

Three magnifying glasses with dark handles and light-colored lenses are arranged on the left side of the slide. One is at the top left, one is in the middle left, and one is at the bottom left.

Conformance Rules – how to follow and comply when specified by multiple sources?

PhUSE EU Connect 2018

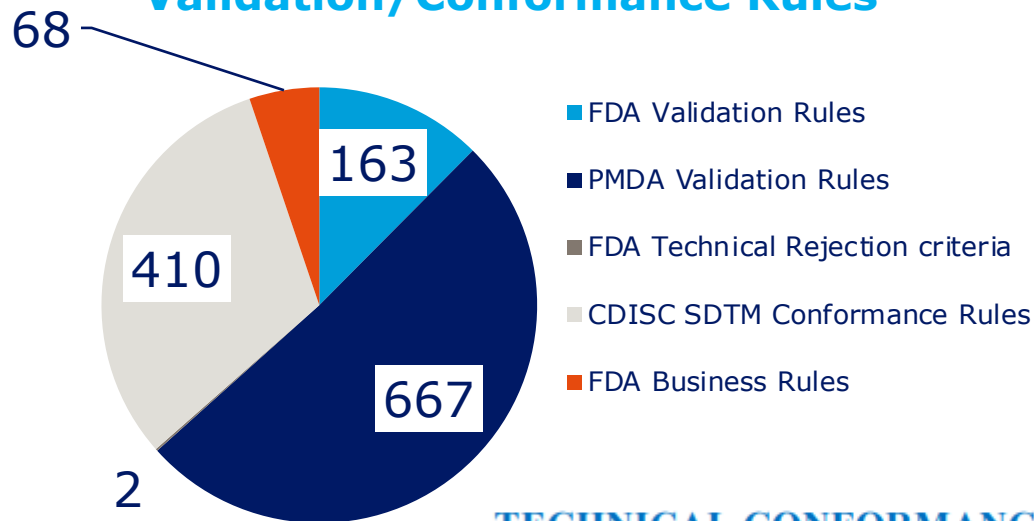
Francis Dsa

Agenda

- Different sources and specifications
- Our process and approach
- Scenario 1
- Scenario 2
- Global Standard Team vs Trial vs Project
- Conclusion

Different sources and specifications

Validation/Conformance Rules



FDA Validation Rules	163
PMDA Validation Rules	667
SDTM Rules	326
Define-XML Rules	105
ADaM Rules	236
FDA Technical Rejection criteria	2
CDISC SDTM Conformance Rules	410
Programmable	356
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Clinical and Nonclinical	33
Clinical Only	21
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TECHNICAL CONFORMANCE GUIDE

October 2017 March 2018

April 27, 2015

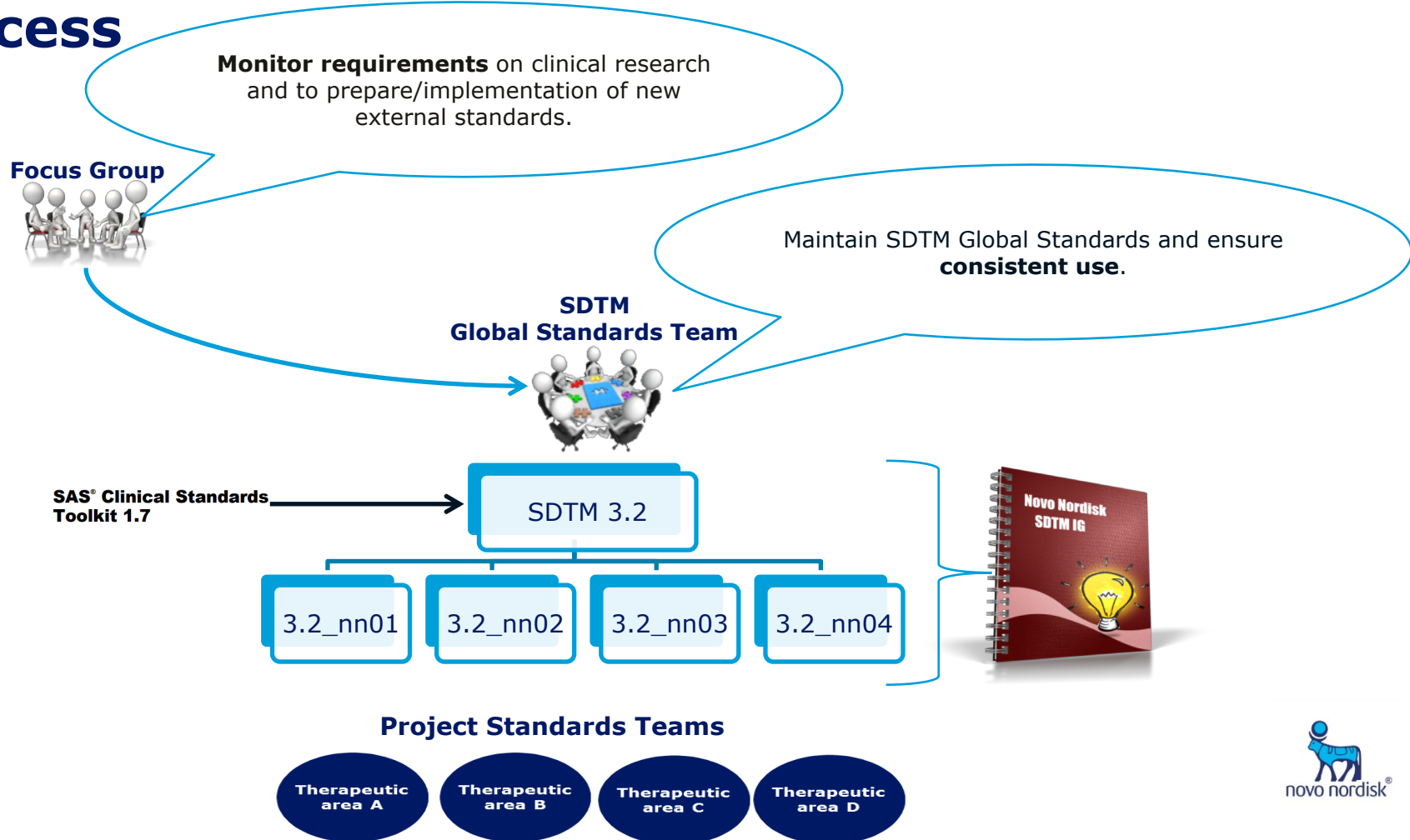
FAQs on Electronic Study Data Submission (Excerpt)

Challenges

There are **no mappings between the different sources** of Validation/Conformance rules and the numbers do not match in the tool provided by vendors.

There are also a number of **conflicting rules** between the different sources that is a **challenge for sponsors as well as vendors**.

Process



Our approach

Handling of Conflicting Rules

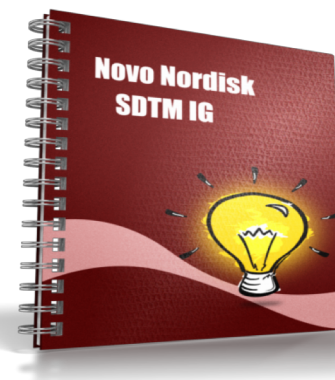
At Novo Nordisk, we have created a document called Novo Nordisk SDTMIG where we document the decisions taken on **conflicting rules and clarify** how they should be implemented consistently. This is controlled and maintained by a SDTM Global Standards Team. This team also monitors and reviews new standards and raises clarifying questions and comments to regulatory agencies and standards organisations.

Novo Nordisk SDTMIG:

Novo Nordisk Interpretation of the CDISC Study Data Tabulation Model Implementation Guide (NN SDTMIG) v1.3 Based on SDTMIG v3.2

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Our approach

Conformance Checks

Based on the submission **learnings from our peers**, we now run conformance checks with **multiple configuration files** in **different versions of Pinnacle 21** for FDA and PMDA.



- Structural checks on define.xml are done by **SAS® Clinical Standards Toolkit**.
- In addition to SDTM data, conformance/consistency checks are conducted on Define.xml as well as between SDTM and ADaM.

Our approach

Documenting in SDRG

Within our Study Data Reviewer's Guide (SDRG) template, we have added sub-sections for each set of conformance checks.

4.2 Issues Summary

Pinnacle 21 ID	Publisher	Datas	Diagnostic Message	Severity	Data Issue	Programming Issue	Explanation
SD1077	FDAC021	All	FDA Expected variable ELEMENT not found	Warning			For eg : All records in the CE domain have the ETCD value 'UNPLAN'. According to the Study Data Tabulation Model Implementation Guide, if ETCD has a value of <<Element Name>> then ELEMENT should be Null. This is not an issue and data is tabulated as per SDTM IG 3.1.3; If ETCD has a value of —UNPLAN then ELEMENT should be Null.

4.2.1 FDA (Pinnacle 21) Issues & Justification SDTM

Dataset	Pinnacle 21 Validator ID	Publisher ID	Diagnostic Message	Severity	Count	Explanation
AE						

4.2.2 FDA (Pinnacle 21) Issues & Justification Define.xml

Dataset	Pinnacle 21 Validator ID	Publisher ID	Diagnostic Message	Severity	Count	Explanation
DEFINE						

4.2.3 PMDA (Pinnacle 21) Issues & Justification SDTM

Dataset	Pinnacle 21 Validator ID	Publisher ID (Optional)	Diagnostic Message	Severity	Count	Explanation
AE						

4.2.4 PMDA (Pinnacle 21) Issues & Justification Define.xml

Dataset	Pinnacle 21 Validator ID	Publisher ID (Optional)	Diagnostic Message	Severity	Count	Explanation
DEFINE						



**Pinnacle 21
Justification database**
This is how we manage
common issues

Scenario 1

“ARM/ARMCD and ACTARM/ACTARMCD”

CDISC

- ARM/ARMCD and ACTARM/ACTARMCD are **required** variables
- Required variables must always be included in the dataset and **cannot be null** for any record

FDA

- **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**.

Our approach

Handling of Conflicting Rules

We have decided to follow the CDISC guidelines (we also prefer non-blank values). This is **documented** in our Novo Nordisk Interpretation of SDTM IG.

Screenshot from Novo Nordisk SDTMIG:

Demographics (DM)

ACTARMCD/ACTARM

All subjects, including screening failures, run-in failures or other subjects not exposed to study treatment, must have ACTARMCD/ACTARM populated.

CRF input	ACTARMCD	ACTARM
Screening failure	SCRNFAIL	Screening failure
Run-in failure, i.e. not fulfilling Randomisation criteria	NOTASSGN	Not assigned
Randomised, but has not received trial product	NOTTRT	Not treated

Table 11 Assigning ACTARM and ACTARMCD



Scenario 2

“ELEMENT and ETCD”

CDER Common Data Standards Issues Document
(Version 1.1/December 2011)

- Based on 2011 [CDER Common Data Standards Issues Document](#), FDA desired **inclusion of** ELEMENT and ETCD (element code) to help reviewers understand timing of events.
- However, in all later FDA published [Study Data Technical Conformance Guide](#) up to V4.1 published in 2018, **only EPOCH** is required.

STUDY DATA
TECHNICAL CONFORMANCE GUIDE

FDA **validator rules version 1.2 published in December 2017** still mentions that variables requested by FDA in Policy documents should be included in the dataset, e.g. EPOCH **and ELEMENT**.

Our approach

Handling of Conflicting Rules

We are following the FDA guidelines for last 6 years . This is **documented** in our Novo Nordisk Interpretation of SDTM IG.

SDTM Global Standards team is currently discussing with our stakeholders “Biostatistics” and “Risk Based Monitoring” about removal of ETCD and ELEMENT. **When** do we **remove** it?

Screenshot from Novo Nordisk SDTMIG:

Appendix L EPOCH, ELEMENT and ETCD

EPOCH, ELEMENT and ETCD are added to all subject level datasets, as suggested in *CDER*

Common Data Standards Issues (see [12]). The variables have been added to the NN SDTM Master Model.

EG	EPOCH	Epoch
EG	EGDTC	Date/Time of ECG
EG	EGDY	Study Day of ECG
EG	EGTPT	Planned Time Point Name
EG	EGTPNUM	Planned Time Point Number
EG	EGELTM	Planned Elapsed Time from Time Point Ref
EG	EGPTREF	Time Point Reference
EG	EGRFTDTC	Date/Time of Reference Time Point
EG	ETCD	Element Code
EG	ELEMENT	Description of Element



Figure 23 EPOCH, ETCD, ELEMENT in NN SDTM Master Model

Our approach

Documenting in SDRG

Within our Study Data Reviewer's Guide (SDRG) template, we have explained it.

Study Data Reviewer's Guide
Trial ID:

Date:
Version:

3 September 2018
1.0

Status:
Page:

Final
49 of 73

Novo Nordisk

4.2.3 PMDA Issues & Justification

Dataset	Pinnacle 21 Validator ID	Diagnostic Message	Severity	Count	Explanation
AE	SD0058	Variable appears in dataset, but is not in SDTM model	Error	2	ELEMENT and ETCD are sponsor-specific variables. The variables are added as suggested in CDER Common Data Standards Issues Document (Version 1.1/December 2011) in the General Considerations section

Global Standard Team vs Trial vs Project

Change process

Global Standard Team and requirements:

- Requirements and conformance rules are moving targets. It evolves over time based on the past learning.
- **Versioning** is the way to get around the new requirements and rules.
- **Training** and guidance document(NN Interpretation of SDTMIG) is the key so we implement the requirements the same way.

Trial team and the project team:

- The trial likes to use the latest model and the tool versions.
- However if the trial is one of the last one for the submission package then they would like to follow the **rest** of the trials to enable **pooling** for Submission.

Meeting with agency is fruitful. We send representative both from Project and the Standard Team to clarify/confirm implementation of requirements.

Conclusion

- Multiple requirements for conformance rules exist from different regulatory agencies and tools versions.
- It is important to run all of the current available conformance rules to ensure that all issues are managed and addressed.
- All identified issues and justifications are described in respective subsections in the SDRG which enables global submissions.

Thank you

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