



**Is it possible to make a
global submission?**

**What are the top five
challenges in complying
with CDISC standards?**

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Agenda

- Is it possible to make a global submission?
- Top Five Challenges in Complying with CDISC Standards
- Questions for you



**Is it Possible to
Make a Global
Submission?**

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

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

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 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, <i>Providing Regulatory Submissions in Electronic Format-Standardized Study Data</i> (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]	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]	

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 Amendment 1	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

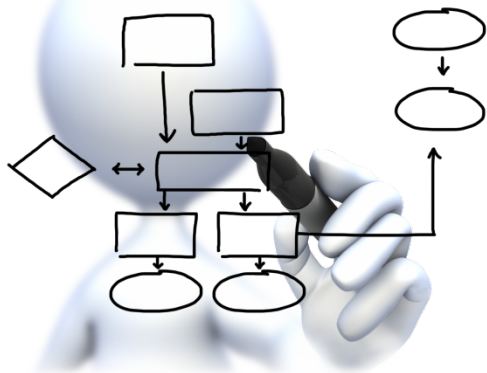
- For controlled terminology versions it is a little more difficult to choose

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 support 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 FDA 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	CDER, 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	CDER, 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	CDER, 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	CDER, 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	CDER, 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

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.

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

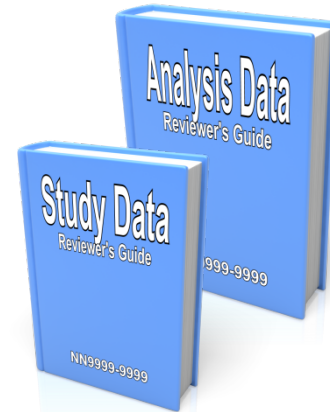
- FDA and PMDA each have a set of conformance checks for checking:
 - SDTM datasets and conformance to the SDTM model
 - ADaM datasets and conformance to the ADaM model
 - Define.xml structure
- FDA and PMDA have different severity categories for checks
 - FDA : Error, Warning, Note
 - PMDA: Rejection 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)

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

Question: Is it possible to make a global CDISC submission?

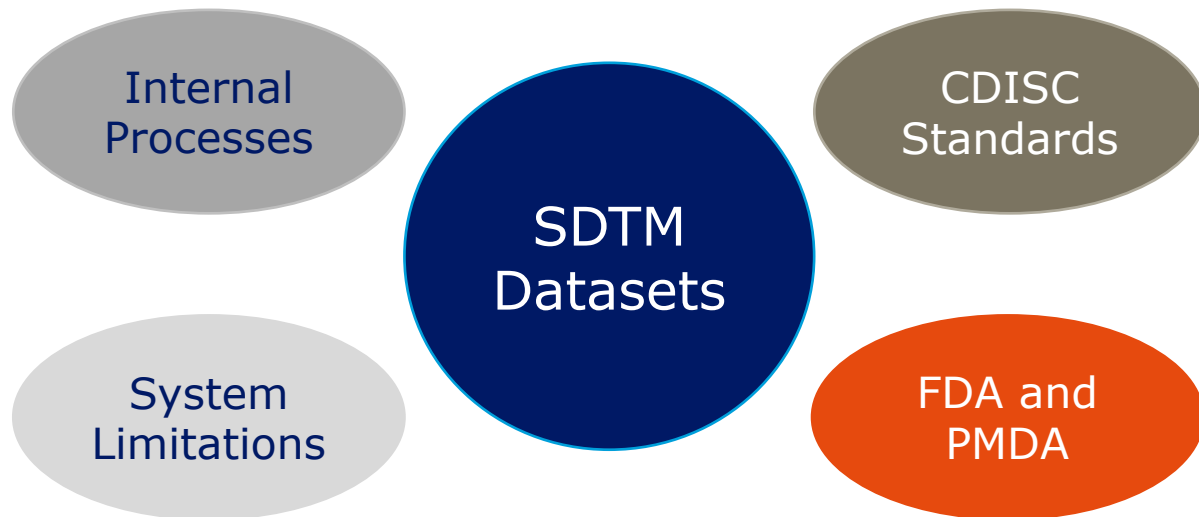
- The answer must be 'No', since the differences in regulatory requirements with respect to implementation and submission deliverables will require that two different packages are created
- As a sponsor you could wish for
 - more alignment between the agencies
 - that the guidance in technical conformance guides and FAQs were implemented in the CDISC Implementation Guides to clear away the inconsistencies



Challenges in complying with CDISC standards

Top 5 Challenges and Requirements

1. Collection of Race & Ethnicity Data
2. Pharmacokinetic Parameters (PP) Domain
3. Standardized Units
4. Event Adjudication Results
5. Associated Person (AP) Domain



Collection of Race & Ethnicity Data

Background

- Between 2008-2013, 20% of new drugs demonstrated some differences in exposure and/or response across racial/ethnic groups
- Critical for identifying population-specific signals
- More consistent demographic subgroup data collection
 - Inside and outside USA

Contains Nonbinding Recommendations

Collection of Race and Ethnicity Data in Clinical Trials

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 26, 2016

For questions about this document, contact the FDA Office of Minority Health at 240-402-5084 or omh@fda.hhs.gov.



Challenges

- The development of the standard is done backwards
 - FDA guidance -> 2 new code lists included in SDTM CT -> SDTMIG pending (Race & Ethnicity details have not changed in the draft version)
- FDA Guidance for Collection of Race & Ethnicity and SDTM code lists 'Race as collected' and 'Ethnicity as collected' are not aligned
 - Which concept to follow?
 - What about other authorities?

Missing Alignment Between FDA Guidance and CDISC CT

FDA guidance on collection of detailed Ethnicity

Ethnicity Data Standard

Are you Hispanic, Latino/a, or of Spanish origin? (One or more categories may be selected)

- a. ☐ No, not of Hispanic, Latino/a, or Spanish origin
- b. ☐ Yes, Mexican, Mexican American, Chicano/a
- c. ☐ Yes, Puerto Rican
- d. ☐ Yes, Cuban
- e. ☐ Yes, Another Hispanic, Latino/a or Spanish origin

Synonyms?

These categories roll up to the Hispanic or Latino category of the OMB standard

How do we map to CDISC CT ?

CDISC CT for Ethnicity as Collected

Code list Name	CDISC Submission Value
Ethnicity As Collected	ETHNICC
Ethnicity As Collected	ASHKENAZI JEW
Ethnicity As Collected	CENTRAL AMERICAN
Ethnicity As Collected	CUBAN
Ethnicity As Collected	CUBAN AMERICAN
Ethnicity As Collected	HISPANIC OR LATINO
Ethnicity As Collected	LATIN AMERICAN
Ethnicity As Collected	MEXICAN
Ethnicity As Collected	MEXICAN AMERICAN
Ethnicity As Collected	NOT HISPANIC OR LATINO
Ethnicity As Collected	PUERTO RICAN
Ethnicity As Collected	SEPHARDIC JEW
Ethnicity As Collected	SOUTH AMERICAN
Ethnicity As Collected	SPANISH

Pharmacokinetic Parameters (PP) Domain

SDTM.PP Challenges

Pharmacokinetic
Parameters as a
derived dataset
instead of source
data

The SDTM standard

SDTM is created
by Data
Management

Internal Processes

SDTM.PP created
based on
ADaM.ADPP

Dataflow

Redundant data
ADaM.ADPP and
SDTM.PP

Datasets

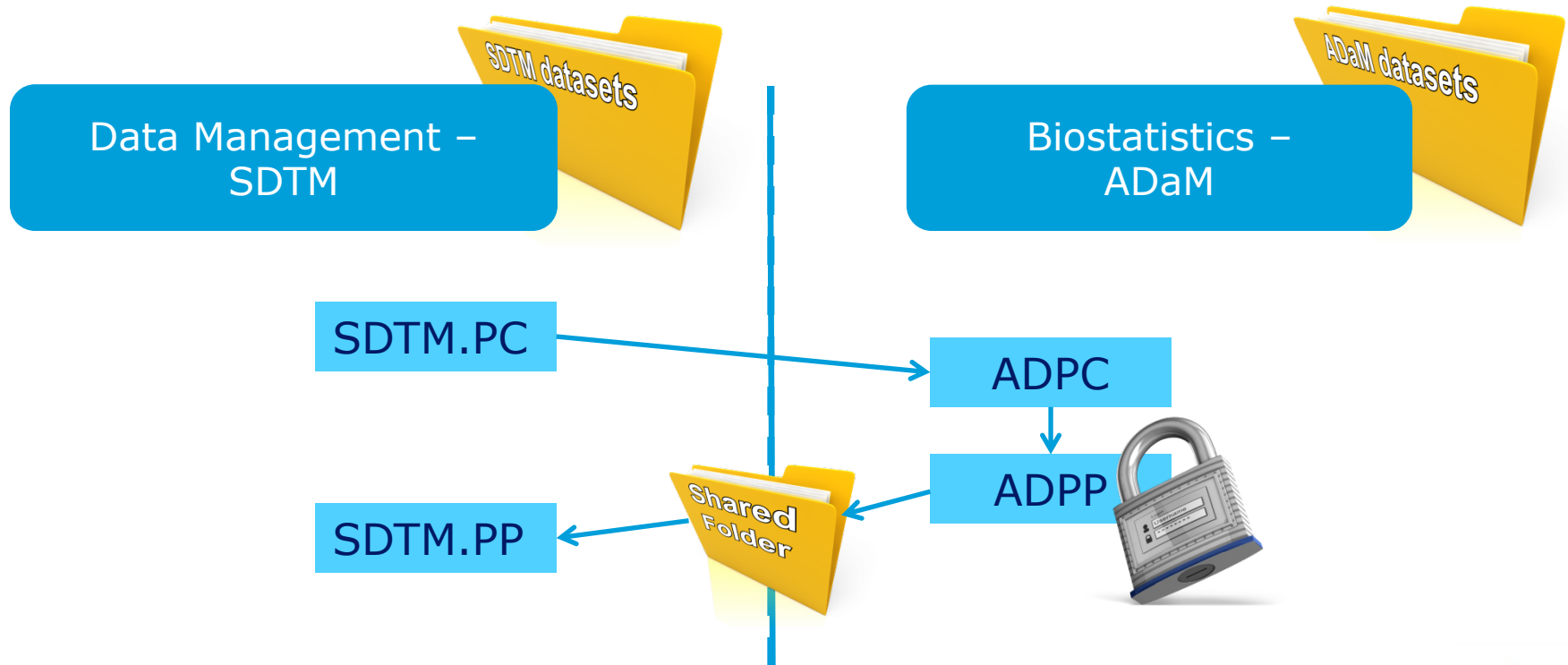
Different
requirements

Regulatory Authorities



From cdisc.org/standards

PP Challenges – The Organisation and Process



Standardized Units in SDTM

What is the 'Standardized' Unit in SDTM?

- The international conventional units used in the Clinical Trial Report?
- The SI units?
- The US conventional units?



'Standardized' Units in SDTM

STRESU Unit
should match
UNIT in PARAM

Unit in PARAM and
AVAL must match
output

We would like to
present results in
international
conventional units

SDTM

TEST	ORRESU	STRESU
Height	inch	cm
Systolic	mmHg	mmHg
Lab1	Xx/zz	mg/dL
Lab2	Zz/xx	mmol/L



ADaM

PARAM	AVAL
Height (cm)	xx
Systolic (mmHg)	xx
Lab1 (mg/dL)	xx.x
Lab2 (mmol/L)	xx.x



Report

Table XYZ – Summary of xyz

	X	Y	Z
Height (cm)	xx	xx	xx
Systolic (mmHg)	xx	xx	xx
Lab1 (mg/dL)	xx.x	xx.x	xx.x
Lab2 (mmol/L)	xx.x	xx.x	xx.x

'Standardized' Units in SDTM

STRESU Unit
should match
UNIT in PARAM

Unit in PARAM and
AVAL must match
output

We will like to
present results in
international
conventional units

SDTM

TEST	ORRESU	STRESU	SI	US
Height	inch	cm		
Systolic	mmHg	mmHg	Pa	
Lab1	Xx/zz	mg/dL	mg/L	
Lab2	Zz/xx	mmol/L		mg/dL



ADaM

PARAM	AVAL
Height (cm)	xx
Systolic (mmHg)	xx
Lab1 (mg/dL)	xx.x
Lab2 (mmol/L)	xx.x



Report

Table XYZ – Summary of xyz

	X	Y	Z
Height (cm)	xx	xx	xx
Systolic (mmHg)	xx	xx	xx
Lab1 (mg/dL)	xx.x	xx.x	xx.x
Lab2 (mmol/L)	xx.x	xx.x	xx.x

**PMDA
request SI
Units**

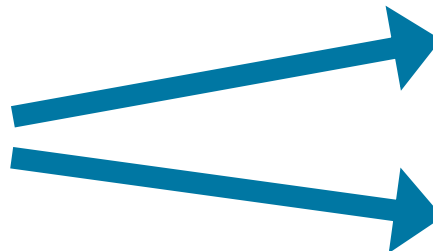
**FDA request US
conventional
Units**

Our Solution for 'Standardized' Units in SDTM

SDTM LB

TEST	ORRESU	STRESU
Lab1	Xx/zz	mg/dL
Lab2	Zz/xx	mmol/L

PMDA
request SI
Units



FDA request US
conventional
Units

SDTM 'ZL'

TEST	ORRESU	STRESU
Lab1	Xx/zz	mg/L
Lab2	Zz/xx	mmol/L

SDTM 'XL'

TEST	ORRESU	STRESU
Lab1	Xx/zz	mg/dL
Lab2	Zz/xx	mg/dL

Our Solution for 'Standardized' Units in SDTM

- Duplicate data in additional sponsor defined domains
 - LB holds data in reported standardized units
 - XL/ZL in regulatory required standardized units
- This support simple traceability from SDTM, ADaM to CTR
 - But give redundant data in domains
 - Preferable compared to having SI unit in –STRESU and values in –STRESN and then have the conventional units and values in supplemental qualifiers
- Currently accepted by FDA and PMDA
 - But must be confirmed for each submission (not a general acceptance)

Event Adjudication Results

Event Adjudication - Requirements

- Event Adjudication – what is it?
- FDA Technical Conformance Guide
 - Clearly identify investigator reported data from adjudication data
- Different types of event data
 - Different diseases with different details
- No existing standards or best practices
 - SDTMIG does not offer explicit guidance



Considerations

- Novo Nordisk has implemented a sponsor defined stand-alone domain based on the SDTM Findings About domain
- Flexible structure that can accommodate various types of adjudication data
- Only the final agreed assessments from the two independent adjudicators are submitted in our SDTM data set

Example of Sample Reported Data

One record per adjudication outcome per result, per date and subject as required by FDA

--LNKID	--REFID	--TESTCD	--TEST	--OBJ	--ORRES	--EVAL	--EVALID	--DTC
14	1	SOURADEV	Source of adjudicated event	ACS	INVESTIGATOR REPORTED	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	
14	1	ADJOUT	Adjudication outcome	ACS	ACUTE MYOCARDIAL INFARCTION	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	
14	1	ADJDATE	Evaluated Event Onset date	ACS	2017-01-01	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	
14	1	MICLASS	Classification of Myocardial Infarction	ACS	ST ELEVATION MYOCARDIAL INFARCTION	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	
14	1	MITYPE	Type of Myocardial Infarction	ACS	TYPE 1 MYOCARDIAL INFARCTION	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	
14	1	CONFVT	Confirmation of event	ACS	FULL DOCUMENTATION AVAILABLE	ADJUDICATION COMMITTEE	PRIMARY ADJUDICATION	

Associated Person (AP) Domain

AP Domain Challenges

CDISC AP IG

Lack of use case in IG related to pregnancy

Data

Differentiate between mothers, foetus and infant data in source

Pregnancy Trial

These are initial learning from latest experiences from implementation

Annotation

One CRF to 7 SDTM domain mapping and relationship among them

System

APID and SUPPQUAL implementation

● External

● Internal

Example on Complexity

APDD=Associated Persons Death Details

APQS=Associated Persons Questionnaires

**APRP=Associated Persons
Reproductive System Findings**

APCE=Associated Persons Clinical Events

APFACE=Associated Persons Findings About Clinical Events

APDM=Associated Persons Demographics

APVS=Associated Persons Vital Signs

CEREFID

FAREFID

VSREFID

QSREFID

RPREFI

D

APID

APID

API

D API

D **AP**

PID A

PID

NOT SUBMITTED

BRTHTDT

C RPDTC

RPORRES when RPTTESTCD=GDUSCAN

RPORRES when RPTTESTCD=LIVEBRTH

DDORRES when DDTESTCD=TMINFDH

DTHDTC

DDDTc

PERINDTH in SQAPDD

RELREC: APDD, AE

RELREC: APDD, APAE

RELREC; APCE, APAE

FAORRES when FATESTCD=CONGANOM

VSORRES when VSTESTCD=UMBCOPH

Summary and Recommendations

Summary

- CDISC standards are open for interpretation
- Regulatory guidance's are not always aligned with CDISC standards

Recommendations

- Using CDISC data standards should not be an implementation issue for pharmaceutical companies requiring individual case-by-case agreements at pre-NDA or e-data consultancy meetings
- CDISC standards should be specific and less open for interpretation
- Regulatory agencies should increase engagement in data standards development to ensure standards fulfil review needs
 - Limit data standard requirements in technical conformance guides

Questions for you!

- What do you see as the biggest challenge preparing for global submissions?
 - Have you experienced contradicting requirements from FDA/PMDA/CDISC?
 - Do you prepare a common or separate submission packages?
- What is the biggest struggle for you with all these changing and new requirements and guidelines?
 - How do you evaluate the impact?
 - How fast do you adapt to the changes?



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