FDA's Study Data Policy Framework and How CDISC Properties Are Evaluated for Inclusion

Helena Sviglin, CDER Office of Strategic Policy

Data Standards Staff

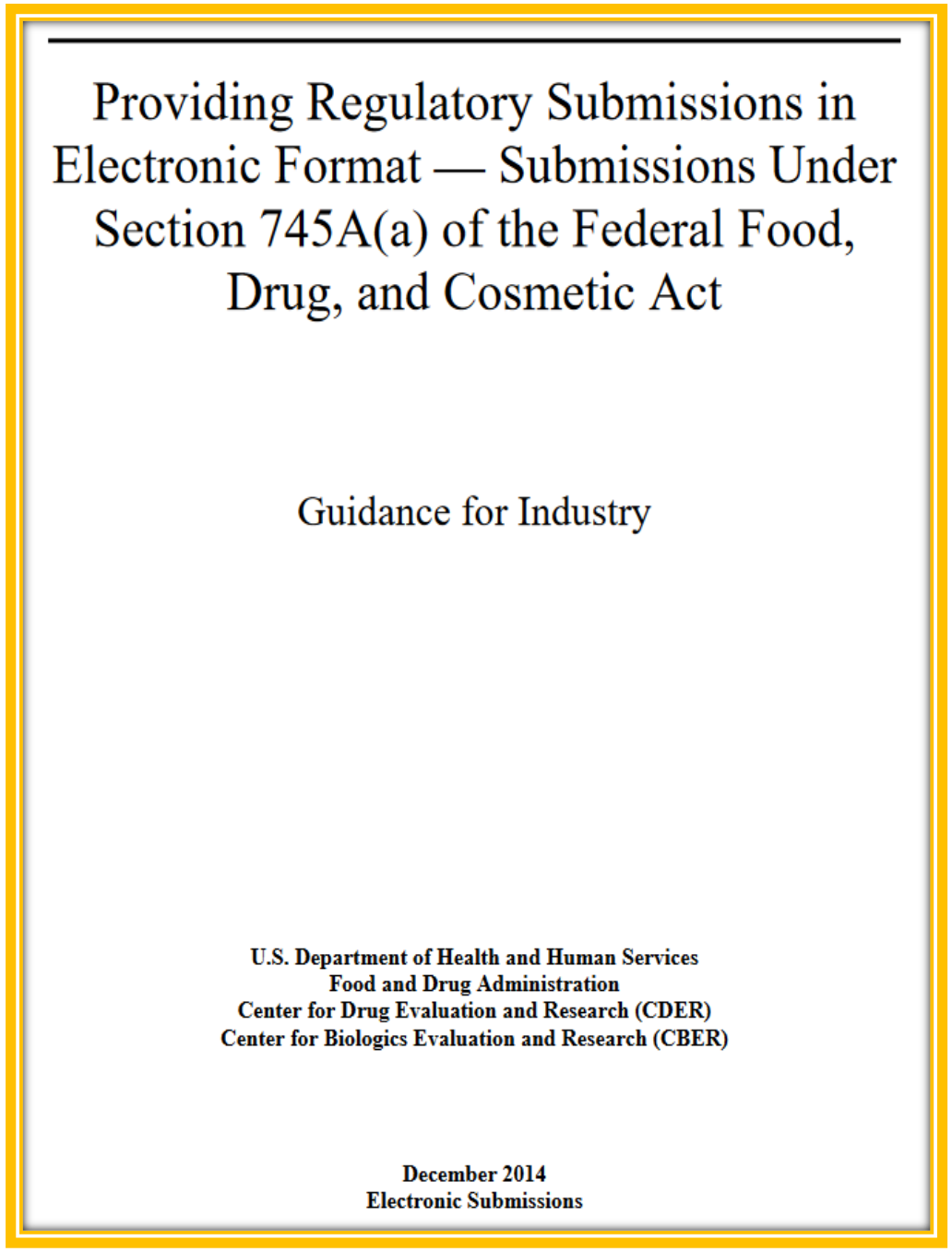
May 2023

Current Contributions:

- Internal policy development and study data governance
- Chair, FDA Study Data Technical Conformance Guide (sdTCG) Working Group
- eData responses
- Chair, FDA Data Standards Catalog Subcommittee
- Chair, FDA Business Rules CCB
- I AM NOT A LAWYER

Helena Sviglin, FDA CDER Office of Strategic Programs

FDA Study Data Policy Framework Overview


Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

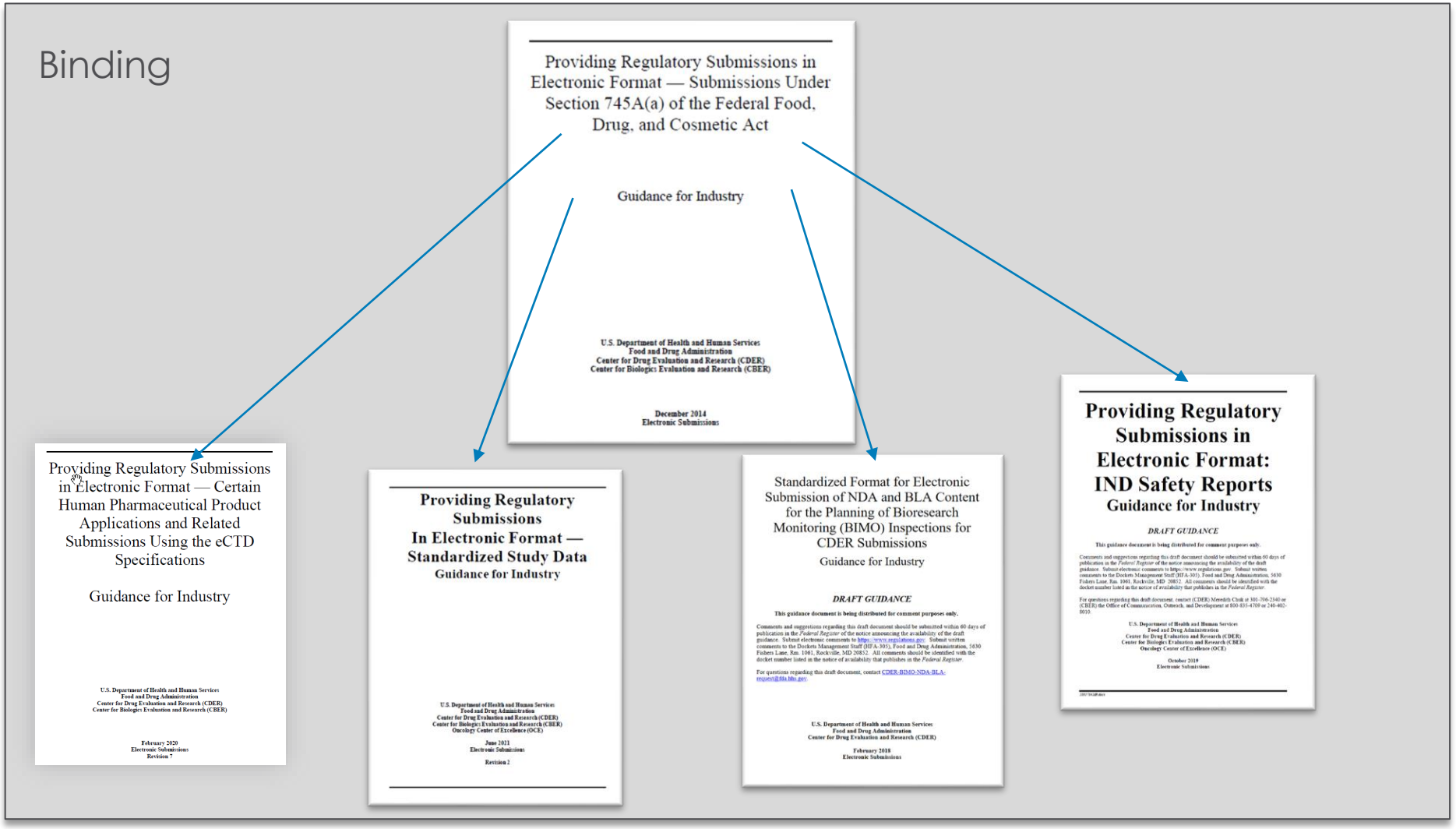
December 2014
Electronic Submissions

Primary Statute

Search for FDA Guidance Documents | FDA (fda.gov/regulatory-information/search-fda-guidance-documents)

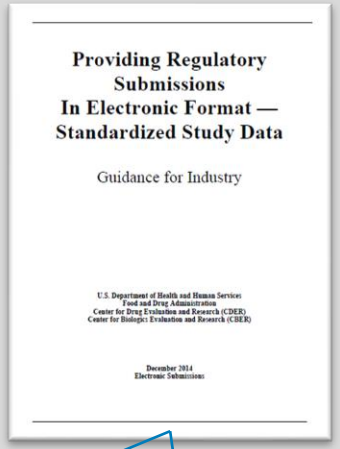
Study Data Standards Resources | FDA (fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources)

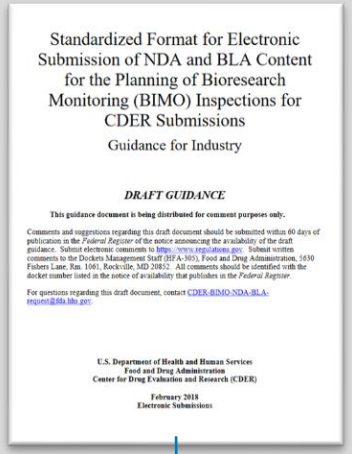
How FDA communicates technical requirements for submitting study data

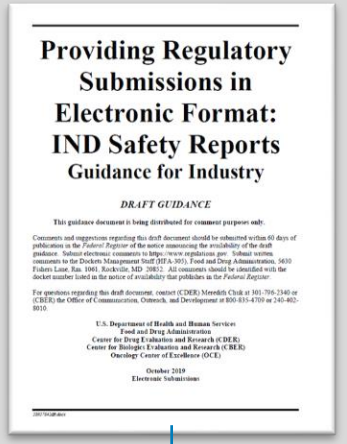


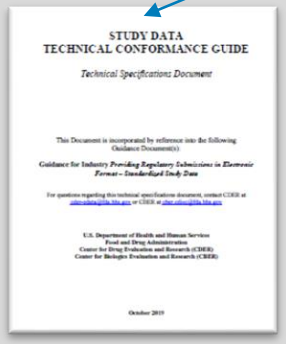
How FDA communicates technical requirements for submitting study data

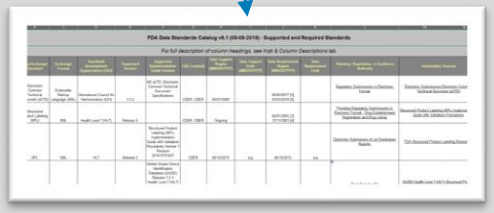
Binding – Level I



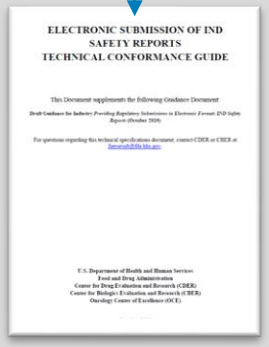








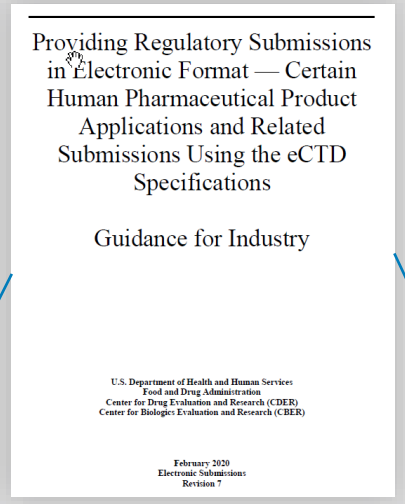
BIMO
TCG



Technically non-binding – Level II – but sit under a binding guidance and are incorporated by reference

Related guidance: eCTD – requires electronic data, eCTD format

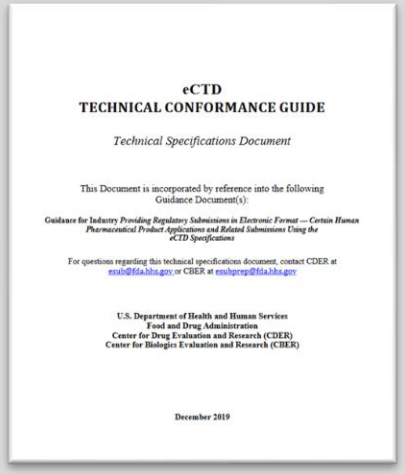
Binding – Level I


Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2020
Electronic Submissions
Revision 7


eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

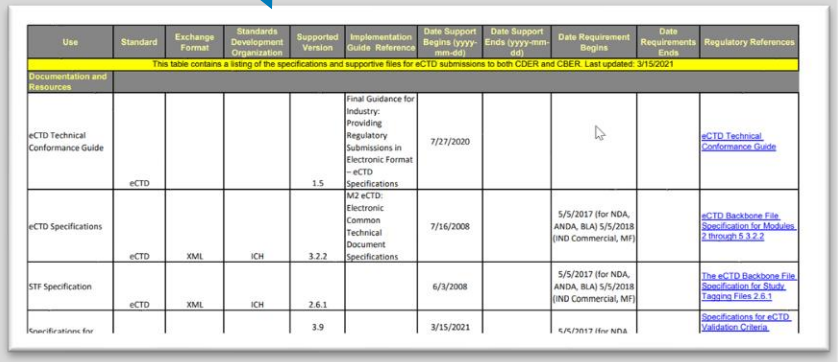
Guidance for Industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2019

Technically non-binding but Level II guidances sit under a binding guidance and are incorporated by reference

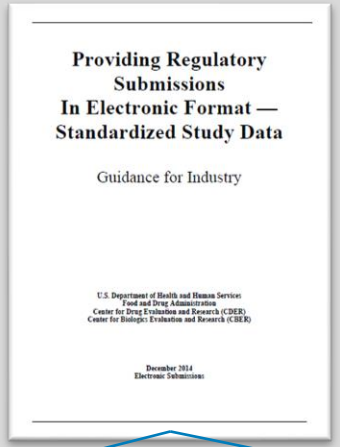


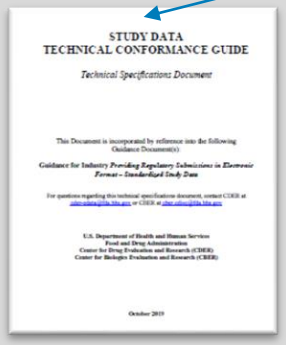
Use	Standard	Exchange Format	Standards Development Organization	Supported Version	Implementation Guide Reference	Date Support Begins (yyyy-mm-dd)	Date Support Ends (yyyy-mm-dd)	Date Requirement Begins	Date Requirements Ends	Regulatory References
This table contains a listing of the specifications and supportive files for eCTD submissions to both CDER and CBER. Last updated: 3/15/2021										
Documentation and Resources										
eCTD Technical Conformance Guide	eCTD			1.5	Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format – eCTD Specifications	7/27/2020				eCTD Technical Conformance Guide
eCTD Specifications	eCTD	XML	ICH	3.2.2	M2 eCTD: Electronic Common Technical Document Specifications	7/16/2008		5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND Commercial, MF)		eCTD Backbone File Specification for Modules 2 through 5 3.2.2
STF Specification	eCTD	XML	ICH	2.6.1		6/3/2008		5/5/2017 (for NDA, ANDA, BLA) 5/5/2018 (IND Commercial, MF)		The eCTD Backbone File Specification for Study Tagging Files 2.6.1
Specifications for				3.9		3/15/2021		5/5/2017 (for NDA		Specifications for eCTD Validation Criteria

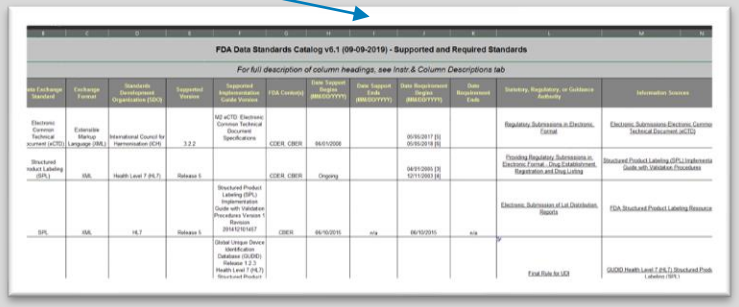
eCTD Data Standards 031521 (fda.gov)

Focus on study data

Binding – Level I







Technically non-binding – Level II – but sit under a binding guidance and are incorporated by reference

Level I vs. Level II Guidance

Level 1 guidances set forth the agency's initial interpretations of new significant regulatory requirements; describe substantial changes in FDA's earlier interpretation or policy; and deal with complex scientific or highly controversial issues.

Level 2 guidances usually address existing practices or minor changes in FDA's interpretation or policy.

Fact Sheet: FDA Good Guidance Practices | FDA

(fda.gov/about-fda/transparency-initiative/fact-sheet-fda-good-guidance-practices#:~:text=In%20general%3A,scientific%20or%20highly%20controversial%20issues.)

Level I vs. Level II Updates to Guidance

Level 1 ***updates*** to guidances describe substantial changes in FDA's earlier interpretation or policy; and deal with complex scientific or highly controversial issues.

Level 2 guidance ***updates*** usually address changes to existing practices or minor changes in FDA's interpretation or policy.

Fact Sheet: FDA Good Guidance Practices | FDA

(fda.gov/about-fda/transparency-initiative/fact-sheet-fda-good-guidance-practices#:~:text=In%20general%3A,scientific%20or%20highly%20controversial%20issues.)

FDA's Study Data Policy Framework

Level I Guidance (sitting under 745A(a))

- eStudy Data Guidance (eStudy)
- Real World Data (RWD) (currently in Draft)
- *eCTD Guidance*

Level II Guidance

- Technical Conformance Guides (TCGs)
- FDA Data Standards Catalog (Catalog)
- Certain Technical Specifications (Tech Specs)

Search for FDA Guidance Documents | FDA (fda.gov/regulatory-information/search-fda-guidance-documents)

Study Data Standards Resources | FDA (fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources)

eStudy Data Guidance Updates

Two Level II Updates were made since 2020

1. Technical Rejection Criteria (TRC) considerations, 2020
2. Scope of SEND, 2021

Providing Regulatory Submissions in Electronic Format -- Standardized Study Data | FDA

RWD Guidance Update

- Establishes that RWD is considered study data at the point of submission and falls under 745A(a)
- Draft Published late 2021
- Review of public comments completed
- This review will inform the final guidance

Providing Regulatory Submissions in Electronic Format -- Standardized Study Data | FDA (fda.gov/regulatory-information/search-fda-guidance-documents)

Technical Conformance Guide (TCG) Recent Updates

- Study Data TCG (sdTCG) updated March 2023
- Biomedical Monitoring (BIMO) TCG updated April 2022
- IND Safety Reports TCG updated April 2022
- FDA Data Standards Catalog updated January 2023

Study Data Standards Resources | FDA

FDA Data Standards Catalog Recent Updates

Catalog continues to be updated to address the current state of requirements for study data at other Centers:

- Annotated ECG (aECG) standard
- Open docket added
- Added CVM as an involved center for UNII Add USCDI+ to the catalog, plus other updates
- S-CAP for CDRH
- ISCR R2 for CDRH
- CDISC Standards ADaM IG v1.2 and 1.3

Data Standards Catalog | FDA

FDA Study Data Technical Specifications (Tech Spec) Recent Updates

1. Submitting Nonclinical Datasets for Evaluation of Rodent Carcinogenicity Studies of Pharmaceuticals, Guidance for Industry, Technical Specifications Document v. 1.0 (May 2021)
2. Submitting Next Generation Sequencing Data to the Division of Antiviral Products v. 1.0 (July 2019)
3. QT Studies Technical Specification Document v. 1.0
4. Bioanalytical Methods Validation (BMV) Tech. Spec. v1.0
5. HIV Technical Specifications Guidance v. 1.0 (March 2018)
6. Vaccines Technical Specification Guidance v2.1
7. Clinical Endpoint BE Studies v1.0
8. Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH) (Jan 2022)

How Does FDA evaluate CDISC properties for inclusion into the Study Data Policy Framework?

1. Organic process
2. Property is identified
3. We work with internal SMEs and contracted SMEs to evaluate the property
    - Check the property for cohesion in key areas
    - Check against existing guidance documents
4. Work internally to develop comments for public comment phases
5. Work internally to develop consensus on what our Agency position will be

Essential Evaluation Areas for Clinical

- Non-Standard variables
- Existing NSV being promoted
- Structural change (vertical -> horizonal/vice versa)
- Changes to core domain structures
- Multiple instances in DM (multiple screenings/enrollments)
- Extension studies and how this impacts SDTM model
- Adjudication data
- Observational Studies
- Sex
- Race/Ethnicity
- Relationships of the evaluated property to other properties (for example, what is the underlying data model behind each thing evaluated)

Non-Clinical Essential Evaluation Areas

U.S. FOOD & DRUG ADMINISTRATION

New Domains	New Variables	New Study Types	New Sub-IGs	Changes to Existing Domains & Variables
Endpoints to include in domain are clearly defined	Definition is clear	Definition of applicable study types is consistent with common use	Rationale and use of Sub-IG, separate from main IG, is clear	Variables can be clarified but not redefined
Any movement of endpoints from existing domains is clear	New variable concept does not overlap existing variable(s)	Can complete study of this type be modeled? If not, what is missing?	Relationship between Sub-IG and reference main iG is clear	Variables upgraded to required – can they be consistently populated?
Variable use in new domain is consistent with existing domains	Variable can be associated with a study concept	Study type is not covered by other Implementation Guides	Creating a study package from the sub-IG and main IG is described	Assess effect of variables downgraded from required on analyses
Use of data for common analyses is possible	Variable added to appropriate domains	Domains/variables to be used for this study type are clear	Consistent use of concepts with referenced main IG	Variables should not be removed without replacement
Clear and consistent examples included	Examples are added to show use	Examples used are relevant to the study type		Variables replaced – is the transition to new variables clear?
Controlled terminology used on appropriate variables	Controlled terminology used when possible	Analyses common to the study type can be done using variables defined		Particular focus on variables used for analysis in FDA tools

Also Document in the Assessment: What is the underlying SDTM version, is that version in the catalog, when was that version

U.S. FOOD & DRUG ADMINISTRATION

Questions?