THE DRIVE TO INCORPORATE STANDARDIZED NONCLINICAL DATA INTO REGULATORY SUBMISSIONS THROUGH COLLABORATION

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SEND Overview

What is SEND?

- The Standard Exchange of Nonclinical Data (SEND) is the FDA's mandate for the submission of nonclinical study data to the Center for Drug Evaluation and Research (CDER).
- The standards are based on the Study Data Tabulation Model (SDTM) and intended to guide the submission of nonclinical data in a consistent format with standard terminology.
- The SEND Implementation Guide (SENDIG), published by Clinical Data Interchange Standards Consortium (CDISC), defines the structure, organization, and format of nonclinical tabulation datasets.
- The SEND data package consists of the datasets (.xpt), Define.xml and a NonClincal Study Data Reviewer's Guide (nSDRG).

Why is SEND Important?

- FDA's efforts to develop an electronic repository for all submitted study data.
- Rapid and easy access to complex data - resulting in faster FDA review and potential for faster approval.
- Analytical and visualization tools to query data rapidly across species, compound class or therapeutic area.

SEND Mandate Current and Future State

SENDIG Version	Study Type	Study Start Date	Submission Type
3.0	Single- and Repeat-Dose Toxicity Carcinogenicity	After 17-Dec-2016	NDA, BLA, ANDA
		After 17-Dec-2017	IND
3.1	Safety Pharmacology in addition to studies listed above for 3.0	After 15-Mar-2019	NDA, BLA, ANDA
		After 15-Mar-2020	IND
Future-TBD	Reproductive Toxicology (DART)	Future-TBD	IND, NDA, BLA, ANDA

Refer to the current FDA Data Standards Catalog and the *Providing Regulatory Submissions in Electronic Format – Standardized Study Data Guidance for Industry* guidance document.

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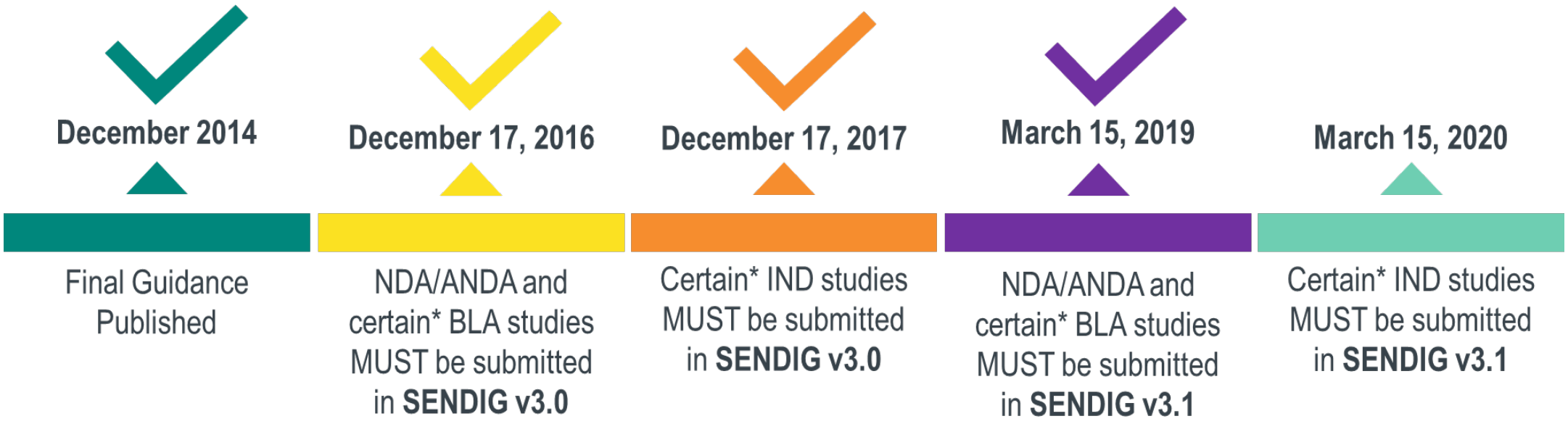
Standards Implementation Timeline



For details, please reference the FDA Study Data Catalog and the *Providing Regulatory Submissions in Electronic Format – Standardized Study Data Guidance for Industry* (December 2014).

SEND Data Coordinator - Responsibilities

- Adapt and harmonize study plans and templates as well as study related processes to fulfill SEND requirements
- Check of study design in terms of SEND requirements and derivation of SEND trial designs
- For internal studies, generate and validate SEND files and supplemental documentation for the submission process
- For external studies, responsible for integrating internal data, quality checks of SEND files and documents and implementation of necessary revisions and finalization in collaboration with Study Monitors and CROs
- Closely interact with key interface partners (e.g. Study Directors, Study Monitors, Laboratory Scientists, Submission Teams) to facilitate completion and technical/scientific accuracy of SEND data
- Prepare Nonclinical Study Data Reviewer's Guide (nSDRG), ensure accuracy of the define.xml, and contribute to the completion of the nonclinical section of the Study Data Standardization Plan (SDSP) to support study and submission level SEND data requirements

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SEND Data Coordinator – Responsibilities (continued)

- Address feedback and inquiries from FDA on SEND data in collaboration with functional scientists, CROs and the submission team
- Manage and implement controlled terminology changes as needed
- Lead the implementation of upcoming new SEND domains and standards and follow-up with regulatory trends on SEND development
- Work closely with software application managers and the vendors to implement necessary SEND application changes/updates
- Develop training processes and conduct training sessions
- For future additional resource needs, identify/qualify/manage external service providers
- Develop/leverage internal and external networks related to SEND processes (e.g. connectivity with CDISC, PhUSE)

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External Team Involvement

- Member of PhUSE and CDISC global organizations
- Influence the development and implementation of SEND
- Define the SEND standards that align with industry practices
- Contribute toward drafting guidance published by the FDA
- Participate in FDA pilots for the evaluation of transmission and SEND compliance of study data
- Collaborate with the FDA at face-to-face sessions to further the standards development

Internal & External Collaboration

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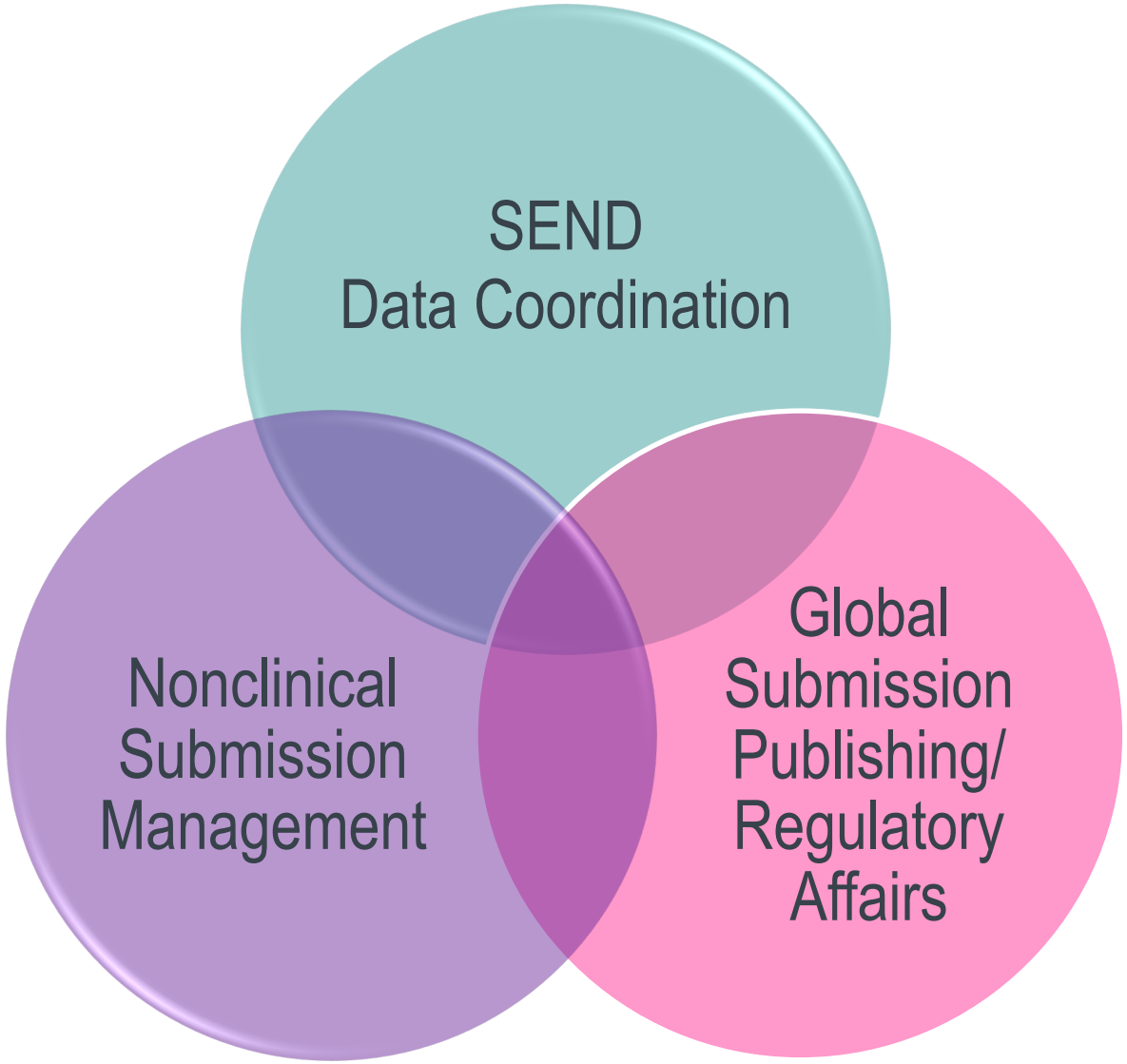
Submission Package Collaboration

- Sponsors must now incorporate the nonclinical study data (SEND) and the clinical study data (SDTM) in the final submission package (M4 & M5).
- This represents a significant change in the established process of planning and preparing a submission package.
- Coordination among multiple teams to compile the requisite study data and review the final eCTD build prior to submission to FDA is critical.



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How will the Agency know what to expect in Module 4?
Study Data Standardization Plan

4. LIST OF STUDIES AND STANDARDS

4.1 Nonclinical

Study Identifier	Brief Title	Study Type	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Module 4.2.3.2 Repeat Dose Toxicity						
Insert Study ID	Insert title	Repeat-Dose Toxicity	Completed	yyyy-mm-dd	SEND IG x.x define.xml x.x	CDISC SEND Terminology yyyy-mm-dd

- For clinical and nonclinical studies, sponsors should provide a plan describing the submission of standardized study data to FDA. The nonclinical table in the SDSP will contain information similar to that presented here.
- The SDSP should be provided as specific stage gates (e.g. IND, End of Phase Mtgs, NDA, etc.).
- Development of the SDSP is a joint effort among specific functional areas including clinical, statistics, nonclinical, and regulatory affairs.
- The SDSP is a “living document” that should be periodically updated (not necessary each time a study is initiated).

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Trial Summary Dataset (ts.xpt) – Full vs Simplified

Study Start Date	Application Type	Data Type	Study Section	Required TS File Type (by Center)	
				CDER	CBER
Prior to or on 17-Dec-16	NDA, BLA, or ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	**Simplified TS**	**Not Required**
		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	**Simplified TS**	
Prior to or on 17-Dec-17	Commercial IND	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	**Simplified TS**	**Not Required**
		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	**Not Required**	
After 17-Dec-16	NDA, BLA, or ANDA	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	**Full TS**	**Not Required**
		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	**Full TS**	
After 17-Dec-17	Commercial IND	Nonclinical	4.2.3.1, 4.2.3.2, 4.2.3.4	**Full TS**	**Not Required**
		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	**Not Required**	

If studies are included in the submission with a study start date (SSD) prior to the applicable standard, a 'simplified' ts.xpt containing the STSTDTC (Study Start Date) should be included as per the guidance from the *Technical Rejection Criteria for Study Data*. This Study start date in the ts.xpt, referenced in the Study Tagging File (STF), indicates to the agency whether or not to expect full datasets.

For nonclinical studies, the study start date is the date on which the study protocol or plan is approved (signed) by the Study Director, also known as the study initiation date.

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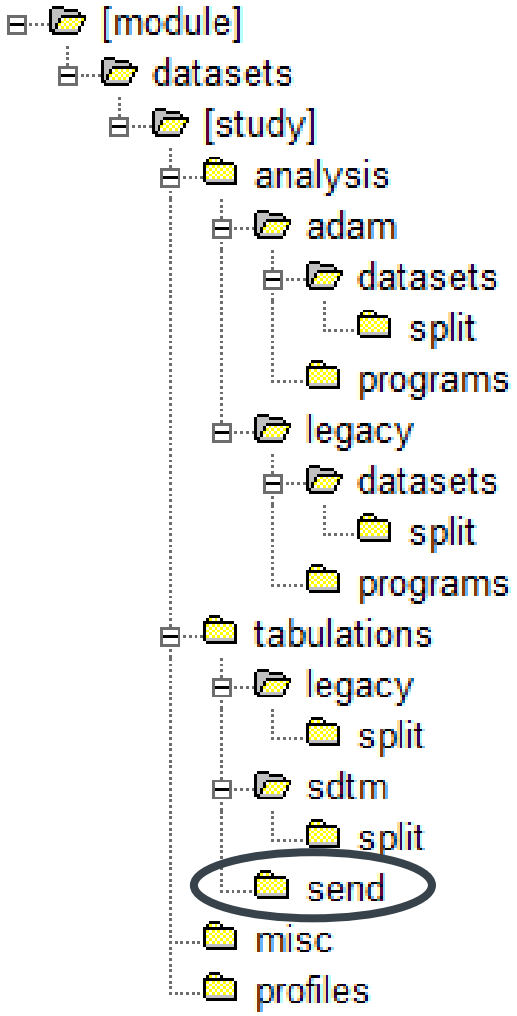
M4 (Non-Clinical) eCTD Folder Structure

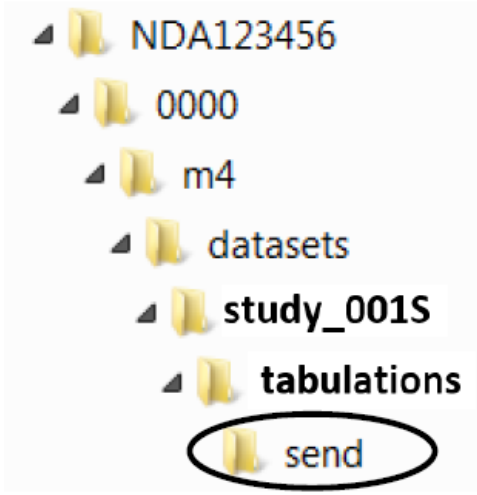
Study datasets and their supportive files should be organized into a specific file directory structure when submitted in the eCTD format.

The file folder structure for study datasets is summarized in these figures.

These folders must NOT be renamed.



Example
Study_001S
(Standardized Data Tabulation SEND Datasets):



Refer to the following guidance documents: *Study Data Technical Conformance Guide* and *Providing Regulatory Submissions In Electronic Format — Standardized Study Data*

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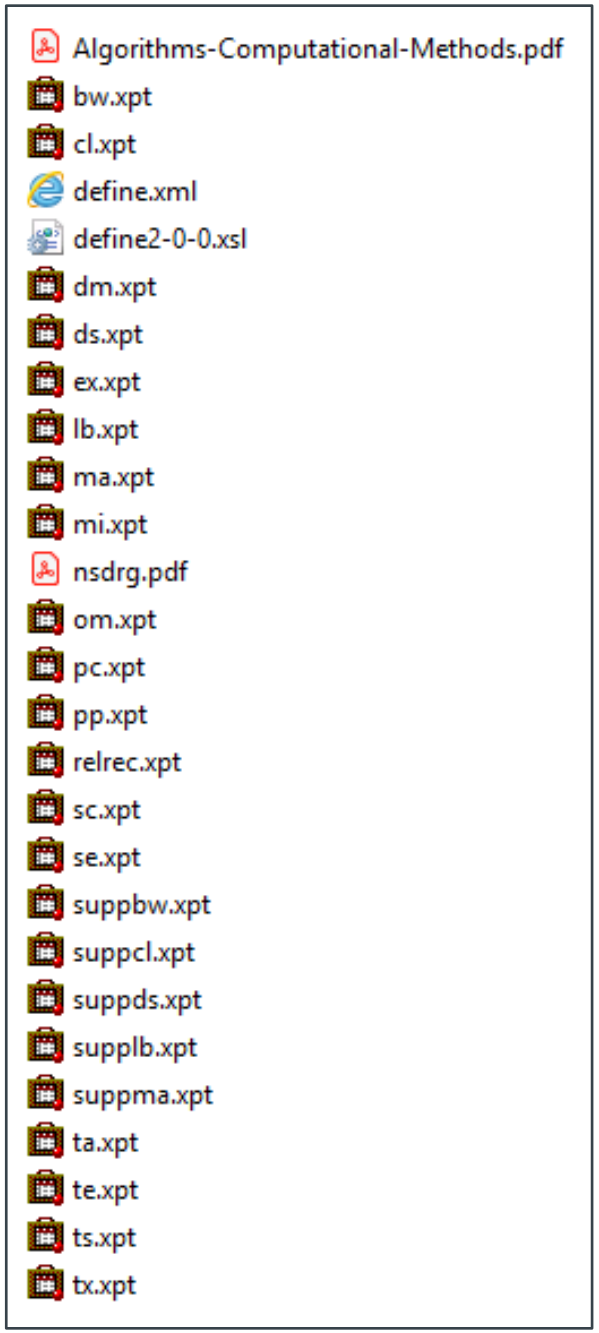

Example of a Nonclinical study dataset package

- Includes the datasets (.xpt), define.xml, nsdrg, and supplement documents (as applicable).
- These files must not be renamed and must be incorporated into the appropriate subfolder of the eCTD in the order provided.

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Assembly Review and Study Data Conformance

- Nonclinical Submission Management and SEND Data Coordinators perform the Assembly Review of the nonclinical study data for all submissions released from Global Submissions Publishing (GSP)/Regulatory Affairs. This check is to ensure the complete, accurate inclusion and organization of all nonclinical submission content files and metadata in the published submission.

- FDA may refuse to file or receive any electronic submission whose study data do not conform to the required standards specified in the *FDA Data Standards Catalog* or comply with the rejection criteria described in the *Technical Rejection Criteria for Study Data* guidance.

- If a file is referenced within a study section in Module 4 or 5, a Study Tagging File (STF) and ts.xpt must be present to identify the study ID and study start date to which the file belongs.

The Study ID must be consistent across all the files being submitted for the same study (i.e. STF, ts.xpt, dm.xpt)

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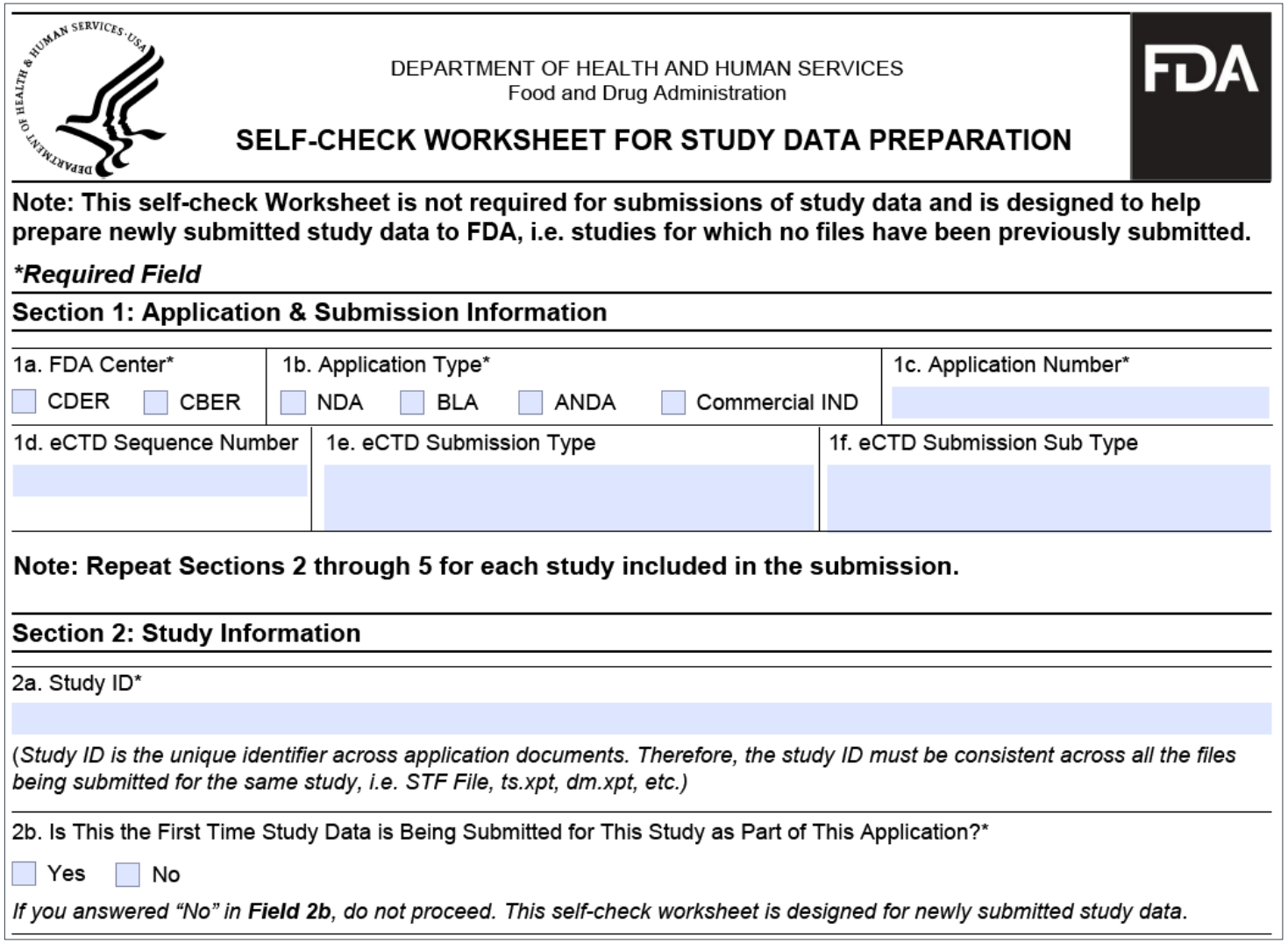
Assembly Review and Study Data Conformance



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

SELF-CHECK WORKSHEET FOR STUDY DATA PREPARATION

FDA

Note: This self-check Worksheet is not required for submissions of study data and is designed to help prepare newly submitted study data to FDA, i.e. studies for which no files have been previously submitted.

Required Field

Section 1: Application & Submission Information

1a. FDA Center*	1b. Application Type*	1c. Application Number*
☐ CDER ☐ CBER	☐ NDA ☐ BLA ☐ ANDA ☐ Commercial IND	

1d. eCTD Sequence Number	1e. eCTD Submission Type	1f. eCTD Submission Sub Type

Note: Repeat Sections 2 through 5 for each study included in the submission.

Section 2: Study Information

2a. Study ID*

(*Study ID is the unique identifier across application documents. Therefore, the study ID must be consistent across all the files being submitted for the same study, i.e. STF File, ts.xpt, dm.xpt, etc.)*

2b. Is This the First Time Study Data is Being Submitted for This Study as Part of This Application?*

☐ Yes ☐ No

*If you answered "No" in **Field 2b**, do not proceed. This self-check worksheet is designed for newly submitted study data.*

To assist sponsors when submitting study data, the FDA has created the *Technical Rejection Criteria Self-Check Worksheet* (PDF); this will help prepare newly submitted study data to the FDA.

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The Journey Continues…

SEND is an evolving standard – and one with several challenges to address before the industry can fully meet requirements – it may take some time for both the FDA and Industry to fully realize the benefits of SEND.

As new implementation guides are issued with new domains, new study types, new standards, we all need to work together, both with our internal and external industry partners, to take the steps necessary for compliance.

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THANK YOU

We would like to acknowledge Linda Hunt from the Submissions Management Group for her contribution and guidance.

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