



Define.xml for ADaM: Clinical Standards Toolkit vs. Pinnacle21?

—
Frederikke Høyer
Ferring Pharmaceuticals

Helping people live better lives

Agenda

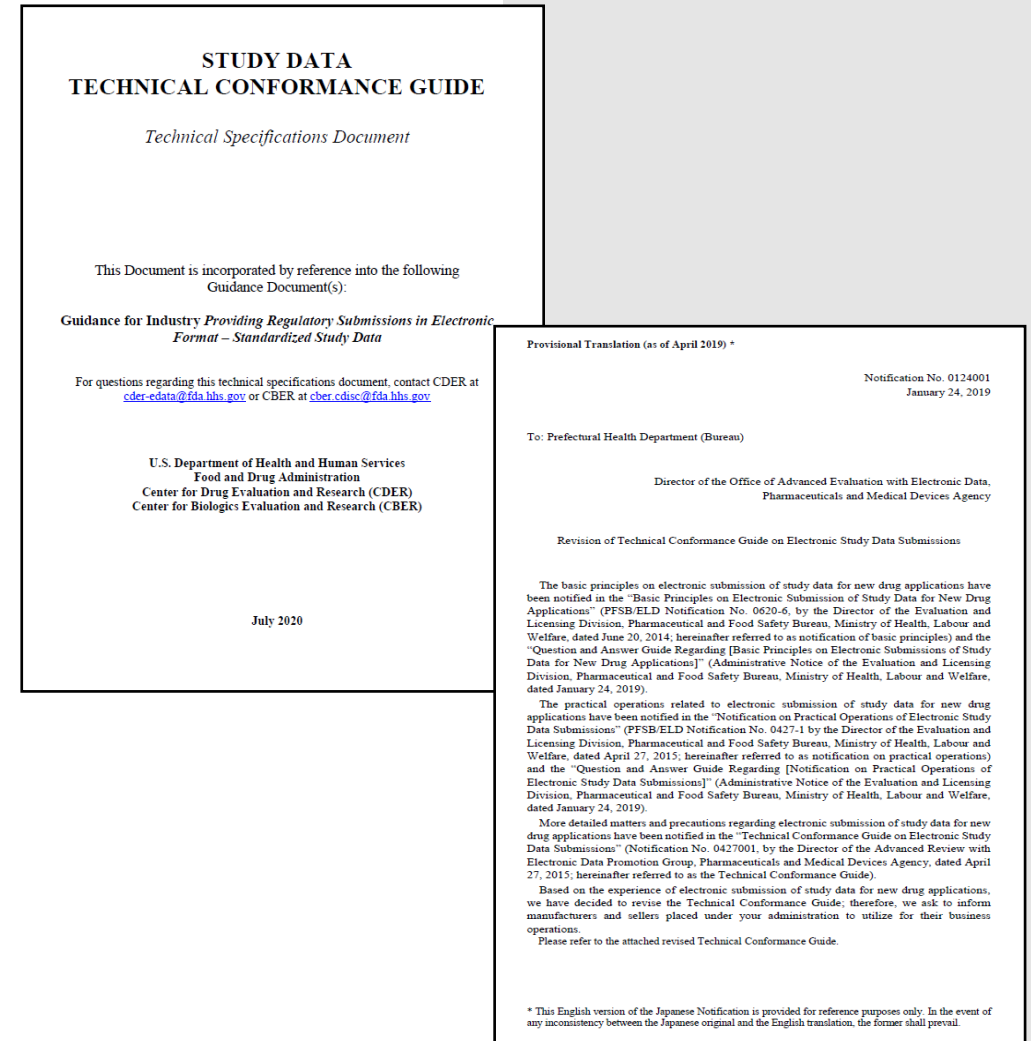
- Process for define.xml generation in SAS Clinical Standards Toolkit and Pinnacle 21 Enterprise
- Differences between the tools regarding automation, related documents, legacy trials and maintenance



The best option

Define.xml for eSubmission

- Define.xml is required by FDA and PMDA for every study in each electronic submission
- Define.xml informs the regulators which datasets, variables, controlled terms, and other specified metadata were used
- Requirements for Define.xml are specified in Technical Conformance Guide documents from both FDA and PMDA



Tools for Define.xml creation

SAS Clinical Standards Toolkit

SAS macro based framework for validation of CDISC data and generation of define.xml.

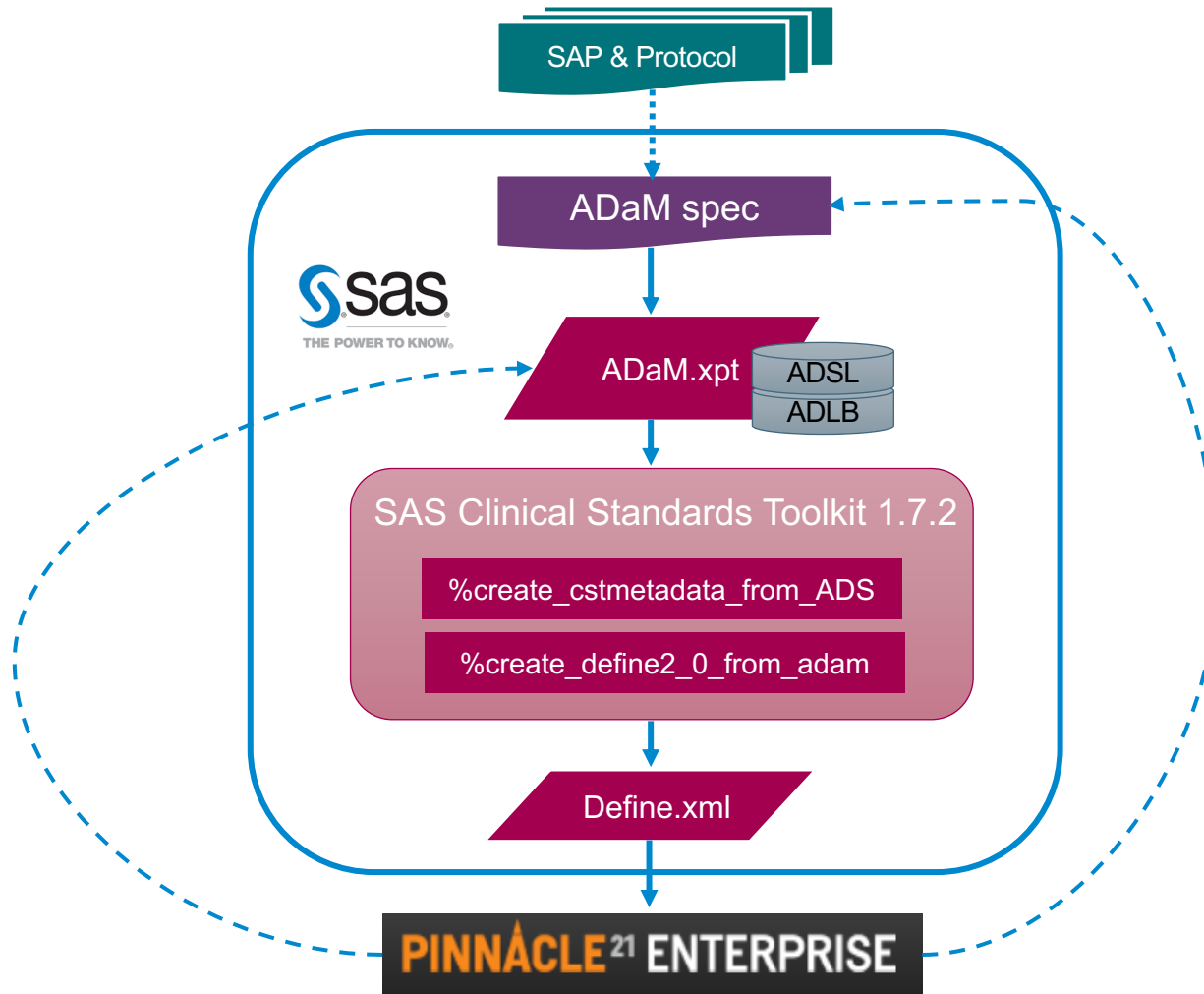
Widely used by the industry



Tool commonly used for CDISC validation of SDTM, ADaM and SEND.

Features a module for Define.xml creation. Also offers a option to pre-populate specific sections in the Analysis Data Reviewers Guide (ADRG)

Using SAS CST for define.xml creation



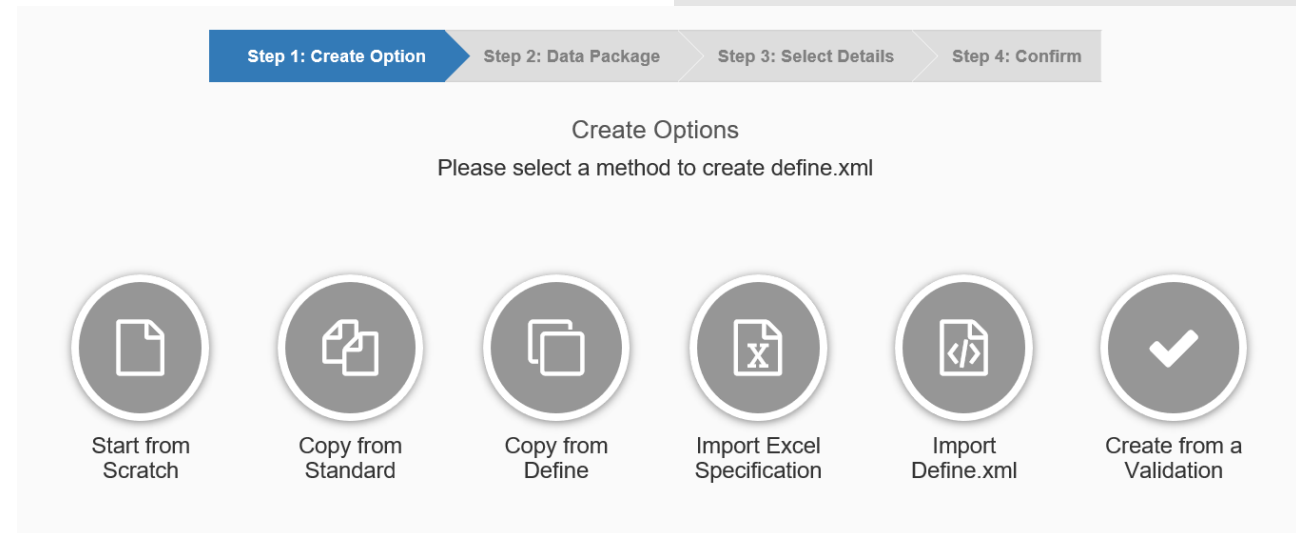
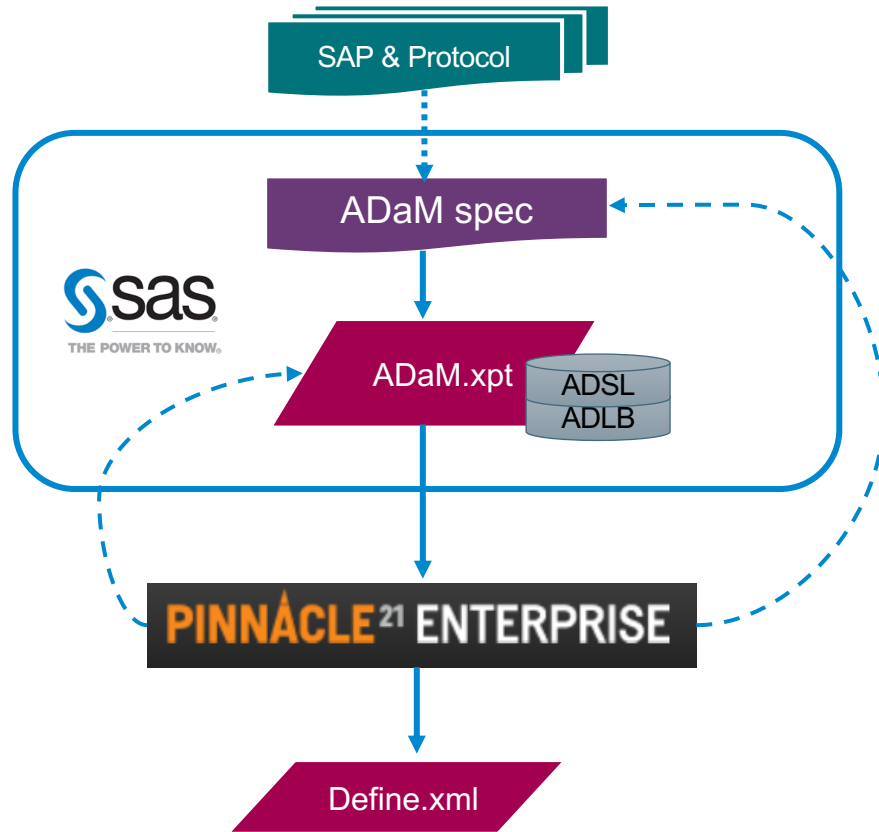
	source_codelists.sas7bdat
	source_columns.sas7bdat
	source_documents.sas7bdat
	source_study.sas7bdat
	source_tables.sas7bdat
	source_values.sas7bdat

```
* Read the source metadata;  
%define_sourcetodefine( _cstOutLib=srcdata  
    , _cstSourceStudy=sampdata.source_study  
    , _cstSourceTables=sampdata.source_tables  
    , _cstSourceColumns=sampdata.source_columns  
    , _cstSourceCodeLists=sampdata.source_codelists  
    , _cstSourceDocuments=sampdata.source_documents  
    , _cstSourceValues=sampdata.source_values  
);
```

```
* Create the Define-XML file;  
%define_write(_cstCreateDisplayStyle=1);
```

```
* Validate the Define-XML file;  
%cstutilxmlvalidate();
```

Using Pinnacle21 Enterprise for define.xml creation



Define.xml creation in Pinnacle21 Enterprise

- Pinnacle 21 Enterprise offers six options for define file creation
- "Create from a Validation" module utilizes transport files (.xpt) previously validated in Pinnacle 21 Enterprise
- User must also select the variables for which Value Level Metadata (VLM) need to be specified (expected for AVAL derivations)



Create from a
Validation

- The metadata from the validation is used to build the Define.xml and used to auto-populate the Define module
- The Define module will appear as a Excel-like format and any field that can be manually changed will alert the user in real-time upon completion of field with non-expected/values or issues

Properties

Datasets

Variables

Value Level

Codelists

Terms

Methods

Comments

Analysis Displays

Analysis Results

Issues356

History

Search

Column

Dataset	Description	Class	Structure	Purpose	Key Variables
ADAE	Adverse Event Analysis Dataset	ADAM OTHER	One record per subject per each AE recorded in SDTM AE domain	Analysis	STUDYID, USUBJID, AEI
ADBL	Baseline Demographics Analysis Dataset	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	
ADCM	Concomitant Medication Analysis Dataset	OCCURRENCE DATA STRUCTURE		Analysis	
ADDS	Subject Disposition Analysis Dataset	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	
ADEG	ECG Test Results Analysis Dataset	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis	Analysis	

Repetitive work

Derivations/Methods/Origin

SAS CST includes the Methods by itself where in Pinnacle, you have to enter them yourself

Timeconsuming, but very straight forward

Properties	Datasets	Variables	Value Level	Codelists	Terms	Methods	Comments	Analysis Displays	Analysis Results	Issues
Search										
Variable	Where Clause	Description	Codelist	Origin						
AVAL	PARAMCD EQ AGE	Age (years)	AVAL.ADBL.PARAMCD.EQ.AGE							
AVAL	PARAMCD EQ RACE	Race	AVAL.ADBL.PARAMCD.EQ.RACE							
AVAL	PARAMCD EQ ETHNIC	Ethnicity	AVAL.ADBL.PARAMCD.EQ.ETHNIC							
AVAL	PARAMCD EQ HEIGHT	Baseline Height (cm)	AVAL.ADBL.PARAMCD.EQ.HEIGHT							
AVAL	PARAMCD EQ WEIGHT	Baseline body weight (kg)								
AVAL	PARAMCD EQ BMI	Baseline BMI (kg/m2)								
AVALC	PARAMCD EQ RACE	Race	AVALC.ADBL.PARAMCD.EQ.RACE							
AVALC	PARAMCD EQ ETHNIC	Ethnicity	AVALC.ADBL.PARAMCD.EQ.ETHNIC							
AVAL	PARAMCD EQ SCREENED	Screening Status	AVAL.ADDS.PARAMCD.EQ.SCREENED							
AVAL	PARAMCD EQ EOT	End of Study Status	AVAL.ADDS.PARAMCD.EQ.EOT							
AVAI	PARAMCD EQ DCSREAS	Reason for Discontinuation	AVAI ADDS PARAMCD EQ DCSREAS							

Properties	Datasets	Variables	Value Level	Codelists	Terms	Methods	Comments	Analysis Displays	Analysis Results	Issues
Search										
ID	Name	Type	Description							

Related documents

➤ Analysis Results Metadata (ARM)

- ARM describes key components of significant analysis results, providing both text and links from a result to metadata and other sources describing the analysis
- Potential to save significant amount of time for regulatory reviewers and thus speed up the drug approval
- Optional component according to ADaM version 2.1.
- Required by PMDA and preferred by FDA

ADaM-IG 1.0

- Analysis Data Reviewer's Guide
- ▶ Analysis Results Metadata
- ▶ Analysis Datasets
- ▶ Parameter Value Level Metadata
- ▶ Controlled Terminology
- ▶ Analysis Derivations
- ▶ Comments

PMDA – Technical Conformance Guide (April 27, 2015)

"In order for the review of clinical study data to progress smoothly, it is important that the relationship between the analysis results shown in the application documents and the analysis datasets is easily understandable. Therefore, the definition documents of the ADaM datasets should preferably include Analysis Results Metadata..."

For the format of the Analysis Results Metadata, the applicant should refer to the Analysis Results Metadata Specification for Define-XML by CDISC to the extent possible, but if it is difficult to include it into the definition document, it is possible to submit it as a separated file in PDF format.

Supported by both Pinnacle 21 Enterprise and SAS CST

Related documents (2)

Include ARM in Define.xml using CST

SAS Clinical Standards Toolkit 1.7.2

★ %create_cstmetadata_from_ADS
★ %create_define2_0_from_adam

	source_codelists.sas7bdat
	source_columns.sas7bdat
	source_documents.sas7bdat
	source_study.sas7bdat
	source_tables.sas7bdat
	source_values.sas7bdat

Add table
Source_analysisresults:
One record per DisplayIdentifier,
ResultIdentifier, Table

	DisplayIdentifier	DisplayName	DisplayDescription	ResultIdentifier
1	RD.Table_14-3.01	Table 14-3.01	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)	AR.Table_14-3.01.R.1
2	RD.Table_14-3.01	Table 14-3.01	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)	AR.Table_14-3.01.R.2

	DisplayIdentifier	ResultIdentifier	AnalysisReason	AnalysisPurpose	ResultDescription
1	RD.Table_14-3.01	AR.Table_14-3.01.R.1	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Dose response analysis for ADAS-Cog changes from baseline
2	RD.Table_14-3.01	AR.Table_14-3.01.R.2	SPECIFIED IN SAP	PRIMARY OUTCOME MEASURE	Pairwise comparisons to placebo for ADAS-Cog changes from baseline

	DisplayIdentifier	ResultIdentifier	ParameterColumn	Table	AnalysisVariables	WhereClause
1	RD.Table_14-3.01	AR.Table_14-3.01.R.1	PARAMCD	ADQSADAS	CHG	(PARAMCD EQ "ACTOT") AND (AVISIT EQ "Week 24") AND (EFFFL EQ "Y") AND (ANL01FL EQ "Y")
2	RD.Table_14-3.01	AR.Table_14-3.01.R.2	PARAMCD	ADQSADAS	CHG	(PARAMCD EQ "ACTOT") AND (AVISIT EQ "Week 24") AND (EFFFL EQ "Y") AND (ANL01FL EQ "Y")

Analysis Results Metadata (Detail) for Study CDISC-Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and sit Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS version 9.2] proc glm data = ADQSADAS; where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;

Related documents (3)

- Analysis Data Reviews Guide (ADRG)
- Pinnacle pre-populated specific sections in ADRG

- All validated datasets
- Issue/error explanation
- Re-use of explanations

Important Links

Trial Summary

Define.xml

Reviewer's Guide

Annotated CRF

All

FDA

PMDA

Dashboard

Analysis Support

Datasets

Issues

History

More Reports

⌵

Actions

Q

AD0047

Filters

Status

Assignee

Tag

Analysis

Category

View by

Dataset

■	Rule	Message	FDA	PMDA	Rate	Status
ADBL - Baseline Analysis Dataset (1 Issues)						
☐	AD0047	Required variable is not present false positive	✓ Error	Error	20% i	Closed
ADDS - Subject Disposition Analysis Dataset (1 Issues)						
☐	AD0047	Required variable is not present false positive	✓ Error	Error	20% i	Closed
ADEF - Efficacy Analysis Dataset (1 Issues)						
☐	AD0047	Required variable is not present false positive	✓ Error	Error	20% i	Closed

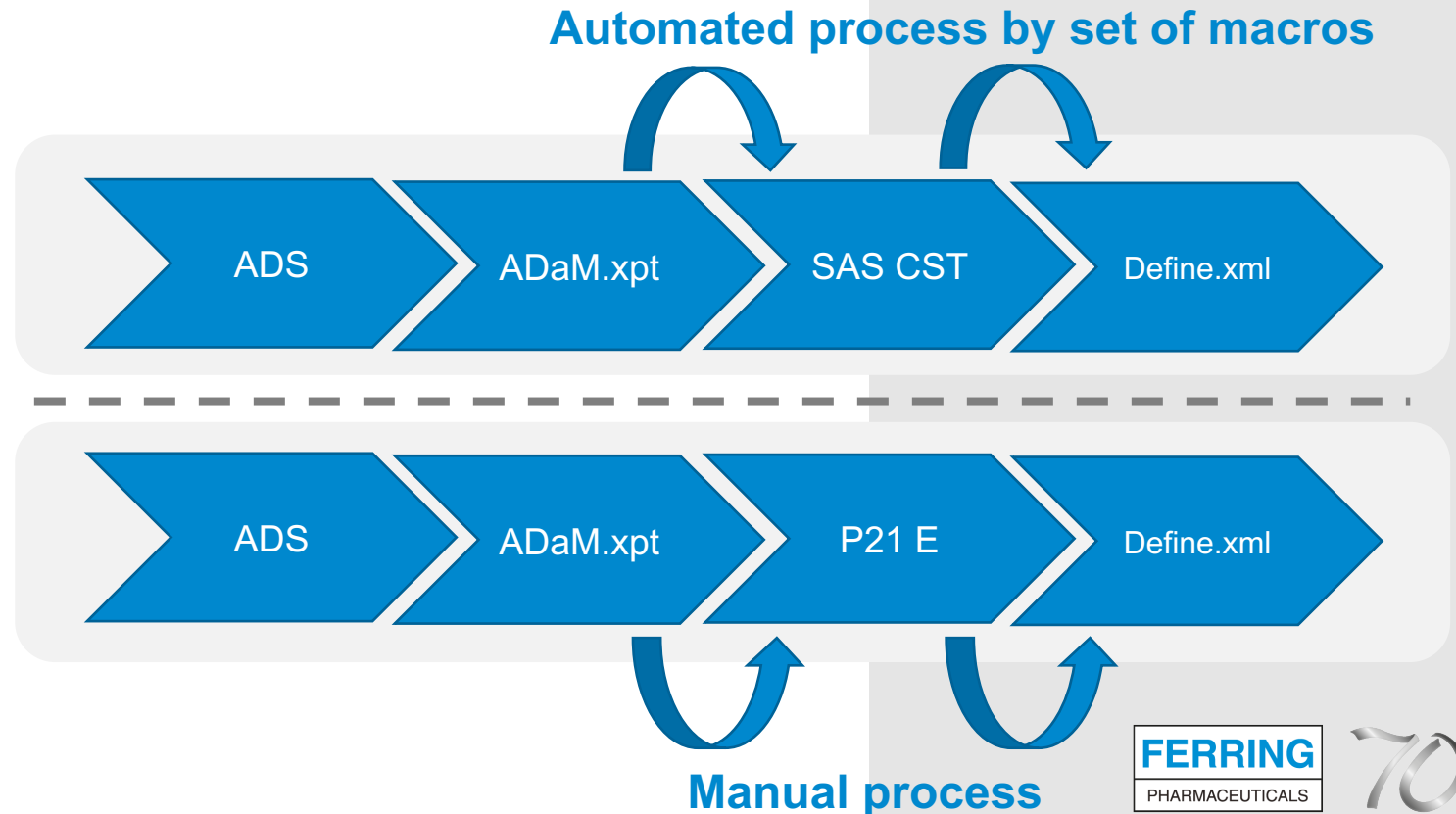
6.2 Issues Summary

Check ID	Diagnostic Message	PMDA Severity	Dataset	Count (Issue Rate)	Explanation
AD0047	Required variable is not present	Error	ADBL	1 (20.00%)	TRTP not required when TRT01P is present
AD0047	Required variable is not present	Error	ADDS	1 (20.00%)	TRTP not required when TRT01P is present
AD0047	Required variable is not present	Error	ADEF	1 (20.00%)	TRTP not required when TRT01P is present

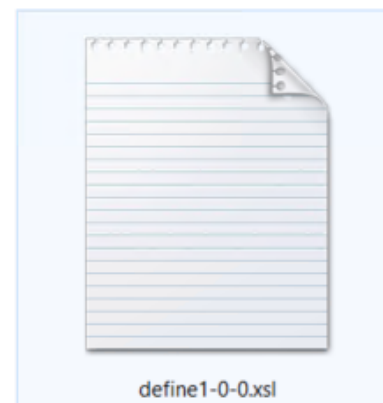
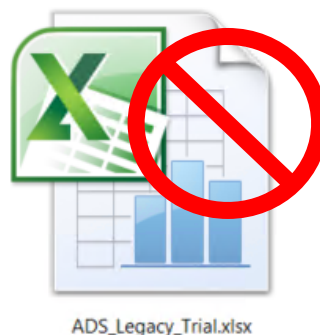
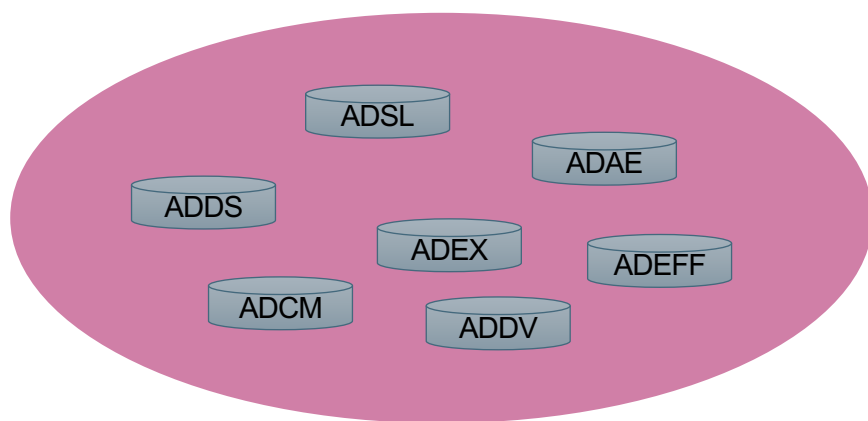
Maintenance

When data changes...

- P21 Enterprise Define module has the ability to import changed metadata after it has been validated again
- Auto-population will over-write any manual changes
 - ➔ Manual rework
- Execution of SAS CST macros will update the Define.xml



Legacy trials



Common issues when preparing legacy trials for submission:

- Define.xml and stylesheet in version 1-0-0
- Links not active
- Mis-match in labels
- ADS missing or not compatible with SAS CST set-up

Datasets for Study CB0102-01-ADAM						
Dataset	Description	Class	Structure	Purpose	Keys	Location
ADSL	Subject Level Analysis Dataset	adsl	one record per subject	Analysis	USUBJID	adsl.xpt
ADAE	Adverse Events Analysis	adae	one record per adverse event per sequence number per subject	Analysis	USUBJID, AEDECOD, AESEQ	adae.xpt
ADCM	Concomitant Medications Analysis	adae	one record for each Prior med or Conmed per sequence per subject	Analysis	USUBJID, CMDECOD, CMSEQ	adcm.xpt
ADDS	Disposition Analysis	adae	one record per disposition instance per subject	Analysis	USUBJID, DSSEQ	adds.xpt
ADDV	Protocol Deviation Analysis	adae	one record per DVSCAT per sequence number per subject	Analysis	USUBJID, DVCAT, DVSCAT, DVSEQ	addv.xpt
ADEFF	Efficacy Analysis	bds	one record per efficacy endpoint per analysis visit	Analysis	USUBJID, PARAMCD, AVISITN	adeff.xpt
ADEX	Exposure Analysis	bds	one record per analysis visit per param code per param category per subject	Analysis	USUBJID, AVISITN, PARCAT1, PARAMCD	adex.xpt

Clinical Standards Toolkit vs. Pinnacle 21

➤ And the winner is....



SAS CST!

- The macro set-up in SAS CST supports a higher level of automation, which in the end saves valuable time for the programmer
- (most) Programmers like to program and the sometimes complex SAS macro set-up and XML syntax should not be a barrier
- Legacy trials might not be fit for SAS CST and will require many hours of preparation. In this case, Pinnacle 21 Enterprise offers a great tool for Define.xml creation
- Pinnacle 21 Enterprise is a useful tool for validation with a user-friendly interface

Clinical Standards Toolkit vs. Pinnacle 21

➤ And the winner is....

SAS CST!

- The macro set-up in SAS CST supports a higher level of automation, which in the end saves valuable time for the programmer
- (most) Programmers like to program and the sometimes complex SAS macro set-up and XML syntax should not be a barrier
- Legacy trials might not be fit for SAS CST and will require many hours of preparation. In this case, Pinnacle 21 Enterprise offers a great tool for Define.xml creation
- Pinnacle 21 Enterprise is a useful tool for validation with a user-friendly interface

CST has hardly evolved for the last few years while P21E has new versions on a regular basis



CST still wins but for how long if SAS does not invest more in it?

Connect with us!



Ferring Pharmaceuticals



@ferring



Ferring Pharmaceuticals



@ferringpharmaceuticals



Ferring Pharmaceuticals

Or me:



Frederikke.hoeyer@ferring.com

