Is it possible to make a global CDISC submission?

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Agenda

- Preparing for the submission
- Planning your trial
- Guidelines, conformance checks, submission deliverables and challenges
- Recommendations
- Conclusion
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Preparing for the submission

• When do you have to comply with the CDISC requirements for your submission?
  • FDA requires all trials with **start date after 16-Dec-2016** to be in CDISC format
  • PMDA requires that **all submissions submitted after 01-Apr-2020** are in CDISC format

• Differences in planning documents and timing:
  • FDA requires the sponsors to fill in the **Study Data Standardisation Plan** at the time of the first IND and no later than end-of-phase II
  • PMDA requires the sponsors to fill in the **Appendix 8** (‘Consultation on data format of submission of electronic study data’) before the first e-data consultation
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Planning your trial

- Plan your trial with the future submission in mind
- Check the Data Standards Catalogue from both FDA and PMDA for supported versions of SDTM, ADaM and controlled terminologies
Choosing SDTM and ADaM versions

- You may want to use the newest standards, but make sure to choose a set which is supported by both FDA and PMDA

Sources: FDA Data Standards Catalogue v. 4.10 (Oct 24, 2017)
Data Standards Catalogue (2017-03-03)
Choosing versions of controlled terminologies

- For controlled terminology versions it is a little more difficult to choose

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Sources: FDA Data Standards Catalogue v. 4.10 (Oct 24, 2017)
Data Standards Catalogue (2017-03-03)
Can we use the same data model?

- Both FDA and PMDA require submission data in CDISC format
- Both agencies require the CDISC SDTM data model
- The CDISC organisation has detailed the implementation of the data model in the IG
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Technical Conformance Guides and FAQs

- The data submission must also comply with the Technical Conformance Guide and recommendations in the FAQ document (PMDA only)

- The Technical Conformance Guides and FAQ instructions are not binding, but sponsors are expected to be compliant
Contradicting guidance from agencies

Example: PP domain in SDTM:

- Novo Nordisk has taken the position, that the PP data are derived data, and hence belong in ADaM
- FDA accepted the Novo Nordisk approach
- The PMDA FAQ states that PP data should be included in the SDTM database regardless of whether it is derived
- Novo Nordisk will bring the question to an e-data consultation

Q5-13: As the pharmacokinetic parameters are derived data, and not the accrual data collected in clinical study, is it necessary to include the PP domain in the SDTM dataset?

A: The pharmacokinetic parameters themselves are considered as data to capture the characteristics of the drug and should be included in database. Therefore, please submit the SDTM dataset with the PP domain.

Sources: FAQs on Electronic Study Data Submission (Excerpt)
Contradictions in guides

• Sometimes the Technical Conformance Guides and the SDTMIG are not aligned

• Example: description of ARM for screening failure subjects
  SDTMIG 3.2:

  Data for screen failure subjects, if submitted, should be included in the Demographics dataset, with ARMCD = “SCRNFAIL” and ARM = “Screen Failure”. Sponsors may include a record in the Disposition dataset indicating when the screen failure event occurred. DM/SE Example 6 shows an example of data submitted for a screen failure subject.

FDA Technical Conformance Guide v. 4.1:

DM Domain (Demographics)
In the DM domain, each subject should have only one single record per study.

Screen failures, when provided, should be included as a record in DM with the ARM field left blank. For subjects who are randomized in treatment group but not treated, the planned arm variables (ARM and ARMCD) should be populated, but actual treatment arm variables (ACTARM and ACTARMCD) should be left blank.24

Sources: SDTMIG 3.2
Study Data Technical Conformance Guide. 4.1 (Mar 2018)
Conformance checks – finding you way

- FDA and PMDA each have a set of conformance checks for checking:
  - SDTM datasets and conformance to the SDTM model
  - ADaM datasets and conformance to the ADaM model
  - Define.xml structure

- FDA and PMDA have different severity categories for checks
  - FDA: Error, Warning, Note
  - PMDA: Rejection criteria, Error, Warning

- Some SDTM checks overlap, but also each agency has additional data model checks
  - FDA has 12 additional checks
  - PMDA has 23 additional checks
  - 111 checks differ in severity
  - 2 checks differ in content
  - 2 checks target different domains

Sources: JPMA (Japan Pharmaceutical Manufacturers Association):
Analysis of differences in FDA/PMDA Validation Rules
SDTM Validation Rules, Pinnacle21:
Submission deliverables

- The two agencies require different submission deliverables:
  - Study Data Reviewer’s Guide:
    - FDA Name: cSDRG filename: csdrg.pdf
    - PMDA Name: SDRG filename: study-data-reviewersguide.pdf
  
  - Analysis Data Reviewer’s Guide:
    - FDA Name: ADRG filename: adrg.pdf

- PMDA requires extra documents for the submission:
  - Attachment 4: dataset definition document for PK analysis, population analysis, physiologically based pharmacokinetic model analysis
  - Attachment 5: detailing procedures for running programs for population analysis

Sources: FDA: Study Data Technical Conformance Guide. 4.1 (Mar 2018)
PMDA: Revision of Technical Conformance Guide on Electronic Study Data Submissions (August 24, 2016)
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• Plan your trial using the latest versions of SDTM, ADaM and controlled terminologies supported by both agencies

• When requirements differ with respect to the domains and variables follow the guidance in this order of priority:
  • Guidance from CDISC Implementation Guides
  • Binding agency guidance
  • Non-binding agency guidance
  • Lastly always talk to your reviewers

• P21 conformance checks:
  • Use the latest version
  • Run both the FDA and PMDA checking rules and update the (c)SDRG/ADRG accordingly
  • Remember to check the define.xml also

• Due to the differences in requirements for the submission deliverables, you will probably need to implement different packages for each agency
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Question: Is it possible to make a global CDISC submission?

- The answer must be ‘No’, since the differences in regulatory requirements with respect to implementation and submission deliverables will require that two different packages are created.

- As a sponsor you could wish for
  - more alignment between the agencies
  - that the guidance in technical conformance guides and FAQs were implemented in the CDISC Implementation Guides to clear away the inconsistencies.
Thank you for your attention!
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