Raising the bar for data standardization:

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

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PINNACLE 21

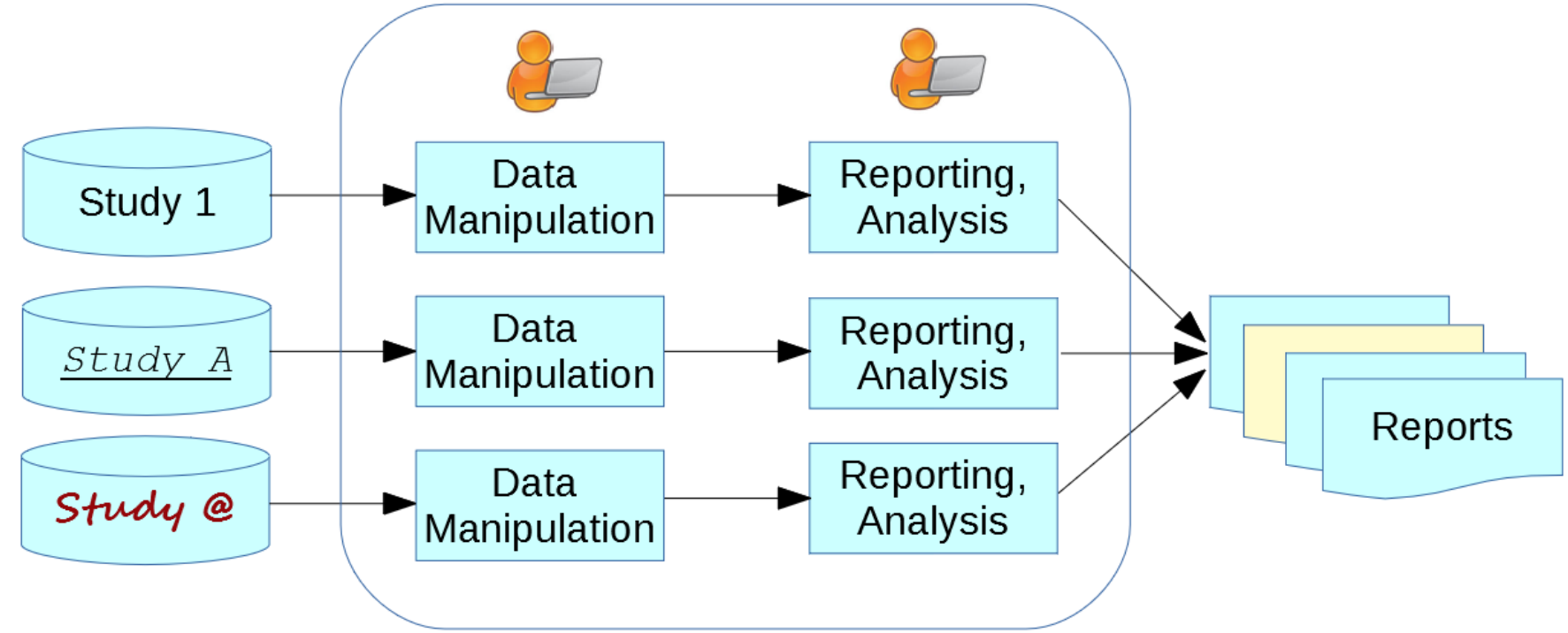
CDISC standards and their adaption

- 1997 – CDISC started as a Volunteer group
- 2005 – SDTM IG 3.1.1, Define-XML 1.0
- 2008 – OpenCDISC
- 2009 – SDTM IG 3.1.2, ADaM IG 1.0
- 2011 – SEND IG 3.0
- 2016 – Required by FDA for new studies
- 2016 (2022) – Required by PMDA

Benefits of standards

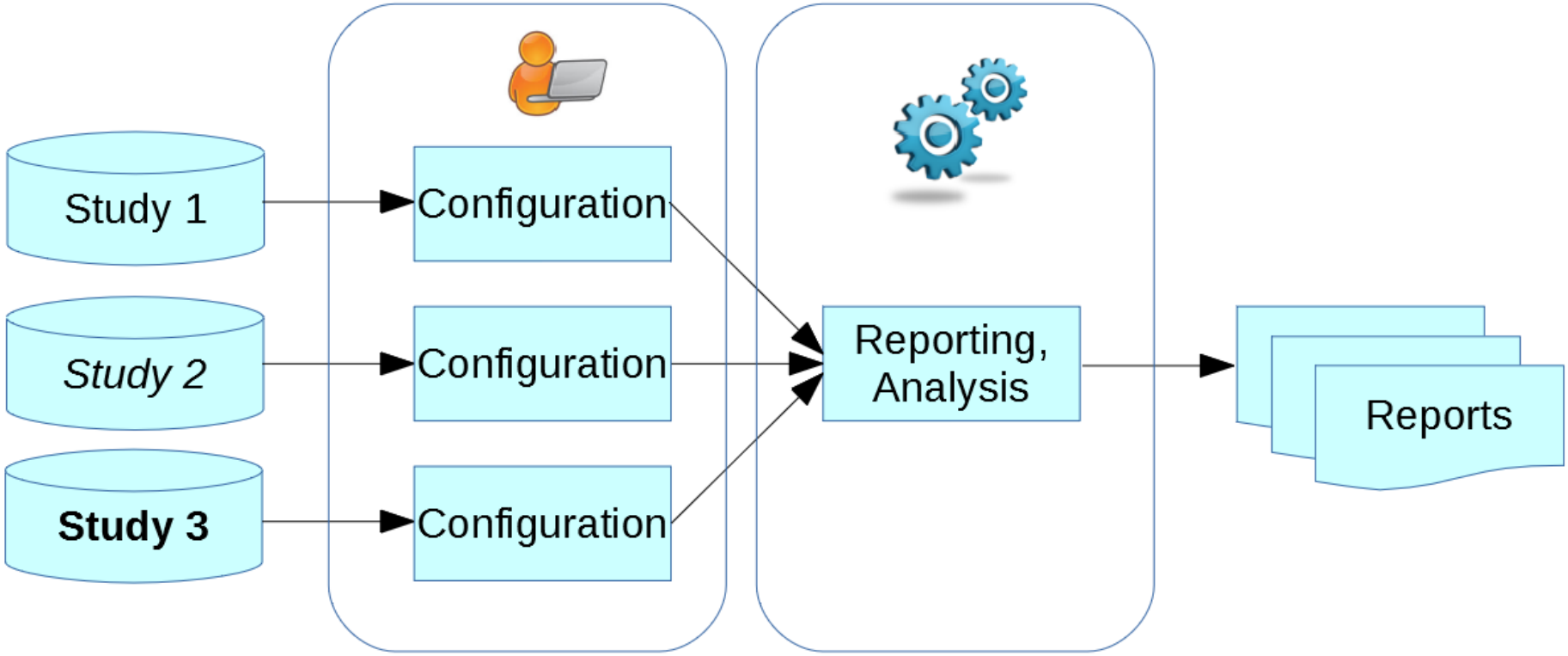
- Similarity across studies
- Ease of integration
- Re-use of code
- Standardized tools
- Automation
- …

Manual programming



- Input data is not standardized
- Data manipulation before reporting and analysis

Standardized tools

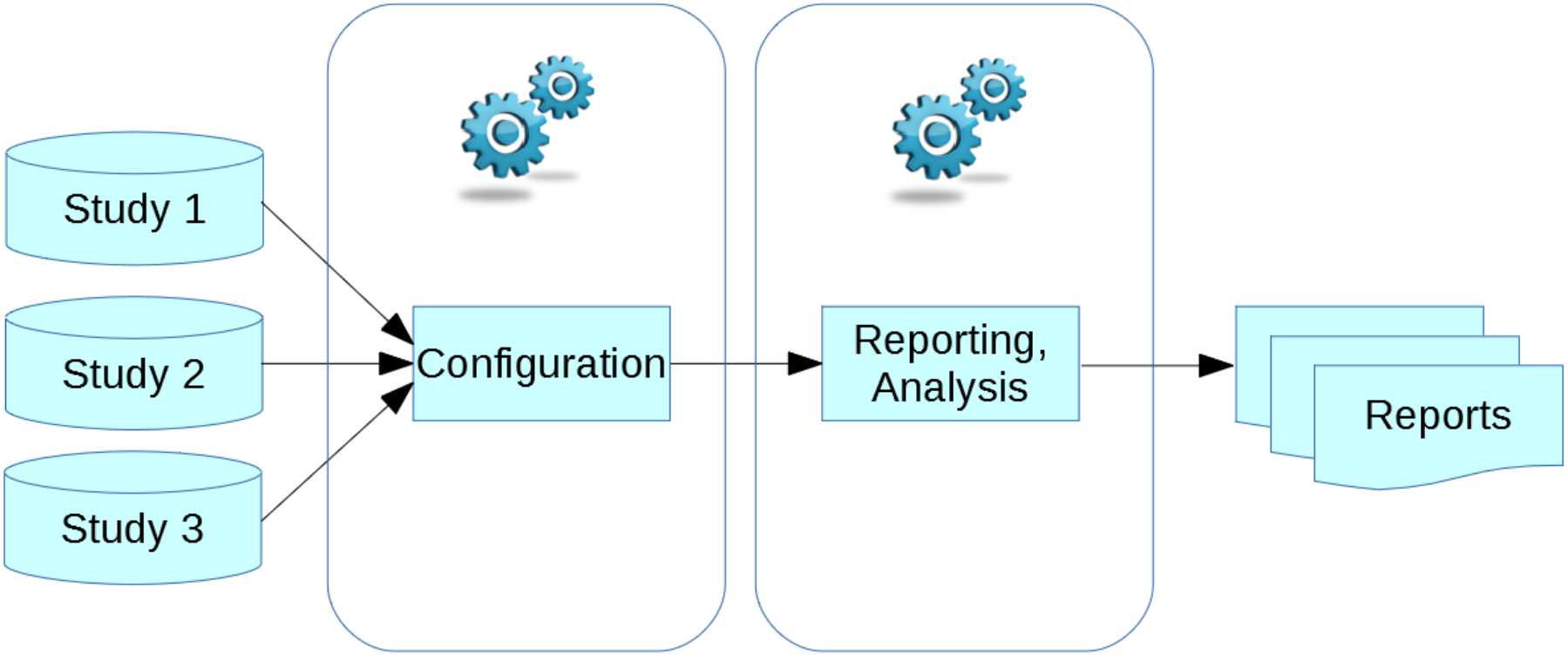


- Input data is partially standardized
- Manual configuration may be needed

Examples

- MAED
  - Subject, Treatment, Adverse Event term
  - One record per AE
- Liver Function Panel
  - Lab results, normal ranges
  - Default use of CDISC, but can be adjusted for non-standard structure and terms (SGOT instead of ASP)

Automated process



- Automated input for standardized tools
- High requirements for standardization

Automation relies on standards

- Location of files
- File names
- Structure
- Control Terminology
- Expected content
- Data quality

Example of wrong Normal Ranges

- Expected

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

- Incorrect

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

- Data is present, but it was implemented incorrectly
- Standard reporting tools will not produce results
- Data manipulation is needed to run analysis
  - LBSTNRHI is Num, LBSTNRC is Char variable

FDA definition for data quality

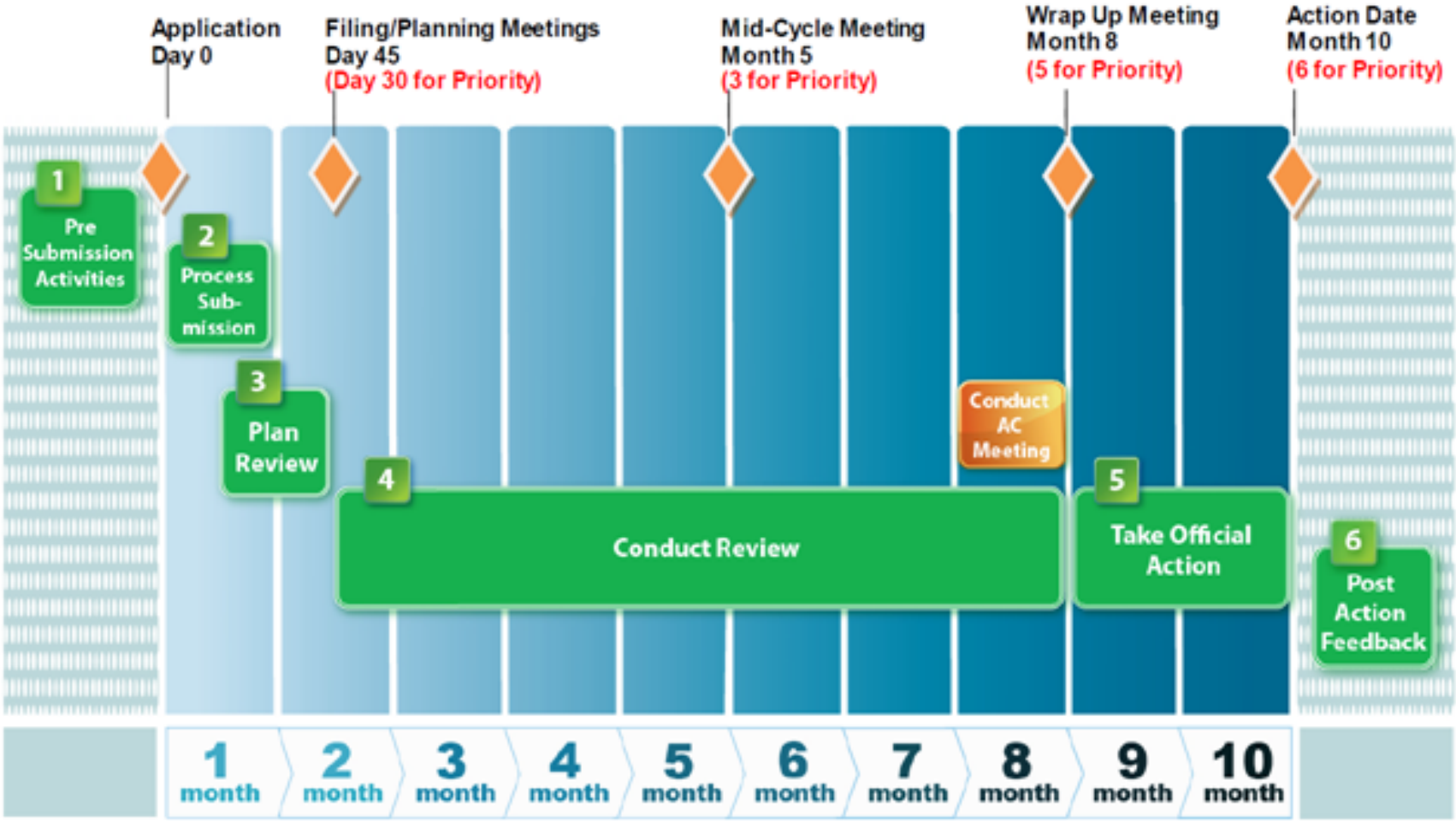
- *"Quality data would therefore be defined as data that sufficiently support conclusions and interpretations equivalent to those derived from error-free data"*

  Janet Woodcock, M.D., 1999

- *"Study data validation helps to ensure that the study data are compliant, useful, and will support meaningful review and analysis"*

  FDA TCG, 2017-10

Overview of the NDA/BLA Review Process and Major Steps for Completing the Review



Note: The timeline for review of NMEs/BLAs under PDUFA V's "Program" Review extends the *Conduct Review* Phase by two months.

See Appendix A for a timeline diagram for PDUFA V.

Increasing demand for data quality

- FDA goal is to make drugs available ASAP
- Manual review process has lower expectations on data quality
  - Often it's more quick for Reviewer to fix or work around issues rather than request fix from Sponsor
  - Data review time is limited
  - Data quality evaluation is difficult
- Automation relies on high quality data
  - Value of standard reporting and analysis for Reviewers increases demand for data quality
  - Standardized data allows early evaluation and enforcement of data quality

PMDA example

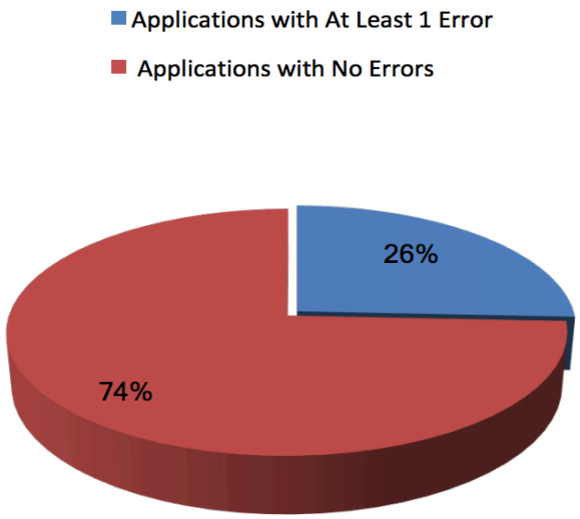
- Submission of data is few weeks before filing the application
- Consultation meetings
- Any Rejection issues (34 rules) must be fixed
- Reconciliation of validation results and Sponsor’s explanations

FDA has just started

- Current 4 FDA Rejection rules are not enough
- *"Trial Summary (TS) dataset must be included in every submission"*
  - Machine-readable metadata about study start date to decide is study must be in CDISC?
  - What about rules to ensure?
    - Presence of this info
    - Use of CDISC CT term for *Study Start Date*
      - *"SSTDTC"* - SDTM
      - *"STSTDTC"* - SEND
    - ISO 8601 format for date

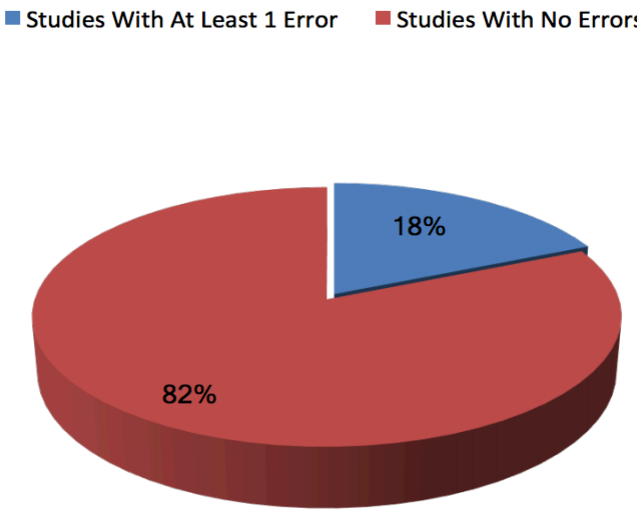
Errors by Application and Study

Potential Rejections



*70 Applications Assessed

Study Errors



*222 Studies Assessed

http://www.phusewiki.org/docs/2017_SDEs/Boston%20SDE/Technical%20Rejection%20Criteria%20for%20Study%20Data%20%E2%80%93%20Preliminary%20Findings.pdf

Automation of validation

- Pinnacle 21 (P21) Community – desktop tool
- P21 Enterprise – web-based application with centralized governance
- FDA DataFit and PMDA P21 Enterprise – P21 Enterprise with additional automation for FDA/PMDA environments based on
  - eCTD structure
  - study metadata

Automation logic

- Automation relies on standards
- Validation is performed according metadata provided by Sponsor (correct or incorrect)
- If study metadata is invalid or missing then some compensation actions are taken
  - For example, the latest versions of standards or dictionaries will be utilized instead

eCTD issues

- Data in incorrect folder is considered as missing
  - *90xxxx\0000\m5\datasets\study-1\tabulations\sdtm* – OK!
  - *90xxxx\0000\m5\datasets\study-1\sdtm* - incorrect
- Files with non-standard or inconsistent names
  - *define-study-1.xml* instead of *define.xml*
  - Define.xml has a reference to "*blankcrf.pdf*", but actual file is "*acrf.pdf*"
- When submitting additional or modified datasets, an update of define.xml for the whole study data is needed

SDTM version in define.xml

- P21C – manual input
- P21E – pre-configured by project manager
- DataFit – from define.xml file

```
def:StandardName="SDTM-IG"
def:StandardVersion="3.2">
```

- Example: study data utilized *SDTM IG 3.1.2*, but define.xml file has reference to *SDTM IG 3.1.3*
  - Unexpected PMDA Reject notification
  - Many false-positive and false-negative messages due to utilization of wrong configuration

https://www.cdisc.org/system/files/all/event/restricted/2017_Japan/Japan%202017_Session%206_Kominami.pdf

Invalid or missing MedDRA version

- DataFit uses define.xml file
  - *<ExternalCodeList Dictionary="MedDRA" Version="19.0"/>*
- If missing then the latest version of MedDRA is utilized
- Incorrectly implemented (e.g., like *Comment* instead of *Dictionary*) MedDRA version means missing info
- MedDRA version is utilized by some reporting tools
- Missing decimal points in version is PMDA Rejection criteria
  - "*19*" instead of "*19.0*"

https://www.cdisc.org/system/files/all/event/restricted/2017_Japan/Japan%202017_Session%206_Oda.pdf

Version of CDISC CT

- Today there is no machine-readable info about CDISC Control Terminology
  - Waiting for Define-XML v2.1
- DataFit utilizes the latest version of CDISC CT
  - 2011 – 104 Codelists
  - 2017 – 730 Codelists
  - Terms for NCI Code = C17988 are used inconsistently across codelists and versions:

Term	2011-07	2017-12
U	6	3
UNK	1	1
UNKNOWN	5	14

  - *U -> UNKNOWN* in SDTM CT 2014-03-28 for 3 non-extensible codelists ENRTPT, STENRF and STRTPT

Other examples Janus CTR

- None of Data Integrity checks are *Rejection* now
  - Missing subjects in DM -> fail to upload study data
- Upload process relies on *def:Class* in define.xml
- Trial Summary data is critical for CTR search

https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM442108.pdf

Summary

- The automation of regulatory review is a game changing event
- Standardized high quality study data is critical for automation
- Expect new Rejection rules and their enforcement from Regulatory Agencies

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