
Providing Regulatory Submissions in Electronic Format—Submission of Manufacturing Establishment Information

Guidance for Industry

DRAFT GUIDANCE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)**

**December 2016
Electronic Submissions**

Providing Regulatory Submissions in Electronic Format—Submission of Manufacturing Establishment Information

Guidance for Industry

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<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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Technical specifications associated with this guidance are provided as a separate document and are updated periodically:

- *Structured Product Labeling (SPL) Implementation Guide with Validation Procedures*

For a complete listing of all documents, supportive files, and terminology for submitting electronically, refer to the Structured Product Labeling Resources Web page at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Contains Binding Provisions and Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	REQUIREMENT TO SUBMIT ELECTRONIC MANUFACTURING ESTABLISHMENT INFORMATION	3
	A. Which submission types require an electronic submission of manufacturing establishment information?.....	3
	B. What are the requirements for electronic submission of manufacturing establishment information?.....	4
	C. When will electronic submission of manufacturing establishment information be required?	5
	D. Are there exceptions to the electronic submission requirements for manufacturing establishment information?	5
	E. Will FDA issue waivers of the electronic submission requirements for manufacturing establishment information?	5

1 **Providing Regulatory Submissions in Electronic Format—**
2 **Submission of Manufacturing Establishment Information**
3 **Guidance for Industry¹**
4

5 **I. INTRODUCTION**
6

7 This draft guidance discusses the requirements and implementation of the Federal Food, Drug,
8 and Cosmetic Act (the FD&C Act) regarding valid electronic submissions of manufacturing
9 establishment information (MEI). Twenty-four months after this draft has been finalized, MEI
10 contained in new drug applications (NDAs), abbreviated new drug applications (ANDAs),
11 biologics license applications (BLAs), and amendments, supplements,² or resubmissions of these
12 application types must³ be submitted electronically in the format specified in this guidance. This
13 draft guidance also applies to drug master files that are submitted for incorporation by reference
14 into an NDA, ANDA, or BLA.

15
16 For additional information on how FDA interprets and intends to implement the electronic
17 submission requirements of section 745A(a) of the FD&C Act, please see the guidance for
18 industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section*
19 *745A(a) of the Federal Food, Drug, and Cosmetic Act* (745A Implementation Guidance).
20

21 In section 745A(a), Congress granted explicit authorization to FDA to specify, by guidance, the
22 electronic format for submissions under section 505(b), (i), or (j) of the FD&C Act and
23 submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act), which
24 include MEI. Accordingly, to the extent that this document provides such requirements under
25 section 745A(a) of the FD&C Act, indicated by the use of the words *must* or *required*, this
26 document is not subject to the usual restrictions in FDA’s good guidance practice (GGP)
27 regulations, such as the requirement that guidances not establish legally enforceable
28 responsibilities (see 21 CFR 10.115(d)).
29

30 To comply with the GGP regulations and make sure that regulated entities and the public
31 understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard
32 language explaining that guidances should be viewed only as recommendations unless specific
33 regulatory or statutory requirements are cited. FDA is not including this standard language in this
34 guidance because it is not an accurate description of this guidance. Insofar as this guidance
35 specifies the format for electronic submissions pursuant to section 745A(a) of the FD&C Act, it
36 will have binding effect.

¹ This guidance has been prepared by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² Efficacy supplements and chemistry, manufacturing, and controls (CMC) supplements.

³ See section 745A(a) of the FD&C Act and the guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and the CBER Web page at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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II. BACKGROUND

Section 505(a) of the FD&C Act requires that FDA approve an application for a new drug before it is introduced or delivered for introduction into interstate commerce. The regulations in 21 CFR 314.50⁴ describe the specific content and format of applications to market new drugs under section 505 of the FD&C Act and supplements to approved applications. 21 CFR 314.50(a) describes the form of application that is required to be submitted to market a new drug, and 21 CFR 314.50(d) describes the “technical sections” of the application. 21 CFR 314.50(d)(1) describes the chemistry, manufacturing, and controls (CMC) section of the application that requires information relating to the composition, manufacture, specification, and manufacturer of the drug substance and drug product.

Sections 351(a) and (k) of the Public Health Service Act (the PHS Act) require that FDA approve an application for a biological product before it is introduced or delivered for introduction into interstate commerce. The content and format of applications submitted to market a new biological product are described in 21 CFR 601.2. In addition, 21 CFR 601.2(a) requires a full description of the manufacturing methods and the address of each location involved in the manufacture⁵ of the biological product.

Thus, under current regulations at 21 CFR parts 314 and 601, applicants and holders of approved applications are required to submit contact information for each manufacturing establishment involved in the manufacture of the drug or biological product, as well as other information relating to the manufacture of the product.

Recently the Agency has noticed that the required information on the manufacturing establishments is often provided in different sections throughout the application. This makes the MEI difficult to find and time-consuming to review. Consolidating the required electronic MEI to appear in a single location will facilitate the complete, timely, and accurate review of all manufacturing establishments involved in the preparation of a drug or biological product.

In addition, this consolidation of the MEI will help eliminate the inclusion and/or maintenance of potentially outdated and erroneous information that, lacking clear information in the submission, might otherwise be retrieved from other Agency files and will enable proper identification and timely evaluation of manufacturing establishments for conformance with requirements, including current good manufacturing practices.

To help resolve these issues, the Agency is requiring that applicants consolidate the MEI into a single list of information about each manufacturing establishment referred to in an application. This list must be submitted as one electronic file and must include the following required information for each manufacturing establishment involved in the manufacture of the drug or biological product. Providing a Field Establishment Identifier (FEI) number is recommended, but not required. However, it helps ensure that the Agency has accurate information about the site.

⁴ For ANDAs, see 21 CFR 314.94(a)(1), (9), (10), and (11).

⁵ See 21 CFR 600.3(u) “Manufacture means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.”

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The MEI encompasses:

- Establishment name and address: Specific information regarding the physical location (e.g., building number on a corporate campus or industrial complex).⁶
- Unique Facility Identifier.⁷
- Contact information⁸ for the person responsible for scheduling inspections.
- Specific manufacturing operations⁹ being conducted.

III. REQUIREMENT TO SUBMIT ELECTRONIC MANUFACTURING ESTABLISHMENT INFORMATION

A. Which submission types require an electronic submission of manufacturing establishment information?

Electronic submissions of MEI will be required for original (i.e., initial) NDAs, ANDAs, and BLAs in the Health Level 7 (HL7) Version 3: Structured Product Labeling (SPL) standard.^{10,11} In addition, MEI must be submitted electronically in this format for efficacy supplements, CMC supplements, and resubmissions to these application types.

As stated in the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, FDA considers master files to be submissions to an NDA, ANDA, or BLA and therefore to fall within the scope of requirements set forth in section 745A(a).¹² These include new drug master files (DMFs), new biological product files (BPFs),¹³ and any amendments to or annual reports on previously submitted DMFs or BPFs. This guidance also applies to

⁶ See 314.50(d)(1).

⁷ See section 510 of the FD&C Act and the guidance for industry on *Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration*.

⁸ For both domestic and foreign firms, the owner's name is required (21 CFR 207.25(a) and 21 CFR 314.50(a)(5)); for foreign firms, however, a U.S. agent is also required. For both foreign and domestic firms, the owner could delegate the responsibility of scheduling inspections.

⁹ See 21 CFR 314.50(d)(1).

¹⁰ This guidance is not applicable to those devices that are regulated by CBER as biological products under section 351 of the PHS Act, including those that do not require the submission of an IND prior to the submission of a BLA. Although a discussion of which devices CBER regulates as biological products under section 351 of the PHS Act is outside the scope of this guidance, as a general matter, this category would include those reagents used in determining donor/recipient compatibility in transfusion medicine. These submissions are subject to the requirements under section 745A(b). See the guidance for industry *eCopy Program for Medical Device Submissions*.

¹¹ This guidance is not applicable to submissions for blood and blood components, including Source Plasma.

¹² See also FDA's Electronic Common Technical Document Web page at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

¹³ See 21 CFR 601.51.

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109 submissions for all combination products filed pursuant to section 505 of the FD&C Act or
110 subsection (a) or (k) of section 351 of the PHS Act.

111
112 Electronic submissions of MEI must include complete information on the locations of all
113 manufacturing sites,¹⁴ including packaging and control sites, for both drug substance and drug
114 product.¹⁵

115
116 For presubmissions, amendments, and annual reports to these original application types,
117 complete MEI must be provided when applicable (e.g., when updated establishment or contact
118 information is necessary).

119
120 **B. What are the requirements for electronic submission of manufacturing**
121 **establishment information?**

122
123 Under section 745A(a) of the FD&C Act, electronic submissions “shall be in such electronic
124 format as specified by [FDA].” FDA has determined that MEI contained in the electronic
125 submissions described in section III.A must be in the electronic format described above, using
126 HL7 Version 3: SPL. Please also refer to the SPL release and the terminologies specified in the
127 Data Standards Catalog¹⁶ posted to FDA’s Data Standards Resources Web page.

128
129 The catalog provides the following:

- 130
- 131 • A listing of supported¹⁷ and/or required standards, their uses, the date FDA will begin (or
132 has begun) to support a particular standard, and the date with which support for a
133 particular standard ends (or will end).
 - 134
135 • The date the requirement to use a particular standard will begin (or has begun) and the
136 date such requirement ends (or will end), as well as other pertinent information.
- 137

138 The MEI file must be included in eCTD Module 3, section 3.2.R Regional information.
139 Applicants must name the file, “establishment-information-[Date of the submission (YYYY-
140 MM-DD)].xml” with a corresponding leaf title of “Establishment-Information-[Date of the
141 submission (YYYY-MM-DD)].”

142
143 To avoid redundancy, the following “Manufacturer” sections must simply link to the single 3.2.R
144 Regional file described above, and no other files may be submitted at these locations:

- 145
- 146 • 3.2.S.2.1 Manufacturer(s) [Drug Substance].

¹⁴ See 21 CFR 207.3(8). “*Manufacturing or processing* means the *manufacture, preparation, propagation, compounding, or processing of a drug or drugs* as used in section 510 of the act and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process....”

¹⁵ See 21 CFR 314.50(d)(1)(i) and (ii)(a) and (b).

¹⁶ Available at <http://www.fda.gov/ForIndustry/DataStandards/default.htm>.

¹⁷ For the purposes of this guidance, *supported* means the receiving Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified file format.

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- 147 • 3.2.P.3.1 Manufacturer(s) [Drug Product].
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149 The Agency may refuse to file or receive an electronic submission unless the MEI conforms to
150 the format specified in this guidance: a consolidated file of MEI in HL7 Version 3: SPL.

151
152 **C. When will electronic submission of manufacturing establishment information**
153 **be required?**
154

155 Twenty-four months after we publish a notice of availability of the final guidance in the *Federal*
156 *Register*, all MEI must be provided electronically, using the HL7 Version 3: SPL standard.
157 Please also refer to the SPL release and the terminologies specified in the Data Standards
158 Catalog.¹⁸
159

160 For a transition from the HL7 Version 3: SPL standard, FDA will publish a *Federal Register* notice
161 announcing the availability of a revised guidance and a timetable for when submissions will be
162 required using the new version of the standard.
163

164 For additional information on how FDA intends to implement the electronic submission
165 requirements of section 745A(a) of the FD&C Act, including timetable for implementation,
166 please see the 745A Implementation Guidance.
167

168 **D. Are there exceptions to the electronic submission requirements for**
169 **manufacturing establishment information?**
170

171 Section 745A(a) allows FDA to establish exemptions from the electronic submission
172 requirements. Accordingly, FDA has exempted all submissions regarding noncommercial INDs
173 from the requirements under section 745A(a).¹⁹ For purposes of this guidance, all
174 noncommercial INDs are exempt from the MEI electronic submission requirements.
175

176 **E. Will FDA issue waivers of the electronic submission requirements for**
177 **manufacturing establishment information?**
178

179 FDA will not provide waivers of the HL7 Version 3: SPL requirement to submit data that do not
180 conform to the standards specified in the catalog, which is available on FDA's Data Standards
181 Resources Web page.²⁰

¹⁸ See section III.B.

¹⁹ See 745A Implementation Guidance, section III.B.

²⁰ See <http://www.fda.gov/ForIndustry/DataStandards/default.htm>.