FDA Validation Rules

New regulatory requirements and how OpenCDISC can help

Sergiy Sirichenko
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PINNACLE 21

Presenter – Sergiy Sirichenko

- Co-founder of OpenCDISC
- FDA Data Fitness Analyst
- The person who answers all your questions on OpenCDISC Forum

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Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the Food and Drug Administration.

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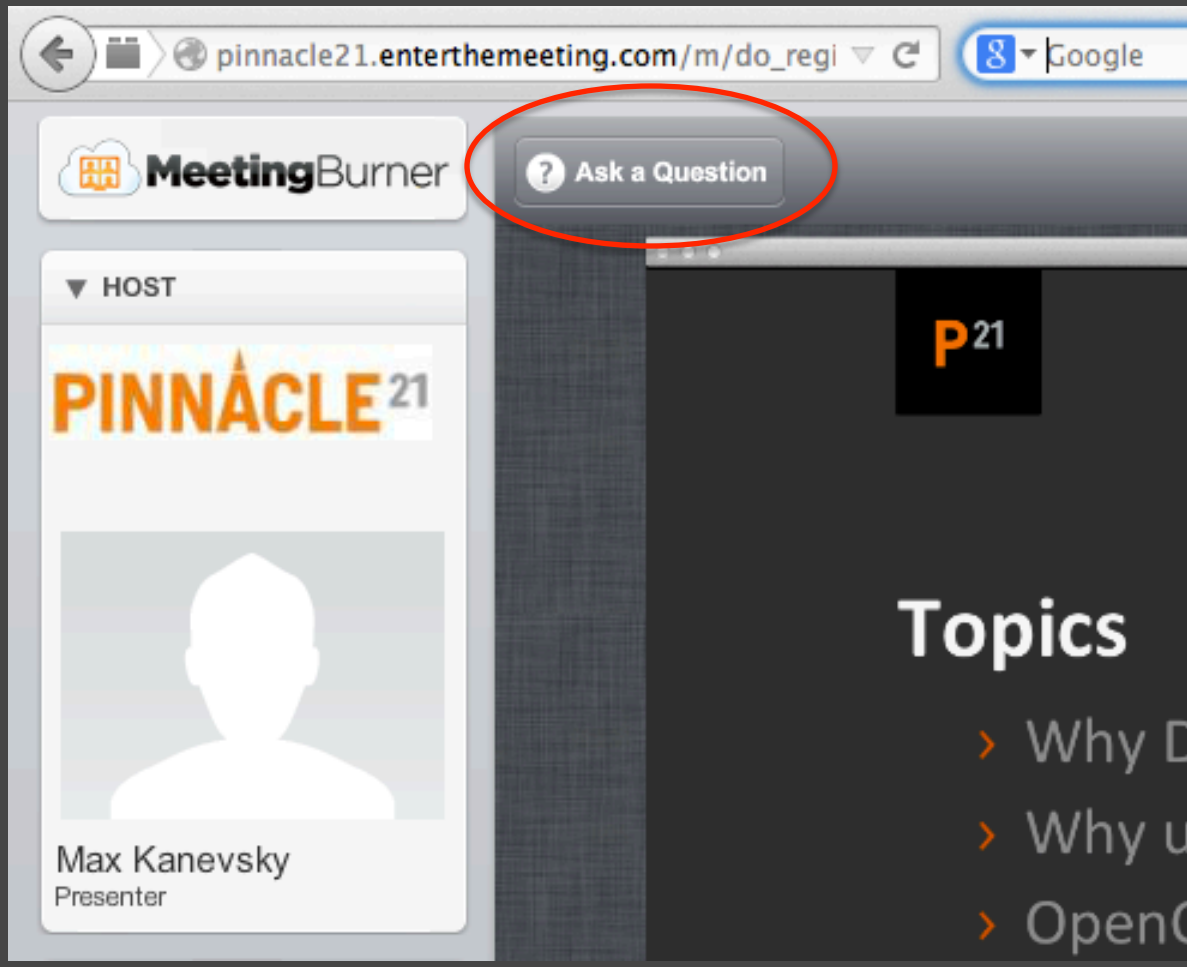
Topics

- New FDA guidance
- Conformance vs. Quality
- Purpose, structure and content
- OpenCDISC Community 2.0
- Comparison FDA rules to OpenCDISC 1.5

Q & A

- At any time during the webinar, click the "Ask a Question" button
- Questions will be answered at the end



FDA Regulations

- New law – FDASIA, Title XI Section 1136
  - Requires usage of standards

- Guidance documents
  - Provide details about the use of specific standard, versions, etc.
  - Can be updated regularly

“Binding” documents

- Guidance on Submissions in Electronic Format
- Guidance on Electronic Submissions: Standardized Study Data
- Study Data Technical Conformance Guide and Data Standards Catalog
- FDA Specific SDTM Validation Rules

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FDA business rules for SDTM data

- Federal Registry/ Vol.79, No. 223
- FDA-2014-N-1840
  - http://www.gpo.gov/fdsys/pkg/FR-2014-11-19/pdf/2014-27384.pdf
- Location:
  - http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
- For further information contact:
  - edata@fda.hhs.gov

Notice

Electronic Study Data Submission; Data Standards; Validation Rules for Study Data Tabulation Model Formatted Studies; Availability

A Notice by the Food and Drug Administration on 11/19/2014

ACTION Notice.

SUMMARY The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) is announcing the availability of a document entitled "Validation Rules for Study Data Tabulation Model (SDTM) Formatted Studies." CDER is making this document available to improve the standardization and quality of clinical data submitted to CDER, as well as to improve the predictability of data quality and usefulness.

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Publication Date:
Wednesday, November 19, 2014
Agencies:

For Industry

Data Standards

- Study Data Standards
- Study Data Standards for Regulatory Submissions Position Statement
- Position on Use of SI Units for Lab Tests
- Data Standards Research Areas and Collaborations
- Janus Clinical Trials Repository (CTR) Project
- Study Design Standard
- Study Participation Standard
- Subject Data Standard

Study Data Standards Resources

Sign up for email updates.

CBER/CDER Study Data Standards for Regulatory Submissions Position Statement

CDER/CBER Position on Use of SI Units for Lab Tests

1. The Agency can process, review, and archive electronic submissions that provide study data using the standards, formats, and terminologies specified in the **Data Standards Catalog** (Click here)

2. **For CDER and CBER: Draft Guidance for Industry - Providing Regulatory Submissions in Electronic Format — Standardized Study Data.** Click here to access the full guidance document. The guidance, when final, will describe how FDA plans to implement the requirements for the electronic submission of standardized study data.

3. ***Draft* Study Data Technical Conformance Guide.** Click here to access the Guide. The Guide, when final, will provide technical specifications, recommendations, and general considerations on how to submit standardized electronic study data.

The following resources remain available until the publication of the final Study Data Technical Conformance Guide:
Study Data Specifications (Click here)

4. Study Data Validation Rules

4a. FDA Specific SEND Validation Rules
The following document outlines FDA's validation rules for SEND formatted non-clinical studies. Nonclinical Validator Specifications (XLS)

4b. FDA Specific SDTM Validation Rules
The following document outlines FDA's validation rules for SDTM formatted clinical studies. SDTM Validator Specification (XLS)

4c. Externally (to-FDA) Defined Validation Rules
When not defined by FDA, the following available resources are used.

The OpenCDISC Validator and the study validation rules are available for download as standard configuration files.

FDA definition for Data Quality

- *"both compliant and useful"*
- *"Compliant means the data conform to the applicable and required data standards.*
- *Useful means that the data can support the intended use (i.e., regulatory review and analysis)"*

*Source: FDA Study Data Technical Conformance Guide

“Intended Use”

- There are many different users with different requirements
  - Medical Reviewer
  - Statistical Reviewer
  - Clinical Trial Repository (JANUS)
  - Integrated Data Analysis
  - Data Storage System
  - Analysis Tools

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"Data validation relies on a set of validation rules that are used to verify that the data conform to a minimum set of quality standards, and the data validation process can identify data issues early in the review that may adversely affect the use of the data"

"Sponsors should validate their study data before submission using the published validation rules and either correct any validation errors or explain in the Data Guide why certain validation errors could not be corrected."

*Source: FDA Study Data Technical Conformance Guide

Purpose of FDA validation rules

- Communicate with industry on specific FDA requirements and enforce them for submission data
- Based on existing Guidance and Standards
  - ICH, Technical Conformance Guide, SDTM, etc.
- Or other FDA specific needs

- Help industry with implementation of high quality data
  - Sponsors are responsible for quality of submission data
  - Data Quality is not limited to a set of any business rules
  - Published FDA data rules are required, but not completely sufficient. They never will be “final”.

FDA rules are specific to FDA needs

- CDISC manages standards compliance
  - ADaM, Define.xml and SDTM
- FDA enhances compliance rules with submission specific business rules
- PMDA might have their own set of business rules

The first release of FDA rules

- Based on OpenCDISC checks
- Introduces additional rules
- Changes in Severity, Message and Description
- Updates planned 1-2 per year
- Comments/feedback can be submitted to FDA eData team

Rules document structure

- Excel format
  - “machine readable”
  - Most commonly used for metadata
  - Easy to use
- Columns
  - FDA Rule ID
  - Message, Description
  - Domains, Severity
  - Standards

FDA Rule ID	MESSAGE	DESCRIPTION	DOMAINS	SEVERITY	3.1.1	3.1.2	3.1.3 (3.1.2 A1
FDAC001	Missing DM dataset	Demographics (DM) dataset must be included in every submission	DM	Error	X	X	X
FDAC002	Missing TS dataset	Trial Summary (TS) dataset must be included in every submission	TS	Error	X	X	X
FDAC003	Missing DS dataset	Disposition (DS) dataset should be included in every submission	DS	Warning	X	X	X
FDAC004	Missing EX dataset	Exposure (EX) dataset should be included in every submission	EX	Warning	X	X	X
FDAC005	Missing AE dataset	Adverse Events (AE) dataset should be included in every submission	AE	Warning	X	X	X
FDAC006	Missing LB dataset	Lab Test Results (LB) dataset should be included in every submission	LB	Warning	X	X	X
FDAC007	Missing VS dataset	Vital Signs (VS) dataset should be included in every submission	VS	Warning	X	X	X
FDAC008	Missing SE dataset	Subject Elements (SE) dataset should be included in every submission	SE	Warning	X	X	X
FDAC009	Missing TA dataset	Trial Arms (TA) dataset should be included in every submission	TA	Warning	X	X	X
FDAC010	Missing TE dataset	Trial Elements (TE) dataset should be included in every submission	TE	Warning	X	X	X
FDAC012	Missing MB dataset, when MS dataset is present	Microbiology Specimen (MB) dataset should be included, when a Microbiology Susceptibility Test (MS) dataset is present	MB	Warning	X	X	X
FDAC013	Incompatible data source	Domain table must have a valid format (e.g., SAS transport (XPORT) v.5 or text-delimited)	ALL	Error	X	X	X
FDAC014	No records in data source	Domain table should have at least one record	ALL	Error	X	X	X
FDAC016	Dataset is greater than 1 GB in size	Large datasets should be split into smaller datasets no larger than 1 GB in size.	ALL	Warning	X	X	X
FDAC017	SDTM Required variable not found	Variables described in SDTM as Required must be included in the dataset	ALL	Error	X	X	X
FDAC018	NULL value in variable marked as Required	Required variables (where Core attribute is 'Req') cannot be NULL for any records	ALL	Error	X	X	X
FDAC020	SDTM Expected variable not found	Variables described in SDTM as Expected should be included in the dataset	ALL	Warning	X	X	X
FDAC021	FDA Expected variable not found	Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH and ELEMENT	ALL	Warning	X	X	X
FDAC022	No Treatment Emergent info for Adverse Event	According to FDA expectations, a treatment-emergent flag should be included in SUPPAE according to SDTM IG v3.1.2 #8.4.3	SUPPAE	Warning	X	X	X
FDAC023	Dataset is not present in define.xml	Datasets included in study data must be described in the data definition document (define.xml)	ALL	Error	X	X	X
FDAC024	Domain referenced in define.xml but dataset is missing	Domains referenced in data definition document (define.xml) should be included in the submission	ALL	Warning	X	X	X
FDAC025	Variable in define.xml is not present in the dataset	Variables listed in the data definition document (define.xml) should be included in the dataset	ALL	Warning	X	X	X
FDAC026	Variable in dataset is not present in define.xml	Variables included in the dataset must be described in the data definition document (define.xml)	ALL	Error	X	X	X
FDAC027	Variable appears in dataset, but is not in SDTM model	Only variables listed in SDTM model should appear in a dataset. New sponsor defined variables must not be added, and existing variables must not be renamed or modified	ALL	Error	X	X	X
FDAC028	Variable prohibited for use in SDTM	Variables described in IG as inappropriate for usage must be not included in the dataset	ALL	Error	X	X	X
FDAC029	Variable which can be used only in SEND	Variables designed only for SEND pre-clinical studies must be not included in the SDTM dataset	ALL	Error	X	X	X
FDAC030	Variable not recommended for use	Variables described in IG as not recommended for usage should be not included in the dataset	ALL	Warning	X	X	X
	Model permissible variable added into	SDTM model variable may be added into standard domains according its domain general class, if there are no restrictions on their usage					

Covered Standards

- SDTM IG 3.1.1
- SDTM IG 3.1.2
- SDTM IG 3.1.3 (3.1.2 Amend 1)
  - Amend 1 is a temporary patch for outdated SDTM IG 3.1.2 standard rather than a separate SDTM version
- SDTM IG 3.2 is still under FDA testing
- SEND 3.0 will be published as a separate document with consistent FDA Rule IDs

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Severity

- Error is a business rule which must always be true
  - Data consistency issues
  - Missing Seriousness Criteria for SAE
  - Missing domains (DM, TS, etc.)
- Warning is a business rule with potential exceptions
  - Extensible Controlled Terminology – new terms may be added if they are not synonyms or subset of standard terms

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- Notice is similar to Warning with difference in probability of exception
  - Warning – it may be an exception, explanation is needed
  - Notice – exception is expected, confirmation of validity is needed
- Notices were retired due to confusion within the industry
  - many users just ignored them

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OpenCDISC Editions

- Community
  - Free open source desktop toolkit
  - www.opencdisc.org
- Enterprise
  - Commercial web-based corporate/project level solution
  - Powers FDA DataFit
  - www.pinnacle21.net
- On-Demand
  - Project level edition of Enterprise

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OpenCDISC Community 2.0

- Release date is December 11, 2014
- Includes 4 tools
  - Validator (CDISC standard + FDA rules)
  - Define.xml Tool (v2.0, Excel based)
  - Data Converter (SAS XPT, Excel, CSV, Dataset-XML)
  - ClinicalTrials.gov Miner (for Clinical team)
- Automatic updates

WEBINAR:

Introducing OpenCDISC Community 2.0

Session 1

- Date: Dec 11, 2014
- Time: 2:00 pm EST
- (11:00 am PST)
- Length: 1 hour

Session 2

- Date: Dec 16, 2014
- Time: 9:00 am EST
- (15:00 CET)
- Length: 1 hour

FDA validation configurations

- FDA configs replace SDTM configs
- config-sdtm-3.1.1 -> SDTM 3.1.1 (FDA)
- config-sdtm-3.1.2 -> SDTM 3.1.2 (FDA)
- config-sdtm-3.1.3 -> SDTM 3.1.3 (FDA)
- config-sdtm-3.2 -> SDTM 3.2
  - Aligned with other FDA configs
- config-send-3.0 -> SEND 3.0
  - Aligned with other FDA configs
  - Will be adjusted and renamed to SEND 3.0 (FDA) after FDA official release

New attribute – Publisher ID

- Introducing "Publisher" for configs and "Publisher ID" for rules
  - In addition to OpenCDISC Rule ID
  - Represents authoring organization
    - FDA, PMDA, CDISC, etc.
  - OpenCDISC ID is same across all configs
  - Usage of OpenCDISC ID and Publisher ID can be interchangeable depending on requirements

How to use OpenCDISC Community 2.0 to comply with FDA validation rules

Comparison of FDA validation rules vs. OpenCDISC Validator 1.5

New checks

- 39 total
- All around Trial Summary data
- Note: some rules will require users to set up proprietary dictionaries due to licensing issues

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Removed checks

- Due to inconsistency between SDTM and FDA requirements
  - SD0094: DSCAT is not 'DISPOSITION EVENT', when EPOCH is provided
  - SD1105: EPOCH variable is populated, when DSCAT='PROTOCOL MILESTONE‘
- Some checks were “missed” and may be added back later
  - SD1094: Incorrect value for --ENDY variable

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Collapsed CT checks

- OpenCDISC Controlled Terminology validation is metadata driven
- ~350 CTxxxx checks were collapsed into just 6 business rules
  - CT2001-CT2006
  - FDAC340-FDAC345
- Driven by terminology assignments in configs similar to Define.xml

Changes in Severity

- OpenCDISC Notice is retired, with a few exceptions
- All extensible codelists checks increased to Warning from Notice
- Severity for ~40 rules increased to Error
  - No records in data source
  - AE start date is after the latest Disposition date
  - Value for --DECOD is in incorrect case
  - See detailed report on www.pinnacle21.net/blog

Changes in Message/Description

- Refining rule descriptions (58) and messages (6)
  - SD1077/FDAC021
    - Old: *"Variables requested by FDA in CDER Common Data Issues document should be included in the dataset"*
    - New: *"Variables requested by FDA in policy documents should be included in the dataset. E.g., EPOCH and ELEMENT"*
  - Algorithm is still the same
  - See "CHANGELOG.txt" for details

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Summary

- FDA-2014-N-1840 is a new guidance document to clarify regulatory expectations for SDTM data
- OpenCDISC Community 2.0 provides executable FDA validation rules for submission data
- Sponsors should catch and fix data issues as early as possible
- OpenCDISC is just a tool, process is also important

Please Submit Feedback

- FDA
  - edata@fda.hhs.gov
- OpenCDISC
  - www.opencdisc.org/forum
  - sergiy@opencdisc.org

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Resources

- Federal Registry, FDA-2014-N-1840
  www.federalregister.gov/articles/2014/11/19/2014-27384/electronic-study-data-submission-data-standards-validation-rules-for-study-data-tabulation-model
- FDA Study Data Standards Resources & Validation Rules
  http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
- FDA Position Statement on CDISC Standards
  http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm368613.htm
- FDA Guidance for Providing Regulatory Submissions in Electronic Standardized Format
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf
- FDA Study Data Technical Conformance Guide
  http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf
- FDA Study Data Specifications v2.0
  http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Questions

Sergiy Sirichenko
ssirichenko@pinnacle21.net