Best Practices from Regulatory Business Process Manager (RBPM) Perspective and Communications

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Objectives

1) Form FDA 356h: Guidance for Industry, Common Errors, and Best Practices

2) Withdrawal of Approved ANDA Supplements

3) Four-Part Harmony in Quality Related Information Requests and Deficiencies

Form FDA 356h: Guidance for Industry, Common Errors, and Best Practices

Guidance for Industry

- Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers

  - Provides instructions on facility information to include in Form FDA 356h
  - It is not binding on FDA or the public.
  - Alternative approach can be used if it satisfies the requirements of the applicable statutes and regulations

- Good ANDA Submission Practices Guidance for Industry

Resources

- Abbreviated New Drug Application (ANDA) Forms and Submission Requirements
- Instructions for completing the Form FDA 356h
- Form FDA 356h

Form FDA 356h Common Errors

- Responsible Official is no longer in the company
- Incorrect phone number and/or fax number
- Misspelling or inadvertent spaces on email address
- Using outdated version of the Form FDA 356h

Form FDA 356h Common Errors

- Incomplete establishment information
  - No DUNS number provided
  - FEI number does not match FDA record
  - Boxes in Establishment Information are not completed

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

Establishment Name			Registration (FEI) Number
Address 1 *(Street address, P.O. box, company name c/o)*			MF Number
Address 2 *(Apartment, suite, unit, building, floor, etc.)*			Establishment DUNS Number
City	State/Province/Region	ZIP or Postal Code	Country

Is the establishment new to the application?	Is this establishment involved in the change described in this supplement?	What is the status of the establishment?
☐ Yes ☐ No	☐ Yes ☐ No	☐ Pending ☐ Active ☐ Inactive ☐ Withdrawn

Form FDA 356h Common Errors

- Submission Subtype and Supplement category if applicable, are not checked

22. Submission Sub-Type		23. If a supplement, identify the appropriate category.	
☐ Presubmission	☐ Amendment	☐ CBE	☐ Prior Approval (PA)
☐ Initial Submission	☐ Resubmission	☐ CBE-30	

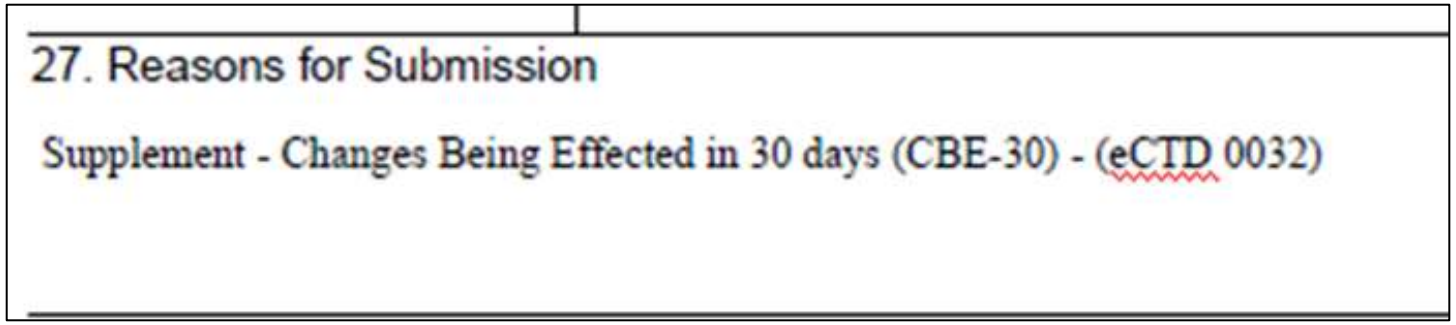
- All drug substance manufacturing facilities referenced in the Drug Master File are not included in the Form FDA 356h.

Best Practices

- Provide up to date contact information
  - Phone and Fax numbers
- Provide secured email address
  - FDA checks if email address is secured before issuing letters to applicants
  - Send request to SecureEmail@fda.hhs.gov to establish a secure email address
- Use most up to date FDA Form 356h

Best Practices

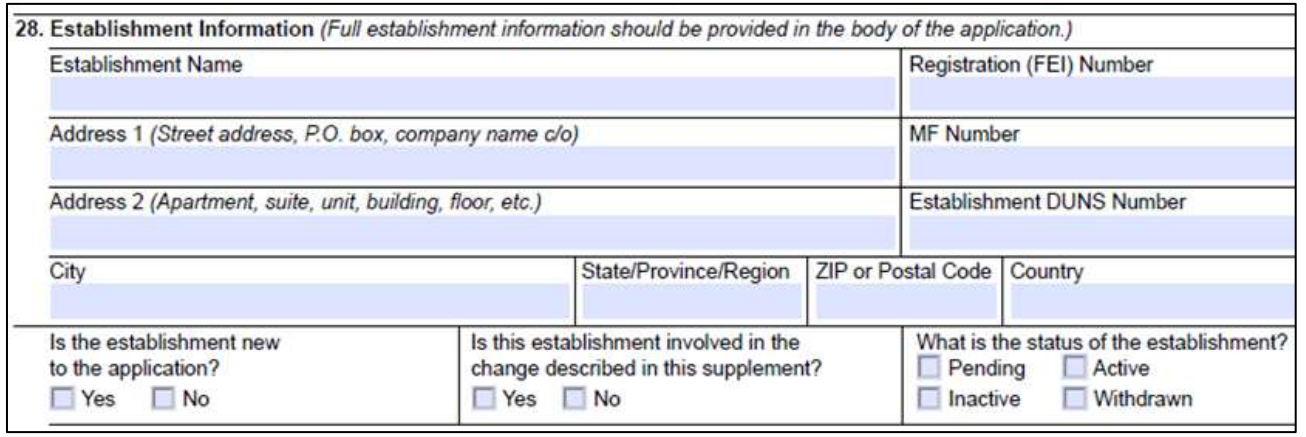
- Provide detailed explanation in Reasons for Submission section
  - For supplements, include all changes not just the type of change



- Complete establishment information completely
  - Check “new” if establishment is new
  - For supplements, check “yes or no” if establishment is involved in the change. If left blank, it may be interpreted as “no”
  - Indicate if establishment is active or withdrawn

Best Practices

- Checking all the necessary boxes leads to less confusion



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- Include all establishments for manufacturing and testing drug substance and drug product

- Include drug substance intermediate facilities

Best Practices

- Include sterilization and micronization sites
- Include facilities used for storing drug substances, in-process material and commercial drug product under quarantine prior to a disposition decision
- Include facility information contained in the DMF properly incorporated by reference
- Include facility withdrawals submitted in a DMF amendment

Best Practices

- Include establishment information with each amendment and supplement
- For combination products, include facilities manufacturing a constituent part of the co-package or single entity combination product or drug-device combination product
- If adding new facility or removing one, include in Form FDA 356h submitted with amendment

Best Practices

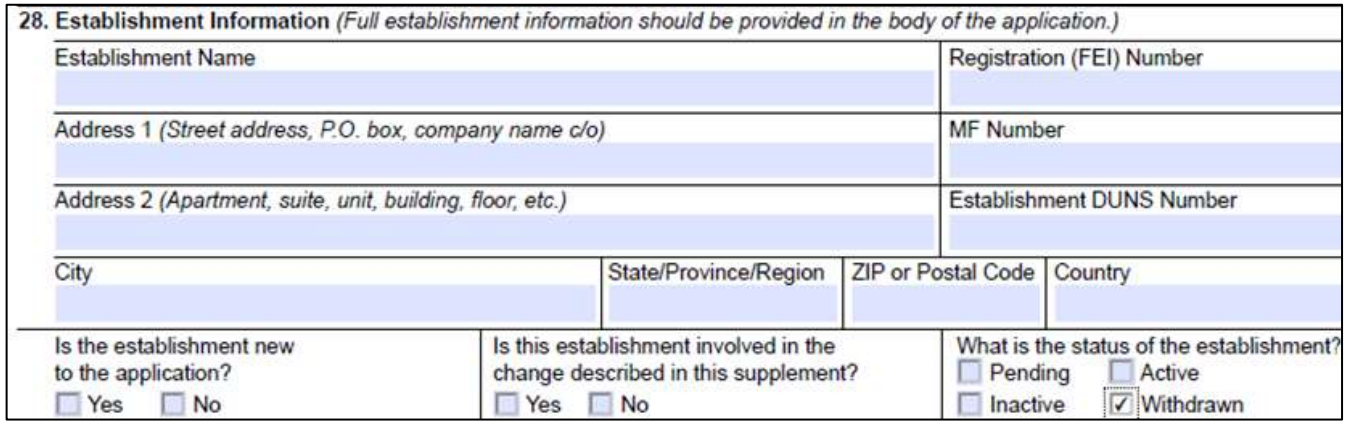
- Include DMF research and development or testing sites that generate release data to support ANDA
- Excipient testers do not need to be included, unless critical to the drug product performance
- Bioequivalence testing sites do not need to be included
- Container/closure manufacturing and testing sites do not need to be included

Best Practices

- Provide up to date FEI # and DUNS

- Facilities associated with the DMF should be included in the 356h.

- If unapproved facility is withdrawn before application is approved, keep in 356h and check withdrawn.



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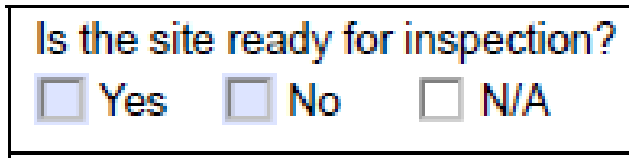
Best Practices

- Check “yes or no” box in “Is the site ready for inspection?” to indicate readiness for inspection



- Do not check “N/A” box for original ANDA submissions

- Check “N/A” box when withdrawing a facility from the ANDA

Challenge Question

The FDA will send an Information Request Letter by email if the applicant's email address is unsecured.

A. True

B. False

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Withdrawing Approved ANDA Supplements

Withdrawing Approved ANDA Supplements

- Guidance for Industry: Changes to an Approved NDA or ANDA
- Applicants should submit a new supplement when withdrawing an approved supplement.
- Refer to “Guidance for Industry: Changes to an Approved NDA or ANDA” for submitting post-approval changes in accordance with 21 CFR 314.70

Challenge Question

Withdrawing an approved supplement is considered a post-approval change?

A. True

B. False

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Four-Part Harmony in Deficiency Communications

Background

- MAPP 5016.8 Rev. 1– Using Four-Part Harmony in Quality-Related Assessment Communications

- This MAPP is intended to promote efficient and effective communication between assessment teams and applicants.

- Clearly stating deficiencies and information requests with a rationale in such requests help applicants address the issue successfully

Background

- Applicant's lack of understanding of the issue may lead to a greater number of assessment cycles

- Continuous improvements on communications (IR and deficiencies) are in progress

Elements of Four-Part Harmony

1. **What was provided?** Acknowledgement of the information submitted and provide reference to relevant modules, sections, pages or tables.
2. **What is the issue?** Identify missing information or information that FDA considers inadequate.
3. **What is needed?** Request additional information or recommend an alternative approach to address the issue.
4. **Why is it needed?** State the basis for the information request or deficiency, and include:
   - The impact of the issue on the overall regulatory decision.
   - References to all or part of applicable regulations, statutes, guidances, and/or FDA-recognized consensus standards, as appropriate.

Example of Four-Part Harmony

Example to demonstrate use of Four-Part Harmony in quality related communications

For your drug product, we acknowledge the X-month accelerated and Y-month long term stability data provided in section 3.2.P.8.3 (**element 1**). The provided stability data do not support the proposed shelf life, because insufficient long-term data were provided to support extrapolation to 2 years (**element 2**). Provide updated stability data to support your proposed shelf life; otherwise, revise your proposed shelf life (**element 3**). For more information, see International Council for Harmonization (ICH) guidance for industry *Q1E Evaluation of Stability Data* (June 2004), including Appendix A, which provides recommendations for evaluating data to estimate a drug product's shelf life (**element 4**).

Using Four-Part Harmony in Quality-Related Assessment Communications

After Receipt of Deficiencies

- Provide complete responses to all deficiencies within the indicated timeframe
- Include information or data requested
- Unsolicited information will alter the goal date
- If extension is needed for response, notify FDA as soon as it is known an extension is needed
- After receiving CR letter, applicants can request Post CR clarification meeting for clarifying questions or Post CR scientific meeting for scientific questions

Challenge Question

Which of the following is true regarding Four-Point Harmony?

A. It is intended to promote efficient and effective communication between assessment teams and applicants.

B. “What is the issue” is an element of Four-Part Harmony?

C. Clearly stating deficiencies and information requests and including a rationale in such requests, helps applicants address the issue successfully.

D. All are true.

References

- Abbreviated New Drug Application (ANDA) Forms and Submission Requirements
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- MAPP 5016.8 Rev. 1– Using Four-Part Harmony in Quality-Related Assessment Communications
- Good ANDA Submission Practices Guidance for Industry

Thank You


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