CDISC Conformance Checking Introduction and Implementation

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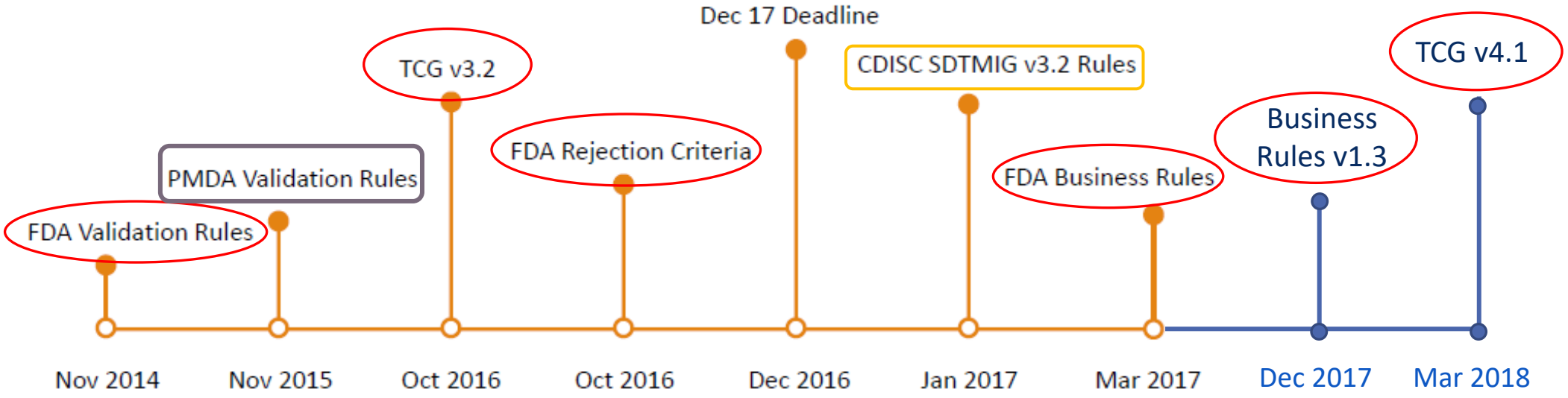
Outline

- Introduction
- Validation Implementation
- Development of Customized Tool
- Summary and Perspective

Axis of Time



From https://www.pinnacle21.com/

FDA Validation Rules

First Validation rules for CDISC SDTM published on Nov 2014

FDA Rule ID	MESSAGE	DESCRIPTION	DOMAINS	SEVERITY	3.1.1	3.1.2	3.1.3 (3.1.2 A:
FDAC001	Missing DM dataset	Demographics (DM) dataset must be included in every submission	DM	Error	X	X	X
FDAC002	Missing TS dataset	Trial Summary (TS) dataset must be included in every submission	TS	Error	X	X	X
FDAC003	Missing DS dataset	Disposition (DS) dataset should be included in every submission	DS	Warning	X	X	X
FDAC004	Missing EX dataset	Exposure (EX) dataset should be included in every submission	EX	Warning	X	X	X
FDAC005	Missing AE dataset	Adverse Events (AE) dataset should be included in every submission	AE	Warning	X	X	X
FDAC006	Missing LB dataset	Lab Test Results (LB) dataset should be included in every submission	LB	Warning	X	X	X
FDAC007	Missing VS dataset	Vital Signs (VS) dataset should be included in every submission	VS	Warning	X	X	X
FDAC008	Missing SE dataset	Subject Elements (SE) dataset should be included in every submission	SE	Warning	X	X	X
FDAC009	Missing TA dataset	Trial Arms (TA) dataset should be included in every submission	TA	Warning	X	X	X
FDAC010	Missing TE dataset	Trial Elements (TE) dataset should be included in every submission	TE	Warning	X	X	X
FDAC012	Missing MB dataset, when MS dataset is present	Microbiology Specimen (MB) dataset should be included, when a Microbiology Susceptibility Test (MS) dataset is present	MB	Warning	X	X	X

Date	Document Number	Version #	Description
2014-Nov-13		1.0	Initial Version - Clinical Data Validation Rules.

FDA Validation Rules – Cont.

Study Data Technical Conformance Guide v3.2 (2016)

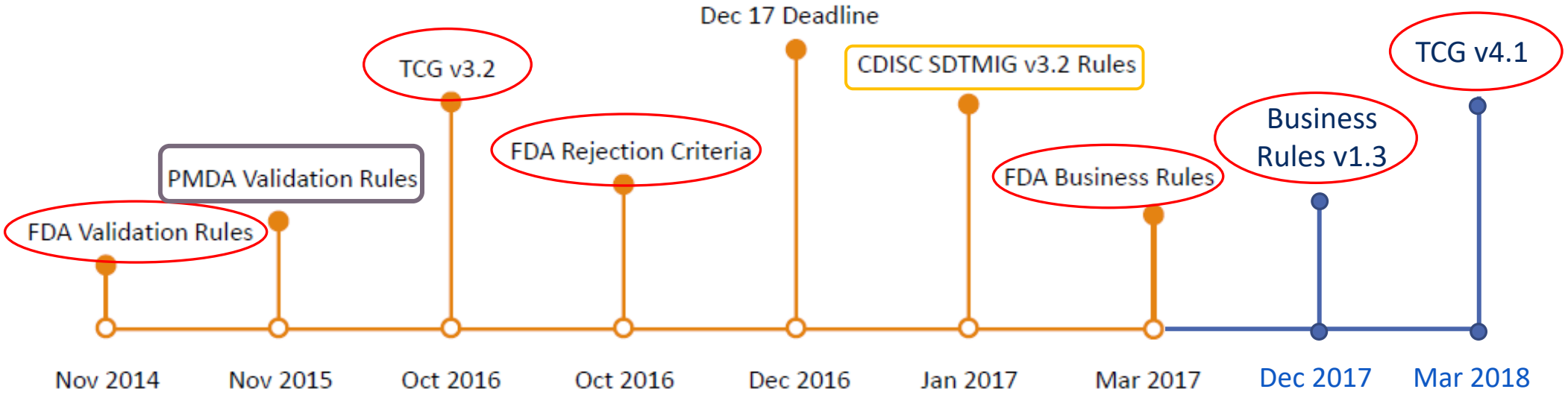
(The latest release v4.1 in 2018)

Expanded validation rules to 3 types

- Introduced Technical Rejection Criteria
- Released FDA Business Rules
- Followed Standards Conformance Rules from CDISC

https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm2005545.htm

Axis of Time



From https://www.pinnacle21.com/

Technical Rejection Criteria

Only two rules #1734 & #1736 published in eCTD validation rule

- #1734: Trial Summary (TS) dataset must be present for each study in Module 4 and 5
- #1736: Demographic (DM) dataset and define.xml must be submitted in Module 4 for nonclinical data
- DM dataset, Subject level analysis dataset (ADSL) and define.xml must be submitted in Module 5 for clinical data

Not new

May expand more in future

FDA Business and Validation Rules

version 1.2, finalized December 2017

FDA Business Rule ID	FDA Business Rule	FDA Validator Rule	Domains	SDTM 3.1.2	SDTM 3.1.3	SDTM 3.2
FDAB001	A treatment-emergent flag must be submitted.	A treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3.	SUPPAE	X	X	X
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	X	X	X
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	X	X	X
		Value for Body System or Organ Class (--BODSYS) variable must be populated using a System Organ Class of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE	X	X	X
		Value for Preferred Term Code (--PTCD) variable must be populated using a Preferred Term Code of the MedDRA dictionary of a version specified in the define.xml.	AE, MH, CE		X	X
		Value for Lowest Level Term (--LLT) variable must be populated using a Lowest Level Term of the MedDRA dictionary of a version specified in the define.xml (Case-insensitive).	AE, MH, CE		X	X

- Implementation of TCG
- Compliance with CDISC
- Previous validation rule stop updating

CDISC Validation Rules

Available CDISC Rules

- SDTMIG v3.2 Conformance Rules
  - Published: v1.0 January 27, 2017

Rule ID	Class	Domain	Variable	Rule	Condition	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	3.2	1.00	C	Dependent on additional non-CDISC metadata	
CG0002	ALL	ALL	--DUR	--DUR collected and not derived	--DUR ^= null	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	3.2	1.00	Y		FDAC112, FDAC127
CG0007	ALL	ALL	--DY	--DY = null	The date portion of --DTC ^= complete date or the date portion of DM.RFSTDTC ^= complete date	3.2	1.00	Y		FDAC125, FDAC126

ht ig-v32

CDISC Validation Rules – Cont.

- ADaMIG v1.0 Conformance Rules
  - Published: v1.0 September 20, 2010
  - Last updated: v1.3 January 20, 2015
  - Adverse Events (ADAE), and Basic Data Structure for Time-to-Event Analyses (BDS-TTE)

https://www.cdisc.org/standards/foundational/analysis-data-model-adam/adam-validation-checks-v13

Pharmaceuticals and Medical Devices Agency (PMDA) Validation Rule

https://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html

PMDA validation rules were published on Nov 18, 2015

Date	Sheet Name	Version #	Description
11/18/2015	SDTM Rules	1.0	Initial version.
11/18/2015	ADaM Rules	1.0	Initial version.
11/18/2015	Define-XML Rules	1.0	Initial version.

PMDA Validation Rules – Cont.

SDTM Rules v1.0

RULE ID	MESSAGE	DESCRIPTION	DOMAINS	PMDA Severity	3.1.2	3.1.3	3.2	PMDA NOTES
SD0001	No records in data source	Domain table should have at least one record.	ALL	Warning	X	X	X	
SD0002	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records.	ALL	Reject	X	X	X	Violation of SD0002 will be considered part of Rejection criteria, except for the following variables in DM domain that will be considered Errors. <Variable Name> ARMCD ARM ACTARMCD ACTARM
SD0003	Invalid ISO 8601 value for *DTC variable	Value of Dates/Time variables (*DTC) must conform to the ISO 8601 international standard	ALL	Error	X	X	X	
SD0004	Inconsistent value for DOMAIN	Domain Abbreviation (DOMAIN) variable should be consistent with the name of the dataset.	ALL	Warning	X	X	X	
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	ALL	Error	X	X	X	

PMDA Validation Rules – Cont.

Severity	PMDA	FDA
Rejection	If violated, will cause the review to be suspended until corrections have been made	Refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs
Error	If violated without any prior explanation, will cause the review to be suspended until corrections have been made	NA
Warning	Even when violated, will not necessarily require any explanation	

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- Introduction
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Pinnacle 21

- FDA and PMDA use Pinnacle 21 Enterprise for validation

Validation Tools and Electronic Submission Validation Criteria in Use				
Tool Name	Standard(s) Being Validated	Tool Version in Use	Tool in Use as of Date	Validation Criteria
GlobalSubmit Validate	eCTD	8.2.6	8/28/2017	See Specifications for eCTD Validation Criteria (above)
Pinnacle 21 Enterprise	SDTM, SEND, ADaM, ASCII, Define, XML	3.2	11/4/2017	FDA Business Rules and FDA Validator Rules

eCTDdataStandards by FDA

TCG on Electronic Study Data submissions

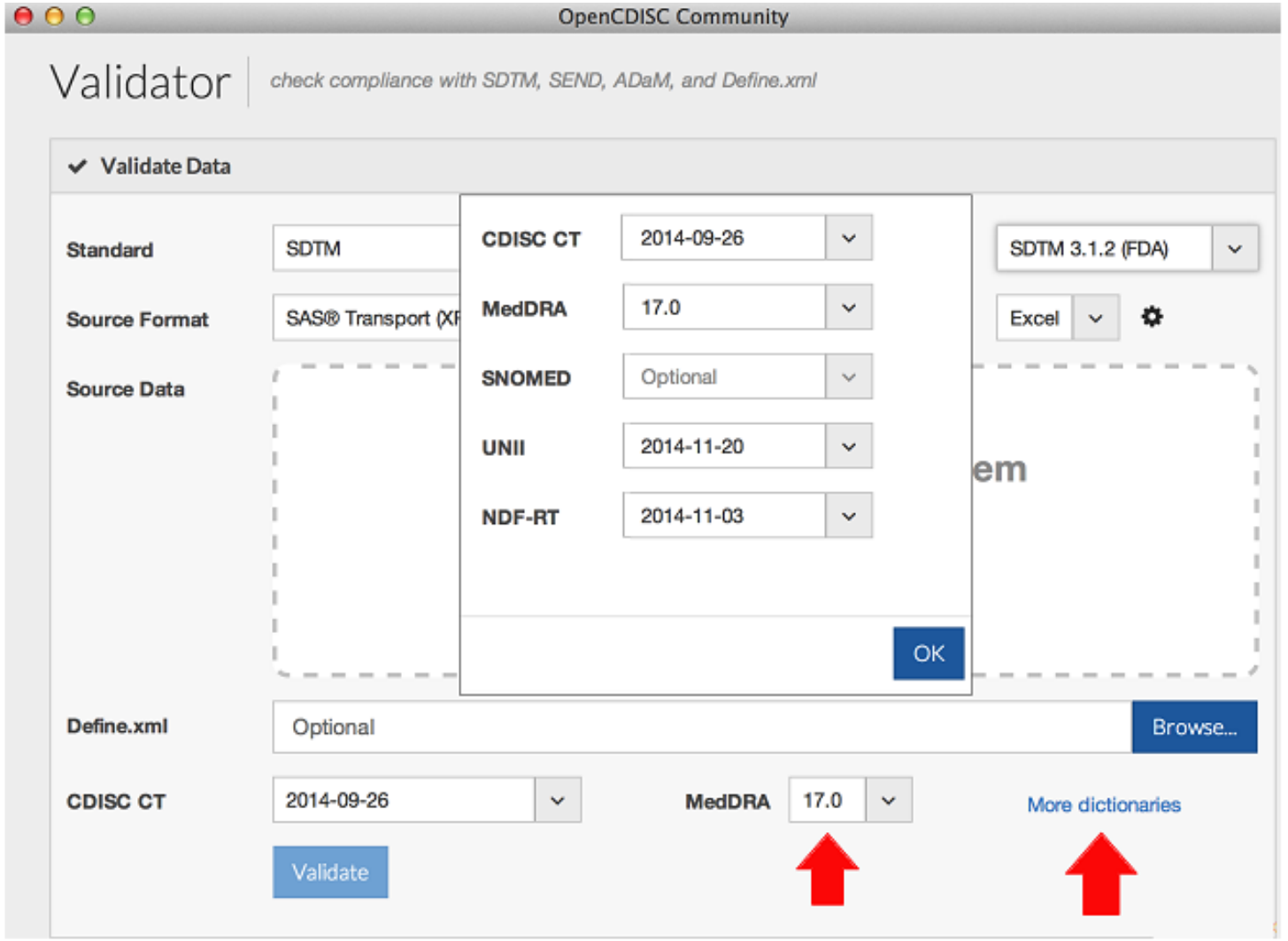
3.6.1 Validation of CDISC-conformant data

The PMDA will perform validation of CDISC-conformant data using OpenCDISC Enterprise.

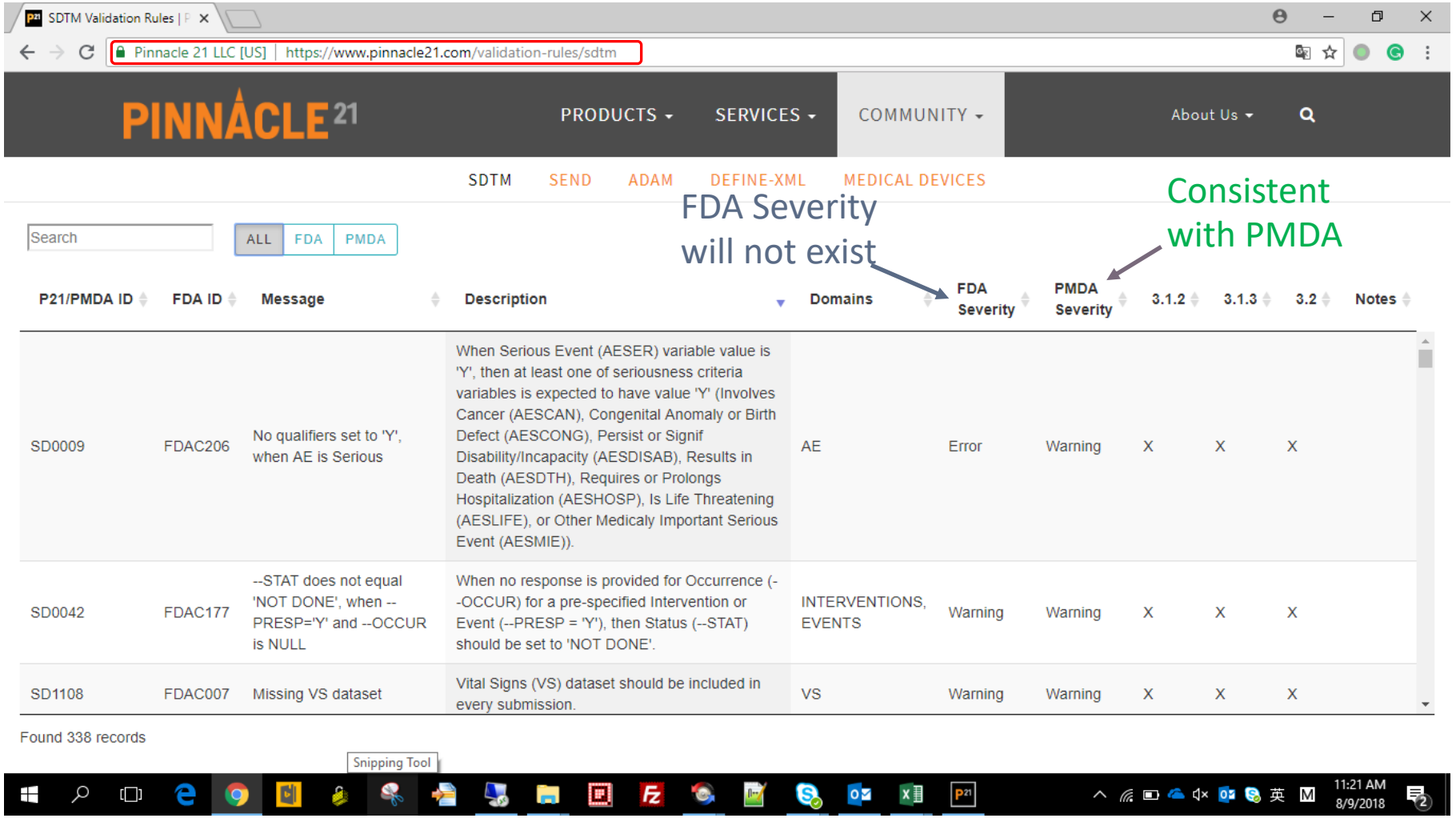
Pinnacle 21 Community

Pinnacle 21 Community.exe

- Downloa
- Don’t for



Pinnacle 21 Validation Rule



P21/PMDA ID	FDA ID	Message	Description	Domains	FDA Severity	PMDA Severity	3.1.2	3.1.3	3.2	Notes
SD0009	FDAC206	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 Disability/Incapacity (AESDISAB), Results in Death (AESDTH), Requires or Prolongs Hospitalization (AESHOSP), Is Life Threatening (AESLIFE), or Other Medicaly Important Serious Event (AESMIE)).	AE	Error	Warning	X	X	X	
SD0042	FDAC177	--STAT does not equal 'NOT DONE', when --PRESP='Y' and --OCCUR is NULL	When no response is provided for Occurrence (--OCCUR) for a pre-specified Intervention or Event (--PRESP = 'Y'), then Status (--STAT) should be set to 'NOT DONE'.	INTERVENTIONS, EVENTS	Warning	Warning	X	X	X	
SD1108	FDAC007	Missing VS dataset	Vital Signs (VS) dataset should be included in every submission.	VS	Warning	Warning	X	X	X	

Pinnacle 21

False Positive

False Negative – How to deal with

- Negative value for PCORRES, PCSTRESN, PCSTRESC.
- Negative value for PPORRES, PPSTRESN, PPSTRESC.
- More than two spaces between two words in character variables.

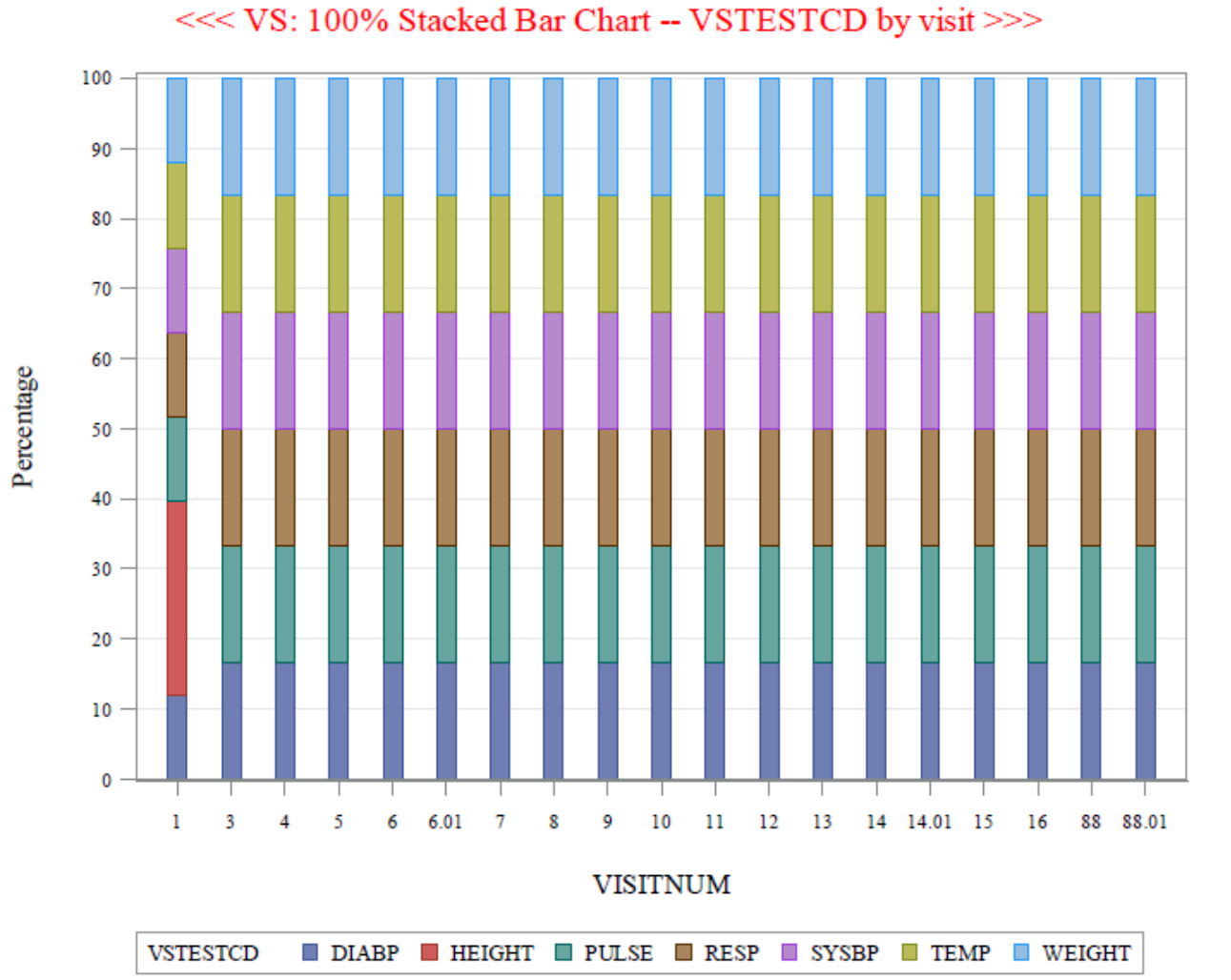
SDTM Check Review – example 1

<<< VS: Checking frequency -- VSTESTCD * VSTEST >>>

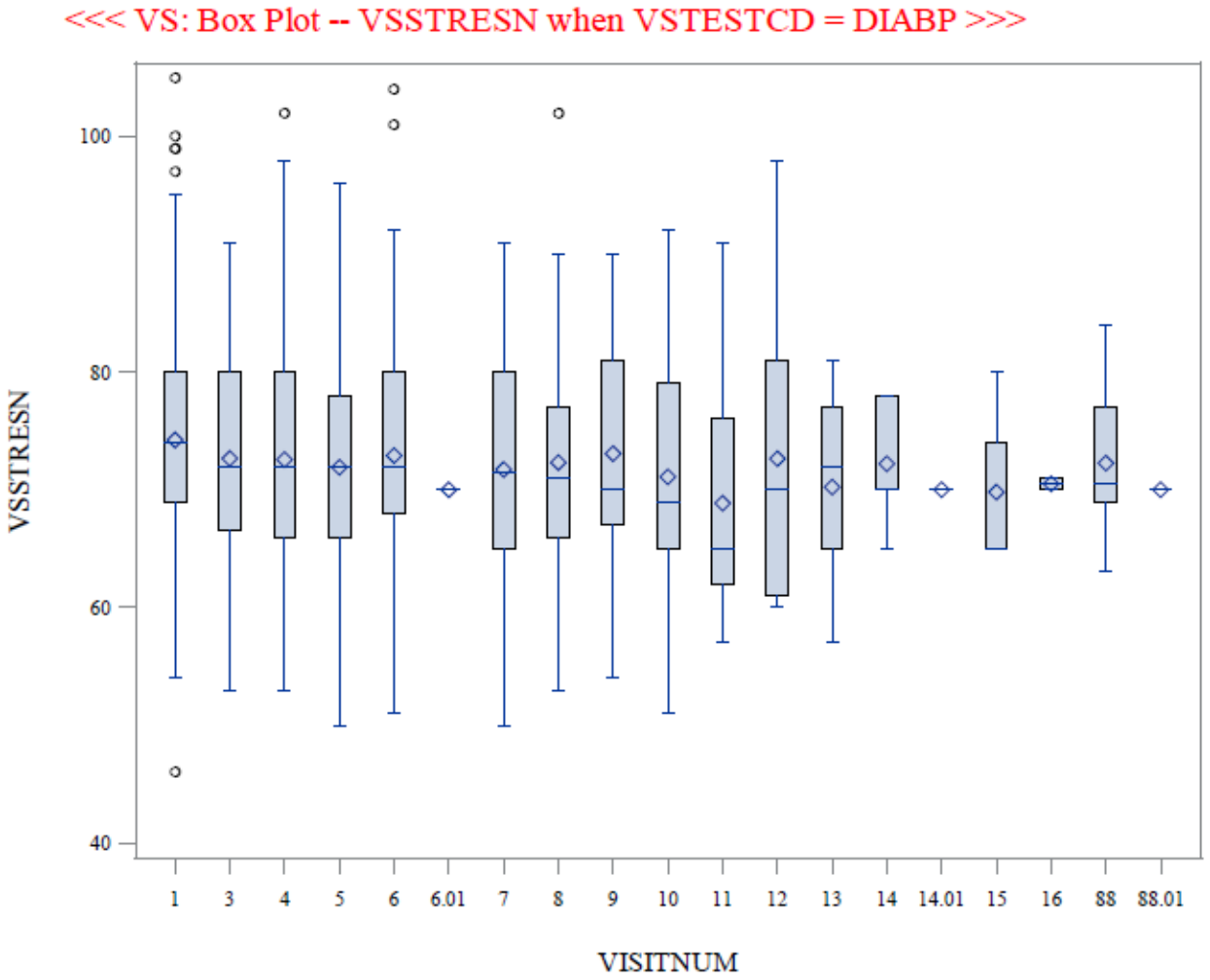
The FREQ Procedure

VSTESTCD	VSTEST	Frequency	Percent	Cumulative Frequency	Cumulative Percent
DIABP	舒张压	729	15.37	729	15.37
HEIGHT	身高	370	7.80	1099	23.17
PULSE	心率	729	15.37	1828	38.53
RESP	呼吸	729	15.37	2557	53.90
SYSBP	收缩压	729	15.37	3286	69.27
TEMP	体温	729	15.37	4015	84.63
WEIGHT	体重	729	15.37	4744	100.00

SDTM Check Review – example 2



SDTM Check Review – example 3



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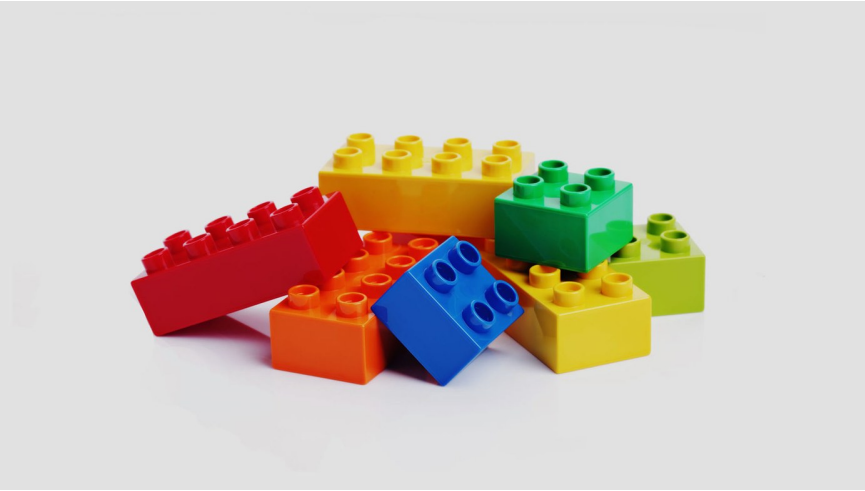
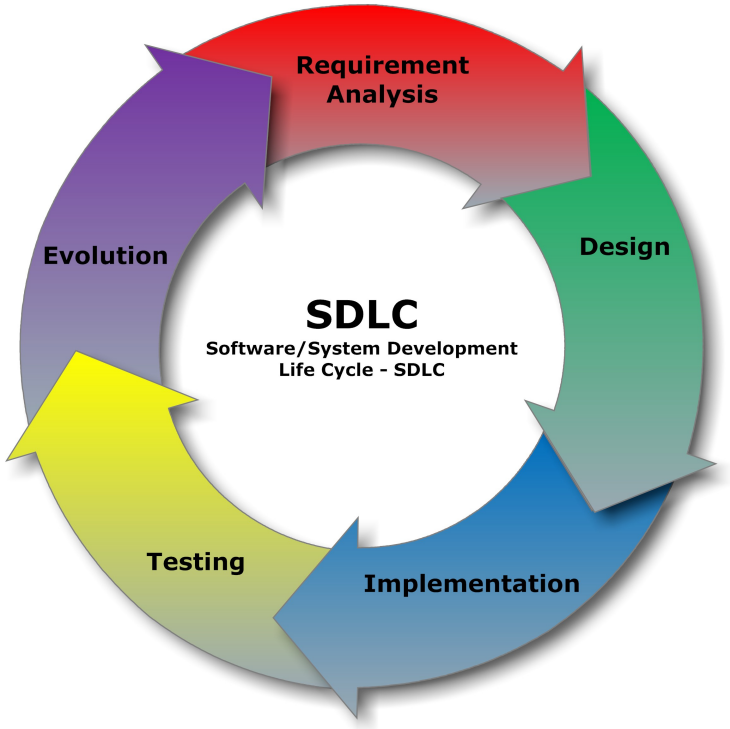
How to build up our repository

Requirement analysis

- False Negative
- ADAM IG v1.1
- Sponsor defined Rule



Development in dMed



- DON’T start coding, design first!

Design the functions

Design the application

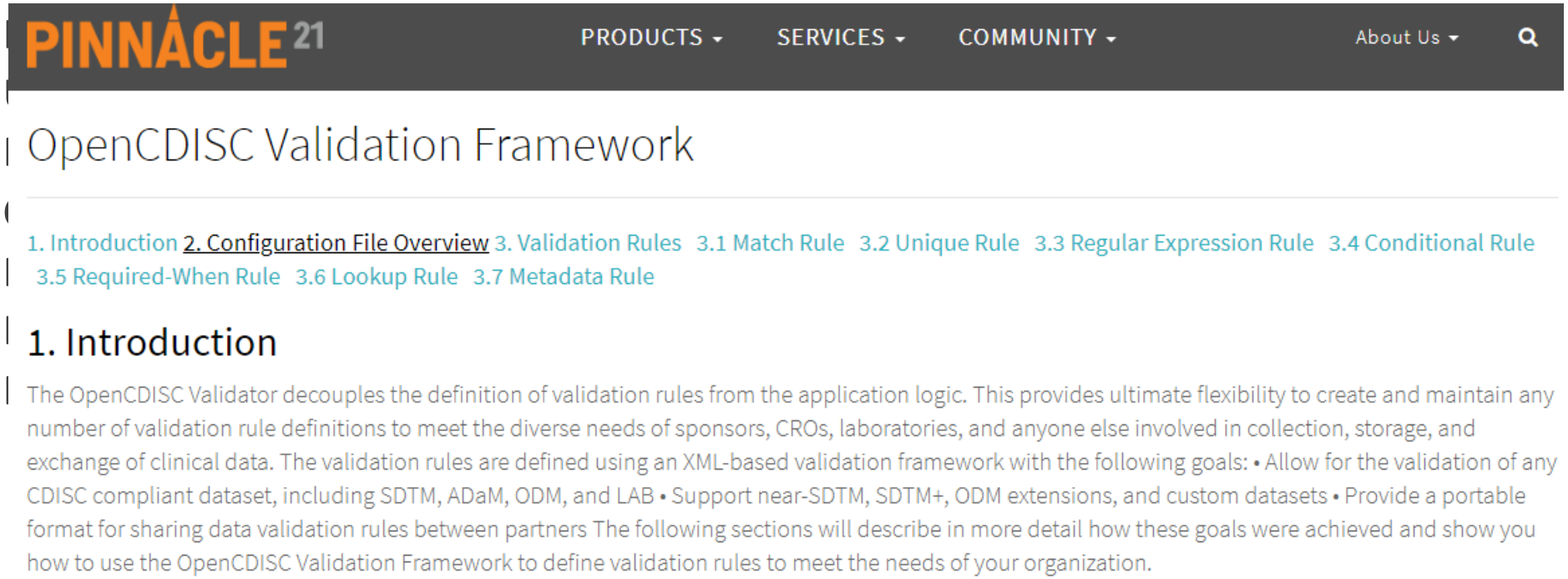
- Input & UI: Java, C#..., SAS
- Validation rules
  - Requirement
  - Code
    - SAS
    - Java or Xquery code to read XML-File
    - …
- Output Report: SAS, Python…

Customized using SAS

SAS Code

Customized using P21

When defining a Validation Rule, the configuration author may choose from one of the following types:



Configuration File

Step 1

\Desktop\pinnacle21-community v2.2\components\config\SDTM 3.2.xml -

```
<ItemRef ItemOID="IT.TA.STUDYID" OrderNumber="1" Mandatory="Yes" KeySequence="1" Role="Identifier" val:Core="Required"/>
<ItemRef ItemOID="IT.TA.DOMAIN" OrderNumber="2" Mandatory="Yes" Role="Identifier" val:Core="Required"/>
<ItemRef ItemOID="IT.TA.ARMCD" OrderNumber="3" Mandatory="Yes" KeySequence="2" Role="Topic" val:Core="Required"/>
<ItemRef ItemOID="IT.TA.ARM" OrderNumber="4" Mandatory="Yes" Role="Synonym Qualifier" val:Core="Required"/>
```

Step 2

```
<val:ValidationRuleRef RuleID="CT2001" Active="Yes"/>
<val:ValidationRuleRef RuleID="CT2002" Active="Yes"/>
<val:ValidationRuleRef RuleID="CT2003" Active="Yes"/>
<val:ValidationRuleRef RuleID="CT2004" Active="Yes"/>
<val:ValidationRuleRef RuleID="CT2005" Active="Yes"/>
<val:ValidationRuleRef RuleID="CT2006" Active="Yes"/>
<val:ValidationRuleRef RuleID="SD0001" Active="Yes"/>
<val:ValidationRuleRef RuleID="SD0002" Active="Yes"/>
```

Step 3

```
</ItemGroupDef>
<ItemDef OID="IT.GLOBAL.STUDYID" Name="STUDYID" DataType="text">
    <Description>
        <TranslatedText xml:lang="en">Study Identifier</TranslatedText>
    </Description>
</ItemDef>
<ItemDef OID="IT.UNRECOGNIZED.STUDYID" Name="STUDYID" DataType="text">
    <Description>
        <TranslatedText xml:lang="en">Study Identifier</TranslatedText>
    </Description>
</ItemDef>
```

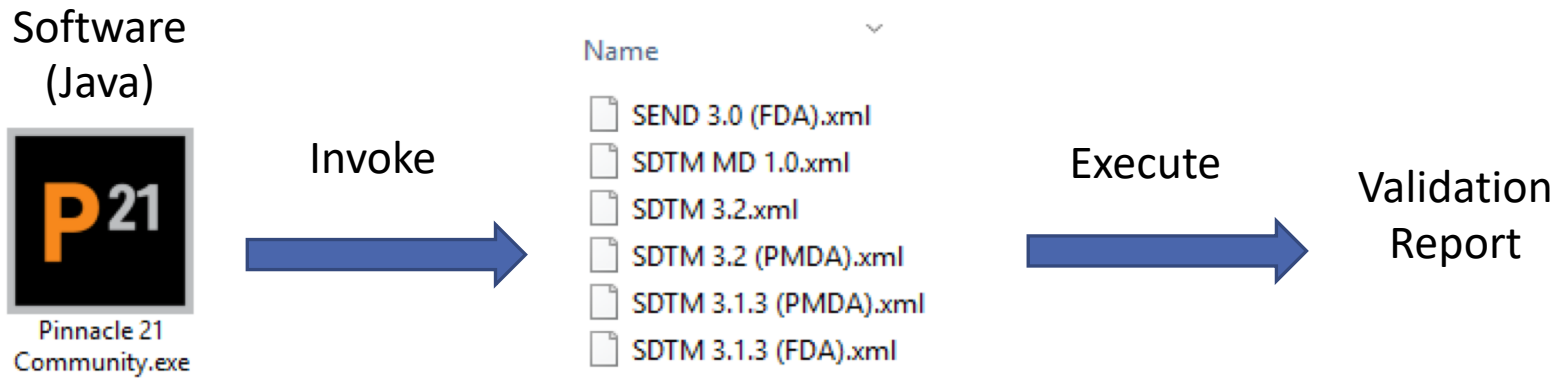
Configuration File

Step 4

```
<val:Match ID="CT2001" PublisherID="FDAC340" Message="%Variable% value not found
<val:Match ID="CT2002" PublisherID="FDAC341" Message="%Variable% value not found
<val:Match ID="CT2003" PublisherID="FDAC342" Message="%Variable% and %Variable.De
<val:Match ID="CT2004" PublisherID="FDAC343" Message="%Variable% value not found
<val:Match ID="CT2005" PublisherID="FDAC344" Message="%Variable% value not found
<val:Match ID="CT2006" PublisherID="FDAC345" Message="%Variable% and %Variable.De
<val:Property ID="SD0001" PublisherID="FDAC014" Message="No records in data sourc
<val:Required ID="SD0002" PublisherID="FDAC018" Message="NULL value in %Variable%
<val:Regex ID="SD0003" PublisherID="FDAC038" Message="Invalid ISO 8601 value for
<val:Match ID="SD0004" PublisherID="FDAC056" Message="Inconsistent value for DOMA
<val:Unique ID="SD0005" PublisherID="FDAC044" Message="Duplicate value for %Domai
<val:Lookup ID="SD0006" PublisherID="FDAC113" Message="No baseline result in %Dom
<val:Unique ID="SD0007" PublisherID="FDAC084" Message="Inconsistent value for Sta
<val:Lookup ID="SD0008" PublisherID="FDAC346" Message="Value for %Domain%DECOD nc
```

Flow

(Software custom code mixed some java code)



Development using XML4Pharma

http://xml4pharmaserver.com/OpenRulesForCDISCStandards/index.html

XQuery

XQuery (XML Query) is a query and functional programming language. It is used to query structured information in XML format.

XQuery To XML

SQL To Database

Advantage:

1, Easy to Learn
2, human-readable
3, machine-executable

Example of XML.File

```
<bookstore>

<book category="COOKING">
  <title lang="en">Everyday Italian</title>
  <author>Giada De Laurentiis</author>
  <year>2005</year>
  <price>30.00</price>
</book>

<book category="CHILDREN">
  <title lang="en">Harry Potter</title>
  <author>J K. Rowling</author>
  <year>2005</year>
  <price>29.99</price>
</book>

</bookstore>
```

XQuery Code

```
doc("books.xml")/bookstore/book[price=30]/title
```

Xquery FLWOR Code

```
for $x in doc("books.xml")/bookstore/book
where $x/price=30
return $x/title
```

Output Result

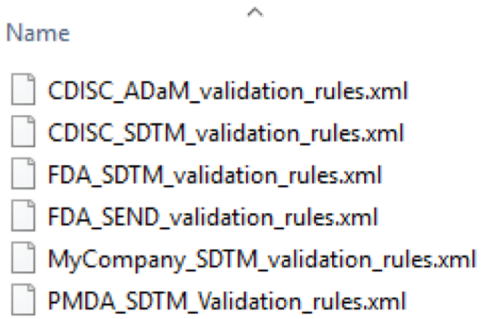
```
<title lang="en">Everyday Italian</title>
```

Flow

Software
(Java or else)

Invoke

Validation rules XML-File
(Xquery Code)



Execute

Validation
Report

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Summary and Perspective

- WHY to thoroughly understand the current checking rules?
- HOW to develop a customized tool?
- Any guidance released from NMPA?


thank
you

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Q & A