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

Check the website: [http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)
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
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
  - Preceeding 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.
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
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
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
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
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)
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:

- 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

(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

(5) HTTP://WWW.FDA.GOV/DOWNLOADS/DRUGS/GUIDANCECOMPLIANCE/REGULATORYINFORMATION/GUIDANCES/UCM292334.PDF

(6) OPENDISC | AN OPEN SOURCE COMMUNITY OF CDISC DEVELOPERS AND USERS

(7) HTTP://WWW.CDISC.ORG/STUFF/CONTENTMGR/FILES/0/0B585DB258D68C43CADC5FAE135D473A/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

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


(12) CDISC Team Updates - Standards in the Electronic Submission Process - 26 Jan 2012 – Webinar

(13) Study Data Standards > Study Data Standards for Regulatory Submissions
Thank you!