Is it possible to make a global CDISC submission?

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changing diabetes®

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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 you 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

FDA Data Standards Catalog v4.10 (10-24-2017) - Supported and Required Standards

a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the y guidance documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FD advance. This catalog is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data* downloads/Drugs/Guidances/UCM292334.pdf).

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends
Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01-28-2015		01-28-2015
SDTM	XPT	CDISC	1.2	Version 3.1.2 Amendment 1	CDER, CBER	08-07-2013	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
SDTM	XPT	CDISC	1.2	3.1.2	CDER, CBER	30-10-2009	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
SDTM	XPT	CDISC	1.3	3.1.3	CDER, CBER	12-01-2012		12/17/2016 [1] 12/17/2017 [2]	
(SDTM)	XPT	CDISC	1.4	3.2	CDER, CBER	08-17-2015		03/15/2018 [1] 03/15/2019 [2]	
Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]
Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.1	CDER, CBER	03-15-2018		03/15/2019 [1] 03/15/2020 [2]	
Standard for									

PMDA Data Standards Catalog (2017-03-03) - Data Exchange Standards

Use	Data Exchange Standard	Supported Version(s)	Implementation Guide Version	Exchange Format	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)
Clinical study datasets - Transport	SAS Transport (XPORT)	5	-	XPT	2016-10-01	
Clinical study datasets	SDTM	1.4	3.2	XPT	2016-10-01	
Clinical study datasets	SDTM	1.3	3.1.3	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2 Amendment1	XPT	2016-10-01	
Clinical study datasets	SDTM	1.2	3.1.2	XPT	2016-10-01	
Clinical study datasets	ADaM	2.1	1.0	XPT	2016-10-01	

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

FDA Data Standards Catalog v4.10 (10-24-2017)

This table contains a listing of the standard terminology code sets. When the Catalog expresses support for more than one terminology for a given type of regulatory information, the submitter any terminology not listed should be discussed with the Agency in advance.
The listing of the data exchange standards developed at FDA are listed in a separate tab. Please look at the "Data Exchange Standards" tab to find data exchange standards information supp have established processes and technology infrastructure to support the process, review, and archive of the data. The submission of standardized data using any standard not listed, or to an F the Agency in advance.

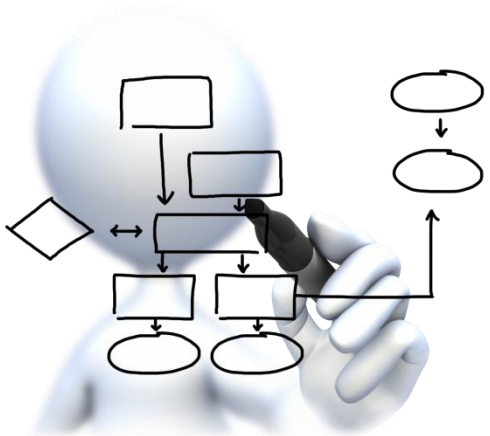
Terminology Standard	Terminology Type	Terminology Standards Development and/or Maintenance Organization	Version(s)	FDA Centers That Use This Terminology	Date Support Begins (MM/DD/YYYY)	Date Support Ends	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Examples of Use
Clinical Data Interchange Standards Consortium (CDISC) Terminology	General Clinical Data	CDISC	2011-06-10 or later	CBER, CDER	06-13-2011		12/17/2016 [1] 12/17/2017 [2]		Use CDISC Submission values
Clinical Data Interchange Standards Consortium (CDISC) Terminology	General Clinical Data	CDISC	All Previous Version	CBER, CDER	Ongoing				Use CDISC Submission Values. Do not use for studies initiated after 2011-06-13.
CDISC Terminology	Non Clinical Data	CDISC	All Previous Version	CDER					SEND Data
Medical Dictionary for Regulatory Activities (MedDRA)	Adverse Events	Maintenance and Support Services Organization (MSSO)	8 or earlier	CBER, CDER	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	CDISC AE Domain
MedDRA	Adverse Events	MSSO	Current Version	CBER, CDER	08/31/2017		03/15/2019 [1] 03/15/2020 [2]		CDISC AE Domain
Event Problem Codes	Adverse Events	CDRH	Latest Version	CDRH	Ongoing				CDISC AE Domain
WHO Drug Dictionary [4]	Medication	Uppsala Monitoring Centre	Not Specified	CBER, CDER	03/31/2015	03/15/2019 [5]	03/15/2018 [1] 03/15/2019 [2]	03/15/2019 [5]	Use in SDTM CMDECOD and CMCLAS

PMDA Data Standards Catalog (2017-03-03) - Terminology Standards

Terminology Standard	Version(s)	Date Support Begins (YYYY-MM-DD)	Date Support Ends (YYYY-MM-DD)	Notes
CDISC Controlled Terminology	Between 2009-02-17 (inclusive) and 2011-06-10 (exclusive)	2016-10-01	2017-06-30	When using the version indicated in "Version(s)" column, consult PMDA at the consultation on data format of the submission of electronic study data.
CDISC Controlled Terminology	2011-06-10 or later	2016-10-01		
MedDRA	8.0 or later	2016-10-01		
WHO Drug Dictionary Enhanced	2008:3 (2008-12-01) or later	2016-10-01		

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]

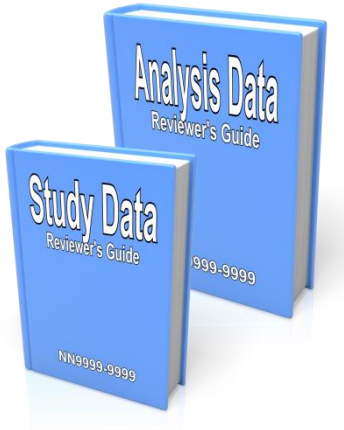
Sources: SDTMIG 3.2
Study Data Technical Conformance Guide. 4.1 (Mar 2018)

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:
https://www.pinnacle21.com/validation-rules/sdtm

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 Name: ADRG filename: analysis-data-reviewers-guide.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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Recommendations

- 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 !

Presenter

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