with experience.
  - all business rules are expected to be followed where applicable.
  - do not redefine conformance or GCP (e.g. deprecated when equal to conformance rules).
  - categorized into those that apply to SEND formatted nonclinical, SDTM formatted clinical data or both.
  - Last version 1.5 June 2019 includes 16 deprecated, 70 current (26 clinical, 17 both, 27 nonclinical).

https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

FDA Validation Rules

- **FDA Validation Rules** provide details regarding FDA's assessment of study data for purposes of review and analysis.
  - also represent the latest understanding of what best supports regulatory review.
  - Last version 1.3 October 2018 contains
    - rules for SDTM-IG v3.1.2, v3.1.3, **v3.2** and SEND v3.0, v3.1.
    - 480 rules, categorized by publisher 185 from FDA Business Rules, 295 from SDTM conformance rules. SDTM CR version
    - 429 rules for **SDTM-IG v3.2**.

FDA Validator Rule ID	FDA Validator Message	Publisher	Publisher ID	Business or Conformance Rule Validated	FDA Validator Rule	Domains
SD1037	Missing value for --TOX, when --TOXGR is populate	FDA	FDAB002	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is greater than 0.	A value for a Toxicity (--TOX) variable should be provided, when a Toxicity Grade (--TOXGR) variable value is populated and greater than 0.	AE, MH, CE, EG, LB, PC, PP
SD0008	Value for --DECOD is not found in the dictionary	FDA	FDAB003	Adverse Events must be coded using 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 define.xml (Case-insensitive).	AE
SD1015	Invalid EPOCH	CDISC	CG0009	. . EPOCH, as a Timing variable, is the name of the Epoch during which --STDTC or --DTC falls. The values of EPOCH are drawn from the Trial Arms domain, Section 7.2 - Experimental Design: Trial Arms (TA)	Epoch (EPOCH) values should match entries in the Trial Arms (TA) dataset.	ALL
SD1078	Permissible variable with missing value for all records	CDISC	CG0015	The sponsor does not have the discretion to exclude permissible variables when they contain data.	Permissible variable should not be present in domain, when the variable has missing value for all records in the dataset.	ALL
SD1023	VISIT/VISITNUM values do not match TV domain data	CDISC	CG0031	For planned visits, values of VISIT, VISITNUM, and VISITDY must be those defined in the Trial Visits dataset,	Combination of Visit Name (VISIT) and Visit Number (VISITNUM) in subject-level domains should match that in the TV domain with the exception of Unscheduled and Unplanned visits.	ALL

Identifier

PMDA Validation Rules 1/2

- **PMDA Validation Rules**
  - The electronic study data, which violates the rules should be corrected prior to the submission of a new drug application and, preferably, all data should be resubmitted.
  - Categorized by level of importance
    - 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.

http://www.pmda.go.jp/english/review-services/reviews/0002.html

PMDA Validation Rules 2/2

- **PMDA Validation Rules**
  - Categorized into those that apply to SDTM, ADaM and Define-XML.
  - Last version 2.0 September 2019.
    - 437 for SDTM: 9 Reject, 175 Error, 253 Warning.
    - 251 for ADaM: 13 Reject, 210 Error, 28 Warning.
    - 136 for Define: 14 Reject, 77 Error, 45 Warning.
  - No correspondent CDISC rules provided

http://www.pmda.go.jp/english/review-services/reviews/0002.html

PMDA Validation Rules – examples

- Examples of Reject Rules, for SDTM,
  for the controlled terminology, for ADaM and for define.xml.

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity
SD0056	SDTM Required variable not found	Variables described in SDTM IG as Required must be included in the dataset.	ALL	Reject
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
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).	ALL	Reject
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.		Reject

PMDA Validation Rules - examples

- Examples of Error Rules, for SDTM, for ADaM and for define.xml.

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity
SD0003	Invalid ISO 8601 value for *DTC variable	Value of Dates/Time variables (*DTC) must conform to the ISO 8601 international standard.	ALL	Error
AD0019	Variable subject-population flag value is null	For subject-level character population flag variables: N = no (not included), Y = yes (included). Null values are not allowed.	ADSL	Error
DD0012	Duplicate Document ID	The ID attribute for Document must be unique within Define.xml. Define-XML specification represents Documents as def:leaf elements within MetaDataVersion element.		Error

- Examples of Warning Rules, for SDTM, for ADaM and for define.xml.

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity
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 Method of Test or Examination (--METHOD).	FINDINGS	Warning
AD0223	Calculation issue: CHG != AVAL - BASE	When all 3 variables are populated, CHG (change from baseline) must equal Analysis Value (AVAL) minus Baseline Value (BASE).	BDS	Warning
DD0078	Document <document> is not referenced	Only Documents that are referenced from a Method or Comment should be included in Define.xml. Define-XML specification represents Documents as def:leaf elements within MetaDataVersion element.		Warning

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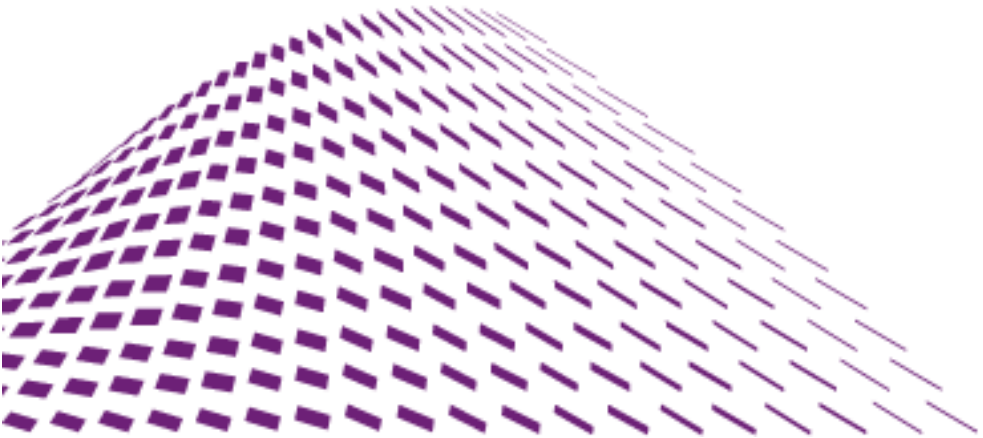
Validation Tools



Validation Tools

- Comparison between two Free validation tools

	Pinnacle 21 Community	PointCross
Open Source	Yes	No
CDISC Conformance Rules	Not available	Not available
FDA validation rules	Available	Available
PMDA validation rules	Available	Available
NMPA validation rules*	Available	Not available
Dataset formats	XPT, XML, CSV	XPT
CDISC-CT	Available with auto-update	Available with auto-update
define.xml validation	Separate	Automatically performed when define.xml is selected.
Define.xml generation	Available	Not available
Reviewer's Guide generation	Not available	Generate nSDRG Template (only SEND)

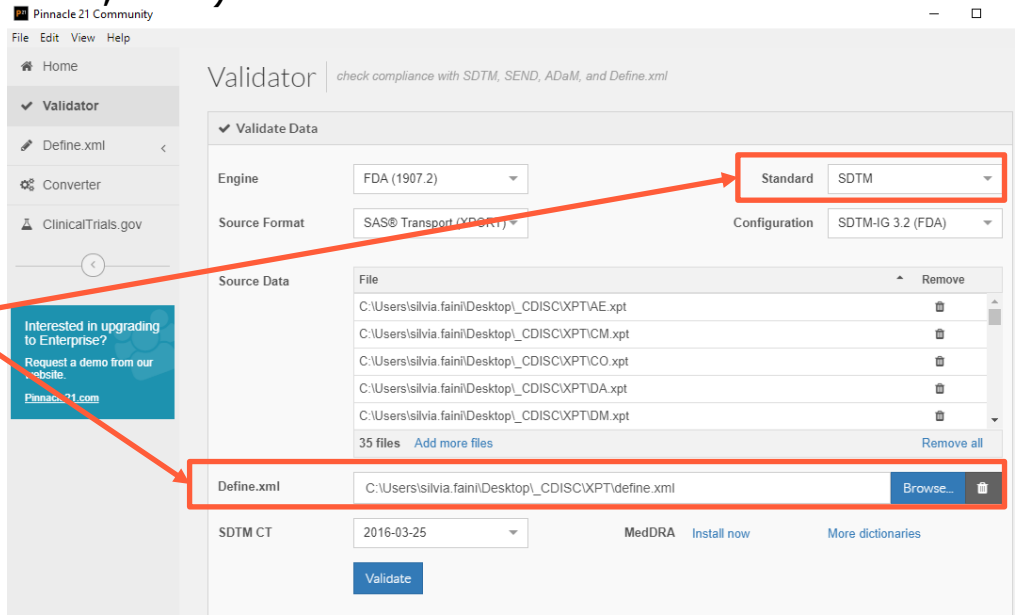
* In March 2019 NMPA issued the first eCTD guidance. Available in P21C since August 2020.

Validation Tools – Pinnacle 21 Community

Validator parameters to be selected:

- CDISC standard, version, FDA/PMDA configuration
- Datasets to be validated (XPT, delimited, XML) + Define.xml
- Controlled Terminology, MedDRA, SNOMED (to be configured)

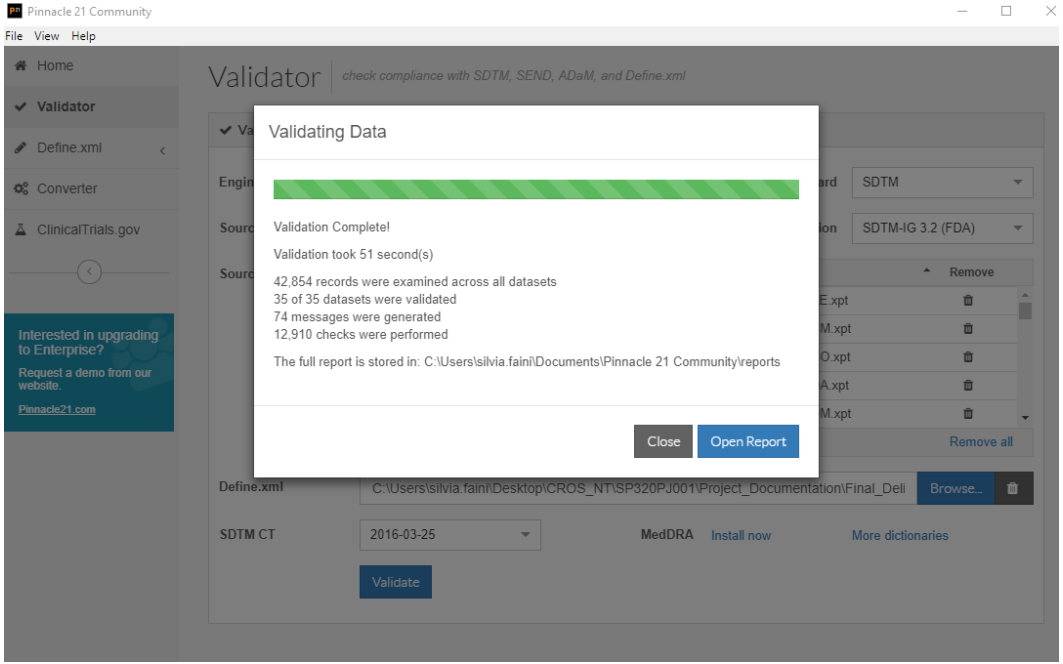
Separate Define-xml validation



Note: Pinnacle21 Community v3.1.0

Validation Tools – Pinnacle 21 Community

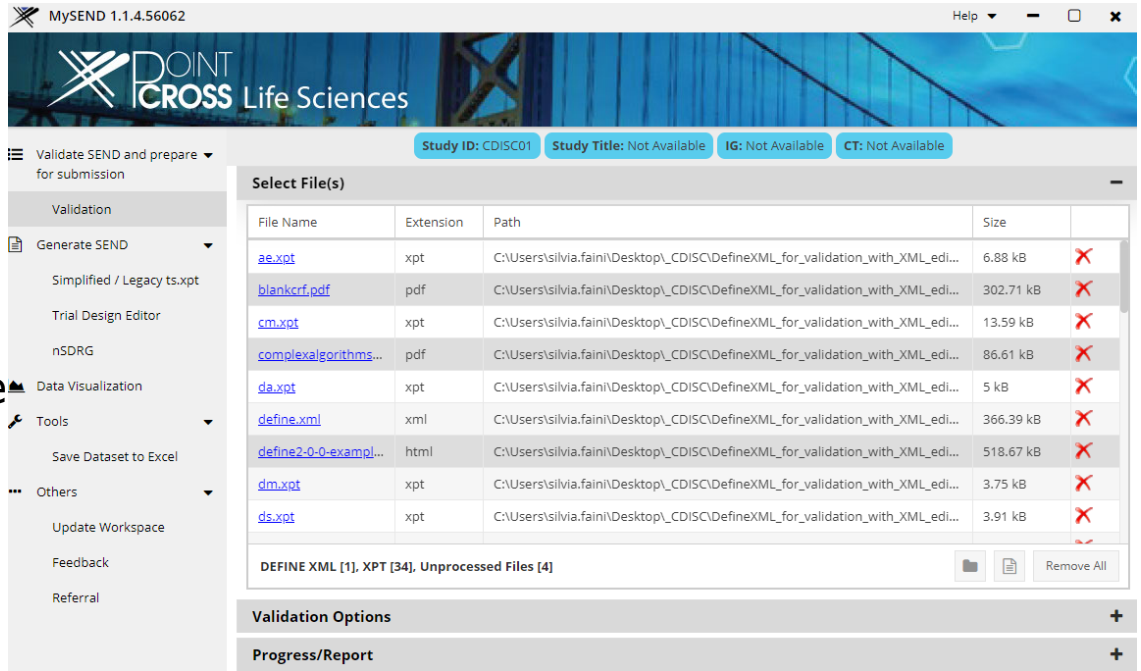
- Validation status in progress/completed
- Excel report name: pinnacle21-report-YYYY-MM-DDTHH-MM
- Link to open the excel report



Validation Tools – PointCross

Validator parameters to be selected:

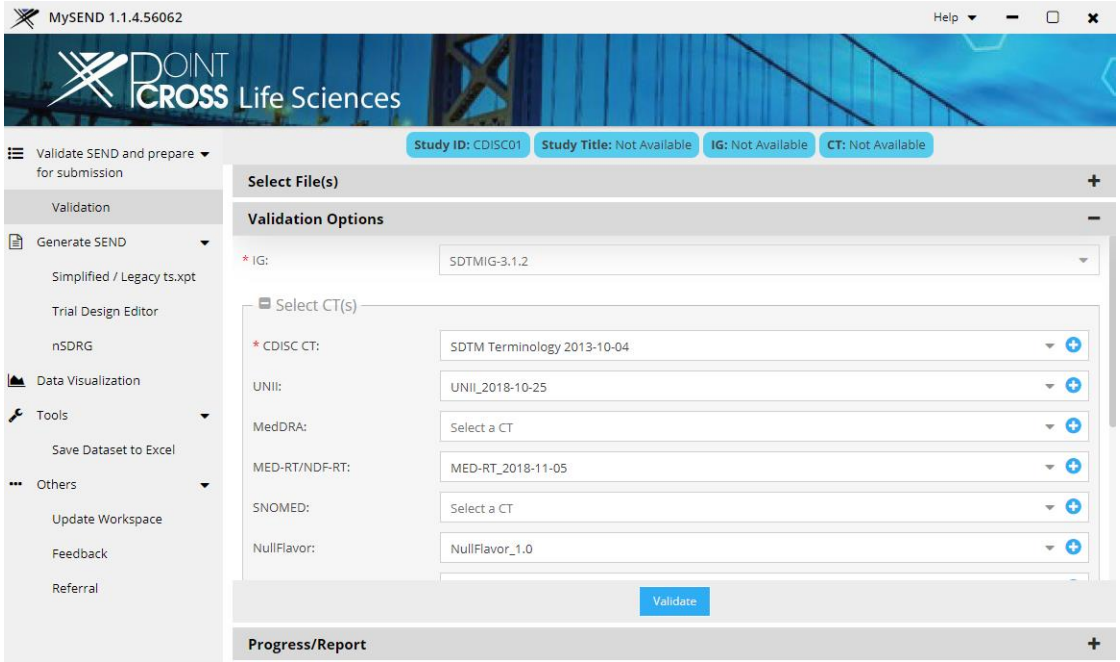
- Select files: select the folder/zip file where datasets and define files are located.
- A summary line with the count of files is provided.
- When a define.xml is in the set, a checkbox is enabled, allowing to do a separate define.xml validation, based on a set of PMDA rules.



Validation Tools – PointCross

Validator parameters to be selected:

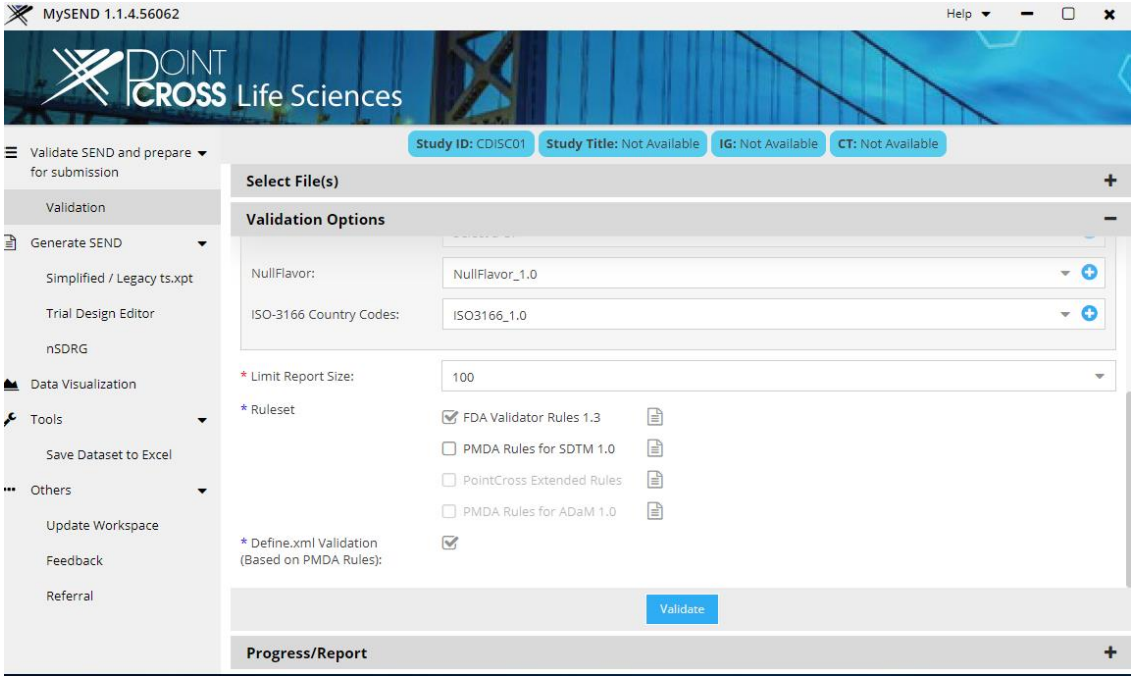
- Validation options: IG version, CDISC CT, UNII, MedDRA (to be configured), MED-RT/NDF-RT, SNOMED (to be configured), NullFlavor, FDA/PMDA rulesets



Validation Tools – PointCross

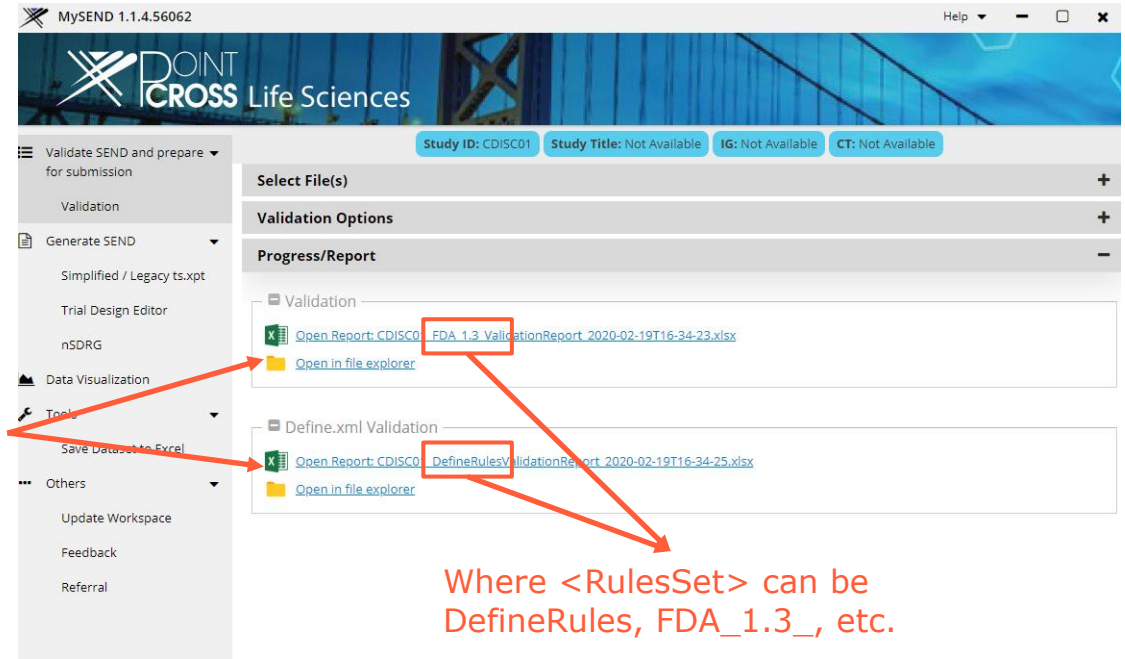
Validator parameters to be selected:

- Validation options: IG version, CDISC CT, UNII, MedDRA (to be configured), MED-RT/NDF-RT, SNOMED (to be configured), NullFlavor, FDA/PMDA rulesets



Validation Tools – PointCross

- Validation status in progress/completed
- Link to open the excel report/folder
- Excel report name: StudyID_<RulesSet>ValidationReport_YYYY-MM-DDTHH-MM-SS



Validation Tools Comparison

Package description:

- 35 SDTM domains: 5 trial domains, 9 supplemental domains, 20 standard domains, 1 ad hoc domain
- define.xml
- Disclaimer looking into one example can have some limits, but at the same time gives some clues.

- Settings used in the example

	SDTM version	Configuration	CDISC SDTM CT
Pinnacle 21 Community	SDTM-IG 3.2	FDA	2016-03-25
PointCross	SDTM-IG 3.2	FDA Validaton Rules v1.3	2016-03-25

Validation Tools Comparison

- Domains with issues: some numbers... discouraging numbers

	Total	Report only in one	Domains with same # of issues	Domains with discrepant # of issues
Pinnacle 21 Community	23	TI	DM, SUPPAE, SUPPCM	19
PointCross	26	FA, IE, SV, SUPPCO	DM, SUPPAE, SUPPCM	19

- Number of issues from the two tools

	AE	CM	CO	DA	DS	DV	EG	EX	LB	MH	PC	PE	QS	SE	SU	TA	TS	VS	ZS
P21C	30	185	1	462	71	2	4303	266	6951	13	3447	31	706	32	2	7	7	1277	1825
PCross	31	87	120	2	962	70	1368	46	3018	95	2759	2	362	2	4	1	22	583	11

... Let's have a look to one domain.

Validation Tools Comparison

- For VS domain P21C 1277 issues, PCross 583 issues.
- Only SD2239 is detected by both, with different number of issues... discouraging numbers

VS					
	SD2239	CG0240	Inconsistent value for VSTPT	Error	1
	CT2002	CG0021	EPOCH value not found in 'Epoch' extensible codelist	Warning	215
	CT2002	CG0021	VSORRESU value not found in 'Units for Vital Signs Results' extensible codelist	Warning	530
	CT2002	CG0021	VSSTRESU value not found in 'Units for Vital Signs Results' extensible codelist	Warning	530
	SD1339	FDAB022	Missing EPOCH value, when a start or observation date is provided	Warning	1

PCID	RULEID	DOMAIN	COUNT	MESSAGE
PCID047	SD1117	VS	570	Duplicate records
PCID198	SD1076	VS	1	Model permissible variable added into standard domain
PCID693	SD1023	VS	9	VISIT/VISITNUM values do not match TV domain data
PCID765	SD2239	VS	3	Inconsistent value for --TPT

Validation Tools Comparison

- **CT2002 (FDA) – CG0021 (SDTM CR)** – VS.EPOCH –EPOCH value not found in 'Epoch' extensible codelist → checking define.xml (see code) this is a FALSE POSITIVE issue.

- P21C provides other false positive issues for CT2002 rule in this example, e.g.: CM.CMDOSFRQ, CM.CMDOSU, CM.CMROUTE, DA.DATEST, DA.DATESTCD, LB.LBSPEC, LB.LBMETHOD.

```
<CodeList OID="CL.EPOCH" Name="Epoch" DataType="text">
   <CodeListItem CodedValue="FOLLOW-UP">
      <Decode>
         <TranslatedText xml:lang="en">FOLLOW-UP</TranslatedText>
      </Decode>
      <Alias Name="C99158" Context="nci:ExtCodeID"/>
   </CodeListItem>
   <CodeListItem CodedValue="SCREENING">
      <Decode>
         <TranslatedText xml:lang="en">SCREENING</TranslatedText>
      </Decode>
      <Alias Name="C48262" Context="nci:ExtCodeID"/>
   </CodeListItem>
   <CodeListItem CodedValue="TAPER" def:ExtendedValue="Yes">
      <Decode>
         <TranslatedText xml:lang="en">TAPER</TranslatedText>
      </Decode>
   </CodeListItem>
   <CodeListItem CodedValue="TREATMENT">
      <Decode>
         <TranslatedText xml:lang="en">TREATMENT</TranslatedText>
      </Decode>
      <Alias Name="C101526" Context="nci:ExtCodeID"/>
   </CodeListItem>
   <Alias Name="C99079" Context="nci:ExtCodeID"/>
</CodeList>
```

Validation Tools Comparison

- **CT2002 (FDA) – CG0021 (SDTM CR)** – VS.EPOCH –EPOCH value not found in 'Epoch' extensible codelist → checking define.xml (see code) this is a FALSE POSITIVE issue.

- P21C provides other false positive issues for CT2002 rule in this example, e.g.: CM.CMDOSFRQ, CM.CMDOSU, CM.CMROUTE, DA.DATEST, DA.DATESTCD, LB.LBSPEC, LB.LBMETHOD.

- This issue for VS.VSORRESU, VS.VSSTRESU (codelist VSRESU) technically is a true positive, but allow to understand that two units are wrongly uppercased:

Units for Vital Signs Results [CL.VSRESU, *C66770*]

Permitted Value (Code)	Display Value (Decode)
BEATS/MIN [*]	BEATS/MIN
BREATHS/MIN [*]	BREATHS/MIN
C [*C42559*]	Degree Celsius
cm [*C49668*]	Centimeter
kg [*C28252*]	Kilogram
mmHg [*C49670*]	Millimeter of Mercury

* Extended Value

Code	Codelist Code	Codelist Extensible (Yes/No)	CDISC Submission Value
C66770		Yes	VSRESU
C49673	C66770		beats/min
C49674	C66770		breaths/min

Validation Tools Comparison

- **SD2239 (FDA) – CG0240 (SDTM CR)** – VS.VSTPT – Inconsistent value for –TPT, Planned Time Point Name (--TPT) value must be consistent for all records with same Subject (USUBJID) and Assessment Date/Time (--DTC).

  → P21C only one record with the wrong VSTPT is detected as issue;

  → PCross, all records with discrepant VSTPT for the same USUBJID, VISITNUM, VSDTC, VSTPT are detected as issues (1 true positive, 2 false positive).

Subject Identifier	Epoch	Visit Name	Date/Time of Measurements	Planned Time Point Name	Vital Signs Test Name	Numeric Result/Finding in Standard Units	Standard Units
1087-002	TREATMENT	Day 1	2014-12-01		Height	129	cm
1087-002		Day 1	2014-12-01	Unscheduled Timepoint 1	Pulse Rate	112	BEATS/MIN
1087-002	TREATMENT	Day 1	2014-12-01		Weight	21.4	kg

→ Check for other datasets if the situation is the same, this issue is present also for EG, LB and PC

Source	Pinnacle	Publisher	Message	Severity	Found
EG	SD2239	CG0240	Inconsistent value for EGTPT	Error	663
LB	SD2239	CG0240	Inconsistent value for LBTPT	Error	1
PC	SD2239	CG0240	Inconsistent value for PCTPT	Error	8

PCID	RULEID	DOMAIN	COUNT
PCID765	SD2239	EG	1323
PCID765	SD2239	LB	38
PCID765	SD2239	PC	22

Validation Tools Comparison

- LBTPT has the only wrong record in the one with LBTPT='Unscheduled Timepoint 1' → which is the only record for LBTEST='SCN1A Analysis', then this record was wrongly included into the dataset (true positive).
- EGTPT has plenty of 'PRE-DOSE' and '2 - 3 HOURS POST-DOSE' for the same USUBJID-EGDTC→ these are false positive in the study context as time was not collected in EGDTC; the only possible wrong record is the one with 'Unscheduled Timepoint 1'.

ject Identifier	Epoch	Visit Name	Date/Time of ECG	Planned Time Point Name	ECG Test or Examination Name	Numeric Result/Finding in Standard Units	Standard Units
1079-005	SCREENING	Day 1	2015-01-02	PRE-DOSE	QTcB - Bazett's Correction Formula	405	msec
1079-005	TREATMEN	Day 1	2015-01-02	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	418	msec
1079-005	TREATMEN	End of Treatment	2015-01-20	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	427	msec
1079-005	TREATMEN	End of Treatment	2015-01-20	PRE-DOSE	QTcB - Bazett's Correction Formula	408	msec
1079-006	SCREENING	Day 1	2015-01-02	PRE-DOSE	QTcB - Bazett's Correction Formula	411	msec
1079-006	TREATMEN	Day 1	2015-01-02	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	428	msec
1079-006	TREATMEN	End of Treatment	2015-01-21	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	422	msec
1079-006	TREATMEN	End of Treatment	2015-01-21	PRE-DOSE	QTcB - Bazett's Correction Formula	418	msec
1080-001	SCREENING	Day 1	2014-12-09	PRE-DOSE	QTcB - Bazett's Correction Formula	410	msec
1080-001	TREATMEN	Day 1	2014-12-09	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	450	msec
1080-001	TREATMEN	End of Treatment	2014-12-30	Unscheduled Timepoint 1	QTcB - Bazett's Correction Formula	441	msec
1080-001	TREATMEN	End of Treatment	2014-12-30	PRE-DOSE	QTcB - Bazett's Correction Formula	436	msec
1080-001	TREATMEN	End of Treatment	2014-12-30	2 - 3 HOURS POST-DOSE	QTcB - Bazett's Correction Formula	446	msec

Validation Tools Comparison

- **SD1339 (FDA) – FDAB022 (FDA BR)** – VS.EPOCH – Missing EPOCH value, when a start or observation date is provided.

  → P21C error detected,

  from trial domains this record should be assigned to EPOCH=TREATMENT as it belongs to Day 1, this mistake should be correct (true positive).

Subject Identifier	Epoch	Visit Name	Date/Time of Measurements	Planned Time Point Name	Vital Signs Test Name	Numeric Result/Finding in Standard Units	Standard Units
1087-002	TREATMENT	Day 1	2014-12-01		Height	129	cm
1087-002		Day 1	2014-12-01	Unscheduled Timepoint 1	Pulse Rate	112	BEATS/MIN
1087-002	TREATMENT	Day 1	2014-12-01		Weight	21.4	kg

Validation Tools Comparison

- **SD1023 (FDA) – CG0031 (SDTM CR)** – VS. VISIT – VISIT/VISITNUM values do not match TV domain data.

  → PCross: one subject has an unscheduled visit, which is not included into TV domain.

Visit Name	Visit Number	Start Date/Time of Visit	Description of Unplanned Visit
Day 1 Unscheduled 1	2.1	2014-12-10	ECG and Vital Signs assessments

  SV.SVUPDES should be used for this visit,

  then this rule is not programmed in the correct way → the correspondent SDTM Conformance Rule is

  "VISIT ^= null and is planned", then the second part of the rule is not checked.

→ Check for other datasets if the situation is the same, this issue is wrongly detected also for EG and SV.

PCID	RULEID	DOMAIN	COUNT	MESSAGE
PCID693	SD1023	EG	10	VISIT/VISITNUM values do not match TV domain data
PCID693	SD1023	SV	1	VISIT/VISITNUM values do not match TV domain data
PCID693	SD1023	VS	9	VISIT/VISITNUM values do not match TV domain data

Validation Tools Comparison

- **SD1117 (FDA) – FDAB021 (FDA BR)** – Duplicate records.

  → Pcross detects 570 duplicate records by the following key variables

  STUDYID, USUBJID, VSTESTCD, VSDTC, VSTPT, VISITDY, VSDY, VISITNUM

  The solution of this issue is into VSPOS variable, then these records are not duplicated, issue to be justified.

ıbject Identifier	Vital Signs Test Short Name	Date/Time of Measurements	Planned Time Point Name	Planned Study Day of Visit	Study Day of Vital Signs	Visit Number	Vital Signs Position of Subject
P-1079-001	DIABP	2014-11-28		-28	-31	1	SITTING
P-1079-001	DIABP	2014-11-28		-28	-31	1	STANDING
P-1079-001	DIABP	2014-11-28		-28	-31	1	SUPINE
P-1079-001	DIABP	2014-12-29T12:00	PRE-DOSE	1	1	2	SITTING
P-1079-001	DIABP	2014-12-29T12:00	PRE-DOSE	1	1	2	STANDING
P-1079-001	DIABP	2014-12-29T12:00	PRE-DOSE	1	1	2	SUPINE
P-1079-001	DIABP	2014-12-29T14:45	2 - 3 HOURS POST-DOSE	1	1	2	SITTING
P-1079-001	DIABP	2014-12-29T14:45	2 - 3 HOURS POST-DOSE	1	1	2	STANDING
P-1079-001	DIABP	2014-12-29T14:45	2 - 3 HOURS POST-DOSE	1	1	2	SUPINE

- Note: FDAB021 rule was deprecated in FDA Business Rule v1.5 (May 2019), but it is still present in FDA Validation Rules v1.3 (October 2018).

Validation Tools Comparison - Conclusions

- Actions after validation run:
  - Fix all possible issues.
  - Justify in RGs the ones that are allowed due to study design, data collected, rules limits.
  - Be careful of how validation rules are implemented into the tool.
- Analysed issues cannot be considered a complete comparison of P21C and PCross.
- Always be aware:
  - issues (positive) can be true or false.
  - False negative are not detected.

True Positive	False Positive
False Negative	True Negative

Issue exists and is reported	Issue does not exist but is reported
Issue exists but is not reported	Issue does not exist and is not reported

Conclusions

- Standards versions vs Conformance Rules vs Regulatory Agencies Rules vs Their implementation in validation tools vs Different tools.
  - How rules consistency can be/not be ensured in this process.
  - Future → try to simplify this chain.

- Work with quality since the beginning, do not think to quality only during validation tool run.

Any question?

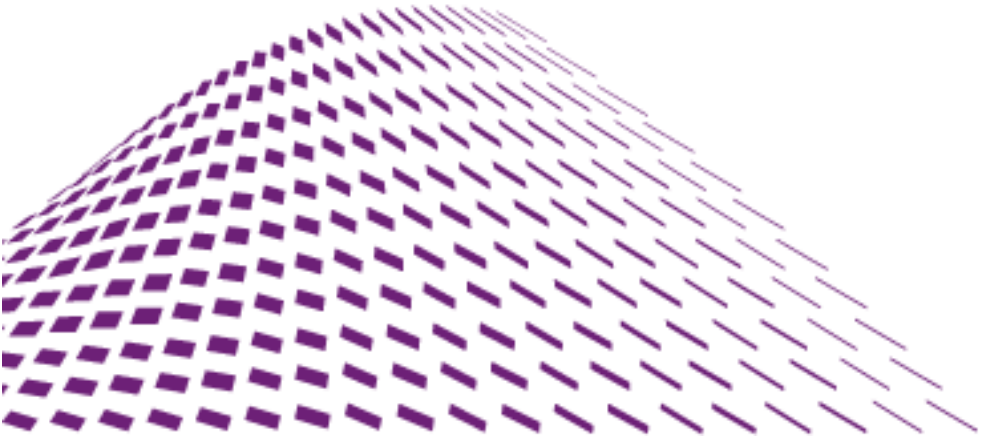
Thank You

Silvia Faini
Principal Statistical Programmer – LivaNova
silvia.faini@livanova.com

LivaNova

Health innovation that matters

Backup Slides
SDTM CR v1.0



CDISC Conformance Rules – SDTM 1/3

SDTM Conformance Rules

- SDTMIG v3.2 Conformance Rules v1.0 released in Q4 2016.
- Based on SDTM v1.4, SDTMIG v3.2, SDTMIG-AP v1.0 released in Q4 2013.
- Scope: standard practices in formulating and documenting compliance and conformance rules.
- Info provided: Rule ID (CGxxxx), Class, Domain, Variable, Rule, Guide, IG Version, Batch, Programmable.

Rule ID	Class	Domain	Variable	Rule	Condition	Guide	Section	Item	IG Versions	Batch ID	Programmable	Programmable Flag Comment	FDA Rule ID (v 1.0)
CG0001	ALL	ALL	DOMAIN	DOMAIN = valid Domain Code published by CDISC	Not custom domain	IG v3.2	2,6	3.d	3,2	1,00	C	Dependent on additional non-CDISC metadata	
CG0002	ALL	ALL	--DUR	--DUR collected and not derived	--DUR ^= null	Model v1.4	2.2.5		3,2	1,00	C	Dependent on additional appropriate metatdata	
CG0006	ALL	ALL	--DY	--DY calculated as per the study day algorithm as a non-zero interger value	Date portion of --DTC is complete and RFSTDTC is a complete date AND --DY is ^= null	IG v3.2	4.1.4.4		3,2	1,00	Y		FDAC112, FDAC127

https://www.cdisc.org/standards/foundational/sdtmig

CDISC Conformance Rules – SDTM 2/3

SDTM Conformance Rules (continue)

- 410 conformance rules:
  - 325 programmable + 85 conditionally programmable (depend on the availability of other documentation)
  - 177 rules have one or more correspondent FDA rules
- Observation class or rule category scope for the rule using an abbreviation of 3-characters or less:
  - ALL – All observation classes, SPC – Special-Purpose Class, FND – Findings Class, EVT – Events Class, INT – Interventions Class, FNA – Findings About, TDM – Trial Design Domains, AP – Associated Persons Domains
- Domain scope for the rule using standard CDISC domain abbreviations, with exceptions being ALL or NOT().
- Variable contains variable name, variable name with dashes as prefix, keyword GEN for rules which apply to all variables.

CDISC Conformance Rules – SDTM 3/3

SDTM Conformance Rules (continue)

- Assumptions for the Rules: to use the conformance rules excel file as input file.
  - General rules
  - Syntax Rules
  - Terminology Rules
  - Potential Rule Implementation as Automated Checks
- In these assumptions there is the effort to set standard rules to create automated controls, but this can be more or less possible depending on several factors:
  - System in which they are implemented
  - Characteristics of the rule

  ... also a part of manual checks is essential to assess adherence to the SDTM guidelines.