Changes in FDA technical Conformance Guide v5.1 to v5.6

Marion Friebel, Parexel

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Revision History

FDA Study Data Technical Conformance Guide v5.1 to v5.6

Section	Title	Version
Footnotes	*Updated links in footnotes referring to FDA Guidance documents*	*5.1*
Footnotes	*Added footnotes relating to the expectation of SEND datasets for nonclinical EFD studies*	*5.1*
Footnotes	*Added links to the FDA Data Standards Catalog and SAS Help Center*	*5.5*
3.3.1	(v5 Transport Format) – Heading changed, content updated	5.1
3.3.2	(Dataset Size) – Updated for clarity	5.5
3.3.3	(Dataset Column Length) – Updated for clarity	5.5
4.1.1.3	(SDTM Domain Specifications) – Addition of Immunogenicity Domain (IS)	5.1
4.1.1.3	(SDTM Domain Specifications) – Updated language under LB Domain (Laboratory)	5.4
4.1.1.3	(SDTM Domain Specifications) – Added PC Domain (Pharmacokinetic Concentration) and PP Domain (Pharmacokinetic Parameters)	5.5
4.1.1.3	(SDTM Domain Specifications) – Added SV Domain (Subject Visits)	5.5
4.1.1.3	(SDTM Domain Specifications) – Updated to address LOINC	5.6
4.1.2.6	(Key Efficacy and Safety Data) – Language added regarding analysis of immunogenicity	5.1
4.1.3.1	*(Definition) – SEND definition updated to match the SDTM definition under Section 4.1.1.1*	*5.1*
4.1.3.2	*(General Considerations) – Updated for clarity*	*5.5*
4.1.3.3.	*(SEND Domain Specification) – Language updated*	*5.1*
4.1.3.3.	*(SEND Domain Specifications) – PC Domain (Pharmacokinetic Concentration) updated for*	*5.5*
4.1.3.3.	*(SEND Domain Specifications) – Updated Custom Domains to include SENDIGv3.1.1*	*5.5*
4.1.3.4.1	*(Scope of SEND for SENDIGv3.0 and v3.1) – Language updated to match the Scope of SENDIG-DARTv.1.1*	*5.1*
4.1.3.4.1	*(Scope of SEND for SENDIGs v3.0, v3.1 and v3.1.1) – Updated to include mentions of SENDIGv3.1.1*	*5.5*
4.1.3.4.1	*(Scope of SEND for SENDIGs v3.0, v3.1 and v3.1.1) – Section C updated for clarity.*	*5.5*
4.1.3.4.2	*(Scope of SEND for SENDIG-Animal Rule v1.0) – Updated for clarity*	*5.6*
4.1.3.4.3	*(Scope of SEND for SENDIG-DARTv1.1 for CDER) – Provided clarification on the expectation of SEND*	*5.1*
4.1.3.4.3	*(Scope of SEND for SENDIG-DARTv1.1 for CDER) – Sections H, I, J, and K, updated for clarity*	*5.5*

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Revision History- Continue

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Section	Title	Version
4.1.4.1	(Variables in SDTM and SEND: CDISC Required, Expected, and Permissible) – Updated to address baselines	5.5
4.1.4.5	(Data Definition Files for SDTM, SEND, and AdaM) – Updated language for Define-XML	5.1
4.1.4.5	(Data Definition Files for SDTM, SEND, and AdaM) – Updated language	5.3
4.1.4.7.1	*(SEND Requirements During the COVID-19 Public Health Emergency) – Updated language due to the expiration of the COVID-19 PHE*	*5.2*
4.1.4.7.1	*(SEND Requirements During the COVID-19 Public Health Emergency) – Language added to address the end of the 180-day wind-down period for the modification to the SEND requirement*	*5.5*
5.3	(List of FDA Technical Specification Documents) – Section updated	5.6
6.1.3	(Maintenance of Controlled Terminologies) – Updated for clarity	5.5
6.5.1.1	(General Considerations) – Updated for clarity	5.1
6.5.1.1	(General Considerations) – Language added to reflect CDER preferences	5.5
6.7	(Laboratory Tests) – Updated for clarity	5.6
Appendix C	*Updated link for MED-RT terminology*	*5.1*
Appendix C	*Added the following TSPARMCDs: PPTCNAM, PPTEGID, PPTEGSYM, PPTMDA*	*5.5*
Appendix D	Updated list of SDO properties that align or do not align with current CBER and CDER business needs	5.5
Appendix F	Table 6 updated for clarity	5.1
Appendix G	Updated for clarity	5.5
Appendix H	*HHS Declared Public Health Emergencies and Modifications to Data Standards Requirements – Added*	*5.2*
Appendix H	*Language added to address the end of the 180-day wind-down period for the modification to the SEND requirement*	*5.5*
Glossary	Addition of MED-RT	5.1
Glossary	Addition of PHE and SDO	5.5

Red marked changes in *italic* not explained in presentation

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Definition

- This Study Data Technical Conformance Guide provides specification, recommendations and general considerations on how to submit standardized study data using FDA–support
- The guide is separated in the same sections as before:

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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Definition- Continue

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 therapeutic area extensions of FDA-supported standards.

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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Changes in Section 3.3.1 , v5.1

3.3.1 v5 Transport Format

The Transport Format (XPORT) Version 5 is the file format for the submission of all electronic datasets.[22] XPORT is an open file format published by SAS Institute for the exchange of study data. Data can be translated to and from XPORT to other commonly used formats without the use of programs from any specific vendor. There should be one dataset per transport file, and the dataset in the transport file should be named the same as the transport file (e.g., 'ae' and ae.xpt, 'suppae' and suppae.xpt, 'lb1' and lb1.xpt).

XPORT files can be created by the COPY Procedure in SAS Version 5 and higher of the SAS Software. SAS Transport files processed by the SAS CPORT cannot be reviewed, processed, or archived by FDA. Sponsors can find the record layout for SAS XPORT transport files through SAS technical document TS-140.[23] All SAS XPORT transport files should use .xpt as the file extension, and the files should not be compressed. Note also that SAS custom formats should NOT be used in submissions to the FDA.

- Type of change: added text

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Changes in Section 3.3.2 , v5.5

- (Dataset Size) – Updated for clarity

Each dataset should be provided in a single transport file. The maximum size of an individual dataset that FDA can process depends on many factors. Datasets greater than 5 gigabytes (GB) in size should be split into smaller datasets no larger than 5 GB. Sponsors should submit these smaller datasets, in addition to the larger non-split datasets, to better support regulatory reviewers. The split datasets should be placed in a separate sub-directory labeled 'split' (See section 7.2). A clear explanation regarding how these datasets were split needs to be presented within the relevant data RG.

- Type of change: not clear to me

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Changes in Section 3.3.3 , v5.5

- (Dataset Column Length) – Updated for clarity

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.

18, not 200. If datasets are split according to section 3.3.2, reduce variable length before datasets are split. Care should be taken to avoid accidental truncation of data through dataset merges.

- Type of change: redundant text deleted or modified

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Changes in Section 4.1.1.3 , v5.1(IS) and v5.4/5.6 (LB)

Immunogenicity Domain (IS)

The IS domain should be submitted for all individual studies where immunogenicity data was collected. Titer results should be included in the IS domain and not as part of supplemental domains. ISTEST and ISTESTCD names should be specific to the test being performed and should not use the same generic name across different tests (i.e., referring to multiple 'Screening', 'Confirming', or 'Titer' neutralizing antibody test results as ISTEST="Antibody').

- Type of change: new text
- (SDTM Domain Specifications) – Updated language under LB Domain (Laboratory) to address LOINC

For clinical studies, please submit two separate domains for lab results. The LB domain should contain SI units in LBSTRESU for the SI results in the LBSTRESC and LBSTRESN fields. An additional custom domain called LC structured identically to LB should contain conventional units in --STRESU for the results in conventional units in the --STRESC and --STRESN variables. It is ideal if both conventional and SI units come directly from the lab vendor.

There is no expectation to submit the new LB variables found in SDTMv2.0 and SDTMIGv3.4, which may support individual parts of a LOINC. These new variables should only be submitted in LB datasets when it is medically or scientifically appropriate to do so.

- Type of change: new text

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Changes in Section 4.1.1.3 , v5.5

> (SDTM Domain Specifications) – Added PC Domain (Pharmacokinetic Concentration) and PP Domain (Pharmacokinetic Parameters)

PC Domain (Pharmacokinetic Concentration)

All planned samples should have a record in this domain. If a sample analysis was planned but no result is available, a reason for why the test was not done should be included in PCREASND. Values for the lower limit of quantitation should be included in PCLLOQ and correspond to those units in PCSTRESU. Naming for all timepoints and visits should be consistent with the data provided in the clinical study report. Naming for all analytes should be consistent with the data represented in the pharmacokinetic parameters (PP) domain. If data for an analyte per subject is present in PP, there should be information for that analyte per subject per sample in PC.

PP Domain (Pharmacokinetic Parameters)

Naming for all visits should be consistent with the data provided in the clinical study report. Naming for all analytes should be consistent with the data represented in the pharmacokinetic concentrations (PC) domain.

› Type of change: new text

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Changes in Section 4.1.1.3 , v5.5

- (SDTM Domain Specifications) – Added SV Domain (Subject Visits)

SV Domain (Subject Visits)
It is the current preference of the Agency that for all clinical studies, subject visit data for scheduled (whether or not they occurred), and unscheduled visits be submitted in one single dataset structured as the current CDISC Subject Visits (SV) domain. It is also Agency preference that three non-standard variables (NSVs) for missed visits, --REASOC (Reason for Occur Value), --EPCHGI (Epi/Pandemic Related Change Indicator), and --CNTMOD (Contact Mode), outlined in the CDISC property "Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic" be included within the SV domain and not within the supplemental SUPPSV domain or in other SDTM datasets. Submitting subject visits information in one single structured dataset allows both the human and technology consumer of this information to operate efficiently and with confidence that all visit data are considered during regulatory review.

- Type of change: new text

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Changes in Section 4.1.2.6 , v5.1

- (Key Efficacy and Safety Data) – Language added regarding analysis of immunogenicity

Sponsors should submit ADaM datasets to support efficacy and safety analyses (including analysis of immunogenicity). At least one dataset should be referenced in the data definition file as containing the primary efficacy variables. Further, variables and parameters pertaining to the primary and secondary endpoints of a study, along with their derivations (as applicable), should be provided as well as documented appropriately (i.e., variable-level metadata or parameter value-level metadata) in the data definition file.

- Type of change: clarification

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Changes in Section 4.1.4.1 , v5.5

- (Variables in SDTM and SEND: CDISC Required, Expected, and Permissible) – Updated to address baselines

FDA recognizes that SDTM contains certain operationally derived variables that have standard derivations across all studies (e.g., --STDY, EPOCH). If the data needed to derive these variables are missing, then these variables cannot be derived and the values should be null. The following are examples of some of the permissible and expected variables in SDTM and SEND that should be included, if available:

1. Clinical baseline flags (e.g., last non-missing value prior to first dose) for laboratory results, vital signs, ECG, pharmacokinetic concentrations, and microbiology results. Nonclinical baseline flags (e.g., last non-missing value prior to first dose in parallel design studies) for laboratory results, vital signs, body weight, cardiovascular test results, respiratory test results, and ECG results. Currently for SDTM and SEND, baseline flags should be submitted if the data were collected or can be derived.

- Type of change: clarification

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Changes in Section 4.1.4.5 , v5.1 and v5.3

- (Data Definition Files for SDTM, SEND, and AdaM) – Updated language for Define-XML
- (Data Definition Files for SDTM, SEND, and AdaM) – Updated language

define.xml.[46] In addition to the define.xml, a printable define.pdf should be provided if the define.xml cannot be printed.[47] 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. The Catalog lists the currently supported version(s) of Define-XML. It should be noted that Define-XML version 2.0 or later is strongly preferred. Sponsors should include a reference to the style sheet as defined in the specification (as listed in the Catalog) and place the corresponding style sheet in the same submission folder as the define.xml file. Within the eCTD study tagging file (STF), valid file-tags for define.xml are 'data-tabulation-data-definition' for SEND or SDTM datasets or 'analysis-data-definition' for ADaM datasets.

- Type of change: clarification

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Changes in Section 5.3 , v5.6

- (List of FDA Technical Specification Documents) – Section updated

5.3.9 Submitting Patient-Reported Outcome Data in Cancer Clinical Trials

5.3.10 Submitting Clinical Trial Datasets and Documentation for Clinical Outcome Assessment Using Item Response Theory

- Type of change: added text

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Changes in Section 6.1.3 , v5.5

- (Maintenance of Controlled Terminologies) – Updated for clarity

- Before

sponsor submit the concept to the appropriate terminology maintenance organization as early as possible to have a new term added to the standard dictionary. FDA considers this *good terminology management practice*. The creation of custom terms (i.e., so-called *extensible* code lists) for a submission is discouraged, because this does not support semantically interoperable study data exchange. Furthermore, the use of custom or extensible code lists should not be interpreted to mean that sponsors may substitute their own nonstandard terms in place of existing equivalent standardized terms. Sponsors should allow sufficient time for a proposed term to be reviewed and included in the terminology, as it is desirable to have the term incorporated into the standard terminology before the data are submitted. If custom terms cannot be avoided, the submitter should clearly identify and define them within the submission, reference them in the relevant RGs, and use them consistently throughout the application.

- After

early as possible to have a new term added to the standard dictionary. FDA considers this *good terminology management practice*. The creation of custom terms for a submission is discouraged. Furthermore, the use of custom or extensible code lists should not be interpreted to mean that sponsors may substitute their own nonstandard terms in place of existing equivalent standardized terms. Sponsors should allow sufficient time for a

- Type of change: redundant text deleted

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Changes in Section 6.5.1.1 , v5.1 and v5.5

- (General Considerations) – Updated for clarity

The Veterans Administration's Medication Reference Terminology (MED-RT)[62] should be used to identify the pharmacologic class(es) of all active investigational substances that are used in a study (either clinical or nonclinical). This information should be provided in the SDTM TS domain when a full TS is indicated. The information should be provided as one or more records in TS, where TSPARM = "Pharmacologic Class".

- Before it was TSPARMCD="PCLAS"

- (General Considerations) – Language added to reflect CDER preferences

pharmacologic classes of approved moieties.[64] If the established pharmacologic class is not available for an active moiety, then the sponsor should discuss the appropriate MOA, PE, and CS terms with the review division. For unapproved investigational active moieties where the pharmacologic class is unknown, the "Pharmacologic Class" record may not be available. FDA does not recommend the use of general terms such as "small molecule," "large molecule" and "peptide" to indicate the pharmacologic class.

- Type of change: new text

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Changes in Section 6.7.1.1 , v5.5

- (Laboratory Tests) – Updated for clarity

The Logical Observation Identifiers Names and Codes (LOINC) is a clinical terminology housed by the Regenstrief Institute LOINC codes are universal identifiers for laboratory and other clinical observations that enable semantically interoperable clinical data exchange. The laboratory portion of the LOINC database contains the categories of chemistry, hematology, serology, microbiology (including parasitology and virology), toxicology, and more. The SDTM standard supports LOINC codes using the LBLOINC variable. LOINC codes should not be added to SEND datasets.

- Type of change: deleted text

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Changes in Appendix D v5.5

- Updated list of SDO properties that align or do not align with current CBER and CDER business needs

Immediately below is a list of SDO properties that have been evaluated by CBER and CDER and are considered to align with their current business needs.

- Occurrence Dataset Structure (OCCDS) v1.0

Immediately below is a list of SDO properties that have been evaluated by CBER and CDER and are not considered to align with their current business needs. Consider refering to FDA comments that were submitted to the SDO for more details. This list may not be comprehensive of all properties and absence form this list does not indicate encouragement to use. Consult with your division for more specific instructions:

- OCCDS v1.1
- ADaM Examples of Traceability v1.0
- ADaM Metadata Submission Guidlinesv1.0
- CDISC Document: Interim User Guide for COVID-19
- CDISC Document: Guidance for Ongoing Studies Disrupted by COVID-19

- Type of change: new text

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Changes in Appendix F v5.1

- Table 6 updated for clarity (changes for clinical studies extracted)

Application Type	Data Type	Modules and Submodules	Expectation by CDER	Expectation by CBER

- Table header before

Data Type	Modules & Submodules	Center	Application Type	Study Start Date	Requirement
Clinical	5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	CDER & CBER	NDA, BLA, ANDA	On/Prior to December 17, 2016	Submit simplified ts.xpt if study contains an xpt dataset (other than ts.xpt)
				After December 17, 2016	Comply with CDISC standards
			Commercial IND	Rejection criteria not applied	

- Type of change: simplify content

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Changes in Glossary v5.1 and v5.5

MED-RT:	Medication Reference Terminology
PHE:	Public Health Emergency
SDO:	Standards Development Organization

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Thank you