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SHANGHAI

Evolution of Data Standards from a Practical Perspective

How to ensure your submission data supports automated review process at FDA and PMDA

Agenda

- Value of Standards - History
- Evolution and implementation at Regulatory Agencies
- What can I do?
  - Automation at FDA and PMDA and examples of standardization issues that break it

Questions

The value of a standard

- Hard to start a new standard, why?
  - If you create a new standard and no one else adopts it, it has little value
  - A standard achieves real value when adopted by others
  - The wider the adoption of the standard, the more value it brings

- Government decree or personal inconvenience can help get standards utilized

Story: Local Times in USA (1883)

- Before Nov 18, 1883
  - Each town had its own local clock in the center of town
- Along came new technology… the Railroads
- Traveling from town to town, organizing time schedules was challenging, and a mistake means a crash
- Railroads, through a lot of work, established a standard so that people could catch their trains on time.
- So follow Railroad time, or you miss your train
- Quickly after this was implemented, the towns that wanted people to catch their trains adopted the standard
- Nice podcast on the subject
  https://www.npr.org/templates/transcript/transcript.php?storyId=730727038

What was it like before electronic submissions?

Shipping Paper files often took 1 or 2 trucks

Imagine the reviewer's job to review a paper submission

Electronic submissions started in 1990s, but…

When you receive data from sponsors in their own format it is all over the place.

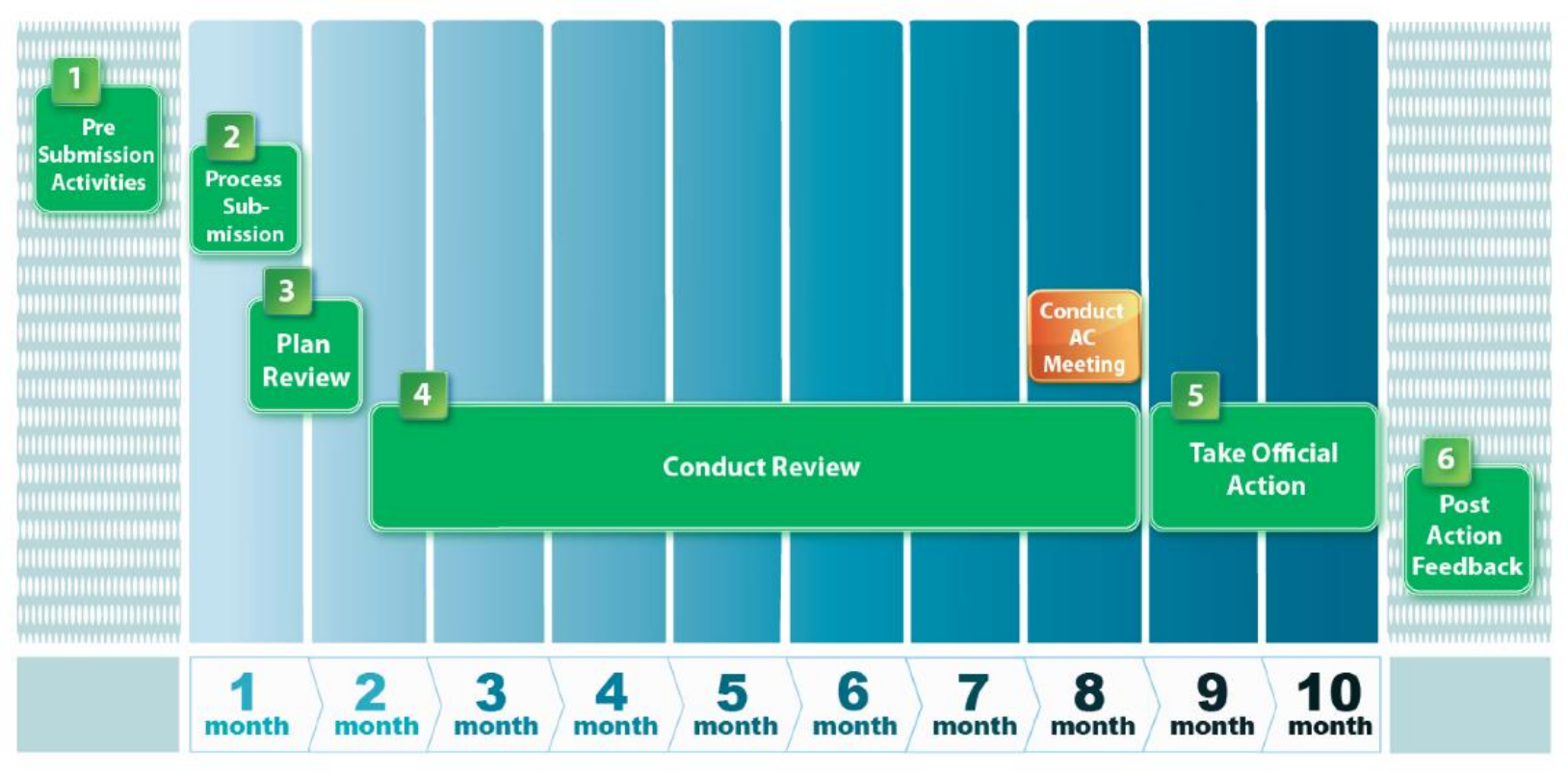
- Filenames different, column names different
- Skinny tables or wide tables with extra columns

File name	Column1	Column2	Column 3	Column 4	Column 5	Column 6	Column 7
Vital Signs	subject id	Visit Num	weignt in kg	systolic bp	pulse		
VS	subjid	Visit Number	sys bp	diastolic bp	weight	weight units	
vital signs screening visit	subject id	Visit	weignt in kg	systolic bp	pulse	height	
AE	subject id	visit number	Visit Date	Start date	End date	adverse experience description	Investigator assessment of causality
Adverse Events	subject number	visit number	AE date	AE description			
Adverse Experiences	subjectid	AEDESC	start	End	causality		
Serious Adverse Events	subject	visit	start date	end date			
Non Serious Adverse Events	subject	visit	start date	end date			

What is it like with no electronic data standards for a regulatory authority?

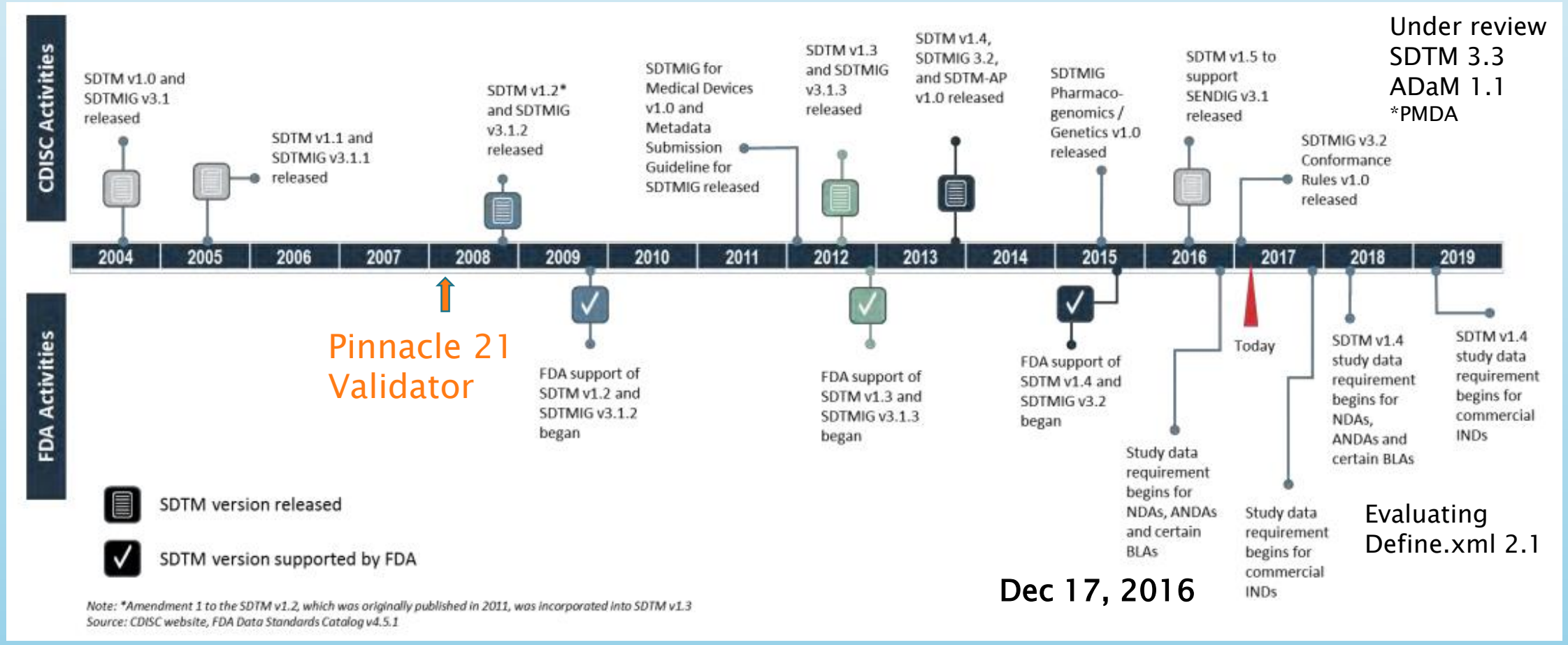
- Can spend forever just figuring out what you've been sent, let alone trying to analyze it
- Every submission was 1 of a kind
- Cannot use develop or use standard tools
- Can never automate this process

21st Century Review Initiative



A set of performance standards to follow during drug review with the goal of making the process more organized, integrated, efficient and effective.

Evolution of SDTM standard since 2004



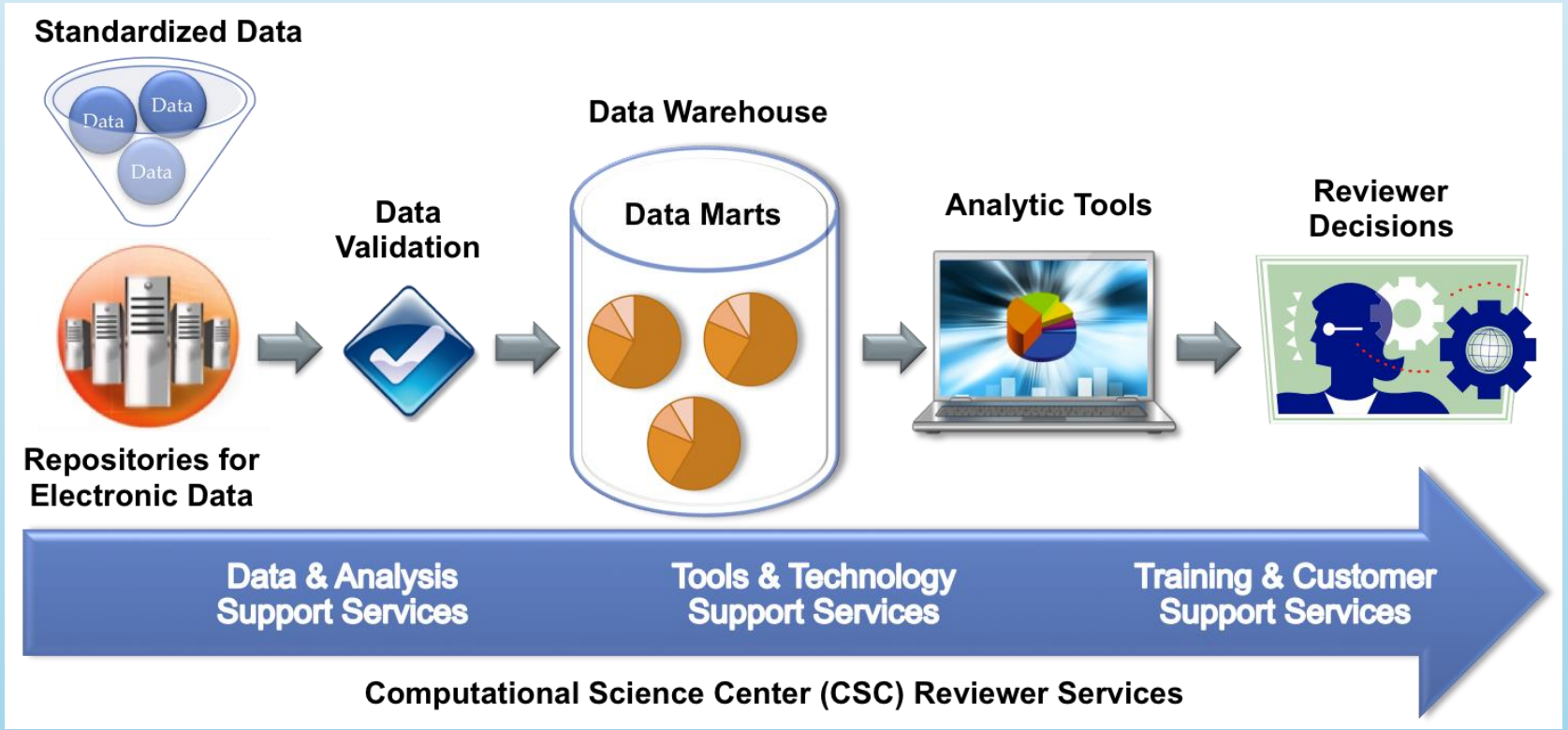
Can I run Pinnacle checks agains EDC data?

- No, because all of their data stores are in different non standardized formats
- Pinnacle would not have standard checks without standardized data

FDA use of CDISC standards drives industry adoption

- Risky to invest in adopting a new standard if you are not sure others will adopt the same standard
- It is worth the investment and up-front costs if it will be used by others and be stable
- Regulatory authority direction enabled the entire industry to settle upon CDISC standards.

Automated data processing



Source: Lilliam Rosario, Ph.D., PhUSE Computational Science Symposium, 2014

High quality data is the key to enabling regulatory reviewers to fully utilize the Computational Science Center's tools and services to support decision making

Source: Lilliam Rosario, Ph.D., PhUSE Computational Science Symposium, 2014

Regulatory Review Tools (15 years ago)

JMP

SAS Viewer

JReview

Standard Regulatory Review Tools (now)

FDA – DataFit Core reports

Tailored views of issues specific to the many types of users

- CBER
- CDER
- Safety reviewers
- Clinical Pharmacology reviewers
- Growing list of constituents want 'their' view of important issues…

Standards Levels of Adoption

- Person
- Team (Therapeutic Area / Drug compound)
- Company
- Industry (CDISC)
- International (CDISC)
  Global – Getting there!

PMDA

- Began receiving data 2016, required 2020
- PMDA expanded the value the industry realizes by utilizing the same standards
- Sponsors and industry gain synergies through re-use of the same Standard.

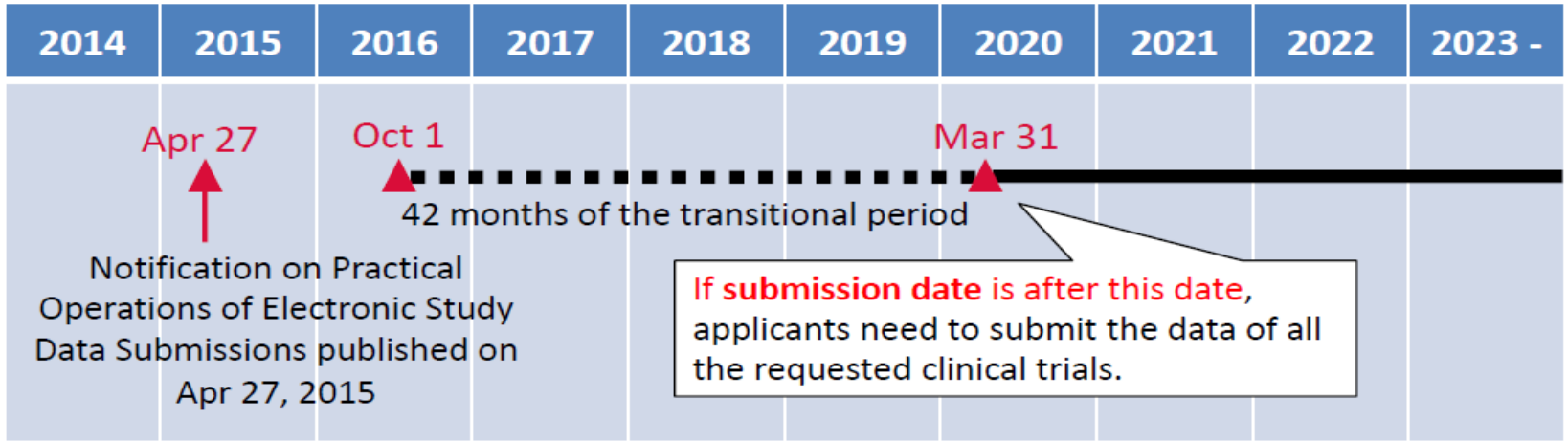
PMDA: Differences in Implementation approach

- PMDA decided to enforce many rejection criteria right away
- Don't do that again!!!

- These rejection criteria help enable automation which relies on certain key items
- Teaches sponsors to get things right the first time
- Now FDA is aiming to expand their own rejection criteria

Transitional period will be ended…

- The transitional period will be ended on March 31, 2020.
  - During the transitional period, applicants can submit the data of at least one clinical trial included in their clinical data packages.
  - After the period, applicants need to submit the data of all the requested clinical trials.



What can I do?

- Enable Regulatory agencies to review our applications efficiently and fast

- Focus on
  - Reviewer's guide
  - Define.xml

- You work with the data everyday, but reviewers need to familiarize themselves with the data
- Explain any and all exceptions in Reviewer's guide
- Reduce queries back to sponsor (can take weeks)
- Reviewers want to approve good medicines for patients, so they try to work around issues whenever possible, but of course this costs time

Automation at FDA and PMDA

- And examples of standardization issues that break it

FDA Rejection Rules (there are just two)

- Rule # 1734:
  - Trial Summary **(TS) dataset must be present** for each study in Module 4 and 5
- Rule # 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
- PMDA has the same requirements as part of their broader rejection criteria

Trial Summary Issues

- Example of issues which break automation

Correct Study Start Date

FDA Rejection Rule

- TSVAL variable value must be in ISO 8601 format, when TSPARMCD = 'SSTDTC'
- Studies started after 2016-12-17 must be in CDISC format

Incorrect

TSPARMCD	TSPARM	TSVAL
SSTDTC	Study Start Date	2016--27

Correct

TSPARMCD	TSPARM	TSVAL
SSTDTC	Study Start Date	2016-12-27

Correct Number of Subjects

FDA Janus CTR Blocking Rule

- TSVAL for this variable needs to be a number. This happens for a number of trial summary parameter codes such as PLANSUB, ACTSUB, RANDQT which are required to be a number

Incorrect

TSPARMCD	TSPARM	TSVAL
ACTSUB	Actual Number of Subjects	51 (56)
PLANSUB	Planned Number of Subjects	50-60

Correct

TSPARMCD	TSPARM	TSVAL
ACTSUB	Actual Number of Subjects	56
PLANSUB	Planned Number of Subjects	55

Correct Minimum and Maximum Age

FDA Janus CTR Blocking Rule

- This happens for TSPARMCDs such as AGEMIN and AGEMAX.
- TSVAL for this variable should be a number or ISO8601 duration as follows: PnYnMnDTnHnMnS or PnW where:[P] precedes the alphanumeric duration.[n] represents is a number >= 0 [W] is used as week designator (e.g., P6W represents 6 weeks of calendar time)

Incorrect

TSPARMCD	TSPARM	TSVAL
AGEMAX	Planned Maximum Age of Subjects	NONE
AGEMIN	Planned Minimum Age of Subjects	18 years

Correct

TSPARMCD	TSPARM	TSVAL	TSVALNF
AGEMAX	Planned Maximum Age of Subjects		PINF
AGEMIN	Planned Minimum Age of Subjects	P18Y	

Define.xml Issues

Example of issues which break automation

Incorrect Name for define.xml File

FDA Rejection Rule

- Name of define.xml file is "*define.xml*"
- Otherwise, it will be considered as a missing file

FDA and PMDA requirements may be different

- For example, requested file names for Reviewers Guide
- FDA: *csdrg.pdf*
- PMDA: *study-data-reviewers-guide.pdf*

Incorrect MedDRA version: as a Comment

Validation will be performed using the latest version of MedDRA since not correctly identified

- Results in tons of false-positives
- Breaks many standardized reports that depend on MedDRA coded AEs

Incorrect

Variable	Label	Controlled Terms or Format	Derivation/Comment
AELLT	Lowest Level Term		MedDRA 19.0
AEDECOD	Dictionary-Derived Term		MedDRA 19.0

Correct

Adverse Events (AE) [Location: ae.xpt]

Variable	Label	Controlled Terms or Format	Derivation/ Comment
AELLT	Lowest Level Term	AE Dictionary	
AEDECOD	Dictionary-Derived Term	AE Dictionary	

External Dictionaries

Reference Name	External Dictionary	Dictionary Version
AE Dictionary (CL.AEDICT)	MEDDRA	19.1

Specify correct SDTM version

```
<MetaDataVersion OID="MDV.CDISCPILOT.CDISC SDTM.3.2"
      Name="Study Updated CDISC PILOT Data Definitions"
      Description="Updated CDISC PILOT Data Definition"
      def:DefineVersion="2.0.0"
      def:StandardName="CDISC SDTM"
      def:StandardVersion="3.1.2">
```

But study data uses 3.2

Tabulation Datasets for Study UpdatedCDISCPILOT (CDISC SDTM 3.1.2)

Dataset	Description	Class	Structure
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm
TE	Trial Elements	TRIAL DESIGN	One record per planned Element
TI	Trial Inclusion/ Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm

Incorrect version of standard

This can result in a PMDA Rejection Rule

- Validation will be performed according to invalid version provided in define.xml
- Validation could result in false-positive Reject messages "*SDTM Required variable not found*"

Invalid Class – can't load data automatically

FDA Janus CTR Blocking Rule

- The actual observation Class of a domain does not match its class as defined by the CDISC define standard
- CTR is using define.xml Class to determine loading routines
- For custom domains if the Class cannot be correctly determined then study cannot be loaded

Incorrect

Dataset	Description	Class
SV	Subject Visits	TRIAL DESIGN
AE	Adverse Events	EVENT
XX	CDISC Certification Results	Findings

Correct

Dataset	Description	Class
SV	Subject Visits	SPECIAL PURPOSE
AE	Adverse Events	EVENTS
XX	CDISC Certification Results	FINDINGS

Other issues

- Example of other issues which break automation

Carriage return or other special characters in data

Can result in errors during load of FDA Janus CTR, JReview, etc.

Incorrect

COVAL
Page break and new line in data make text user-friendly. That's why they are often utilized during data collection.

Correct

COVAL
Page break and new line in data make text user-friendly. That's why they are often utilized during data collection.

Some software programs "choke" on carriage returns

PINNACLE 21

Missing or Wrong location for Upper Limit Normal

Breaks Liver Lab Analyses, Liver Toxicity, Hy's law, etc.

Incorrect

LBTESTCD	LBSTRESN	LBSTNRHI	LBSTNRC
ALT	42		<42
AST	5		<20
BILI	28		<38

Correct

LBTESTCD	LBSTRESN	LBSTNRHI	LBSTNRC
ALT	42	42	
AST	5	20	
BILI	28	38	

Resources

- Data Standards Catalogue
  https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
  Includes links TCG, business rules & validator rules

- Video on FDA Data standards program:
  https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review

- PMDA FAQ:
  http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0007.html

- Questions regarding submission of datasets to CDER may be sent to edata@fda.hhs.gov

Benefits of shared use of Standards

Automation is an advanced stage of value obtained through use of standards by

- Regulatory Agencies
- Sponsors
- Service providers
- Software companies

And most importantly…

- Patients – all over the world
  - Saves costs and time in developing new medicines!

Thank You!

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