
Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics and Evaluation Research (CBER)**

**October 2019
Pharmaceutical Quality/CMC**

Revision 1

Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER

Questions and Answers

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information

Center for Drug Evaluation and Research

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

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

and/or

Office of Communication, Outreach and Development

Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Bldg. 71, Room 3128

Silver Spring, MD 20993-0002

Phone: 800-835-4709 or 240-402-8010

Email: ocod@fda.hhs.gov

<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics and Evaluation Research (CBER)
October 2019
Pharmaceutical Quality/CMC**

Revision 1

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	QUESTIONS AND ANSWERS.....	2
	Form FDA 356h Questions/Answers.....	2
	Module 3 Questions/Answers	6
	General Questions/Answers.....	8

Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to clarify Agency expectations regarding facility information that should be included in original new drug application(s) (NDA); abbreviated new drug application(s) (ANDA); original biologics license application(s) (BLA); amendments; supplements; chemistry, manufacturing, and controls (CMC) supplements; and resubmissions to these submission types. Submission of Form FDA 356h fulfills the requirement for applicants to submit an application form (21 CFR 314.50(a) and 314.94(a)(1); 601.2(a)). Form FDA 356h serves as both a summary of administrative information, as well as a repository of complete information on the locations of all manufacturing, packaging, and control sites for both drug substance and drug product facilities associated with the application. This guidance addresses questions related to the inclusion and withdrawal of proposed commercial facilities and development facilities, the appropriate location within an application for facility information, and the type of facility information that should be included in applications. Applications that include appropriate and complete facility information in the establishment information section of Form FDA 356h will reduce the frequency of Information Request (IR), Refusal to File (RTF), and Refuse to Receive (RTR) actions and increase the efficiency of the application assessment process. This guidance describes the recommended placement of all facility information for both original and supplement applications.

This guidance applies to BLA products licensed under section 351 of the Public Health Service Act, including In-Vitro Diagnostics regulated as BLAs and drug products marketed (or to be marketed) under an NDA or an ANDA under the Federal Food Drug and Cosmetic Act. This guidance applies to all manufacturing locations, including facilities that perform functions under contract.

¹ This guidance was prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics and Evaluation Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at <https://www.regulations.gov/docket?D=FDA-2017-D-6821>). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

Contains Nonbinding Recommendations

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Agency frequently receives questions regarding expectations for inclusion of manufacturing establishment information in applications (Module 3) and Form FDA 356h. In some instances, this lack of clarity results in FDA receiving applications that contain extraneous information, misplaced information (i.e., not readily accessed by Agency reviewers), or missing information. These issues result in delays to the assessment process and in some instances, unnecessary IR, RTF, and RTR actions. This guidance offers detailed recommendations regarding the placement of facility information in applications.

III. QUESTIONS AND ANSWERS

Form FDA 356h Questions/Answers

1. What facility information should I include in the establishment field on Form FDA 356h?

For original NDA, ANDA, and BLA applications, amendments, efficacy supplements, CMC supplements, and resubmissions to these submission types, the applicant should include complete information on the locations of all manufacturing, packaging, and control sites for both drug substance and drug product on Form FDA 356h. This should include:

- All drug product (in-process material and final) manufacturing (including primary, packaging, and labeling sites) and testing sites, including stability testing, that are proposed to be involved in the disposition² of commercial product. Stability testing information associated with the drug substance and drug product should be included in Module 3 (see below).
- All intermediate (performing operations addressed by the International Conference on Harmonisation guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)) and final drug substance manufacturing and testing sites that are proposed to be involved in the disposition of commercial product. This includes sterilization and micronization sites.

² For purposes of this guidance the term disposition is the result of a decision to assign a status within the commercial supply chain. Examples of disposition include lot release, quarantine awaiting further data, or lot rejection. Assays and resulting data, which are used to make disposition decisions, are a part of the commercial process control strategy.

Contains Nonbinding Recommendations

- For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part. For more detailed information on combination products please see guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).³
- All facilities used for storing or warehousing drug substance, in-process material, and commercial drug product under quarantine prior to a disposition decision, including any facilities that solely store the stability samples.

2. Should I list all facilities in Modules 2 and 3 on Form FDA 356h?

No. Facilities that do not impact or inform the commercial control strategy do not need to be listed on Form FDA 356h. Examples of such facilities can be found below in response to Question 1 under Module 3 Questions/Answers.

3. What facilities should be identified in the establishment field on Form FDA 356h when submitting an amendment or a supplement?

Submissions should include complete facility information for existing facilities and any changes to previously submitted facility information. If an applicant is adding a new facility or removing a previously submitted facility, this information should be captured on Form FDA 356h submitted with the amendment or supplement. The appropriate box should be checked:

Pending:	Introducing a new facility to the application.
Active:	Already approved for use for that application.
Inactive:	Approved for use to manufacture the drug under the application, but is not currently being utilized.
Withdrawn:	Any facility withdrawn from the current, pending, original, or supplemental submission.

4. If I have withdrawn a facility, how should I revise Form FDA 356h?

If a facility not previously approved is withdrawn before the application (e.g., original or supplement) adding the facility is approved, or if a previously approved facility has been withdrawn in a post-approval notification under 21 CFR 314.70 or 601.12, the facility should remain on Form FDA 356h with the box “withdrawn” checked. For amendments, this starts with the first amendment notifying FDA that the facility is being withdrawn and all subsequent amendments until the application is either

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

withdrawn or approved. The withdrawn facility should be omitted from the list in any subsequent supplement.⁴

5. For combination products, should I list the device constituent part manufacturer?

Yes. For a combination product, any finished device constituent part manufacturing facilities that are proposed to be involved in the disposition of commercial products should be listed on Form FDA 356h. This includes facilities that conduct design controls activities, including verification and validation, in accordance with 21 CFR 820.30 for the device constituent part. In addition, Form FDA 356h should list the facilities that manufacture the combination product.

6. Should I have an FDA Establishment Identifier (FEI) number and Data Universal Numbering System (DUNS) number for a given facility? If so, how do I obtain the FEI number and DUNS number or alternatively how can I check to see if a facility has already obtained these identification numbers?

Having an FEI number and DUNS number will facilitate the application process and establishment registration.

The FEI number is needed by the Agency to proceed with the facility evaluation portion of the application assessment.

Section 510 of the Food, Drug, and Cosmetic Act requires that each initial and annual drug establishment registration include a Unique Facility Identifier (UFI) (21 U.S.C. 360(b), (c), and (i)). The Agency's preferred UFI for a drug establishment is the DUNS number, assigned and managed by Dun & Bradstreet.⁵

21 CFR 207.21(a) states that "Registrants must register each **domestic** establishment no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug..."

21 CFR 207.21(b) states that "Registrants must register each **foreign** establishment before a drug ...manufactured, repacked, relabeled, or salvaged at the establishment is imported or offered for import into the United States."

FDA recommends that at the time of registration, the owner or operator obtain an FEI number. Although the absence of the FEI number may hinder the timeline for assessment of the establishment information contained within your application, you should not delay submitting your application due to the absence of an FEI number. Rather, you should request an FEI number as soon as possible.

⁴ If further clarification is needed regarding the appropriate action to be taken when a facility is withdrawn, please consult with the appropriate FDA review division.

⁵ See guidance for industry *Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration* (November 2014).

Contains Nonbinding Recommendations

To obtain an FEI number for a GDUFA-related facility, email FDAGDUFAFEIRequest@fda.hhs.gov.

To obtain an FEI number for a PDUFA- or BsUFA-related facility, email PDUFABSUFAFEIRequest@fda.hhs.gov.

Your email should include the following data points:

- (a) Subject: Foreign or Domestic FEI request for (firm name)
- (b) Company Legal Name for the location for which the activity is being conducted
- (c) Company Address for the location for which the activity is being conducted
- (d) Company Point of Contact (name, email, telephone number)
- (e) Activities the firm is going to participate in regarding the drug product (manufacturing, labeling, testing, etc.)
- (f) Known drug products (API, finished dose, intermediary)
- (g) Registered with FDA (if so, include the registration number)

Note: An FEI number is a facility specific identifier. Thus, if a particular facility has already been assigned an FEI number (through registration of any commodity, GDUFA, PDUFA, BsUFA, etc.), you should not request a second FEI number for that location.

To obtain a DUNS number:

- DUNS numbers can be obtained, or DUNS information modified, through Dun & Bradstreet's website:
<https://www.dnb.com/solutions/government/duns-number-request-guide.html>
- To find or verify a previously obtained FEI or DUNS number go to FDA's registration site for drug establishments:
<https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm>

7. If a facility is listed on Form FDA 356h or elsewhere in my application, will it be subject to a user fee?

Form FDA 356h is not linked to the assignment of a user fee. The function performed by the establishment determines the assessment of a user fee, not the inclusion of a facility on Form FDA 356h.

If you have questions about user fee assessments, please review the various guidances specific to the relevant user fee program: GDUFA, PDUFA, MDUFA, and BsUFA.⁶

Note: For PDUFA and BsUFA applications, as of October 1, 2017, manufacturing facilities/establishments referenced in NDAs and BLAs are no longer subject to user fees.

⁶ See <https://www.fda.gov/forindustry/userfees/>.

Contains Nonbinding Recommendations

Module 3 Questions/Answers

1. What facility information should I list in Module 3?

Module 3 should contain all facilities listed on Form FDA 356h, as well as research and development manufacturing and testing sites that generated data in support of the application. This includes facilities that manufactured or tested any lots of the product.

Module 3 should also contain testing labs that perform functions integral to the control strategy, including but not limited to characterization and comparability of molecules and analytical similarity. This includes any testing sites that generate release data, stability testing to support the application, and commercial testing sites.

For combination products⁷ only:

- Provide a detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly filling, sterilization, testing, other); and what constituent parts are at the site (e.g., drug only, device only, both drug and device). For each facility that has at least two different constituent part manufacturing operations (e.g., drug and device) identify which CGMP operating system is established at the site per 21 CFR 4.4(a).
- For each facility manufacturing a single entity or co-packaged combination product⁸ that is subject to 21 CFR Part 4, identify which CGMP operating system approach is established.
- If the CGMP operating system complies with 21 CFR 4.4(b), identify the elected approach (i.e., 21 CFR 4.4(b)(1) for full 21 CFR 211 compliance with additional 21 CFR 820 provisions, or 21 CFR 4.4(b)(2) for full 21 CFR 820 compliance with additional 21 CFR 211 provisions).

2. Where should I list the facilities in Module 3?

All manufacturing and control sites should be in either the drug substance (3.2.S.2.1) or drug product (3.2.P.3.1) sections of Module 3. If you are not sure if the site should

⁷ For additional information, see guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (July 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁸ The CGMP requirements for constituent parts of cross-labeled combination products that are entirely manufactured at separate facilities are the same as those that would apply if these constituent parts were not part of a combination product (e.g., for a drug/device combination product, only parts 210 and 211 (21 CFR parts 210 and 211) would apply to the manufacture of the drug constituent part(s) of the cross-labeled combination product, and only part 820 (21 CFR part 820) would apply to the device constituent part(s)).

Contains Nonbinding Recommendations

be included, add it to Module 3. If you do not know whether the site should be listed in the substance or product section, list it in the section that you think is the most applicable. Failure to list a manufacturing facility in the application or listing a facility in an incorrect area (i.e., other than 3.2.S.2.1 and 3.2.P.3.1) could result in an extension to the review period.

3. Should I consolidate facility information in each respective section of Module 3 of an application?

Yes. To facilitate FDA's assessment and inspection planning process, the Agency recommends that you clearly identify all facilities associated with your application in a table format at the beginning of the relevant section in Module 3. We also recommend that you include this summary table at the beginning of each relevant section in Module 2.

FDA further recommends including the full establishment name and the establishment address where the manufacturing function is performed. Include the FEI number and specific manufacturing operations and responsibilities for each facility, including type of testing and drug master file (DMF) number, if applicable.

Additionally, FDA recommends that you provide the name and title of an onsite contact person, including their phone number, fax number, and email address.

Each facility should be ready for an inspection at the time of submission. If a facility is not ready for inspection, indicate when the facility will be ready for inspection.

If you decide to use a table format, FDA recommends that you use the format below.

Facility information:

Site Name	Site Address	FDA Establishment Identifier (FEI)	Drug Master File Number (if applicable)	Specific Manufacturing Responsibilities or Type of Testing [Establishment Function]
1.				
2.				

Contains Nonbinding Recommendations

Corresponding names and titles of each facility's onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4. If I use a firm to develop analytical method(s), should I list these facilities in the application?

Yes. The information for such firms should be provided in Module 3 of the application.

General Questions/Answers

1. If a DMF is referenced in my marketing application, should I list the facilities associated with the DMF in my NDA/ANDA application?

Yes. The facility information contained within a DMF properly incorporated by reference should be included on both Form FDA 356h and in Module 3 of the application, as appropriate. The recommended placement of the DMF facility information in the application follows the same logic as any other facility that is not part of a DMF (see Question 1 under Form FDA 356h Questions/Answers for facility information to include on the Form FDA 356h and Question 1 under Module 3 Questions/Answers for the facility information to include in Module 3.) The Agency will consider all facilities that are listed in a DMF apply to the referencing NDA or ANDA application unless explicitly stated in the DMF Letter of Authorization (LOA) that only certain facilities will be used by the referencing application.

The DMF LOA, which permits the Agency to review the DMF and permits the authorized party (i.e., the company or individual who submits an application or another DMF) to incorporate information from the DMF into an application or another DMF by reference, should specify which facilities will be utilized in the commercial manufacturing. If the LOA specifies a subset of facilities that will be utilized in commercial manufacturing, then only these facilities should be listed in Form FDA 356h and in Module 3 of the application. Absent this specificity, all facilities that could be potential sources of the materials for which the DMF is being referenced by the NDA/ANDA should be listed in the application.

Facility withdrawals submitted in an amendment to the DMF should also be submitted on Form FDA 356h for referencing applications if the facilities were included on the applicant's Form FDA 356h (see Question 4 under Form FDA 356h Questions/Answers).

Contains Nonbinding Recommendations

2. Do I need to list research and development or testing site DMF facilities that generate release data or stability testing data to support my NDA or ANDA?

Yes. If a facility referenced in a DMF is to be utilized for research and development or testing, this is considered part of the commercial control strategy and should be included in your application. Thus, if you intend to accept a LOA from a DMF testing facility, we recommend that this facility be listed in your application. The recommended placement of the DMF facility information in the application follows the same logic as any other facility that is not part of a DMF (see Question 1 under Form FDA 356h Questions/Answers for facility information to include on the Form FDA 356h and Question 1 under Module 3 Questions/Answers for the facility information to include in Module 3 of the application).

3. Should I list excipient testers in the application?

In general, excipient testers do not need to be listed in the application. FDA expects the drug product manufacturers to have adequate testing/controls in place to determine if the excipient meets established acceptance criteria per 21 CFR 211.84. However, if an excipient is considered critical to the drug product performance (e.g., liposomes), the testing facilities should be listed in Module 3.

4. Do I need to include crude heparin manufacturing sites?

Yes. All crude heparin manufacturing sites and heparin testing sites should be listed on Form FDA 356h and in Module 3. If there are any changes in the crude heparin sites, inform FDA as soon as possible through an appropriate amendment or post-marketing submission.

5. For a Priority ANDA where an applicant is eligible to pre-submit facility information (i.e. Pre-Submission Facility Correspondence, PFC), what facility information should I include on Form FDA 356h that accompanies this pre-submission?

See the guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)* (November 2019)⁹ for the facility information that should be submitted on Form FDA 356h.

⁹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.