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FDA Guidance on Standardized Study Data for Electronic Submissions

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ABSTRACT

In February 2014 the FDA released several draft guidance documents on standardized study data for electronic submissions with a 90-day window for public comment. The final guidance is expected to be released 2015. Two of the three guidance documents will be considered binding once they are released as final. From the time the final guidance documents are released sponsors will have between 24 and 36 months (depending on the submission type) to comply with the binding guidance documents.

This paper will highlight what impact the two binding guidance documents will have on sponsors as they prepare their submissions in the period following the finalization of the binding guidance. We will also discuss some of the content of the non-binding guidance that may require a change in how sponsors are implementing CDISC standards within their organization.

INTRODUCTION

At the time of writing this paper, all guidance documents are still considered draft. The content is due to be finalized and released by the FDA in early 2015. Readers are reminded that content may be subject to change based on the public comments received by the FDA. This paper references the content of the draft guidance documents and may not reflect the content of the final versions.

For many years, the industry has been waiting for the FDA to officially mandate the use of CDISC standards in electronic submissions, and sponsors have been concerned about the timeframe in which they will be required to fully comply. The Food and Drug Administration Safety and Innovation Act (FDASIA) laid the groundwork for how this will be done, but did not give specific details. The following draft guidance documents were released for public review early in 2014 in order to support the purpose as stated in FDASIA:

> FDA-2014-D-0092 - Study Data Technical Conformance Guide and Data Standards Catalog
>
> FDA-2012-D-0097 - Guidance on Electronic Submissions: Standardized Study Data
>
> FDA-2014-D-0085 - Guidance on Submissions in Electronic Format--Submissions under the Federal Food, Drug, and Cosmetic Act

These finally provide some insight into how this will work and sets the framework for more formally documenting the FDA's requirements with respect to data standards. The four documents are related to each other in a hierarchical manner as shown below. This paper will explain the relationship between these as well as their relevance to other regulatory documents.

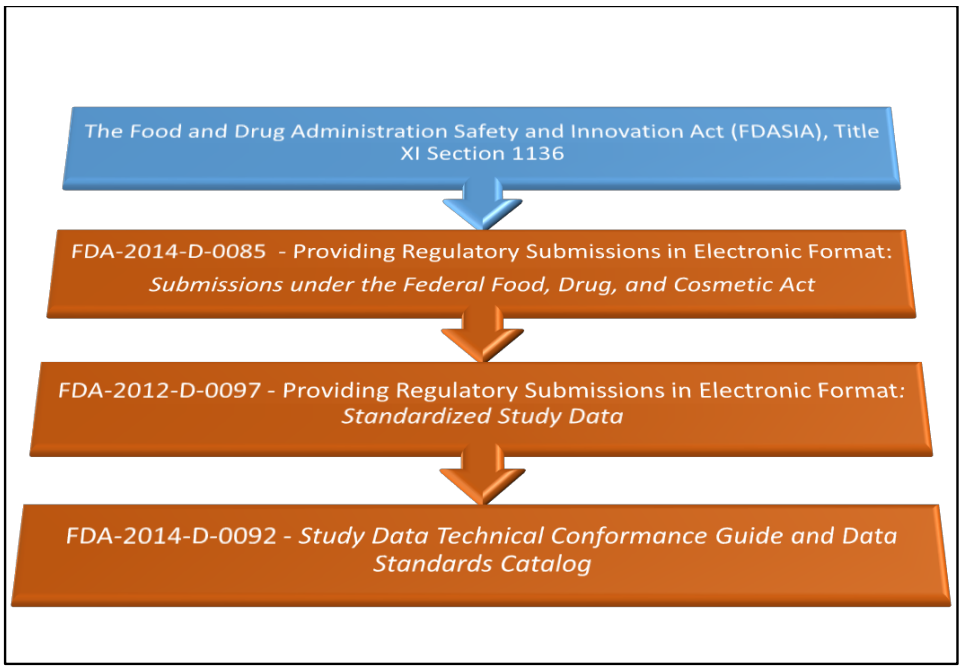

Figure 1: Hierarchy of documents

BACKGROUND

At the top of the document hierarchy is the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012. This expanded the FDA's authorities and strengthened the agency's ability to safeguard and advance public health by:

SEC. 1136. ELECTRONIC SUBMISSION OF APPLICATIONS.
Subchapter D of chapter VII (21 U.S.C. 379k et seq.) is amended by inserting after section 745 the following:
''SEC. 745A. ELECTRONIC FORMAT FOR SUBMISSIONS.
''(a) DRUGS AND BIOLOGICS.—
''(1) IN GENERAL.—Beginning no earlier than 24 months after the issuance of a final guidance issued after public notice and opportunity for comment, submissions under subsection (b), (i), or (j) of section 505 of this Act or subsection (a) or (k) of section 351 of the Public Health Service Act shall be submitted in such electronic format as specified by the Secretary in such guidance.
''(2) GUIDANCE CONTENTS.—In the guidance under paragraph (1), the Secretary may—
''(A) provide a timetable for establishment by the Secretary of further standards for electronic submission as required by such paragraph; and
''(B) set forth criteria for waivers of and exemptions from the requirements of this subsection.
''(3) EXCEPTION.—This subsection shall not apply to submissions described in section 561.
''(b) DEVICES.—
''(1) IN GENERAL.—Beginning after the issuance of final guidance implementing this paragraph, presubmissions and submissions for devices under section 510(k), 513(f)(2)(A), 515(c), 515(d), 515(f), 520(g), 520(m), or 564 of this Act or section 351 of the Public Health Service Act, and any supplements to such presubmissions or submissions, shall include an electronic copy of such presubmissions or submissions.
''(2) GUIDANCE CONTENTS.—In the guidance under paragraph (1), the Secretary may—
''(A) provide standards for the electronic copy required under such paragraph; and
''(B) set forth criteria for waivers of and exemptions from the requirements of this subsection.''.

1. Giving the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products;
2. Promoting innovation to speed patient access to safe and effective products;
3. Increasing stakeholder involvement in FDA processes; and
4. Enhancing the safety of the drug supply chain.

Within FDASIA, Title XI Section 1136 specifically addresses Electronic Format for Submissions. However, it really only states the scope for future guidance on use of standards in electronic submissions, allows for exemptions and states that a timetable will be given. It also applies to all aspects of an electronic submission, not just to the submitted data.

The most important detail included in FDASIA (as it relates to this paper) is that it allows the FDA to issue "guidance" documents that are binding. This goes against the Good Guidance Practices" that all prior FDA Guidance for Industry has followed. Namely, these "binding guidance" are really not "guidance" at all, they are "requirements". Two of the three draft documents discussed in this paper are considered to be binding. We will discuss this in the relevant sections below.

The FDA determined that is would not be feasible to describe and implement electronic formats that would apply to ALL submissions covered by Section 745(a) in a single guidance. Therefore, they have divided the information into three separate guidance documents to make it more manageable.

1. "Providing Regulatory Submissions in Electronic Format: Submissions under the Federal Food, Drug and Cosmetics Act" takes the scope of FDASIA Section 1136 and describes how the FDA will accomplish this for all parts of an electronic submission. *This is will be binding.*

2. "Providing Regulatory Submissions in Electronic Format: Standardized Study Data" is a direct result of the first guidance and focuses only on electronic study data. It includes the details on requirements, timelines for implementation, and how to request an exemption. *This will be binding.*

3. "Study Data Technical Conformance Guide and Data Standards Catalog" provides specific expectations on what standards the FDA can accept and how they would like the data to be structured. *This will NOT be binding.*

Guidance for SUBMISSIONS UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

Purpose

The first of the three draft guidance documents, "Providing Regulatory Submissions in Electronic Format: *Submissions under the Federal Food, Drug and Cosmetics Act*", takes the very general information from FDASIA and provides a high-level descriptions of the overall process for how the FDA will communicate the requirements described within Title XI, Section 1136. The scope of this document remains the same as FDASIA, in that it includes all aspects of electronic submissions, not just study data.

This document is intended to be binding once it becomes approved. It is not subject to the usual restrictions of the FDA's good guidance practice regulations and uses terms such as "must" and "required".

The purpose of this document is to describe how FDA plans to implement the requirements of §745(a) and the overall process for how FDA will communicate the requirements for electronic submission formats (not just for study data).

This document describes and covers:

- Submission types that must be submitted electronically
- Exemptions from and waivers of the eSubmission format requirements
- Timetable and process for implementation of the requirements

Content

The document describes which submission types that will require eSubmission and which are excluded. It also describes how the requirements will be implemented and when will electronic submissions be required. There are also example situations provided that clarify how the process is expected to work.

What kind of Submissions are included?

- Certain INDs
- NDAs
- ANDAs
- Certain BLAs
- All subsequent amendments, supplements and reports to the above (even if original submission was not electronic)

Submissions Types not included:

- Those described in section 561 of FD&C Act
- Devices regulated by CBER as biological products under §351 of PHS act (e.g. devices intended for screening donated blood)

- Other exemptions & waivers will be described in the applicable individual guidance

Unless exempted or requirements waived, any submission not in the electronic format will not be filed

How will requirements be implemented?

1. Individual draft guidance documents (by type of submission) will describe the electronic format requirements
    - Posted on FDA's Drug Guidance page and Vaccines, Blood and Biologics page
    - Announced in a list of new, revised & withdrawn guidances
    - Notice published in Federal Register announcing comment period for draft guidance

2. After review of comments, final guidance will be made available
    - Same announcements as above, plus
    - Federal Register will announce the date on which the new electronic format will be required

3. Revisions/updates to formats will follow same process

When will electronic submissions be required?

Sponsors will have at least 24 months from the date the final guidance is issued for a type of submission. Each guidance will specify the exact timetable for specific submissions.

For revisions to existing formats, timetable may be less than 24 months. Revisions to a required format include:

- Version updates and maintenance enhancements
- Minor changes (corrections of typos) may have immediate effect

Example situations provided

The document does a very good job translating the details into what this really means for sponsors by providing several example scenarios that clearly show how the process would work in practice.

You may think of this as similar to a "Standard Operation Procedure (SOP)" that outlines a process but still leaves out many specific details. The second guidance document focuses on study data specifically.

GUIDANCE FOR SUBMISSIONS UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

Purpose

The second guidance document applies the process described in the first guidance document to the case of submission of electronic study data. The scope is specifically on standardized study data contained in submissions for CDER and CBER. As with the first guidance described above, this guidance will be considered as binding, not recommendations.

What is covered?

The document describes which submission types that will require standardized data and which are excluded. It also describes how the requirements will be implemented and when will electronic study data be required. There are also example situations provided that clarify how the process is expected to work.

It follows the same scope as the "parent" guidance described above, namely:

Submission types included are:

- Certain INDs
- NDAs
- ANDAs

- Certain BLAs
- All subsequent amendments, supplements and reports to the above (even if original submission was not electronic)

Submissions Types not included:

- Those described in section 561 of FD&C Act
- Devices regulated by CBER as biological products under §351 of PHS act (e.g. devices intended for screening donated blood)
- Other exemptions & waivers will be described in the applicable individual guidance

The document lists the specific exemptions for which the FDA will accept these in standardized electronic format but it is not required:

- All submissions regarding devices that are regulated by CBER as biological products under §351 of the PHS Act
- Study data contained in non-commercial INDs (includes investigator-sponsored INDs, emergency use INDs and treatment INDs

What are the requirements?

Submissions must be in a format the FDA supports unless a waiver has been approved (the process for applying for a waiver will be discussed in an upcoming section of this paper). Currently, the supported standards include:

- File format standards (PDF, XPT, TXT, XML)
- Study Data Exchange standards (e.g. SDTM)
- Analysis Standards (e.g. ADaM, some SDTM datasets)
- Terminology Standards (e.g. CDISC CT, MedDRA, NDF)

Waivers

No waivers will be granted for submission of data in non-FDA supported study data standard. However, it will be possible for a sponsor to request waiver to allow the use of a non-current version of a supported standard. This must be a written request containing:

1. Specific requirements for which a waiver is requested
2. Justification for why the waiver is needed
3. Description of the alternative that the sponsor intends to use

The FDA will notify in writing if the waiver has been granted. The FDA encourages discussions of waivers prior to or at end of pre-IND meeting with review division and submission of request prior to submitting IND.

Timetable

According to this draft version of the guidance, NDAs, ANDAs and certain BLAs must follow details in the Data Standards Catalogue for all studies with earliest informed consent date 24 months after Federal Register notice of final guidance availability.

Certain INDs must use specified formats in studies with earliest informed consent date 36 months after Federal Register notice of availability.

Assuming the guidance documents are finalized in 1Q2015, this could mean that NDAs, ANDAs and certain BLAs will need to meet the stated requirements by 1Q2017 and that certain INDs will need to plan for these requirements if informed consent will be staring after 1Q2018.

Support

Sponsors may use established FDA-sponsor meetings to discuss data standardization issues as early as possible (ideally Pre-IND and end of Phase 2). In general, premarketing application meeting is considered too late for these discussions.

Technical questions may be submitted to the appropriate FDA e-mail list, which is included in the guidance.

This guidance then refers sponsors to the Draft Study Data Technical Conformance Guide (Conformance Guide) for non-binding details on submitting standardized study data.

STUYD DATA TECHNICAL CONFORMANCE GUIDE AND DATA STANDARDS CATALOG

Purpose

These documents supersede CDER Common Data Standards Issues document and previous Study Data specifications documents. The benefit of this is that any changes to the documents will go through a public review period. This will reduce the likelihood of the FDA requesting data to be represented in a manner that contradicts CDISC rules. It may however place more stringent requirements for implementation than is found in the relevant CDISC standards. For example, a permissible variable in SDTM may be identified as expected or required by the FDA.

Documentation

The guidance includes a section on the planning for providing standardized study data and describes what documentation is expected to be included along with the electronically submitted study data. While the other two guidance documents were binding, this one is not. It is also the most specific of the three with respect to what the FDA would like to receive. This includes a Study Data Standardization Plan and a Study Data Reviewer's Guide.

The Study Data Standardization Plan is intended to assist both the sponsor and the FDA in identifying potential data standardization issues early in the development process. The plan should include:

- A list of the planned studies and types (Phase I, II, III)
- A description of the Study Designs
- Planned data standards, formats and terminologies including versions to be used in the submission
- A list of and justification for studies that may not conform to standards

The Study Data Reviewer's Guide is a document that should be familiar to most sponsor as this is not a new document. The guidance simply provides the details on what is expected to be included for each study in a submission, as listed below:

- Study protocol title, number and version
- Study design
- Data standards, formats and terminologies including versions
- Description of study datasets (including method for splitting large datasets)
- Data standards conformance validation rules, versions and issues

Content

This document is where the FDA will describe in detail their expectations for specific SDTM and ADaM domains and variables, controlled terminologies and dataset naming, among other things. The content combines information that has previously been proved in the CDER Common Data Issues Document plus some new sections. There is a placeholder section for information for Therapeutic Area standards once they become available.

CONCLUSIONS:

These draft guidance documents are a welcome step in the right direction. They are the most specific descriptions on how and when sponsor's will need to comply with data standards as part of electronic submissions. It is expected that additional guidance documents will be forthcoming that address parts of the electronic submission other than the study data.

The division of the guidance documents into two binding and one non-binding guidance should improve the flexibility of the FDA to respond to updates to the details of the data standards use that is covered in the Study Data Technical Conformance Guide while avoiding the more strict processes described in the binding guidance from interfering with updates.

The inclusion of a public comment period for all guidance will help reduce confusion by sponsors on what the FDA expects. Sponsors should be able to provide comments back to the FDA on any proposed updates that are unclear or problematic prior to finalization.

When the final versions of these documents become available they will be invaluable in allowing sponsors to finally plan a timeline for full compliance with FDA requirements.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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