FDA-CTP AND CDISC DEVELOP TOBACCO DATA STANDARDS TO ACHIEVE EFFICIENCIES FOR ALL STAKEHOLDERS

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CENTER FOR TOBACCO PRODUCTS

THE TOBACCO CONTROL ACT BECAME LAW ON JUNE 22, 2009

- To regulate tobacco products and ensure that FDA had the authority to address issues of concern, especially tobacco dependence and the use of tobacco by young people – Congress passed the Tobacco Control Act

- FDA's goal is to reduce the harm from all regulated tobacco products across the entire U.S. population:
  - Reducing the number of people who start using tobacco products
  - Encouraging more people to stop using these products
  - Reducing the adverse health impact for those who continue to use these products

THE TOBACCO CONTROL ACT'S AUTHORITIES

The Tobacco Control Act amended the Federal Food, Drug, and Cosmetic Act (FD&C) to provide FDA authority for:

- Premarket review of new and modified risk tobacco products
- Postmarket surveillance
- Product standards
- Testing and reporting of ingredients
- Reporting of harmful and potentially harmful constituents
- Adverse event reporting
- New warning labels
- Advertising and promotion restrictions
- User fees

FDA'S TOBACCO REGULATORY AUTHORITIES

In general, FDA's tobacco regulatory authorities do not extend to:

- Setting tax rates for tobacco products
- Regulating therapeutic products, such as those marketed to treat tobacco dependence (regulated by other parts of FDA)
- Setting clean indoor air policies
- Regulating tobacco growing
- Requiring the reduction of nicotine yields to zero
- Providing cessation services
- Banning all cigarettes, smokeless tobacco products, little cigars, other cigars, pipe tobacco, or roll-your-own tobacco products
- Changing the minimum age of sale for tobacco products

ABOUT CTP

- Vision Statement

  To make tobacco-related death and disease part of America's past, not America's future and, by doing so, ensure a healthier life for every family

- Mission Statement

  To protect Americans from tobacco-related death and disease by regulating the manufacture, distribution, and marketing of tobacco products and by educating the public, especially young people, about tobacco products and the dangers their use poses to themselves and others

- Key Strategic Priorities
  - Product Standards
  - Comprehensive FDA Nicotine Regulatory Policy
  - Pre & Post-Market Controls; Regulations & Product Reviews
  - Compliance and Enforcement
  - Public Education

CTP AND DATA STANDARDS

- CTP Data Standards Strategy 2021-2025
  - Purpose: Strategies for the development and dissemination of data standards to better support the programs of CTP through better, more meaningful data
  - Areas that are included
    - **Electronic Data Exchange Standards**
    - **Premarket and Postmarket Review**
    - Quality
    - Policy
    - Planning and Governance

CTP AND DATA STANDARDS

- Electronic Data Exchange Standards
  - Technical Specification Document
    - Electronic Submissions through CTP Portal or Electronic Submission Gateway (ESG)
    - Utilize the Appendix A example for Organization of Folders and Documents
    - Electronic submissions must be packaged using eSubmitter
    - Data files such as Excel (xls, xlsx) or sas transport files (xpt or xport) should not be converted to a PDF
  - Best Practices
    - Obtain an Industry Account Manager account for CTP Portal
    - Submit applications electronically utilizing eSubmitter and CTP Portal
    - Follow recommendations in the Technical Specification Document
  - Future State
    - Functionality and/or tools to assist submitters in organizing and packaging submissions
    - Validations built into tools to assist submitters in correcting issues prior to submission

CTP AND DATA STANDARDS

- Premarket and Postmarket Review
  - OMB Forms
    - Required forms for Premarket Tobacco Product Application and Substantial Equivalence Applications were released when the rules were published 10/4/2021 and the supporting OMB Forms were published in January 2022
    - **Form 4057b: Product Application Grouping Spreadsheet** is utilized to standardize product information contained within a submission until such time that a data standard is available
    - Similar forms are forthcoming for Substantial Equivalence and Exemption applications
  - Best Practices
    - Always obtain the most recent form from FDA.gov. Do not re-use previously downloaded forms
    - Submit 4057b with all PMTA applications
    - Complete the required fields defined by product category and sub-category
    - Do NOT change form fields, data drop downs or file format. Submit the file as an .xlsx
  - Future State
    - Evaluating development of tools to assist submitters in populating form prior to submission

CTP AND DATA STANDARDS

- CTP DATA STANDARDS GRANT PROGRAM
  - The Grant program has published for public participation under RFA-FD-22-002
  - This is a Cooperative Agreement grant which is a support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, FDA scientific or program staff will assist, guide, coordinate, or participate in project activities.
    - THE GRANTEE IS THE LEAD
  - Outlines CTP Data Standards Program strategic goals
    - Support open, consensus-based, data standards development
    - Maintain and promote a well-defined data standards governance function,
    - Promote electronic submission of regulatory data using established standards
    - Optimize CTP's regulatory review process to fully leverage data conformed to standards

CTP AND DATA STANDARDS

- Benefits to Industry
  - Reduces time for reviewers to locate and identify required documents
  - Validations can be built into the portal and/or packaging tools to assist Industry in submitting the necessary information required for a particular submission
  - Standardized structured data allows for validation criteria to be built into tools
  - Aligns CTP with FDA Data Standards Catalog in the use of data standards and supporting tools
  - Standardized data helps CTP to streamline the review process by organizing files and data and enabling search and automation capabilities
  - Controlled terminology ensures that the same words mean the same thing to both industry and FDA
  - Improves collaboration and communication between FDA and Stakeholders
  - FDA leverages form data to obtain administrative information, help determine review types, and populate databases to enable the use of technology for review and analysis

TOBACCO IMPLEMENTATION GUIDE (TIG)

- Tobacco Implementation Guide (TIG):
  - Supports the CTP Data Standards Strategy 2021-2025 through provision of standards and terminologies to facilitate tobacco research, scientific review, harm reduction, and information exchange
  - Is a collaborative initiative with FDA-CTP, CDISC, and industry stakeholders
  - To develop non-proprietary, consensus-based, vendor-neutral, platform-independent submission data standards for tobacco product data
  - Will develop a set of standards, collectively referred to as **TIG v1.0**, to be freely available on the CDISC website with publication planned in 2023

TOBACCO IMPLEMENTATION GUIDE (TIG) V1.0

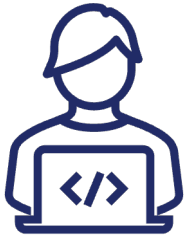
- A single, comprehensive implementation guide designed for use cases unique to tobacco studies

An overview of standards and general implementation

With guidance by topics and use cases; e.g.

- Product Description
- Nonclinical
- Individual Health
- Population Health

Key scientific concepts and maps



Data Collection (*CDASH eCRFs*, *ODM-XML*)

Data Tabulation (*SEND*, *SDTM Human Clinical*, *Define-XML*)

Analysis (*ADaM, Define-XML*)

Common Language (*Controlled Terminology*)

Measures of Adherence (*Conformance Rules*)

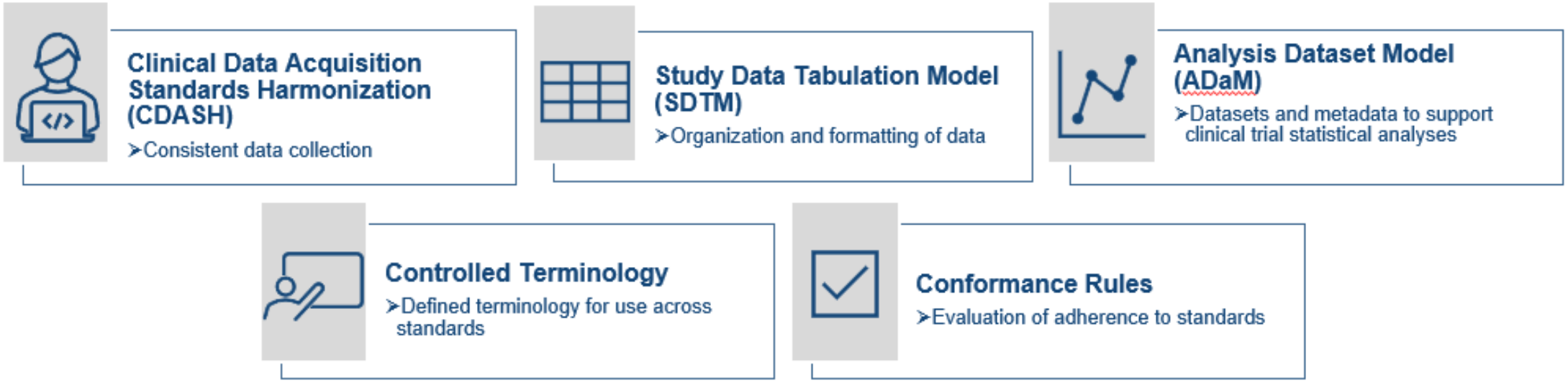
Accessible in platforms which optimize use (including *CDISC website*, *CDISC Library*)

Education and Outreach (including *webinars*, *formal training*)

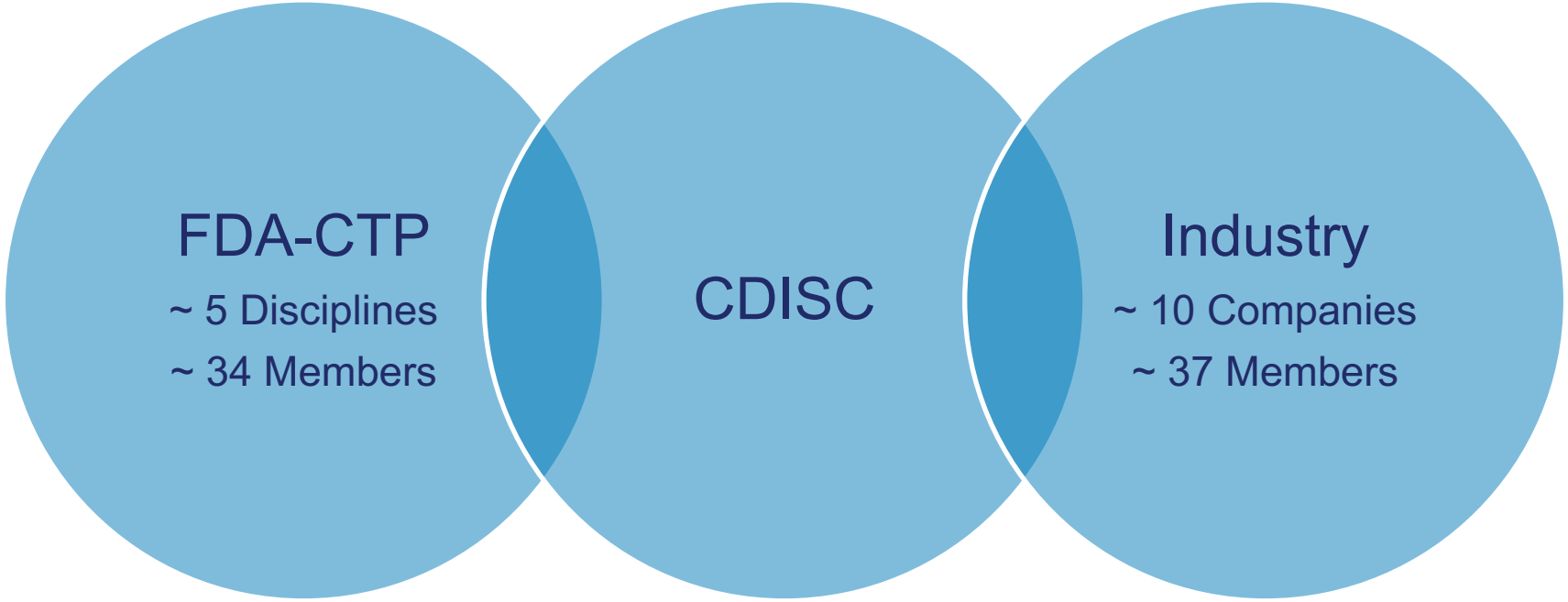
DATA STANDARDS

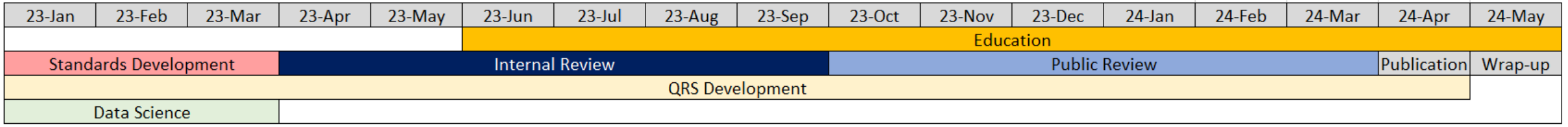
- Addresses concepts for tobacco studies and translates them into CDISC standards for both:
  - Established CDISC standards
  - New CDISC standards to fill gaps identified by FDA-CTP and Industry SMEs

- Standards you will see as part of this project include:



TIG TEAM AND TIMELINES

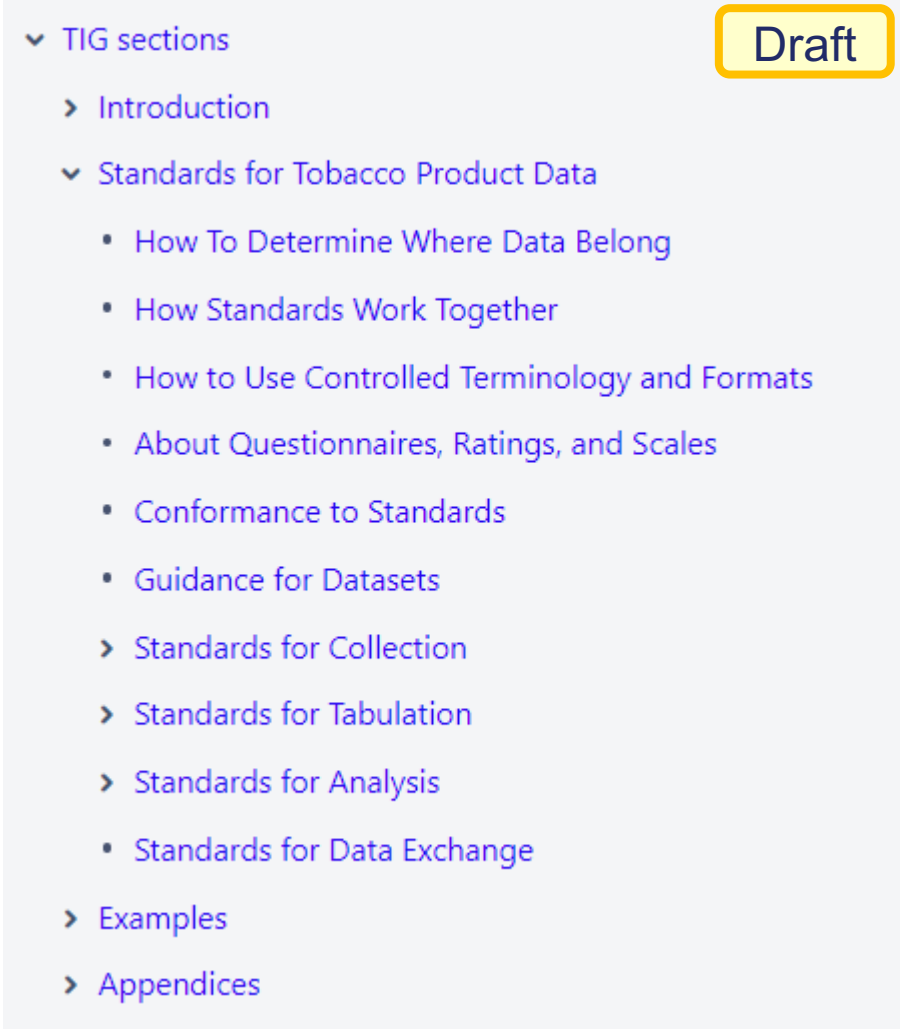




❑ Internal Review comment resolution

PROGRESS

- ✓ Scope and Requirements for TIG v1.0 are complete
- ✓ Key concepts are identified
- ✓ Standards development is complete via four workstreams
- ❑ Internal Review comment resolution is in progress
- ❑ Data Science strategy/platforms are in progress
- ❑ Education & Communication started; training development in progress
- ✓ Conference presentations in 2022 and 2023 to raise awareness



INNOVATION HIGHLIGHTS

The TIG v1.0 is CDISC's first *hybrid* implementation guide.

- Developed in partnership with the FDA-CTP, the TIG v1.0 is a stand-alone CDISC **foundational standard** that serves as a comprehensive resource for the collection, tabulation, analysis, and exchange of tobacco product data for submissions to FDA-CTP.

- The TIG v1.0 implements the following models:
  - CDASH Model v1.2
  - SDTM v2.1
  - ADaM v2.1
  - With references to standards and resources including Define-XML v2.1 and CDISC eCRF Portal

HYBRID IMPLEMENTATION GUIDE STRATEGY

Philosophy for development:

- Adhere to Plain Writing: It's the Law! | FDA
  - https://www.plainlanguage.gov/guidelines/, as much as possible
- Orient implementation guide to 1) Data, 2) Users, and 3) Standards - in this order
- Ensure guidance is simplified, concise, and organized from highest level concepts to detailed concepts
- Adhere to scope of implementation of standards only (i.e., like an instruction manual)
- Limit content related to:
  - Historical or theoretical topics better covered in CDISC Knowledge Base articles, glossaries, and/or training
  - Regulatory requirements that are defined and managed by FDA-CTP
  - Guidance for using external standards, e.g., ISO 8601, best covered by the external organization

Suggested in team kick-off.

INNOVATION HIGHLIGHTS

- The TIG v1.0 focuses on implementation for use cases inherent to tobacco product data comprised of concepts identified by one or more stakeholders as important in the context of tobacco product research.

The following use cases are specifically addressed in the TIG: Draft

- *Product Description*, which refers to concepts used to characterize tobacco products.
- *Nonclinical*, which refers to concepts used to identify potential risks and effects on biological processes for tobacco products via in vitro and in vivo nonclinical studies.
- *Product Impact on Individual Health*, which refers to concepts used to assess the impact of tobacco products on individuals.
- *Product Impact on Population Health*, which refers to concepts used to assess the impact of tobacco products on populations of individuals.

PRODUCT DESCRIPTION EXAMPLE

Tobacco Product Identifiers and Descriptors – New, Predicate, Original, and Comparison Products (TO)

Draft

The example below illustrates TO concepts using a cigarette product and its predicate product for demonstration purposes. The Product Design Parameters and Conformance Testing section additionally demonstrates this dataset for an ENDS product and a portioned snus product.

to.xpt

Rows 1-10: Show the identifying and descriptive parameters for a new product. Note that the category variable (TOCAT) is "NEW PRODUCT" for these records. The applicant chose to further sub-categorize each parameter as either an identifying or descriptive parameter in the variable TOSCAT.

Rows 1-4: Show the records for the product identifiers for the tobacco product identified in SPTOBID.

Rows 11-21: Show the records for the product descriptors for a predicate tobacco product identified in SPTOBID. Note that the category variable (TOCAT) is "PREDICATE PRODUCT" for these records. The applicant chose to further sub-categorize each parameter as either an identifying or descriptive parameter in the variable TOSCAT.

Row 13: Shows the FDA Submission Tracking Number (STN) associated with the predicate product. This parameter should be included for all products for which an FDA STN is available.

to.xpt

Row	STUDYID	DOMAIN	SPTOBID	TOSEQ	TOPARMCD	TOPARM	TOCAT	TOSCAT	TOVAL	TOVALU
1	TOB07	TO	CIG01a	1	TBPRDCAT	Tobacco Product Category	NEW PRODUCT	PRODUCT IDENTIFIER	Cigarette	
2	TOB07	TO	CIG01a	2	TBPRSCAT	Tobacco Product Subcategory	NEW PRODUCT	PRODUCT IDENTIFIER	Filtered, Combusted	
3	TOB07	TO	CIG01a	3	MANUF	Manufacturer	NEW PRODUCT	PRODUCT IDENTIFIER	Joes Cigs USA	
4	TOB07	TO	CIG01a	4	TRADENAM	Trade Name	NEW PRODUCT	PRODUCT IDENTIFIER	Treetop Menthol King Size	
5	TOB07	TO	CIG01a	5	PACKTYP	Package Type	NEW PRODUCT	PRODUCT DESCRIPTOR	HARD PACK	
6	TOB07	TO	CIG01a	6	PRDQUAN	Product Quantity	NEW PRODUCT	PRODUCT DESCRIPTOR	20	CIGARETTE

NONCLINICAL IN VITRO EXAMPLE

Bacterial Reverse Mutation Test (Ames) (GT) Draft

Rows 1-5: Show the number of revertant colonies per plate collected for each of five observational units GTREFID=0_1 through 0_5 (see description in the relref dataset).

Rows 6, 7: Show summary values collected (MEAN, STANDARD DEVIATION) for GTREFID=A that apply to the entire trial set, SetA, as indicated by LEVEL=1 and LVLDESC=TRIAL SET for this REFID as shown in the relref dataset.

Rows 8-13: Revertent colonies were counted for each of three plates/observational units (GTREFID=6_1 through 6_3) and each value is associated with a record to show a postfix code of "V" = "Very thin background bacterial lawn"

Rows 14-16: Show summary values collected (MEAN, STANDARD DEVIATION, and FOLD INCREASE) for GTREFID=F that apply to the entire trial set, SetF, as indicated by LEVEL=1 and LVLDESC=TRIAL SET for this REFID in the relref dataset.

Rows 17-19: Show three plates/observational units (GTREFID=5_1 through 5_3) where no revertant colonies were counted due to too much cytotoxicity and a postfix code of "T".

Rows 20-22: Show the number of revertant colonies per plate collected for each of three observational units (GTREFID=18_1 through 18_3).

Rows 23-25: Show summary values collected (MEAN, STANDARD DEVIATION, and FOLD INCREASE) for GTREFID=R that apply to the entire trial set, SetR, as indicated by LEVEL=1 and LVLDESC=TRIAL SET for this REFID in the relref dataset.

gt.xpt

Row	STUDYID	GNTXAID	DOMAIN	GTSEQ	GTREFID	GTTESTCD	GTTEST	GTORRES	GTORRESU	GTCOLSRT	GTSTRESC	GTSTRESN	GTSTRESU	GTSTAT	GTREASND	GTMETHOD	GTDTC
1	8325064	Ames	GT	1	0_1	RPP	Revertant Numbers Per Plate	26	COLONIES		26	26	COLONIES			INSTRUMENT COUNTED	2015-08-03
2	8325064	Ames	GT	2	0_2	RPP	Revertant Numbers Per Plate	35	COLONIES		35	35	COLONIES			INSTRUMENT COUNTED	2015-08-03

DATA SCIENCE INNOVATION

CDISC Library

- End-to-end standards for tobacco studies
- Inclusion of informative content (e.g., domain assumptions and examples)
- Biomedical Concepts available
- ODM-XML representations of case report forms

HOW YOU CAN BE INVOLVED

- We invite you to contribute to development of TIG standards.
  - Become a Tobacco Implementation Guide (TIG) volunteer
    - www.cdisc.org/volunteer
    - Click link to *Become a Volunteer*
    - Time commitment is generally a one-hour weekly meeting
    - It is never too late to volunteer.
  - Review draft standards as they are released
  - Please reach out with any questions or support you may need.
    - Christine Connolly, CDISC Head of Standards Projects: cconnolly@cdisc.org

THANK YOU

- We welcome your questions and feedback!