

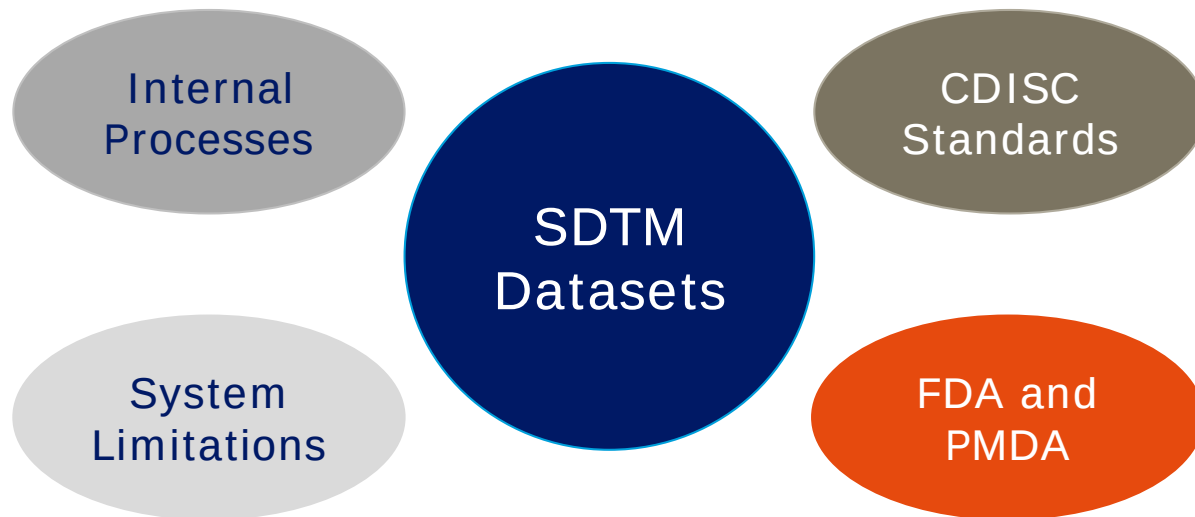


Top Five Challenges in Complying with CDISC Standards

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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

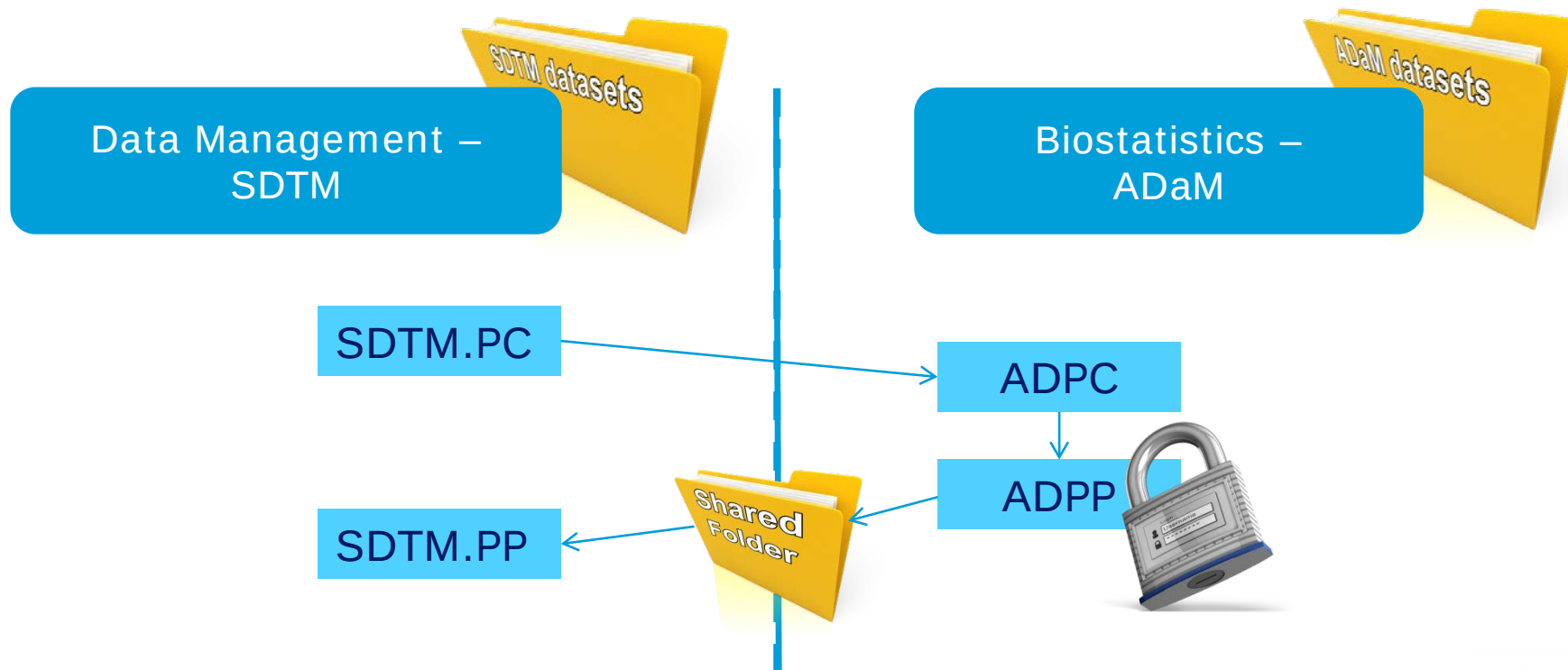
Datasets



Different
requirements

Regulatory Authorities

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

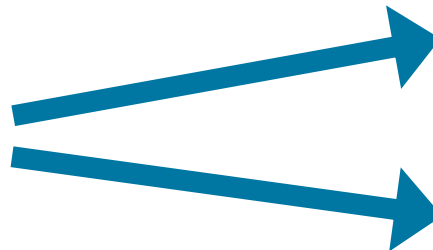
FDA request US
conventional
Units

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	CONFVET	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

Congenital anomalies

If a congenital anomaly is observed at ultrasound during pregnancy and reported as an SAE, but not confirmed after birth, the AE description should be updated with "No adverse effect" or "No adverse drug effect".

1. Seq. No.

[Seq. No.]

2. Fetus/Infant ID

Note: Fetus/Infant ID will be populated only after submitting the form

[Fetus/Infant ID]

3. Fetus/Infant No.

(Note: In case of single fetus/infant use fetus/infant No. 1. In case of multiple fetus/infant use 1, 2 and so forth, e.g. the fetus/infant ID will be 101001X1 and 101001X2. Use the same fetus/infant ID consistently throughout the trial.)

[Fetus/Infant No.]

4. Date of delivery

[Date of delivery]

5. Gestational age at time of delivery

(Completed weeks and days, based on ultra sound scan or based on investigator judgement)

[Gestational age]

6. Did the pregnancy result in a live birth?

(Live Birth)

[Live Birth]

7. Congenital anomalies

If yes,
[1] report the congenital anomalies as serious adverse events in the new-born infant(s)
[2] fill out Maternal Form 2 and Fetal Form
[3] fill out Congenital Anomaly Event Adjudication Form
[4] Congenital anomalies

Infant Health Status

8. Umbilical cord pH

[pH]

CEREFID

FAREFID

VSREFID

QSREFID

RPREFID

APID

APID

APID

APID

APID

NOT SUBMITTED

BRTHDTC

RPDTC

RPORRES when RPTTESTCD=GWUSCAN

RPORRES when RPTTESTCD=GDUSCAN

RPORRES when RPTTESTCD=LIVEBIRTH

DDORRES when DDTESTCD=TMINFDH

DTHDTC

DDDTTC

PERINDTH in SQAPDD

RELREC: APDD, AE

RELREC: APDD, 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

Thank you for your attention 😊



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