

Manufacturing Establishment Facility Submission Expectations

SBIA 2020

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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)

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Pharmaceutical Quality/CMC

Revision 1

OBJECTIVE

To provide an overview of the new Q &A 356h guidance issued in 2019

Background

- According to 21 CFR 314.50(a) and 314.94(a)(1); 601.2(a), Applicant has to submit a Form FDA 356h for manufacturing facilities information.
- Agency has issued many **IR or RTF/RTR** due to
 - Missing facility information in FDA Form 356h
 - Incorrect information provided in FDA Form 356h
 - Inconsistent information between Form 356h and the Module 3.

* IR: Information Request

* RTF: Refusal to File

* RTR: Refuse to Receive

What Facility Information Should Be Included in Form FDA 356h

- All commercial drug product manufacturing and testing sites
- All intermediate and final drug substance manufacturing and testing sites
- Facilities that manufacture a constituent part of a co-package or single entity combination products or drug-device combination product that are proposed to be involved in the disposition of commercial product
- Any facilities used for storing or warehousing drug substance, in-process material, and commercial drug product under quarantine prior to a disposition decision.

Drug product manufacturing and testing sites

- Drug product manufacture sites
 - Testing sites including the stability testing and release testing
 - Primary packaging site
 - Sites that store the drug products or in-process materials or stability samples
-
- ❖ Sites for Commercial Production have to be reported in Form 356h AND Module 3
 - ❖ Sites for Registration batches/clinical batches can be reported in Module 3
 - ❖ R & D sites that generated data in support of the application should be listed in Module 3
 - ❖ Critical Excipients testing sites or packaging testing sites can be reported in Module 3

Drug Substance manufacturing and testing sites

- Drug substance commercial manufacturing and testing sites
- All critical intermediate manufacturing and testing sites
- The sites that conduct the sterilization and micronization of the drug substance
- ❖ Sites for Commercial Production have to be reported in Form 356h and Module 3
- ❖ Sites for Registration batches/clinical batches can be only reported in Module 3
- ❖ R & D sites that generated data in support of the application should be listed in Module 3
- ❖ Critical Excipients testing sites or packaging testing sites can be reported in Module 3

Combination Product

- Facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product is subject to 21CFR Part 4
 - Final kitting facilities
 - Facilities that conduct design control activities including verification and validation of a device constituent part

Device Constituent Part Manufacturer

- Any sites involved in the disposition of commercial products should be listed in Form 356h
 - Facility that has two different constituent part manufacturing operations should be clearly stated in field #28 (e.g. drug and device with the cGMP operating system)
 - Facility that manufactures a single entity or co-package combination products should identify which cGMP operating system approach is established
- Sites involved in the disposition of development batches should be listed in Module 3
- Device component manufacturer does not need to be listed in Form FDA 356h

What Information Has to Be Provided in 356h Form

28. Establishment Information (Full establishment information should be provided in the body of the application.)			
Establishment Name			
Address 1 (Street address, P.O. box, company name c/o)		Registration (FEI) Number	
Address 2 (Apartment, suite, unit, building, floor, etc.)		MF Number	
City	State/Province/Region		
Country	ZIP or Postal Code		
Is the establishment new to the application? <input type="checkbox"/> Yes <input type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn	
Establishment Contact Information at the site/facility			
Name of Contact for the Establishment		Telephone Number (Include area code)	
Address 1 (Street address, P.O. box, company name c/o)		FAX Number (Include area code)	
Address 2 (Apartment, suite, unit, building, floor, etc.)		Email Address	
City	State/Province/Region		
Country	ZIP or Postal Code		
Manufacturing Steps and/or Type of Testing		Is the site ready for inspection? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A If No, when will site be ready? (mm/dd/yyyy)	
		Continuation Page for #28	
29. Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, MAFs, and DMFs referenced in the current application.)			
Contin. Page for #29			

- FEI # / DUN#
- Indicate whether it is new to this application
- Indicate the current status
- Manufacturing steps and type of testing has to be the same as the one listed in Module 3

What information is often seen missing/wrong in FDA Form 356h

- No FEI # / DUNS # or wrong FEI # / DUNS #
- The facility is new to the application, but
 - the “Yes” box in 356h form is not checked
 - not mentioned in the cover letter
- The facility is withdrawn from the application, but it is
 - mentioned in the cover letter but not checked in the 356h form
 - checked in the 356h form but not mentioned in the cover letter
- The manufacturing steps and function is not consistent between Form 356h and Module 3
- Only new facilities of the Amendment or Supplement are listed in Form 356H, or in Module 3

What information is often seen missing in the 356h Form

No FEI # /DUNS# or wrong FEI # /DUNS#

- ✓ To obtain a FEI # or get an updated FEI #, For a GDUFA-related facility, email

FDAGDUFAFEIRequest@fda.hhs.gov

- ✓ For a PDUFA- or BsUFA-related facility , email

PDUFA BSUFAFEIRequest@fda.hhs.gov

- ✓ To obtain a DUNS #, go to

<https://www.dnb.com/solutions/government/duns-number-request-guide.html>

- ✓ To verify a previously obtained FEI # or DUNS #, go to

<https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm>

When to Withdraw a Facility

- **Amendment**
 - The application is not approved yet
 - The withdrawal facility still needs to be listed in the amendment and subsequent amendments until the application is approved or withdrawn

28. Establishment Information (Full establishment information should be provided in the body of the application.)
Establishment Name

28. Establishment Information (Full establishment information should be provided in the body of the application.)			
Establishment Name			
Address 1 (Street address, P.O. box, company name c/o)		Registration (FEI) Number	
Address 2 (Apartment, suite, unit, building, floor, etc.)		MF Number	
City	State/Province/Region		
Country	ZIP or Postal Code		
Is the establishment new to the application?		What is the status of the establishment?	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Pending <input type="checkbox"/> Active <input type="checkbox"/> Inactive <input checked="" type="checkbox"/> Withdrawn	
Establishment Contact Information at the site/facility			

When to Withdraw a Facility

Supplement

The withdrawal facility is previously approved under 21 CFR 314.70 or 601.12

- Check the box “No” in 356h form and mark “withdrawn”
- The withdrawn facility should not be listed in the subsequent supplement.

28. Establishment Information (Full establishment information should be provided in the body of the application.)			
Establishment Name			
Address 2 (Apartment, suite, unit, building, floor, etc.)		MF Number	
City	State/Province/Region		Establishment DUNS Number
Country	ZIP or Postal Code		
Is the establishment new to the application?		What is the status of the establishment?	
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		<input type="checkbox"/> Pending <input type="checkbox"/> Active <input type="checkbox"/> Inactive <input checked="" type="checkbox"/> Withdrawn	
Establishment Contact Information at the site/facility			
Name of Contact for the Establishment		Telephone Number (Include area code)	
Address 1 (Street address, P.O. box, company name c/o)		FAX Number (Include area code)	
Address 2 (Apartment, suite, unit, building, floor, etc.)			

What information is often seen missing/wrong in FDA Form 356h

continue

- The manufacturing steps and function is not consistent between Form 356h and Module 3
- Only new facilities of the Amendment or Supplement are listed in Form 356H, or in Module 3
- Incomplete supplier chain - e.g. the applicant withdrew the drug substance manufacturer, however, there is no new drug substance manufacturer proposed.

What Information Has to be Provided in Module 3

- Facility information listed in a table

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.				

- Name, title and contact information of an onsite contact person
- A site that is developing analytical method(s) should be included in Module 3

What information is often seen Wrong or Missing in Module 3

- The facilities used during the drug product development or used for clinical batches manufacture
- The facilities that manufacture the critical drug substance intermediate
- The facilities that developed and validated the test method
- Inconsistent or unclear information provided in Module 3

Crude Heparin Sites

- All crude heparin sites and heparin testing sites should be listed on Form 356h and in Module 3
- If there are any changes in the heparin site and/or crude heparin sites, inform FDA, and
 - List all current crude heparin sites including current and new crude heparin sites in Form 356h and Module 3
 - Mark “Withdrawn” or “New” clearly in Form 356h
 - If adding a new heparin site, list all crude heparin sites that supply the crude heparin to this site.

Challenge Question #1

If you don't know the FEI # of a firm that supplies the crude heparin, what should you do?

- A. Use number 99999 in field 28 for FEI #
- B. Email FDA to get the correct FEI #
- C. Email the heparin manufacturer and ask them to get the FEI# from the crude heparin supplier

Challenge Question #2

If I want to switch a critical DS intermediate site, do I need to report it to FDA?

- A. Don't need to report since it is not the drug product or drug substance site
- B. Only need to report it in Module 3
- C. Need to report it in both Form 356h and Module 3

Acknowledgements

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