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

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Data Standards Staff
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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
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)

May 2023 Sviglin
How FDA communicates technical requirements for submitting study data

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How FDA communicates technical requirements for submitting study data

- **Binding – Level I**
  - Providing Regulatory Submissions In Electronic Format — Standardized Study Data
    - Guidance for Industry
  - Standardized Format for Electronic Submission of Nonclinical Data for INDs (mRNA and CRISPR)
    - Guidance for Industry
  - Providing Regulatory Submissions in Electronic Format: IND Safety Reports
    - Guidance for Industry

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

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Related guidance: eCTD – requires electronic data, eCTD format

Binding – Level I

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

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
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
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
FDA Study Data Technical Specifications (Tech Spec) Recent Updates

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 -> horizontal/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

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

Also Document in the Assessment: What is the underlying SDTM version, is that version in the catalog, when was that version added to the catalog.
Questions?