PhUSE 2018

Paper DS05

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

Francis Dsa, Novo Nordisk A/S, Copenhagen, Denmark

ABSTRACT /INTRODUCTION

At Novo Nordisk, we have worked on producing high quality SDTM datasets that follow conformance and validation rules published by CDISC, FDA and PMDA. In FDA Study Data Technical Conformance Guide, the types of study data validation rules are:

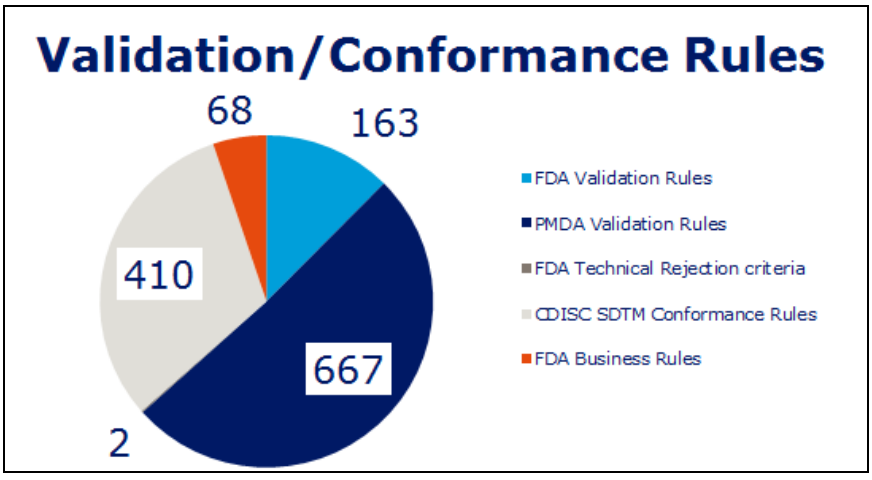
1. Standards Development Organizations (e.g., CDISC) provide rules that assess conformance to its published standards (See www.CDISC.org).
2. FDA eCTD Technical Rejection Criteria for Study Data that assess conformance to the standards listed in the Catalog.
3. FDA Business and Validator rules to assess that the data support regulatory review and analysis.

We do multiple checks for data issues and conformance rules during the data collection and SDTM generation process. This includes data cleaning checks, SDTM generation checks, Define.xml checks, and multiple Pinnacle 21 configuration file checks. This presentation will share some of our approach on how we interpret and implement multiple conformance rules in various systems/tools and documentation of such in SDRG.

DIFFERENT SOURCES AND SPECIFICATIONS

The different sources are listed below:

PMDA Validation Rules		667
	SDTM Rules	326
	Define-XML Rules	105
	ADaM Rules	236
FDA Validation Rules		163
FDA Technical Rejection criteria		4
CDISC SDTM Conformance Rules		410
	Programmable	356
	non-Programmable	54
FDA Business Rules		68
	Clinical and Nonclinical	33
	Clinical Only	21
	Nonclinical Only	14



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.

Example of conflict in rules:
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.

NOVO NORDISK'S APPROACH

HANDLING OF CONFLICTING RULES

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

Below is an example from Novo Nordisk SDTMIG:

Demographics (DM)

ACTARMCD/ACTARM

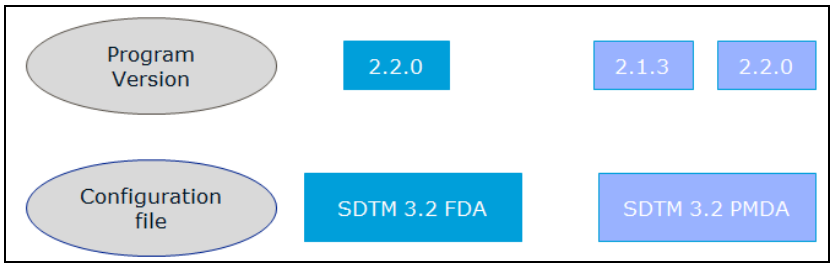
All subjects, including screening failures, run-in failures or other subjects not exposed to study treatment, must have ACTARMCD/ACTARM populated.

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

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.



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

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

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						

CONCLUSION AND LEARNINGS

- 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 sub-sections in the SDRG which enables global submissions.

CONTACT INFORMATION

Francis Dsa
Principal Standards Specialist
Novo Nordisk A/S
Vandtårnsvej 114
2860 Søborg
Work Phone: +45 3079 0799
Email: frd@novonordisk.com