Fake it till you make it with Global SDTM Laboratory Submissions

Éanna Kiely

ClinBuild

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Agenda

- Problem Statement
- Multiple Lab Units Representation Team
- Options and Considerations
  - Options inside/extend/outside SDTM/IG
  - Considerations and Open Questions
- Next Steps

Problem Statement: FDA Flexibility on Standard Unit Types

- The FDA Position on Use of SI Units for Lab Tests 2013-10-23 states that the FDA aims to transition to generally accepting SI units:
  - *CDER and CBER are evaluating an approach to transition to general acceptance of laboratory data in clinical trials that are measured and reported in Système International (SI) units instead of U.S. Conventional units.*
- While acknowledging the challenges of adopting SI units.
  - *... the majority of U.S. healthcare providers are trained using U.S. conventional units. Lab results reported using U.S. conventional units often convey the most clinical meaning to U.S. healthcare providers, including CDER and CBER reviewers.*

Problem Statement (contd.)

- To facilitate this transition conversions of some SI units to US conventional units may be required.
  - *... conversion of certain lab test results to U.S. conventional units may be a necessary interim step toward a transition to full SI unit reporting.*
- Sponsors are encouraged to check if conversions are required.
  - *...sponsors are strongly encouraged to solicit input from review divisions as early in the development cycle as possible to minimize the potential for conversion needs during NDA/BLA review.*
- Based on this position paper we can assume that the FDA will accept SI units unless US conventional units are requested.

PMDA Recommends SI Units

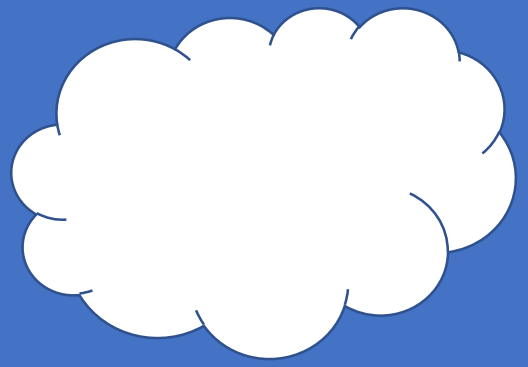
- The PMDA recommends that SI units are used in the --STRESC/N variables in Notification on Practical Operations 0124-4 2019-01-24 section 3.1.c.
  - 3. Details on the electronic data to be submitted
    - (1) Electronic data that conforms to the CDISC standards
      - c. Controlled Terminology, code lists, and units that are recommended
  - *The use of SI units is recommended.*
- An exception is made for mmHg for diastolic and systolic blood pressure according to FAQs on Electronic Study Data Submission (translation 2019-04) Q4-8
  - *...it is acceptable to store only the data in mmHg in the SDTM dataset without storing the converted data in SI unit for test results (e.g. blood pressure) collected in mmHg as conventional unit.*

SDTM/IG on Standard Unit Types

- No information is provided in the SDTM/IG on the standard unit type to use e.g. US conventional units vs SI units.
- In SDTM 1.7 the --STRESC variable is described as “copied or derived from --ORRES in a standard format or standard unit” and --STRESU is the standardized units.
- In SDTMIG 3.3 section 4.5.1.1 Original and Standardized Results it states:
  - *The variable, --STRESC, is populated either by the conversion of values in --ORRES to values with standard units.*

Multiple Lab Units Representation Team

- Cross Team Collaboration between the SDS and Lab CT Team
  - https://wiki.cdisc.org/display/CTC/SDS+Lab+Units+Subteam
- Aims to provide options for submitting multiple standard unit types to regulators.
- Options and Considerations have been developed and reviewed by the Lab CT and SDS Team
- Will be presented to the CDISC Global Governance Group (GGG) for a consultation on the 22NOV2019 & 13DEC2019
- Outcome of GGG consultation will be added to the FDA/CDISC Technical Meeting for FDA review and possible implementation



Blue Sky Thinking

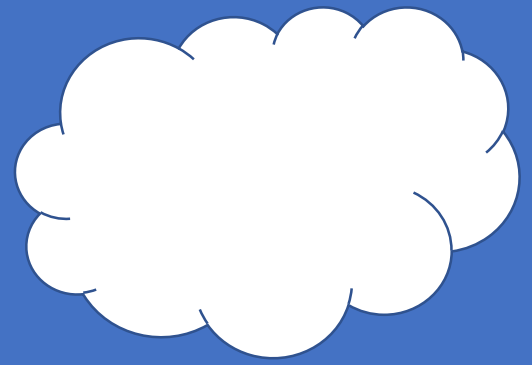


Table of Options

#	Option	Pros	Cons	Status
1	FDA Manages Multiple Units Representation In-House	Reduce sponsor resources No SDTM update required	Increase FDA resources	Possible longer term solution Outside of CDISC's remit
2	Sponsor Submits Two LB Type Datasets	FDA can compare two datasets Easier to manage for global submissions and on a company standards level No SDTM update	Increase sponsor resources	Most in use currently Some FDA reviewers have expressed a preference for this
3	Sponsor Submits One LB Dataset with SI and US Conventional Units as Requested	FDA only receives the requested units. No SDTM update	Increase sponsor resources Difficult to manage for global submissions/ sponsor standards level	Difficult to manage without a formal communication document. Should only be recommended in conjunction with Consideration 2
4	Sponsor Uses LBSCAT to Group the Different Unit Types	FDA can compare within same dataset No SDTM update	LBSCAT cannot be used	LBSCAT is needed for other purposes
5	Represent Additional Units in Supplemental Variables / SUPPLB	In use by the PMDA No SDTM update	Increase sponsor resources Large SUPPLB file	The Lab CT team recommended not to include this option. The SDS team proposed to keep it in.
6	Additional Variable to Indicate Unit Type	Allows for additional unit types FDA can compare within same dataset	Increase sponsor resources Potential for unit mixup? Requires update to SDTM	
7	Add Result Variables for SI and US Conventional Units similar to LBSTRESC/N etc.	FDA can compare within same dataset	Increase sponsor resources Does not allow for additional unit types Requires update to SDTM	Certain sponsors favors this approach
8	New LB Domain Model	Separate out normal ranges into a separate table, support multiple standard units	Could be a very large update with impact on multiple findings domains	May work with CDISC 2.0
9	LAB Model	Existing standard No SDTM update	Standard may not be widely adopted and require training. In XML format not .xpt	Addresses multiple lab unit representation/reported results.

Table of Considerations / Open Questions

#	Consideration	Comments	Status
1	Define-XML Stores the SI and US Conventional Units and Conversions	Moves information to Define-XML.	
2	PhUSE Lab Units team's Test Unit Plan	Improves communication between FDA and sponsor	Needed for Option 3
3	Unified Code for Units of Measure (UCUM)	Could aid the conversions	Will require implementation Lab team is already incorporating UCUM Does not address representing multiple standard lab unit types
4	CDISC/Lab Consortium/Other Lab Units Conversion Team	Could be a very useful resource but would require a large amount of resources to implement and maintain.	

#	Open Question	Comments
1	Is it possible to find metrics on the FDA requests for US conventional units?	Sponsors have submitted SI datasets only to be requested to provide US conventional units during review Can the FDA provide this information or should CDISC/PhUSE do a survey?
2	Should the sponsor proactively provide SI and US conventional units to the FDA?	It takes a lot of effort to maintain lab test in both SI and US conventional units
3	How does this impact SEND / ADaM?	Can be discussed at the GGG

Options Within SDTM/IG (1.7/3.3)

Option 2: Sponsor Submits Two LB Like Datasets

- The sponsor submits two LB type datasets e.g. LB (SI) and XB (US conventional units)

LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESU
SODIUM	Sodium	136	mmol/L	136	mmol/L
GLUC	Glucose	3.9	mmol/L	3.9	mmol/L
XBTESTCD	**XBTEST**	**XBORRES**	**XBORRESU**	**XBSTRESC**	**XBSTRESU**
SODIUM	Sodium	136	mmol/L	136	mEq/L
GLUC	Glucose	3.9	mmol/L	70.2702703	mg/dL

Pros	Cons
Allows FDA reviewers to compare different standard units types in separate datasets	* Increases use of sponsor resources maintaining multiple lab test results, units, normal ranges, etc.
Easier to manage on global/standards level since LB is single source of truth in SI and is used for PMDA. XB is a view in US conventional units based on LB.	* US conventional units may not be requested for all submissions or requested consistently
Within the current SDTM	Increases the submission package file size

Option 3: Sponsor Submits One LB Dataset with both SI and US Conventional Units as Requested

- The sponsor submits one LB dataset that has individual tests in SI or US conventional units according to the requests made by the review division*
- Row 1 is in US conventional units and row 2 is in SI units.

LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESU
SODIUM	Sodium	136	mmol/L	136	mEq/L
GLUC	Glucose	3.9	mmol/L	3.9	mmol/L

Pros	Cons
Reduced file size compared to option 2	Same as option 2: managing multiple standard unit types
The FDA reviewers only see the requested units	Difficult to manage for global submissions and on a sponsor standards level.
Within the current SDTM	Units requests may change per submission

* Requires a communication document between FDA and the sponsor see Consideration 2: PhUSE Lab Unit team's Test Unit Plan

Option 5: Represent Additional Units in Supplemental Variables / SUPPLB

- The sponsor adds SI to the parent domain and the US conventional units to SUPPLB

LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESU
SODIUM	Sodium	136	mmol/L	136	mmol/L
GLUC	Glucose	3.9	mmol/L	3.9	mmol/L

IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
LBSEQ	1	LBUSRESC	Character Result/Finding in USC Format	136
LBSEQ	1	LBUSRESN	Numeric Result/Finding in USC Units	136
LBSEQ	1	LBUSRESU	US Conventional Units	mEq/L

Pros	Cons
Within the current SDTM	Same as option 2: managing multiple standard unit types
Recommended by the PMDA FAQ Q4-8	Would create large SUPPLB with (~8) US conventional unit variables: LBSTRESC, LBSTRESN, LBSTRESU, LBSTNRLO, LBSTNRHI, LBSTNRC, LBSTREFC, LBSTREFN

Option 5: SUPPLB in line with the PMDA on Domestic/International Conventional and SI units

- FAQs on Electronic Study Data Submission (Excerpt)
  - Provisional Translation (as of April 2019)
- 4. Questions on CDISC-conformant electronic study data
  - Q4-8
- *... it is acceptable to store only the data in mmHg in the SDTM dataset without storing the converted data in SI unit for test results (e.g. blood pressure) collected in mmHg as conventional unit.*
- Examples of how to store data in conventional units and SI units into SDTM
  - [Example 1] When values in domestically conventional units and internationally conventional units both exist: Store values in domestically conventional units under “--ORRES” and values in internationally conventional units under “SUPP--.” Store SI values under “--STRESC” (or “--STRESN” if necessary).
- [Example 2] When central clinical laboratory values and in-hospital clinical laboratory values both exist: Store central values under “--ORRES” and in-hospital values under “SUPP--.” Store SI values under “--STRESC” (or “--STRESN” if necessary) after unifying them into a single unit per parameter and then converting.
- https://www.pmda.go.jp/files/000229469.pdf

Options that Extend SDTM/IG (1.7/3.3)

Option 6: Additional Variable to Indicate Standard Unit Type

- New variable added to LB (Findings domains?) to show which standard unit type is used e.g. LBSTRSUT (Standard Unit Type)

LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESU	LBSTRSUT
SODIUM	Sodium	136	mmol/L	136	mmol/L	SI
GLUC	Glucose	3.9	mmol/L	3.9	mmol/L	SI
SODIUM	Sodium	136	mmol/L	136	mEq/L	US CONVENTIONAL
GLUC	Glucose	3.9	mmol/L	70.2702703	mg/dL	US CONVENTIONAL
CKMB	Creatine Kinase MB	17	IU/L	17	IU/L	OTHER

Pros	Cons
Allows for additional unit types (e.g. SI units, US conventional, Chinese conventional or other)	Conventions will be needed: if test/method/specimen use the same unit in both SI and US conventional units are two rows added or is “BOTH” added to LBSTRSUT?
Compare different units in single dataset	Managing multiple standard unit types and increased file size
	Requires an update to the current SDTM

Option 7: Add Result Variables for SI and US Conventional Units similar to LBSTRESC/N etc.

- Create specific standard variables for SI and US Conventional Units.
- Either these or the LBSTRESC/N etc. could be used.

				Character Result/Finding in SI Format	SI Units	Character Result/Finding in USC Format	US Conventional Units
LBTESTCD	**LBTEST**	**LBORRES**	**LBORRESU**	**LBSIRESC**	**LBSIRESU**	**LBUSRESC**	**LBUSRESU**
SODIUM	Sodium	136	mmol/L	136	mmol/L	136	mEq/L
GLUC	Glucose	3.9	mmol/L	3.9	mmol/L	70.27027	mg/dL

Pros	Cons
Allows FDA reviewers to compare different units in single dataset	Requires an update to the current SDTM with the addition of ~16 new variables
In use is some sponsors operational standard	What happens to the current LBSTRESC/N type variables?
	Does not allow for additional unit types like option 6 can.

* Very similar to Option 9: Lab Model

Option Outside of the SDTM/IG

Option 9: LAB Model

- The CDISC LAB Model 1.0.1 (2003-03-02) section 3.4.13 **Base Result** provides an exchange standard for collected/reported, SI and US conventional units.
  - *It is recognized that results may be preferred in more than one unit system...*

Pros	Cons
Within the current ~SDTM (CDISC Standards)	Provides the information in an XML format not .xpt
Existing standard could be incorporated into the SDTM table structure as in Option 7	Standard may not be widely adopted in sponsors SDTM teams (widely in large laboratories ~60%)
Reported results are *"are the results reported to the investigator sites"* unlike LBORRESU	Would require roll out and training
Available in multiple transmission formats: Excel, XML, pipe delimited. Could also be updated to .xpt	Naming conventions that do not conform to SDTM (variables do not contain domain code).

Option 9: LAB Model Base Result Variables

FIELD NAME	SAS VARIABLE NAME	EXPLANATION
Base Test Level		
Lab Test ID	LBTESTCD	The ID of the test performed as defined by the data provider.
Lab Test Name	LBTEST	The name of the test performed as defined by the data provider.
Base Result Level		
Reported Text Result	RPTRESC	Reported text result by laboratory.
Reported Units	RPTU	Reported result units by laboratory.
Conventional Text Result	CNVRESC	Conventional text result at laboratory.
Conventional Units	CNVU	Conventional result units at laboratory.
SI Text Result	SIRESC	SI text result at laboratory.
SI Units	SIU	SI result units at laboratory.

Example variables from Lab1-0-1-BaseDataFields.xls

Considerations / Open Questions

Consideration 2: PhUSE Lab Units Team's Test Unit Plan

- The PhUSE Lab Units team created the Test Unit Plan (TUP). This is a communicative document between the FDA and sponsor to agree on a submission level, the units to be used for each lab test/specimen/method.
- The TUP is an extension of the Study Data Standardization Plan.
- If Option 3 (One LB Dataset with both SI and US Conventional Units) is to be used the TUP (or other communicative document) should be used.

- Should the PhUSE Lab Units team restart to work on the TUP?

Open Questions

- What is the impact of the FDA requesting both SI and US conventional units?
  - How many requests do sponsors receive and what is the delays (workload) to review timelines
  - Should CDISC/PhUSE/FDA? send a survey / do a workshop?
- Should the sponsor maintain both SI and US conventional units?

- How does this impact SEND/ADaM?

Next Steps

Next Steps

- The options will be presented to the GGG for consultation (22NOV2019 & 13DEC2019) before being presented to the FDA at the FDA/CDISC Technical Meeting
- If an option inside the current SDTM/IG is selected it could be rolled out as an update to the FDA Technical Conformance Guide (TCG) (~March 2020).
- If an option that is an extension to the SDTM/IG is selected it is most likely to be added to SDTM/IG (2.1?/3.5) (~November 2022/3)
- A mix of both types could be used with a short term solution that is within the SDTM/IG before a longer term solution that updates the SDTM/IG is implemented.

Project Timelines & Next Steps

Task	Date
Project Initiation	14DEC2018
Project Approval Sent/Received	05MAR2019/10SEP2019
Lab Team Reviews	Multiple, final 13NOV2019
SDS Team Review	Multiple, final 04NOV2019
GGG 1	Scheduled 22NOV2019
GGG 2	Scheduled 13DEC2019
FDA CDISC Technical Meeting	? 2020
Outcome Driven by FDA	? 2020
Within SDTM/IG	March/November 2020
Extends SDTM/IG	SDTM/IG (2.1?/3.5) November 2022/3

Lab Units Representation Team Members

Name	Role	Team	Company	Contact
Éanna Kiely	Project Lead/SDTM Expert	SDS	ClinBuild	eanna.kiely@clinbuild.com
Erin Muhlbradt	Lab Expert	Lab	NCI-EVS	erin.muhlbradt@nih.gov
Alan Meier	SDTM Programing Expert	SDS	Cytel	alan.meier@cytel.com
You?		ADaM /SEND	Your company?	

Questions

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Thank you!

eanna.kiely@clinbuild.com

Conversions from SI units to US conventional units taken from the AMA (American Medical Association) Manual of Style SI Conversion Calculator
http://www.amamanualofstyle.com/page/si-conversion-calculator

Back Up Slides

Laboratory Data Process