CHANGES IN FDA TECHNICAL CONFORMANCE GUIDE

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DEFINITION

- This Study Data Technical Conformance Guide provides specification, recomendations and general considerations on how to submit standardized study data using FDA – support

- The guide is separated in sections:

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.

Section 3: **Exchange Format** - **Electronic Submissions** – presents the specifications, considerations, and recommendations for the file formats currently supported by FDA.

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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 Standards** – presents supplemental considerations and specific recommendations when sponsors submit study data using FDA-supported therapeutic area standards (TA).

Section 6: **Terminology** – presents general considerations and specific recommendations when using controlled terminologies/vocabularies for clinical trial data.

Section 7: **Electronic Submission Format** – provides specifications and recommendations on submitting study data using the electronic Common Technical Document (eCTD) format.

Section 8: **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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v2.2

v2.3

EC Domain (Exposure as Collected)
The Exposure as Collected domain provides for protocol-specified study treatment administrations, as-collected. The EC domain may address some challenges in providing a subject's exposure to study medication. However, testing and acceptance has not been completed on the EC and it is not supported at this time.

DD (Death Details)
The Death Details domain provides for supplemental data that are typically collected when a death occurs, such as the official cause of death. The DD domain may has not completed testing and acceptance and it is not supported at this time.

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TESTING AND ACCEPTANCE FOR „EC" AND „DD" COMPLETED AND NOW SUPPORTED

v2.2	v2.3
4.1.2 Analysis Data Model	**4.1.2 Analysis Data Model**
4.1.2.1 Definition	**4.1.2.1 Definition**
4.1.2.2 General Considerations	**4.1.2.2 General Considerations**
4.1.2.3 Key Efficacy and Safety Variables	**4.1.2.3 Dataset Labels**
4.1.2.4 Timing Variables	**4.1.2.4 Subject Level Analysis Data**
4.1.2.5 Core Variables	**4.1.2.5 Core Variables**
4.1.2.6 Dates	**4.1.2.6 Key Efficacy and Safety Variables**
4.1.2.7 Labels	**4.1.2.7 Timing Variables**
4.1.2.8 Software Programs	**4.1.2.8 Numeric Date Variables**
	4.1.2.9 Imputed Data
	4.1.2.10 Software Programs

TIMING AND DATES VARIABLES   FOR ANALYSIS BETTER EXPLAINED

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v2.2   v2.3

4.1.4.5   Data Definition Files for SDTM, SEND, and ADaM
The data definition file, i.e., define file, describes the metadata of the submitted electronic datasets, and is considered arguably the most important part of the electronic dataset submission for regulatory review. This data definition specification for submitted datasets defines the metadata structures that should be used to describe the datasets and variables. An insufficiently documented define file is a common deficiency that reviewers have noted. Consequently, the sponsor needs to provide complete detail in this file, especially for the specifications pertaining to derived variables. In addition, sponsors should also make certain that the code list and origin for each variable are clearly and easily accessible from the define file. The version of any external dictionary should be clearly stated both in the define file and, where possible, in the updated Trial Summary (TS) domain (SDTMIG 3.1.2 or greater; SENDIG 3.0 or greater). The internal dataset label should also clearly describe the contents of the dataset. For example, the dataset label for an efficacy dataset might be "Time to Relapse (Efficacy)."

Separate define files should be included for each type of electronic dataset submission, i.e., a separate define file for the SDTM datasets, a separate define file for the SEND datasets, and a separate define file for the ADaM datasets. The define file should be submitted in XML format, i.e., a properly functioning define.xml[28]. In addition to the define.xml, a printable define.pdf should be provided if the define.xml cannot be printed [29]. To confirm that a define.xml is printable within the CDER IT environment, it is recommended that the sponsor submit a test version to cder-edata@fda.hhs.gov prior to application submission. If a define.xml version 2.0 or later version is submitted, then a define.pdf does not need to be included in the submission. The *Standards Catalog* lists the currently supported version(s) of define.xml. Sponsors should include a reference to the style sheet as defined in the specification and place the corresponding style sheet in the same submission folder as the define.xml file.

4.1.4.5   Data Definition Files for SDTM, SEND, and ADaM
The data definition file describes the metadata of the submitted electronic datasets, and is considered arguably the most important part of the electronic dataset submission for regulatory review. This data definition specification for submitted datasets defines the metadata structures that should be used to describe the datasets and variables. An insufficiently documented data definition file is a common deficiency that reviewers have noted. Consequently, the sponsor needs to provide complete detail in this file, especially for the specifications pertaining to derived variables. In addition, sponsors should also make certain that the code list and origin for each variable are clearly and easily accessible from the data definition file. The version of any external dictionary should be clearly stated both in the data definition file and, where possible, in the updated Trial Summary (TS) domain (i.e., SDTMIG 3.1.2 or greater; SENDIG 3.0 or greater). The internal dataset label should also clearly describe the contents of the dataset. For example, the dataset label for an efficacy dataset might be "Time to Relapse (Efficacy)."

Separate data definition files should be included for each type of electronic dataset submission, i.e., a separate data definition file for the SDTM datasets of a given clinical study, a separate data definition file for the SEND datasets of a given nonclinical study, and a separate data definition file for the ADaM datasets of a given clinical study. The data definition file should be submitted in XML format, i.e., a properly functioning define.xml[27]. In addition to the define.xml, a printable define.pdf should be provided if the define.xml cannot be printed [28]. To confirm that a define.xml is printable within the CDER IT environment, it is recommended that the sponsor submit a test version to cder-edata@fda.hhs.gov prior to application submission. If a define.xml version 2.0 or later version is submitted, then a define.pdf does not need to be included in the submission. The *Standards Catalog* lists the currently supported version(s) of define.xml. Sponsors should include a reference to the style sheet as defined in the specification and place the corresponding style sheet in the same submission folder as the define.xml file.

SOME DIFFERENCES IN WORDING TO BE MORE SPECIFIC IN V2.3

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CONTINUE   - *UPDATE IN SECTION 5.1*

v2.2

v2.3

5.1 General

The following SDTM domains associated with the listed therapeutic area user guide have not completed testing and acceptance and are not supported at this time.

	SDTM IG Domain	Therapeutic Area User Guide
1.	Healthcare Encounters	Cardiovascular Studies, 1.0; Polycystic Kidney Disease, 1.0; Asthma, 1.0
2.	Microscopic Findings	Tuberculosis, 1.0; Parkinson's,1.0
3.	Morphology	Cardiovascular Studies,1.0; Parkinson's,1.0; Polycystic Kidney Disease,1.0; Alzheimer's,1.0; Multiple Sclerosis,1.0
4.	Procedures	Cardiovascular Studies,1.0; Polycystic Kidney Disease,1.0; Alzheimer's,1.0
5.	Reproductive System	Polycystic Kidney Disease, 1.0
6.	Disease Response	Tuberculosis,1.0
7.	Skin Response	Asthma,1.0

5.1 General

For an SDTM domain associated with a therapeutic area user guide, sponsors should contact the appropriate review division.

*THIS MEANS THAT THE LISTED TAUGS   ARE ACCEPTED , TESTED AND **SUPPORTED***

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CONTINUE - *SECTION 7.1 AND 7.2 ADDED*

v2.2

v2.3

7. Electronic Submission Format

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7.1 eCTD File Directory Structure

Study datasets and their supportive files should be organized into a specific file……

Only headline added for the first part

7.2 eCTD Test Submission

CDER would like to work closely with people who plan to provide a submission using the eCTD specifications and offer to help smooth the process. The agency also offers a process for submitting sample standardized datasets for validation. Sample submissions are tests only and not considered official submissions. They are not reviewed by FDA reviewers at any time. The Electronic Submissions page provides more information regarding test submission process[48]

Very important part

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