FDA Technical Conformance Guide v5.0

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Revision History - Versions 4.8.x

Date	Version	Change / Modification
September 2021	4.8	Section 4.1.3.4 (Scope of SEND) Section 4.1.3.4.1 (Scope of SEND for SENDIGs v3.0 and v3.1), Section 4.1.3.4.2 (Scope of SEND for SENDIG - Animal Rule v1.0) – Provided clarification on the expectation of SEND for studies listed in the referenced SENDIGs.
October 2021	v4.8.1	Footnotes were updated to fix web links and other typos and formatting issues.

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Revision History - Version 4.9

Date	Version	Change / Modification
March 2022	4.9	Section 3.3.3 (Dataset Column Length) – Provided clarification Section 3.3.7 (Variable and Dataset Labels) – Provided clarification Section 4.1.1.2 (SDTM General Considerations) – Provided clarification Section 4.1.1.3 (SDTM Domain Specifications) – Provided clarification Section 4.1.3.2 (General Considerations) – Provided clarification Section 5.3 – Added section “List of Technical Specifications Documents” Added technical rejection criteria for study data documentation information in the following: Section 7.1 Section 8.2.2 Appendix F Appendix G Section 7.2 (Electronic File Directory) – Added this section ‘to focus on recommended file folder structure Appendix B – Provided clarification Appendix C – Updated table

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Revision History - Version 5.0

Date	Version	Change / Modification
October 2022	5.0	Document first paragraph – added link to Docket for entering comments on this document Purpose – Added clarification to the use of the word ‘require’ Footnotes – Updated links in footnotes referring to FDA Guidance documents Section 4.1.2.10 – Clarified language concerning acceptable file extensions that aligns with eCTD file format specification Section 4.1.3.3 – Under BG Domain (Body Weight Gain), removed ‘CDER’ as this applies to both CBER and CDER submissions Section 4.1.4 – General Considerations: SDTM, SEND, and/or ADaM; clarified the use of the word ‘required’ Section 4.1.4.1 – Clarified headings Section 6.5.1.1 – Updated the link to the document entitled Established Pharmacologic Class Text Phrase Appendix B and C – Clarified use of TS Parameters

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Background and Structure

- The Study Data Technical Conformance Guide (SDTCG) provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards.
- No changes to the general organization/structure of the documents
  - Section 1: **Introduction** – provides information on regulatory policy and guidance background, purpose, and document control.
  - Section 2: **Planning and Providing Standardized Study Data** – recommends and provides details on preparing an overall study data standardization plan, a study data reviewer's guide and an analysis data reviewer's guide.

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Background and Structure (continued)

- Section 3: **Exchange Format: Electronic Submissions** – presents the specifications, considerations, and recommendations for the file formats currently supported by FDA.
- Section 4: **Study Data Submission Format: Clinical and Nonclinical** – presents general considerations and specifications for sponsors using, for example, the following standards for the submission of study data: Study Data Tabulation Model (SDTM), Analysis Data Model (ADaM), and Standard for Exchange of Nonclinical Data (SEND).
- Section 5: **Therapeutic Area Topics** – presents supplemental considerations and specific recommendations when sponsors submit study data using therapeutic area extensions of FDA-supported standards

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Background and Structure (continued)

- Section 6: **Terminology** – presents general considerations and specific recommendations when using controlled terminologies/vocabularies for clinical trial data or nonclinical study data.
- Section 7: **Electronic Submission Format** – provides specifications and recommendations on submitting study data using the electronic Common Technical Document (eCTD) format.
- Section 8: **Study Data Validation and Traceability** – provides general recommendations on conformance to standards, data validation rules, data traceability expectations, and legacy data conversion

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Preface (added text) and General Changes (reference updates)

- Preface: Added link to Docket for comments on this document [SDTCG]

STUDY DATA
TECHNICAL CONFORMANCE GUIDE

This technical specifications document represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, send an email to cder-edata@fda.hhs.gov or cber-edata@fda.hhs.gov. You can submit comments to this document online at https://www.regulations.gov and searching Docket No. FDA-2018-D-12160002.

- Footnotes: Updated links referring to FDA guidance documents

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Section 1.2 - Purpose (added text)

- Clarification to the use of the word "require"

> Not every data element included in a standard's underlying data model is fit for purpose for every trial. The use of the word 'required' in this document generally indicates a requirement by the Agency and not any external organization. Any use of the word 'required' that would have a different meaning will be explained in the text. For example, the Study Data Tabulation Model Implementation Guide (SDTMIG)[6] classifies variables as required, expected, or permissible. This use of the word 'required' by the Standards Data Organization does not necessarily indicate an Agency requirement. What data are collected and submitted is a decision that should be made based on scientific reasons, regulation requirements, and discussions with the review division. However, all study-specific data necessary to evaluate the safety and efficacy of the medical product should be submitted in conformance with the standards currently supported by FDA and listed in the Catalog.

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Section 3.3.3 - Data Column Length (added text)

- Allotted variable length across datasets to avoid accidental truncation when merging dataset in the later processing.

> The allotted length for each column containing character (text) data should be set to the maximum length of the variable used across all datasets in the study except for suppqual datasets. For suppqual datasets, the allotted length for each column containing character (text) data should be set to the maximum length of the variable used in the individual dataset. This will significantly reduce file sizes. For example, if USUBJID has a maximum length of 18, the USUBJID's column size should be set to 18, not 200. Care should be taken to avoid accidental truncation of data through dataset merges. Ensure that variable length reduction happens before datasets are split. For example, if PARAM is set to a length of 20 in ADLB1 and 25 in ADLB2, when ADLB2 is concatenated with ADLB1 data loss will occur. SAS uses the length of 20 for the width which will truncate data in ADLB2 when the contents of the PARAM field is longer than 20 characters.

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Section 4.1.1.2 - SDTM General Considerations (added text)

- When datasets are updated, define.xml and cSDRG should be updated as well.

> The SDTMIG should be followed unless otherwise indicated in this Guide or in the Catalog. The conformance criteria listed in the SDTMIG should not be interpreted as the sole determinant of the adequacy of submitted data. If there is uncertainty regarding implementation, the sponsor should discuss application-specific questions with the review division and general standards implementation questions with the specific center resources identified elsewhere in this Guide (See section 1.2). Each submitted SDTM dataset should have its contents described with complete metadata in the define.xml file (See section 4.1.4.5) and within the cSDRG as appropriate (See section 2.2). When updated datasets (e.g., 'ae.xpt', 'lb.xpt') are submitted, updated and complete define.xml and cSDRG covering all datasets should be submitted using the "replace" lifecycle operator to update the original file.

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Section 4.1.1.3 - SDTM Domain Specification (updated wording)

- Clarification dataset name vs. file name

LB Domain (Laboratory)
The size of the LB domain dataset submitted by sponsors is often too large to process (See section 3.3.2). This issue can be addressed by splitting a large LB dataset into smaller datasets according to LBCAT and LBSCAT, using LBCAT for initial splitting. If the size is still too large, then use LBSCAT for further splitting. For example, use the dataset name lb1 (file name 'lb1.xpt') for chemistry, dataset name lb2 (file name 'lb2.xpt') for hematology, and dataset name lb3 (file name 'lb3.xpt') for urinalysis. Splitting the dataset in other ways (e.g., by subject or file size) makes the data less useable. Sponsors should submit these smaller files in addition to the larger non-split standard LB domain file. Sponsors should submit the split files in a separate sub-directory/split that is clearly documented in addition to the non-split standard LB domain file in the SDTM datasets directory (See section 7). FDA may require laboratory data using conventional units for reviewing submissions and labeling. Sponsors should discuss with the review divisions what laboratory data should utilize conventional units prior to submission.

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Section 4.1.2.10 - Software Programs (updated text)

- Update file extensions, alignment with eCTD file format specification

Sponsors should provide the source code used to create all ADaM datasets, tables, and figures associated with primary and secondary efficacy analyses. Sponsors should submit source code in single byte ASCII text format. Files with MS Windows executable extensions (.cmd, .com, and .exe) should NOT be submitted. For a list of acceptable file extensions, refer to the document entitled *Specifications for File Format Types Using eCTD Specifications*.[31]

Furthermore, sponsors should submit the source code used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information,[32] if applicable. The specific software utilized (version and operating system) should be specified in the ADRG.

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[31] Available at https://www.fda.gov/media/85816/download.

[32] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-human-prescription-drug-and-biological-products-implementing-plr-content-and-format.

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Section 4.1.3.2 - General Considerations (updated text)

- Additional clarification regarding submission of SEND datasets

> For submissions to CDER, SEND datasets are required when submitting a draft report as these data form the basis of regulatory decisions regarding nonclinical support for clinical development. SEND datasets will not be required for CBER submissions until after March 15, 2023. If there are changes to the SEND datasets requiring resubmission with the final study report, resubmit the updated datasets using the 'replace' operator. Information about using the 'replace' operator to update datasets can be found in Section 7.1. SEND datasets would not need to be resubmitted with the final report if there were no changes to the dataset from the draft report. Even when SEND datasets do not need to be resubmitted, it is recommended that an updated nSDRG is submitted with the final study report. This updated nSDRG should include the current study report version (Section 1.1), any date (or administrative) changes, and a notation that no changes to SEND datasets were made or needed other than the notation of the version change (e.g., STRPSTAT change) after the draft report was submitted.

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Section 4.1.3.3 - SEND Domain Specification (removed text)
Section 4.1.3.4 - Scope of SEND (new section)

- Section 4.1.3.3 BG Domain, removed restriction to CDER

  Body Weight Gain (BG) Domain
  It is not necessary to include a BG domain in ~~CDER~~ submissions.

- Section 4.1.3.4 - Scope of SEND
  - New section presenting a general discussion on the FDA's "current thinking" on SEND.
    - Section 4.1.3.4.1 - Scope of SEND for SENDIGs 3.0 and 3.1
    - Section 4.1.3.4.2 - Scope of SEND for SENDIG-Animal Rule 1.0
  - The Agency's current interpretation of the scope of SEND is subject to change as new SENDIGs are supported and required by the Agency.

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Section 4.1.4.1 - Variables in SDTM and SEND: Required, Expected, and Permissible (added text)

- Clarification of the wording "required".

4.1.4 General Considerations: SDTM, SEND, and/or ADaM

4.1.4.1 Variables in SDTM and SEND: CDISC Required, Expected, and Permissible

CDISC uses the word “required” to describe variables in their data models (SEND, SDTM, ADaM). This use does not indicate a requirement by the Agency.

For the purposes of SDTM and SEND submissions, all required, expected, and permissible variables that were collected, plus any variables that are used to compute derivations, should be submitted.

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Section 5.3 - List of Technical Specification Documents (added section)

- List of additional FDA technical specifications for specific topics

> Technical specification documents provide detailed information for content on specific topics, where applicable, submitted to FDA for an application. Sponsors should consult with the review division early in the process to discuss issues with trial design or conduct that may affect the content of the study data being submitted. Technical specifications can be found here.[47]

[47] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-standardized-study-data.

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Section 5.3 - List of Technical Specification Documents (continued)

5.3.1 Submitting Nonclinical Datasets for Evaluation of Rodent Carcinogenicity Studies of Parmaceuticals, Guidance for Industry

5.3.2 Submitting Next Generation Sequencing Data to the Division of Antiviral Products

5.3.3 Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs

5.3.4 Bioanalytical Methods Templates

5.3.5 Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus-1 Infection

5.3.6 Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

5.3.7 Technical Specifications-Comparative Clinical Endpoint Bioequivalence Study Analysis Datasets for Abbreviated New Drug Applications

5.3.8 Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)

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Section 6.5.1.1 - General Considerations [Medical Reference Terminology]

- Footnote 59, Link update

Pharmacologic class is a complex concept that is made up of one or more component concepts: mechanism of action (MOA), physiologic effect (PE), and chemical structure (CS).[59] The established pharmacologic class is generally the MOA, PE, or CS term that is considered the most scientifically valid and clinically meaningful.

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[59] See the guidance for industry and review staff *Labeling for Human Prescription Drug and Biologic Products —Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*, available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

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Section 7 - Electronic Submission Format (re-structured, added text)

- Section 7.1 - eCTD Specifications
  - Reference to Technical Rejection Criteria added

> For information on how to incorporate datasets into the eCTD, please reference the Guidance to Industry *Providing Regulatory Submissions in Electronic Format: Certain Human Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document Specifications*.[63] Information on eCTD Validations, including those referenced in the "Technical Rejection Criteria for Study Data Important Information" (Appendix F), can be found in the *Specifications for eCTD Validation Criteria*. Details on the expectations for validations applying to study data can be found in Section 8.2.2 (Support on Data Validation Rules) and Appendix F (Technical Rejection Criteria for Study Data Important Information) of this Technical Conformance Guide.

  - Descriptions of Electronic File Directory moved into new section 7.2

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Section 7 - Electronic Submission Format (continued)

- Section 7.2 - Electronic File Directory
  - New section created from corresponding paragraphs of old section 7.1
  - High-level description of the Electronic Files Directory
  - Figure 1 (Folder Structure for Study Datasets) and Table 2 (Study Dataset and File Folder Structure and Description) moved into this section
  - No change to text
- Section 7.3 - eCTD Sample Submission
  - Section re-numbered from 7.2 to 7.3
  - No change to text

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Section 8.2.2 - Support on Data Validation Rules

- References to Technical Rejection Criteria (TRC) added section
- New structure and re-phrased
  - Section 8.2.2 - "Introduction" paragraph
  - Section 8.2.2.1 - TRC for Study Data
  - Section 8.2.2.2 - TRC and Use of Simplified ts.xpt for Clinical Studies
  - Section 8.2.2.3 - TRC and Use of Simplified ts.xpt for Nonclinical Studies for CDER
  - Appendix F: Technical Rejection Criteria for Study Data Validation Important Information
  - Appendix G: Examples of [simplified] ts.xpt Datasets

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Appendix B & C: Trial Summary (TS) Parameters for Submission

- Appendix B: TS Parameters for Submission - Clinical
  - Parameter SPREFID added

FDA Desired - Clinical	TSPARMCD	TSPARM	FDA Notes
Conditional	SPREFID	Sponsor's Study Reference ID	If applicable.

- Appendix C: TS Parameters for Submission - Nonclinical
  - Parameter SLENGTH removed

FDA Desired - Nonclinical	TSPARMCD	TSPARM	FDA Notes
~~Y~~	~~SLENGTH~~	~~Study Length~~	

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Thank you