10 Years of FDA Study Data Technical Conformance Guide. Have you missed any FDA Data Submission Requirements?

Presented by Angelo Tinazzi, Senior Director, Cytel Inc.

Meet the Speaker

Angelo Tinazzi

Title: Senior Director - Standards, Systems, CDISC Consulting, Statistical Programming, Project Based Service

Organization: Cytel Inc.

Angelo Tinazzi is **Senior Director, Statistical Programming**, Project Based Service (PBS), **responsible for Clinical Data Standards and Data Submission**, working at Cytel since 2012. Angelo has about **30 years' of experience** working with different organizations in Italy, UK, and Switzerland.

In his role at Cytel, **Angelo lead data standards initiatives** as well as **advising clients** and internal teams on **best strategies for implementing data standards** for **submission with health authorities such as FDA, PMDA, and NMPA**. He also **supports applications development** and **automation initiatives** for the Cytel PBS Statistical Programming Group.

Angelo is a **CDISC ADaM Authorized Instructor** and **member of the CDISC European Coordinating Committee** where he is also **leading Italian speaking User Network**.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *I have no real or apparent conflicts of interest to report.*
- ***Focus is on clinical data standards e.g., no SEND***

Agenda

1. TCG 2014-2024 “Timelapse”
2. 2021-March 2024 Key Update
3. Conclusions

TCG 2014-2024 “Timelapse”

FDA Data Technical Specifications Guidance

TCG Content

Timelapse

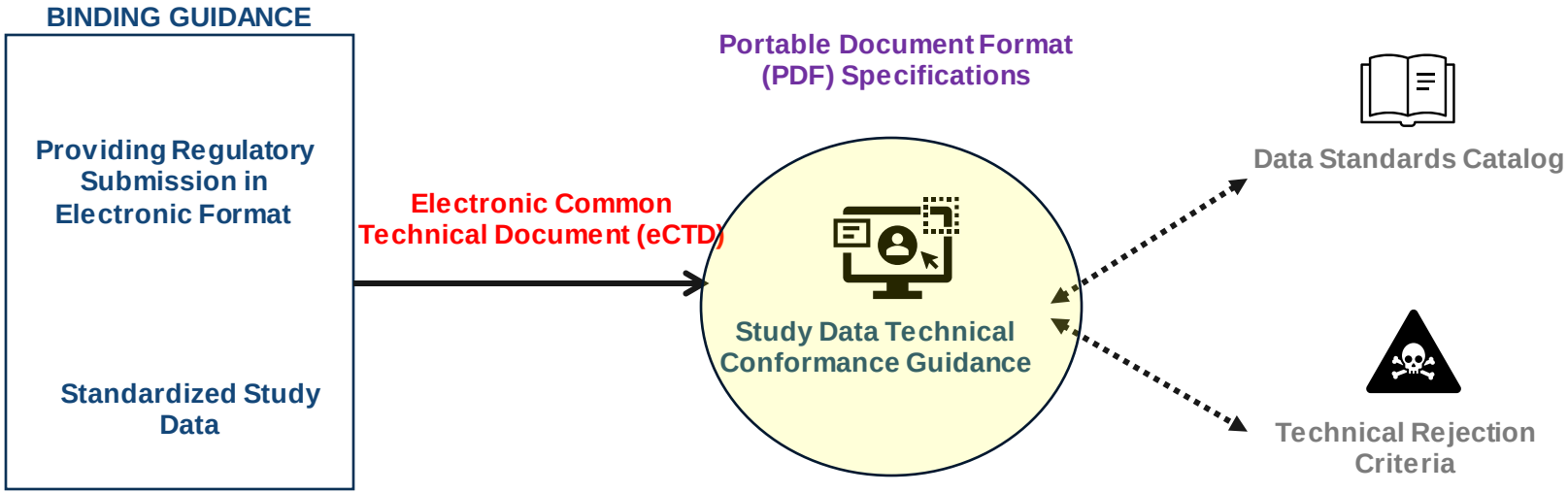
A long time ago in a galaxy far, far away...

TCG 2014-2024 “Timelapse”

Are we going into the Future?

AI 2041, Kai-Fu Lee – Chen Qiufan

FDA Data Technical Specifications Guidance



Raising Awareness for Additional FDA Data Standards Submission Recommendations
A Tinazzi, CDISC EU 2023

TCG 2014-2024 Timelapse – TCG Content

- Background and Purpose
- Relationship to other Documents

- Planning (SDSP)
- Reviewer Guide, nsdrg, csdrg, adrg

- PDF, XML
- SAS XPT Key Requirements, Use of "Special Chars"

- CDSIC, General Consideration for SEND, SDTM, ADaM
- Specific FDA Requirements for SEND, SDTM, ADaM

- Supported CDISC TAUGs
- List of FDA Technical Specification Documents

- CDISC-CT Controlled Terminology FDA Spec Req e.g., use of OTHER
- Medical Dictionary e.g.., MedDRA and support for other Terminologies

- eCTD
- Sample Submission

- Type of Study Data Validation Rules
- Traceability when Converting Legacy Datasets

- Interoperability, Trial Summary (TS) FDA Required Parameters
- Additional Documents Evaluated By FDA
- Example of Study Data Folder Structure
- Technical Rejection Criteria, Examples of simplified ts.xpt

TCG 2014-2024 Timelapse

2014 Public Review Comment

Version 1 – January 2014

PUBLIC SUBMISSION

Comment from Jozef Aerts

Posted by the **Food and Drug Administration** on May 15, 2014

„… Version 5, is an open file format … Data can be translated to and from XPORT to other commonly used formats without the use of programs from SAS Institute or any specific vendor“.

I wonder whether any programmer at the FDA ever tried this without using SAS. The specification as being published by SAS („TS-140“) is completely insufficient to accomplish this task.

…..

So, it is high time to switch to a real open standard, like XML.

https://www.regulations.gov/comment/FDA-2014-D-0092-0008

TCG 2014-2024 Timelapse

JSON is one way towards 2041

Thursday April 25th

11:00 - 12:30
Session 6B: Pivoting JSON

Silvia Faini, Cytel
Europa 6

11:00 - 11:30
Key Takeaways from the Dataset JSON Pilot
Sam Hume, CDISC

11:30 - 12:00
The Need for Speed: Why Dataset JSON is so Important
Jozef Aerts, XML4Pharma

12:00 - 12:30
ARD Generator : A SAS Tool for Metadata Driven Analysis Using the Analysis Standard Result
Karl Wallendszus, Oxford Population Health

TCG 2014-2024 Timelapse

Version 2.0
1st official version

Version 3.0
Increased Dataset Size (5GB)

Version 4.2
Added TS Appendix
Multiple Enrolment

Version 4.7.2
Rejection Criteria and simplified TS incorporated

Version 5.7
March-2024

MED-RT
~~NDF-RT~~

Jan 2014 — 2015 — 2016 — 2017 — 2018 — 2019 — 2020 — 2021 — 2022 — 2023 — 2024

Dec 2014

Various Alignments With Evolving Standards - Overall 34 Releases

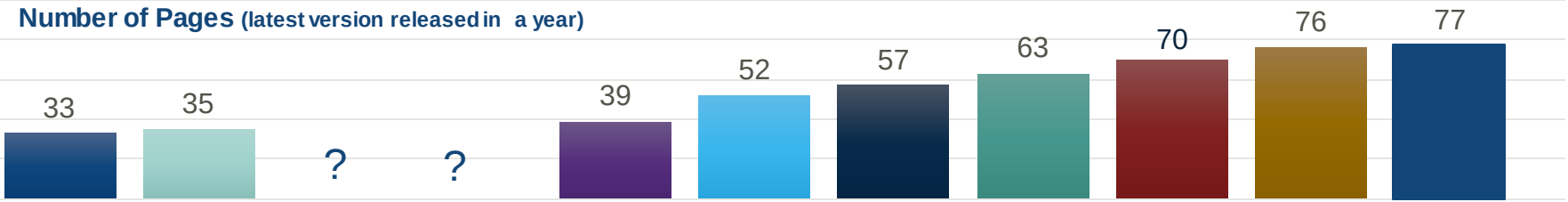
Version 1
Public Review

Version 4.1
PHUSE SDSP

Version 4.9
Added Section "List of Technical Specifications Documents"

Version 5.1
Requirement for dual LB unit

Number of Pages (latest version released in a year)



2021-March 2024 Key Update

Handling of Subjects with Multiple Enrollments in SDTM (2018)

Immunogenicity

Custom LC Domain

SV domain Requirements

More FDA Technical Specification Guidance

2021-March 2024 Key Update

Handling of subjects with multiple enrollments in SDTM [TCG October 2018]

- Custom domain with a similar structure to DM
- Not yet a domain name reserved in the CDISC-CT e.g., DC

Working Progress CDISC wiki, SDTM Ig 4.0?

- Same USUBJID within same application- Regular concern from FDA interactions

The Facts in the Case of Subject X
Cytel Blog, February 2023

2021-March 2024 Key Update

Immunogenicity – Not all "labs" are LB [TCG March 2023]

- Added IS to section 4.1.1.3 "SDTM Domain Specifications"
- **Regular concern from FDA interaction e.g., CBER**

The Laboratory Test Results (LB) domain should only contain laboratory test data such as hematology, clinical chemistry and urinalysis. This domain should not include microbiology or immunogenicity data, which are stored in separate domains, MB or IS, respectively

LB, MB & IS Domain Scope Changes for the SDTM IG v3.4 and Impact on Controlled Terminology
CDISC Webinar, June 2023

2021-March 2024 Key Update
Custom LC domain [TCG June 2023]

- Named LC with TCG March 2024 (will it be added to CDISC –CT?)
- Copy of LB with Standard Results Variables in US conventional unit
- **Clear requirements from previous FDA meetings e.g., end Phase-2 meeting November 2021**

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials

2021-March 2024 Key Update

Custom LC domain [TCG June 2023]

- Named LC with TCG March 2024 (will it be added to CDISC –CT?)
- Copy of LB with Standard Results Variables in US conventional unit
- Clear requirements from previous FDA meetings e.g., end Phase-2 meeting November 2021
- **Which parameters could be impacted? Mainly 'mol', but not only…..**

Parameter	SI Unit	US Conv Unit
Bicarbonate Chloride Cortisol Sodium	mmol/L	mEq/L
Bilirubin Urate	umol/L	mg/dL
Calcium Cholesterol (any) Glucose Phosphate Triglycerides Urea Nitrogen	mmol/L	mg/dL

Parameter	SI Unit	US Conv Unit
Creatinine Cl.	mL/s/m2	mL/min
Magnesium	mmol/L	mg/L
Albumin Protein	g/L	g/dL
WBC differentials	10^9/L	10^3/uL
Hematocrit	L/L	%

2021-March 2024 Key Update
Custom LC domain [TCG June 2023]

Submitting Laboratory Data in Multiple Standard Units
Éanna Kiely, Alexion/AZ – Thursday 14:30-15:00 (Session 7C)

2021-March 2024 Key Update
SV domain requirements [TCG October 2023]

*It is the current preference of the Agency that for all clinical studies, subject visit data for scheduled (**whether or not they occurred**), and unscheduled visits be submitted in one single dataset structured as the current CDISC Subject Visits (SV) domain* [Section 4.1.1.3]

Stop using VE !!! This was an initial recommendation from CDISC "Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic", 2020

2021-March 2024 Key Update

SV domain requirements [TCG October 2023]

It is also Agency preference that three non-standard variables (NSVs) for missed visits, ***--REASOC*** *(Reason for Occur Value),* ***--EPCHGI*** *(Epi/Pandemic Related Change Indicator), and* ***--CNTMOD*** *(Contact Mode), outlined in the CDISC property "Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic"* ***be included within the SV*** *domain and* ***not within the supplemental SUPPSV*** *domain or in other SDTM datasets*

Standard Variables now available with SDTM Version 2.0 / IG 3.4

2021-March 2024 Key Update

More FDA Technical Specification Guidance [TCG December 2023]

- Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessments (COA) Using Item Response Theory
- Submitting Patient-Reported Outcome (PRO) Data in Cancer Clinical Trials
- **More Additional Technical Specification Guidance Previously Released**

Understand PFDD Guidance Series and Impact on Data Submission
Jintao Shi, Boehringer Ingelheim – Wednesday 11:30-12:00 (Session 2C)

Raising Awareness for Additional FDA Data Standards Submission Recommendations
A Tinazzi, CDISC EU 2023

Data Standards Conformance Checks for Vaccine Trials
Estella Sani, GSK – Wednesday 13:00-14:00 (Poster)

2021-March 2024 Key Update

Various Update [TCG March 2024]

- Section 4.1.4.3 (Naming Conventions in SDTM and SEND) To the extent possible, **naming for drugs and metabolites** should be **consistent** across different clinical and nonclinical studies and across domains within a study. This includes, but it is not limited to, the **TS, EX, PC, and PP domains**.
- Appendix B **New TSPARMCD** (Required)
  - ONGOSIND (Ongoing Study Indicator)
- Appendix D **New Additional Documents Evaluated By FDA**
  - CDISC ADaM popPK Implementation Guide-v1.0

2021-March 2024 Key Update
Others Update Worth to Mention

- Handling QS questions "**Logically Skipped**" [October 2017]
- If **you need to split a file that exceeds file size limits**, you should submit the smaller split files in the 'split' sub-folder in addition to the larger non-split file in the original data folder. **There is no need for a second define.xml file to be submitted within the split subfolder**. [March 2022]
- For the **PC and PP** domains, **when referencing timepoints like visits**, **consistency with other domains is crucial**. **PCLLOQ** should now also include a lower limit of quantitation. [October 2023]

Conclusions

Conclusions

- FDA TCG more than **doubled** in 10 Years, so the FDA expectations
- For certain topics, certain **FDA divisions expect you to act quickly**
- Suggest to **update ongoing studies** whenever doable
- High risk of **violating standards e.g., SDTM**

Thank You!

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cdisc

References

1	"Raising Awareness for Additional FDA Data Standards Submission Recommendations" (A. Tinazzi, CDISC EU Interchange, April 2023) https://www.cytel.com/blog/therapeutic-area-user-guidance-the-hidden-gems
2	"DC - SDTM Section 3.2.2(new) Demographics for Multiple Participations" (Draft CDISC Wiki) https://wiki.cdisc.org/pages/viewpage.action?spaceKey=SDD&title=DC+-+SDTM+Section+3.2.2%28new%29+Demographics+for+Multiple+Participations
3	"The Facts in the Case of Subject X" (A. Tinazzi, Cytel Blog, February 2023) https://www.cytel.com/blog/the-facts-in-the-case-of-subject-x
4	"LB, MB & IS Domain Scope Changes for the SDTMIG v3.4 and Impact on Controlled Terminology" (CDISC Webinar, 2023) https://www.cdisc.org/events/webinar/lb-mb-domain-scope-changes-sdtmig-v3-4-and-impact-controlled-terminology
5	"Watch out, the FDA Rejection Criteria are Now in Place" (A. Tinazzi, Cytel Blog, January 2022) https://www.cytel.com/blog/watch-out-the-fda-rejection-criteria-are-now-in-place

Abstract

It was January 2014 the FDA issued first version of its Technical Conformance Guide for public review. The final version (2.0) was then released December 2014, a pivotal moment occurred when the FDA stopped the clock, providing sponsors with a two-year window adapting their methods of creating clinical dataset packages. This adaptation was necessary to comply with the FDA's required data standards for any study commencing after December 16th, 2016.

Fast forward through approximately 30 versions, with latest version 5.6 released last December, the guidance has undergone significant changes. These changes include more pages, from 38 to 88, but also substantial alterations in content, so that the requirements for sponsors set forth by the FDA have been consequently impacted.

Between 2021 and 2023, the FDA released 13 versions. If you find yourself fatigued from spotting differences, fear not! This presentation will simplify things, highlighting most substantial changes / new requirements.