Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

DRAFT GUIDANCE

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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)

February 2014
Electronic Submissions
Revision 1
Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Standardized Study Data

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I. INTRODUCTION

This draft guidance provides, among other things, the requirements for a valid electronic submission of standardized study data under section 745A(a) of the FD&C Act. In accordance with section 745A(a), following the issuance of a final guidance on this topic, study data contained in the submission types identified in this guidance must be submitted electronically in a format that FDA can process, review and archive. For additional information on how FDA intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act please see the “Guidance for Industry Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act” (745A Implementation Guidance).

When finalized, this guidance (eStudy Data guidance) will implement the electronic submission requirements of section 745A(a) of the FD&C Act for study data contained in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) by specifying the format for the electronic submission of such submissions. Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed, unless exempted from the electronic submission requirements (see section II.B).

In section 745A(a), Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements by specifying the format for such submissions in guidance. Accordingly, to the extent that this document provides such requirements under section 745A(a) of the FD&C Act, indicated by the use of the words must or required, this document is not subject to the usual restrictions in FDA’s good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d).

To comply with the GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in

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1 This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

2 For purposes of this guidance, quality control or validation data submitted in support of licensure of blood components are not considered study data.
this guidance because it is not an accurate description of the effects of this guidance. Insofar as
this guidance specifies the format for electronic submissions, or provides “criteria for . . .
exemptions” pursuant to section 745A(a) of the FD&C Act, it will have binding effect.

This guidance supersedes the draft guidance for industry Providing Regulatory Submissions in
Electronic Format – Standardized Study Data that was issued in February 2012.

II. REQUIREMENT TO SUBMIT ELECTRONIC STANDARDIZED STUDY DATA

A. For what submission types is an electronic submission of standardized study
data required?

Electronic submissions of standardized study data will be required for the following submission
types:

- Certain investigational new drug applications (INDs)
- New drug applications (NDAs)
- Abbreviated new drug applications (ANDAs)
- Certain biologics license applications (BLAs)

This also includes all subsequent submissions, including amendments, supplements, and reports
to one of the submission types identified above. Study data contained in amendments,
supplements, and reports must be submitted electronically in the specified format, even if the
original application was submitted to FDA prior to implementation of the electronic submission
requirements. Study data in submissions that are not submitted electronically will not be filed,
unless exempt from the electronic submission requirements or unless FDA has granted a waiver.

See section II.D below for information on waivers of the requirement to use the specified
standards, formats, or terminologies.

B. What types of submissions are exempted from the electronic submission
requirements for standardized study data?

The statute allows FDA to set forth criteria for exemptions from the electronic submission
requirements. Accordingly, FDA will exempt all submissions regarding devices that are
regulated by CBER as biological products under Section 351 of the PHS Act,\(^3\) and study data
contained in noncommercial INDs from the electronic submission requirement under section
745A(a). For purposes of this guidance, the term “noncommercial products” refers products that
are not intended to be distributed commercially and includes investigator-sponsored INDs,
emergency use INDs, and treatment INDs. Although these submissions of study data will be
exempt, FDA also accepts their submission in a standardized electronic format as described in
this guidance document.

\(^3\) Devices regulated by CBER as biological products under Section 351 of the PHS Act are generally those intended
for use in screening donated blood for transfusion-transmissible diseases.
C. What are the requirements that must be followed for electronic submission of standardized study data?

Under section 745A(a) of the FD&C Act, electronic submissions “shall be in such electronic format as specified by [FDA].” FDA has determined that study data contained in the electronic submissions described in section II.A must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of study data that use the standards, formats, and terminologies specified in the Data Standards Catalog to the FDA’s Study Data Standards Resources Web page and incorporated by reference into this document.

The Data Standards Catalog provides a listing of supported and/or required standards, their uses, the date FDA will begin (or has begun) to support a particular standard, and the date support ends (or will end), the date the requirement to use a particular standard will begin (or has begun) and the date such requirement ends (or will end), as well as other pertinent information. The Agency may refuse to file an electronic submission unless its study data conforms to the required standards, formats, and terminologies specified in the Data Standards Catalog.

When planning a study (including the design of case report forms, data management systems, and statistical analysis plans), the sponsor or applicant must determine which FDA-supported standards, formats and terminologies to use or request a waiver as described in section II.D. FDA-supported standards include the following:

1. File Format Standard

A file format standard specifies a particular way that information is encoded in a computer file. Specifications for a format permit the file to be written according to a standard, opened for use or alteration, and written back to a storage medium for later access. Some file formats in widespread use are proprietary; others are open source. Examples of file format standards currently supported by FDA include: Adobe Acrobat Portable Document (.pdf), SAS Institute Transport File format (.xpt), text files (.txt), and Extensible Markup Language (.xml).

2. Study Data Exchange Standard

Study data exchange standards describe a standard way of exchanging data between computer systems. Exchange standards may describe the data elements and relationships necessary to achieve the unambiguous exchange of information between disparate information systems. The Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) is an example of an exchange standard for study data that is currently supported.

3. Analysis Standard

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4 Available at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

5 For the purposes of this document, “supported” means the receiving Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified file format.
Analysis standards describe a standard presentation of the data intended to support analysis. Analysis standards include extraction, transformation, and derivations of the original data. An example is the CDISC Analysis Data Model (ADaM) which specifies standards for analysis datasets currently supported by FDA. As a practical matter, most of the existing data standards are not in one-to-one correspondence with the various types of data standards. For example, the CDISC SDTM may be used as an exchange standard (when combined with the SAS transport file format standard) and as an analysis standard to support simple analyses (e.g., simple analyses of demographics or adverse events).

4. Terminology Standard

The use of terminology standards, also known as controlled terminologies or vocabularies, is an important component of study data standardization and is a critical component of achieving semantically interoperable data exchange. Terminology standards specify the key concepts that are represented as preferred terms, definitions, synonyms, codes, and code system. Terminology standards are maintained by external organizations (i.e., external to the sponsor or applicant). Sponsor- or applicant-defined custom terms are not considered controlled terminologies. Examples of controlled terminologies include:

- The National Drug File (NDF)—Reference Terminology for drug classifications
- CDISC Controlled Terminology
- Medical Dictionary for Regulatory Activities (MedDRA)

D. Will FDA issue waivers of the electronic submission requirements for standardized study data?

Electronic submissions of study data must be in a format that FDA can review, process, and archive. Currently, the Agency can process, review, and archive electronic submissions of study data that use the standards, formats, and terminologies specified in the Data Standards Catalog posted to the FDA’s Study Data Standards Resources Web page.

FDA will not provide waivers to submit data that do not conform to any FDA-supported study data standard. However, sponsors or applicants may apply for a waiver from the requirement to use specific versions of standards, formats, or terminologies. If granted, the waiver enables a

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8 CDISC Controlled Terminology is available at http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc.
9 MedDRA is available at http://www.meddra.org/.
10 Available at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.
sponsor or applicant to submit study data electronically using a non-current version of a standard that was previously supported by FDA.

To apply for a study-specific waiver from the requirement to submit study data in a non-current version of the standards set forth in the Data Standards Catalog, a written request should contain the following:

1. The specific requirement or requirements from which the sponsor or applicant is requesting a waiver
2. The reason the sponsor believes that the waiver is necessary
3. A description of the alternative or alternatives that the sponsor intends to use

FDA encourages the sponsor or applicant to discuss the waiver request prior to or at the pre-IND meeting with the appropriate review division in CDER or CBER and submit the request in writing prior to submitting the IND. If no pre-IND meeting is held, sponsors or applicants are encouraged to contact the review division prior to the pre-BLA meeting to discuss a waiver request.

E. When will electronic submission of standardized study data be required?

For additional information on how FDA intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, including timetable for implementation, please see the 745A Implementation Guidance.

1. Initial Timetable for the Implementation of Electronic Submission Requirements

After we publish a notice of availability of the final guidance in the Federal Register, all studies with a start date twenty-four months after the Federal Register notice must use the appropriate FDA-supported standards, formats, and terminologies specified in the Data Standards Catalog (see section II.C) for NDA, ANDA, and certain BLA submissions. Study data contained in certain IND submissions must use the specified formats for electronic submission in studies with a start date thirty-six months after the Federal Register notice of availability.

The following is an example of how a new electronic submission requirement would be implemented:

On November 15, 2016, FDA publishes a Federal Register notice announcing the availability of the final eStudy Data Guidance. For studies with a start date after November 15, 2018, sponsors or applicants must use the appropriate FDA-supported standards, formats and terminologies specified in the Data Standards Catalog for NDA,
ANDA, and certain BLA submissions. The Data Standards Catalog will list November
15, 2018 as the “date requirement begins.”

2. Version Updates to FDA-Supported Standards, Formats and Terminologies

Periodically, version updates to FDA-supported study data standards, formats, and terminologies are released by Standards Development Organizations (SDOs). Version updates may include:
(1) Content or structural changes (e.g., new SDTM domains or variables) and (2) Typographical errors, corrections, or clarifications that do not result in content or structural changes. Generally, version updates that include content or structural changes would require FDA to execute a testing and acceptance process, while errata, corrections or clarifications would not.

After this guidance is finalized (and the 24- and 36-month timeframes described in section II.E.1 have passed), content or structural version updates will be required in submissions for studies with a start date\(^\text{13}\) that is no earlier than 12 months after the Federal Register notice of availability. The Federal Register notice of availability will specify the effective date for all version updates that will correspond to a specific calendar month (e.g., in the examples below, March).

The following are examples of these types of updates and how they would be implemented:

**Example 1:** CDISC releases a data exchange standard SDTM 4.1 as a version update to SDTM 4.0 on February 15, 2016. The version update includes domain and variable changes to the standard. Following the release by CDISC, FDA will execute an acceptance testing process to determine whether it is able to support the updated version, SDTM 4.1. The acceptance testing process confirms that FDA is able to support the updated version. On May 6, 2016, FDA publishes a Federal Register notice announcing support for the new version, SDTM 4.1, and updates the Data Standards Catalog. The effective date posted in the Federal Register notice is March 15, 2017. Although the new SDTM version 4.1 is supported by FDA as of May 6, 2016 and sponsors or applicants are encouraged to begin using it, the new version will only be required in submissions for studies that start after March 15, 2018. The Data Standards Catalog will list March 15, 2018 as the “date requirement begins.”

**Example 2:** CDISC releases a data exchange standard SDTM 4.1.1 as a version update to SDTM 4.1 on September 18, 2016. The version update SDTM 4.1.1 includes clarifications and corrections to typographical errors in SDTM version 4.1, but no new content or structural changes. FDA will determine when it is able to support the updated version, SDTM 4.1.1, but generally FDA testing will not be required for version updates for errata. On October 3, 2016, FDA updates the Data Standards Catalog indicating

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\(^{13}\) For purposes of this guidance, the study start date is the earliest date of informed consent among any subject that enrolled in the study. For example, see Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC), http://www.cdisc.org.
support for the new version, SDTM 4.1.1. The effective date posted in the Federal
Register notice is March 15, 2017. Although the new SDTM version 4.1.1 is supported
by FDA as of October 3, 2016 and sponsors or applicants are encouraged to begin using
it, the new version will only be required in submissions for studies that start after March
15, 2018, according to the date when SDTM 4.1 was supported by FDA (see example 1
above). The Data Standards Catalog will list March 15, 2018 as the “date requirement
begins.”

Example 3: On January 15, 2018, the SDO releases the PDF version 2.X file format as
an update to PDF version 1.7. Following the release by the SDO, FDA will execute an
acceptance testing process to determine whether it is able to support PDF version 2.X for
study data submissions. The acceptance testing process confirms that FDA is able to
support the updated version. On June 28, 2018, FDA publishes a Federal Register notice
of availability announcing support for the new version, PDF 2.X, and updates the Data
Standards Catalog. The effective date posted in the Federal Register notice is March 15,
2019. Although the new PDF version is supported by FDA and sponsors or applicants
are encouraged to begin using it, PDF 2.X will only be required in submissions for
studies that start after March 15, 2020. The Data Standards Catalog will list March 15,
2020 as the “date requirement begins.”

3. New Standards, Formats and Terminologies

After this guidance is finalized (and the 24- and 36 month milestones discussed above have been
reached), FDA may announce in a Federal Register notice of availability (and guidance, if
necessary) its support for new standards, formats and terminologies. New standards, formats and
terminologies are those that have not been supported by FDA and are not listed in the Data
Standards Catalog at the time this draft guidance is finalized. The Federal Register notice of
availability will specify the effective date for new standards, formats and terminologies that will
correspond to a specific calendar month (e.g., in the examples below, March). New standards,
formats or terminologies will be required in submissions for studies that start 24 months (for
NDAs, ANDAs, and certain BLAs) and 36 months (for certain INDs) after the publication of a
notice of availability in the Federal Register.

The following is an example of a new standard and how it would be implemented:

Following an evaluation, pilot testing, and public input, FDA publishes a Federal
Register notice on March 15, 2016 announcing the retirement of the SAS Transport File
Format version 5 standard, FDA’s support of a new open study data transport standard,
and FDA’s update to the Data Standards Catalog. The effective date posted in the
Federal Register notice is March 15, 2017. Although the new study data transport
standard will be supported by FDA as of March 15, 2016 and sponsors or applicants will
be encouraged to use it, the new standard for study data transport will only be required
in submissions for studies that start after March 15, 2019. The Data Standards Catalog
will list March 15, 2019 as the “date requirement begins.”
III. ADDITIONAL SUPPORT

A. Meetings with FDA

Sponsors and applicants may use established FDA-sponsor meetings (e.g., pre-IND, and end-of-phase 2) to discuss the study data standardization plan and quality parameters, and raise data standardization issues (if any). Discussions about nonclinical study data standardization plans may be initiated at the pre-IND stage and should continue throughout development. Initial discussions about which data standards to use for clinical study data should take place as early as possible during drug development, especially for safety data, but should occur no later than the end of phase 2. In general, the premarketing application meeting is considered too late to initiate data standardization discussions.

Sponsors and applicants may submit technical questions related to data standards at any time to the technical support team identified by each Center (see the Study Data Standards Resources Web page for specific contact information14). Sponsors and applicants may also request a separate Type C meeting to discuss substantive data standardization issues. An example of such an issue might be a sponsor's desire to use a non-supported standard. The request should include adequate information to identify the appropriate FDA staff necessary to discuss the proposed agenda items.

B. Implementation Support

The Draft Study Data Technical Conformance Guide (Conformance Guide) provides nonbinding specifications, recommendations, and general considerations on how to submit standardized study data. The Conformance Guide supplements the requirements described in this guidance and is intended to assist sponsors and applicants in the electronic submission of standardized study data. Once FDA completes its review of the draft Conformance Guide, including comments submitted (if any), the Agency will publish a notice in the Federal Register announcing the availability on the FDA Web site of the final Conformance Guide. After the Conformance Guide is finalized, FDA will update the Conformance Guide on a regular basis and announce the availability of any updates in a Federal Register notice.

Sponsors and applicants with questions on how to implement the FDA-supported study data standards should contact and work with FDA technical staff. Contact information is provided on the Study Data Standards Resources Web page. Sponsors and applicants may also arrange to submit sample data for a pre-submission technical review. The technical staff also welcomes any additional feedback or comments regarding the information posted on the Web page.