Science For A Better Life

# ADaM Standards - Organizing the Unorganized

(Heike Reichert, PhUSE SDE, Frankfurt, April 2013)

# Preamble

- Expenses for developing new drugs are very high
- Concentration not on only one single market
- For the US market all drugs must be FDA approved
- The FDA's safety team monitors the effects of more than 3,000 prescription drugs on 200 million people

This data is not really searchable

→ Request for submissions of standardized study data in electronic format

# Agenda/ Content

- Why Standards?
- Analysis Dataset Standards at Bayer
- Advantages of a standardized ADaM submission
- Challenges of an ADaM submission
- CDISC Standards Issues by the FDA

# Why standards?

# Why standards? (1)

**Imagine your fridge looks like this:**

- Disarrangement, topsy-turvy
- Where to store different kinds of food?
- What goes into the fridge?
- How can I relocate food?
- How can I locate expired food?

# Why standards? (2)

**And now, this fridge:**


- Neat
- Clear definition where to store what
- Well-arranged
- Easy locating of food
- Easy location of expired food

# Why standards? (3)

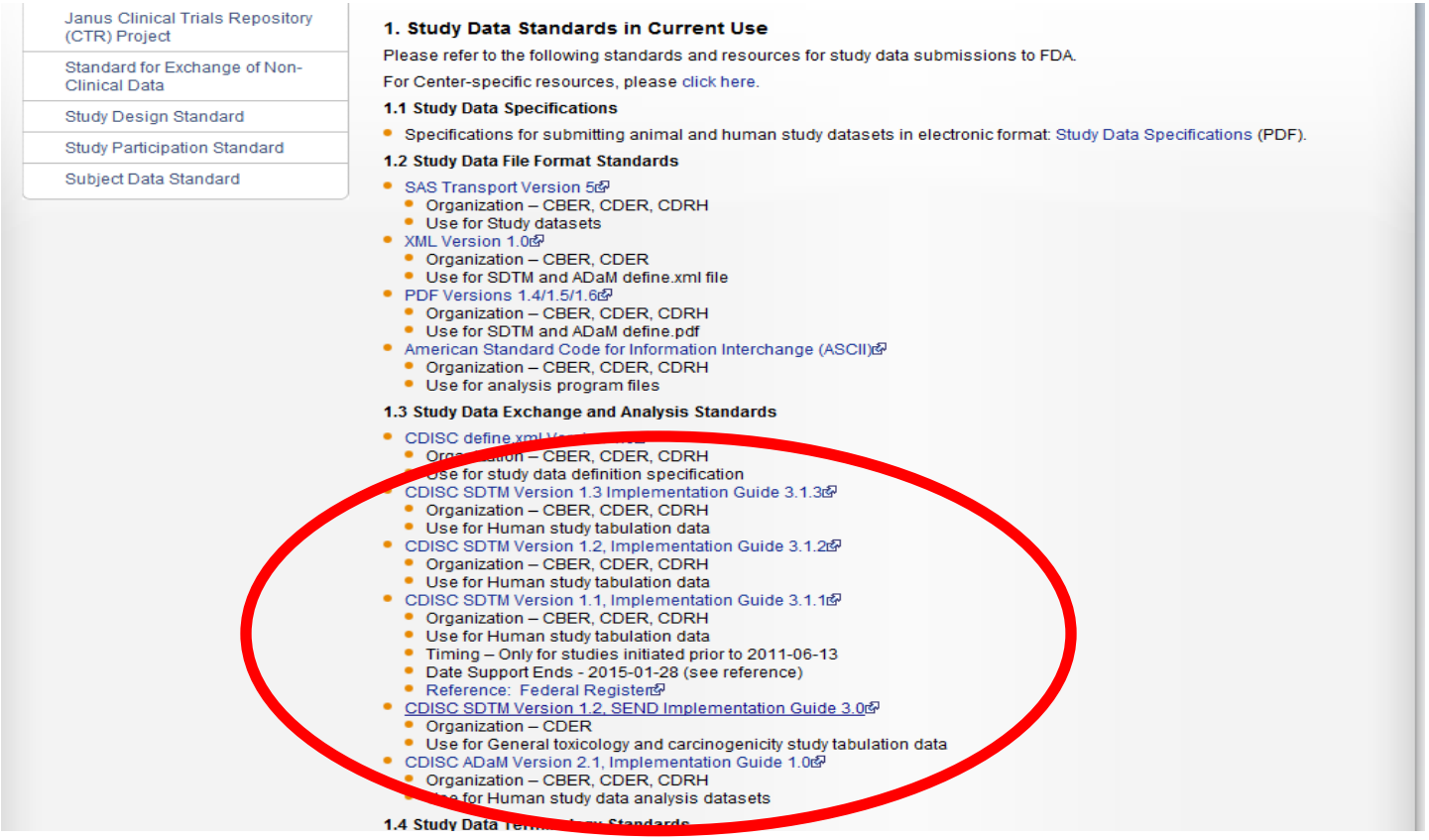
**Standardization helps to**

- specify unambigous metadata
- specify which data goes to which dataset
- locate your data
- implement metadata updates a lot easier
- locate retired data

# Why standards? (4)

## FDA supports CDISC standards (SDTM, ADaM) for submission

Check the webside: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm



- Janus Clinical Trials Repository (CTR) Project
- Standard for Exchange of Non-Clinical Data
- Study Design Standard
- Study Participation Standard
- Subject Data Standard

**1. Study Data Standards in Current Use**

Please refer to the following standards and resources for study data submissions to FDA.

For Center-specific resources, please click here.

**1.1 Study Data Specifications**

- Specifications for submitting animal and human study datasets in electronic format: Study Data Specifications (PDF).

**1.2 Study Data File Format Standards**

- SAS Transport Version 5
  - Organization – CBER, CDER, CDRH
  - Use for Study datasets
- XML Version 1.0
  - Organization – CBER, CDER
  - Use for SDTM and ADaM define.xml file
- PDF Versions 1.4/1.5/1.6
  - Organization – CBER, CDER, CDRH
  - Use for SDTM and ADaM define.pdf
- American Standard Code for Information Interchange (ASCII)
  - Organization – CBER, CDER, CDRH
  - Use for analysis program files

**1.3 Study Data Exchange and Analysis Standards**

- CDISC define.xml
  - Organization – CBER, CDER, CDRH
  - Use for study data definition specification
- CDISC SDTM Version 1.3 Implementation Guide 3.1.3
  - Organization – CBER, CDER, CDRH
  - Use for Human study tabulation data
- CDISC SDTM Version 1.2, Implementation Guide 3.1.2
  - Organization – CBER, CDER, CDRH
  - Use for Human study tabulation data
- CDISC SDTM Version 1.1, Implementation Guide 3.1.1
  - Organization – CBER, CDER, CDRH
  - Use for Human study tabulation data
  - Timing – Only for studies initiated prior to 2011-06-13
  - Date Support Ends - 2015-01-28 (see reference)
  - Reference: Federal Register
- CDISC SDTM Version 1.2, SEND Implementation Guide 3.0
  - Organization – CDER
  - Use for General toxicology and carcinogenicity study tabulation data
- CDISC ADaM Version 2.1, Implementation Guide 1.0
  - Organization – CBER, CDER, CDRH
  - Use for Human study data analysis datasets

**1.4 Study Data Terminology Standards**

# Why standards? (5)

**Ongoing discussions with the EMA if proactive publication of clinical trial data will be demanded**

- access to full data sets by interested parties
- workshop on clinical-trial data and transparency with the help of five advisory groups
  - One group focuses on Clinical-trial-data formats
    - ensure that clinical-trial data can be shared
    - clear and understandable format
    - appropriate analyses
    - swift implementation without undue burden to stakeholders
- come into force on 1 January 2014.

(European Medicines Agency - News and Events - Workshop on clinical-trial data and transparency)

# Analysis Data Standards at Bayer

# Analysis Dataset Standards at Bayer (1)

## Analysis Datasets at Bayer (1)

- According to CDISC ADaM standard
  - Starting point for ADS: SDTM+
  - Traceability: certain SDTM+ - variables are transferred to ADS
- Code - decode principle
  - Codelist/format use:
    - Code variable = start
    - Decode variable = label
  - Controlled use of character strings → controlled terminology beyond CDISC requirements
  - Study can only use codes and decodes that are available in pre-defined codelist
- Used for pooling for integrated analyses

# Analysis Dataset Standards at Bayer (2)

## Analysis Datasets at Bayer (2)

- Generation supported by macro system
  - Creation of ADS format catalog
  - Take over of selected SDTM+ - variables with their attributes
  - Automatic derivation of variables if algorithm is fix (e.g. CHG = AVAL-BASE)
  - Automatic derivation of decode variables with specified attributes
  - Setting of labels, formats, length etc. according to metadata (ATTRIB-statement unneeded)
  - Checks of data against metadata (completeness, rules)

# Analysis Dataset Standards at Bayer (3)

## Analysis Datasets at Bayer (3)

Nevertheless:

- In ADaM: big scope of interpretation
- Align handling among programmers
- Align possible variations within different projects
- Align possible variations of different studies

Standardization was necessary

# Analysis Dataset Standards at Bayer (4)

## Standardization of Analysis Datasets at Bayer

- Standardization of metadata and codelists
- Standardization on different hierarchical levels
  - Global metadata of about 30, mainly safety analysis datasets (e.g. ADAE, ADVS, ADLB)
  - Project-specific metadata of mainly efficacy datasets (e.g. ADMB, ADTU)
  - Studies just select the appropriate metadata and codelists

→ Limited creativity for each programmer

→ Only few adaptions and updates of metadata for the studies necessary

# Advantages of a standardized ADaM submission

# Advantages of a standardized ADaM submission

- Data structure and terminology is unique within a submission
- Preparation of integrated analysis is supported
- Reduction of variability in submissions across studies and sponsors
  - Authorities:
    - Facilitated review
    - Standardized data analysis tools to re-evaluate study results
    - Standardized tools for data review
    - Shortened review time
  - Sponsor:
    - Standardized programs and tools for generation of datasets
    - Standardized programs and tools for generation of documentation
    - Saving of time for the deliverables in the long run

# Challenges of an ADaM submission

# Challenges of an ADaM submission (1)

- Tough job to implement ADaM standards

All this stuff

has to go into this small fridge

# Challenges of an ADaM submission (2)

**Challenges of an ADaM submission:**

- Time consuming documentation for all types of metadata
- Learning curve for programmers
  - Understanding the principles of CDISC
    - Additional records instead of additional variables
    - Harmonization principle: same name, same value, same label
- Learning curve for authorities
  - „please add columns LOCF, WOCF to your efficacy dataset“
- Changes of specification in CDISC have high impact on
  - metadata – variable names, variable types
  - Programs
  - Possible structure of datasets

# CDISC Standards Issues by the FDA

# CDISC Standards Issues by the FDA (1)

- **Waste of space**
  - correlation between dataset sizes and allotted column variable length (e.g. i.e. actual length = 8, allotted length = 200)
- **Creation of sponsor defined domains and variables**
- **Validation errors**
  - Codelist mis-match for extensible codelists
  - End date is prior to start date
  - Required and expected variables should be present in the dataset
  - Variable labels in the dataset should match CDISC naming conventions
- **Extended Codelists:** values of variables are not included
- **Invalid ISO 8601 values**
- **Missing traceability:** CRF -> SDTM -> ADaM -> CSR
- **Inadequate documentation**

# CDISC Standards Issues by the FDA (2)

**Can be avoided by**

- Open CDISC validator
  - Errors and warnings that can be fixed should be fixed
  - If errors/warnings inherently exist: Reviewer‘s Guide
- Standardization
- Development and use of standard tools

**→ Authorities may also reject submissions if submitted data does not adhere to standards/PDUFA V**

# CDISC Standards Issues by the FDA (3)

## Conclusion

- FDA expects high quality data, metadata and documentation
- Industry has to reconsider the submission deliveries
- In worst case: discarding of all processes and starting from scratch


Bringing the fridge to the bone yard

# CDISC Standards Issues by the FDA (4)

# CDISC Standards Issues by the FDA (5)

- To make the fridges at FDA look really nice!

# References


- **CDISC Team Updates - Standards in the Electronic Submission Process** - *26 Jan 2012* - Webinar
- **Center for Drug Evaluation and Research** – Wikipedia
- European Medicines Agency - News and Events - Workshop on clinical-trial data and transparency
- http**://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm**

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# Thank you!