



Science For A Better Life

ADaM Standards - Organizing the Unorganized

(Heike Reichert, PhUSE, Brussels, October 2013)

Introduction



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

→→ great deal of work

→→ Especially as each company has its own submission standard

→→ **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:



- Disorganized, 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? (4)

Standardization helps to

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

Why standards? (5)

Standards at the FDA



FDA supports CDISC standards (e.g. SDTM, ADaM) for submissions

Check the website: <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 Version 1.2](#)
 - 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? (6)

Standards at the FDA

Guidance for Industry Providing Regulatory Submissions in Electronic Format (DRAFT)

- Current and future requirements how data has to be provided to the agency
- Submitted data must fit validations rule (openCDISC validator)
- Recommendations:
 - No retrospective mapping of study data
 - Discussions with agency about standard implementation as early as possible, e.g. before pre-IND meeting
- After guideline is published, submissions
 - for BLA and NDA, supplements and amendments must comply within 24 months
 - for IND must comply within 36 months

Why standards? (7)

Standards at the FDA



FDA released a **CDISC position paper** on 13 September 2013

- Study data must be in conformance to CDISC standards for electronic submissions.
- Replacement of CDISC standards for study data is not foreseen.
- Implementation of new standards will not be done without public input on the cost and utility.

Why standards? (8)

Standards at the EMA



Draft policy: "Publication and access to clinical-trial data"

- Proactively publish raw de-identified clinical trial data in an analyzable format for interested parties.
- CDISC standard shall be the required standard.
- Result of the "Clinical Trial Data Transparency Initiative"
 - Preceding workshop with participants of Academia, Media, Industry, Patients, a European Ombudsman's representative and the assistant of European Data Protection Supervisor to collect and evaluate interests, views and concerns.

Why standards? (9)

Standards at the EMA



Draft policy: "Publication and access to clinical-trial data"

- Expected to come into force on 1 January 2014
- Implementation impacted by
 - Outcome of some court cases related to the "European Medicines Agency policy on access to Documents" of 2010
 - Legal action to clarify the legal situation for publication of commercially confidential information



Analysis Data Standards at Bayer

Analysis Data Standards at Bayer (1)



Bayer Analysis Datasets

- According to CDISC ADaM standard
 - Starting point for analysis datasets: SDTM+
 - SDTM+: SDTM variables and Bayer specific variables
 - Traceability: certain SDTM+ - variables are taken over
- SDTM specifies a lot of character variables
 - Error-prone to select via text string
 - Variability among different programmers



introduction of code-decode principle

Analysis Data Standards at Bayer (2)



■ ■ 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
- If required code is missing it has to be requested.
 - Evaluation by an expert team
- ■ Analysis datasets are used for pooling for integrated analyses

Analysis Data Standards at Bayer (3)



Standardization of Analysis Datasets at Bayer

- Standardization of metadata and codelists
- Standardization on different hierarchical levels
 - (1) Global
 - metadata of about 30, mainly safety analysis datasets
 - e.g. ADAE (adverse events), ADVS (vital signs) , ADLB (laboratory)
 - but also efficacy datasets
 - e.g. ADTTE (time-to-event) or ADQS (questionnaires)
 - Lower levels must adhere

Analysis Data Standards at Bayer (4)



Standardization of Analysis Datasets at Bayer

(2) Therapeutical Area Standard (TAS)

- metadata, e.g. Oncology, of mainly efficacy datasets, e.g. ADTU (Tumor)

(3) Project standard

- defines all datasets and variables used in studies within a project
- Variables from global and TAS as well as project specific new variables and datasets
- Studies have to use the metadata and codelists available on project level

- ➔ Limited creativity for each programmer
- ➔ Well-defined permissible changes possible
- ➔ Study specific definitions of datasets or codelists are not allowed

Analysis Data Standards at Bayer (5)



Creation of Analysis Datasets (1)

Generation supported by macro system

- Creation of an analysis dataset 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 not needed)
- Checks of data against metadata (completeness, rules)

Analysis Data Standards at Bayer (6)



Creation of Analysis Datasets (2)

- ➔ Macro system supports the generation of ADaM compliant analysis dataset
- ➔ Limited possibilities for own interpretation and data handling
- ➔ Standardization of analysis datasets and SDTM+ datasets necessary beforehand

Advantages of a standardized ADaM submission

Advantages of a standardized ADaM submission



- „ Similarity of Data structure and terminology
- „ 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**

Use of OpenCDISC validator

- **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**

CDISC Standards Issues by the FDA (3)

Conclusion

- ■ Expectations: high quality data, metadata and documentation
- ■ Industry has to reconsider the submission deliveries
- If worst comes to the worst: discarding of all processes and starting from scratch and ...



Bringing the fridge to
the waste container

CDISC Standards Issues by the FDA (4)



CDISC Standards Issues by the FDA (5)

The outer shell is provided by CDISC. Now the empty fridges have to be filled with content in order to make them look really nice for the agencies!



References

REFERENCES

- (1) [CENTER FOR DRUG EVALUATION AND RESEARCH - WIKIPEDIA, THE FREE ENCYCLOPEDIA](#)
- (2) [MISSION STATEMENT AND CORE PRINCIPLES](#)
- (3) [STANDARDS & IMPLEMENTATIONS](#)
- (4) [HTTP://WWW.FDA.GOV/FORINDUSTRY/DATASTANDARDS/STUDYDATASTANDARDS/DEFAULT.HTM](http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm) (5)
[HTTP://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCEREGULATORYINFORMATION/GUIDANCES/UCM292334.PDF](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292334.pdf)
- (6) [OPENCDISC | AN OPEN SOURCE COMMUNITY OF CDISC DEVELOPERS AND USERS](#)
- (7) [HTTP://WWW.CDISC.ORG/STUFF/CONTENTMGR/FILES/0/0B585DB258D68C43CAD5FAE135D473A/FILES/MALLA_CBER_CDISC_SESSION_8_OCT_2012_MALLA.PDF](http://www.cdisc.org/stuff/contentmgr/files/0/0b585db258d68c43cad5fae135d473a/files/malla_cber_cdisc_session_8_oct_2012_malla.pdf)
- (8) [FEDERAL FOOD, DRUG, AND COSMETIC ACT \(FD&C ACT\)](#)
- (9) [HTTP://WWW.EMA.EUROPA.EU/DOCS/EN_GB/DOCUMENT_LIBRARY/OTHER/2013/06/WC500144730.PDF](http://www.ema.europa.eu/docs/en_GB/document_library/other/2013/06/WC500144730.pdf) (10)
[European Medicines Agency - News and Events - Workshop on clinical-trial data and transparency](#)
- (11) http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144734.pdf
- (12) [CDISC Team Updates - Standards in the Electronic Submission Process - 26 Jan 2012 – Webinar](#)
- (13) [Study Data Standards > Study Data Standards for Regulatory Submissions](#)



Science For A Better Life

Thank you!