# Facility Quality Assessment for Pre-market Applications

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OPQ | CDER | FDA

**Regulatory Education for Industry (REdI)**
**Generic Drugs Forum 2017**
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# Agenda

- Goals of a Facility Quality Assessment
- Facility vs. Process Quality Assessment
- Risk-based Facility Quality Assessments
- PAI decisions and outcomes
- Types of Information Requests
- Facility recommendations

# Facility Requirement

The FD&C Act states the FDA cannot approve an application to market if:

"the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of such drug are inadequate to preserve its identity, strength, quality, and purity"

§§ 505(d) and 505(j)(4)(A) (21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))

# Goals of the Facility Quality Assessment:

- Identify manufacturing risks from a CGMP perspective based on the proposed process and control strategy
- Evaluate the inspectional history of each facility while considering its ability to implement the proposed process and control strategy
- Determine whether an on-site PAI should be conducted at each of the facilities named using risk-based decision criteria (collaboration with other members of the OPQ review team)
- Make a decision on the final commercial acceptability for each facility named in the application

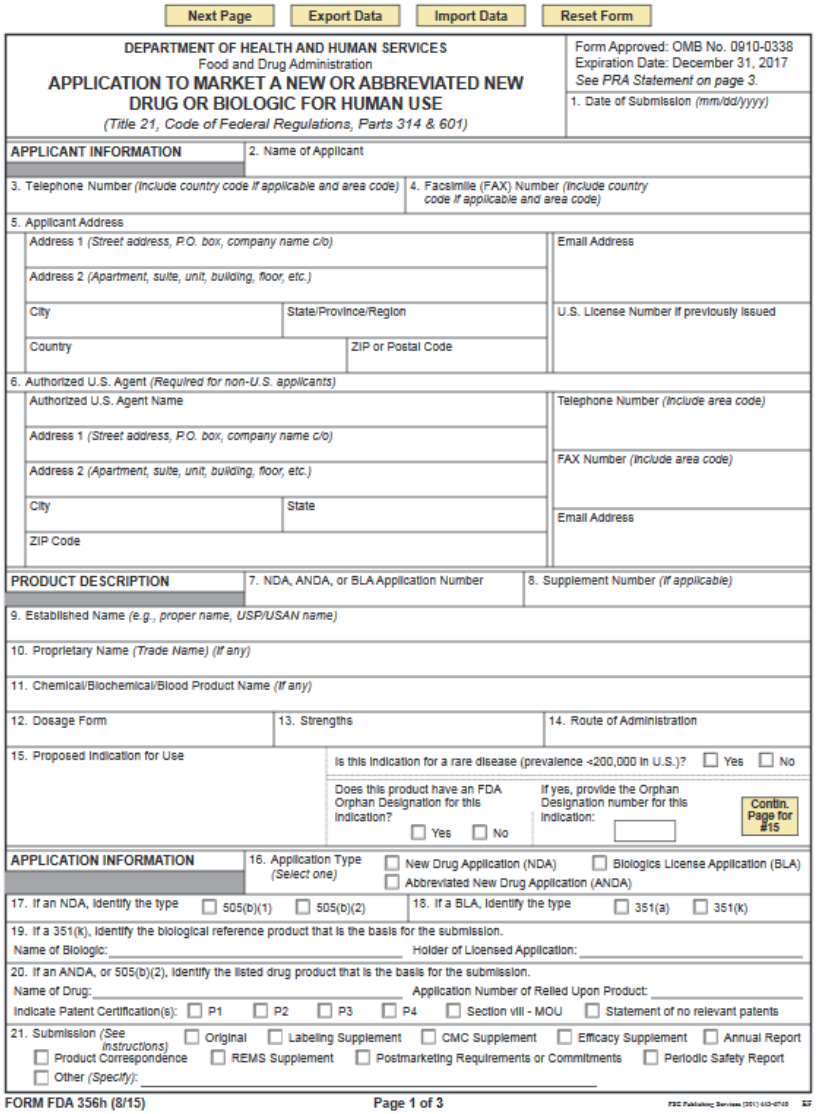
# Facility vs. Process

- The Process Quality Assessment will examine the appropriateness of the design and control strategy of the manufacturing process.
- The Facility Quality Assessment will examine the implementation of these controls and assess Quality systems at the proposed manufacturing facilities.
  - Maintain the control strategy on-site over the life cycle of the product.

*The Process and Facility Reviews are complementary and synergistic. Taken together, these reviews provide a comprehensive assessment of the manufacturing operations proposed in the submission.

# Facilities in the Submission

## Form FDA 356h



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

Form Approved: OMB No. 0910-0338
Expiration Date: December 31, 2017
*See PRA Statement on page 3.*

1. Date of Submission *(mm/dd/yyyy)*

**APPLICANT INFORMATION**

2. Name of Applicant

3. Telephone Number *(include country code if applicable and area code)*

4. Facsimile (FAX) Number *(include country code if applicable and area code)*

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City | State/Province/Region | Country | ZIP or Postal Code
Email Address
U.S. License Number if previously issued

6. Authorized U.S. Agent *(Required for non-U.S. applicants)*

Authorized U.S. Agent Name
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City | State | ZIP Code
Telephone Number *(include area code)*
FAX Number *(include area code)*
Email Address

**PRODUCT DESCRIPTION**

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15. Proposed Indication for Use

Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

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**APPLICATION INFORMATION**

16. Application Type *(Select one)* ☐ New Drug Application (NDA) ☐ Biologics License Application (BLA) ☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type ☐ 505(b)(1) ☐ 505(b)(2)

18. If a BLA, identify the type ☐ 351(a) ☐ 351(k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is the basis for the submission.
Name of Drug: _____ Application Number of Relied Upon Product: _____
Indicate Patent Certification(s): ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

21. Submission *(See instructions)* ☐ Original ☐ Labeling Supplement ☐ CMC Supplement ☐ Efficacy Supplement ☐ Annual Report ☐ Product Correspondence ☐ REMS Supplement ☐ Postmarketing Requirements or Commitments ☐ Periodic Safety Report ☐ Other *(Specify)*: _____

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## Module 3: Quality

**Drug Substance**

| | |
|---|---|
| 3.2.S.2 | **Manufacturer**<br>**Drug Substance (Active Pharmaceutical Ingredient)**<br>Must correlate to the establishment information submitted in annex to Form FDA 356h<br>1. Name and Full Address(es) of the Facility(ies)<br>2. Contact name, phone and fax numbers, email address<br>3. U.S. Agent's Name (if applicable)<br>4. Specify function or responsibility<br>5. Type II DMF number(s) for API(s)<br>6. CFN, FEI, or DUNS number (if available)<br>7. Additional sources of API and information (1 through 6) as applicable |

**Drug Product**

| | |
|---|---|
| 3.2.P.3.1 | **Drug Product Manufacturer(s)**<br>Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories.<br>1. Name and Full Address(es) of the Facility(ies)<br>2. Contact name, phone and fax numbers, email address<br>3. U.S. Agent's name (if applicable)<br>4. Specify function or responsibility<br>5. cGMP Certification (from both applicant and drug product manufacturer, if different entities)<br>6. CFN, FEI, or DUNS numbers (if available) |

**Guidance for Industry*

- *ANDA Submissions – Refuse-to-Receive Standards, Dec 2016, Revision 2*
- M4Q: CTD — Quality, Aug 2001

# OPF analysis of Facilities

## Commercial Facilities

- Finished Dosage Manufacturers
- API manufacturers
- Finished dosage & API External testing sites
- Primary Packaging and Labeling sites
- Animal derived APIs ( performs crude extraction facility)

## Supporting Facilities

- Intermediate API facility
  - Case-by-case (critical)
- Exhibit batch manufactures
  - Not a proposed commercial site
  - Subject to PAI if concern(s) identified
- Component manufacturers
  - For-cause if concern identified
  - DP manufactures responsibility to qualify their suppliers
- Excipient manufactures
  - Generally not evaluated, unless novel excipient / critical step in process
- Secondary Packagers

* Note all of these sites are required to meet the statutory CGMPs per the FD&C Act and may be routinely inspected

# What goes into the Facility Risk Assessment

- Develop a broad understanding of risk for each facility which the Reviewer then uses to justify and recommend facilities for PAI
- OPF uses a RISK BASED approach to evaluate facilities listed in application
  - Facility Risk
  - Process Risk
  - Product Risk

# What goes into the Facility Risk Assessment

## FACILITY RISK

- *What is the firm's CGMP compliance status?*
  - Previous inspectional history/outcomes

- *Is there confidence that the firm can maintain quality operations given their manufacturing commitments?*
  - CGMP issues
  - FARs
  - Recalls
  - Production load

# What goes into the Facility Risk Assessment

## PROCESS RISK

- *What is the firm's related experience with the proposed operations or operational profile code?*
  - New or different process
  - New Manufacturing building/space/lines
  - New Profile or unrelated profile
    - IR tablet (TCM) vs. IR (CHG) capsule both with similar drug load
    - IR Tablet (TCM) vs. IR Capsule (CHG) with different drug load

- *Are the facility's proposed operations inherently difficult to execute or monitor*?
  - High/Medium Risk process (complex)

- Incomplete Development Data
- API Source (derived from Animal tissue, etc.)

# What goes into the Facility Risk Assessment

## PRODUCT RISK

- *Do the product attributes and manufacturing process contribute additional risks?*
    - Known issues with the referenced RLD
    - NME
    - Intended patient population
    - Sponsors first application
    - Complex supply chain/multiple suppliers

# Examples of PAI Triggers

- Facility named in application for the first time
- Facility has no inspectional history
  - Facility only inspected for non-application products
- First ANDA filed (coverage of FDF and testing)
- Numerous Application submissions
- Certain site/process/product changes that are expected to pose significant challenge to the state of control

*Note: Recent "favorable" Surveillance inspections (NAI/VAI) or previous PAIs does NOT indicate a PAI will not be needed

# Pre-Approval Inspection (PAI)
# Compliance Program 7346.832

- PAI is Requested from OPQ/OPF to ORA and assignment is created
- ORA schedules PAI
- Inspection Team may include:
  - ORA Drug Investigator (*lead)
  - CDER Reviewers
    - Chemistry SME
    - Microbiology SME
    - Process/Facility SME
    - Formulation SME

*BLA PAIs may be performed by OPF, OBP, and ORA

- Knowledge Transfer Memos (KTMs)


Publicly available CPGM defines program expectations

- Defines criteria for on-site inspection versus desk file review
- Discusses coverage during inspection and provides guidance for inspection outcomes
  https://www.fda.gov/ucm071871.pdf

# PAI Outcomes

- Lead investigator will make ***recommendation*** at the conclusion of the inspection:
  - Recommend Approval
    - Inspection found no significant issues or violation to the PAI CP
    - None of the Withholding criteria apply from the Compliance Program
  - Recommend Withholding Approval
    - Investigators observed that the site is not GMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete (violation of one or more of the PAI objectives)
    - Criteria for Withholding outlined in Compliance program

*****CDER's Office of New Drugs or Office of Generic Drugs makes the final decision on whether to approve or withhold approval of the application or licensure**.

# After the PAI

1. Inspection team writes the EIR Narrative and generates a package to include exhibits and attachments (482, 483, affidavits…etc.)
2. Endorsed EIR Package is sent to the Center for review by OPF
   - small differences exist for Domestic vs. Foreign Firms in the PAI EIR review process
   - Final Decision remains with the Center
3. OPF-performs the PAI EIR review
   - Narrative Report and Exhibits
   - 483s and the firm's responses

# Types of Information Requests

Following inspection and EIR review, Reviewers can ask additional questions to a firm using a Request for Additional Information (RAI) Letter. These requests are an extension of the inspection and ask for clarification or further information following a PAI.

## Request For Additional Information (RAI):

focused exclusively on CGMP issues and operations performed on-site, should follow a recent inspection, and are sent to a inspected facility directly.

## Vs.

## Information Request (IR):

questions related to the manufacturing operations at that site but in the context of the application review and sent to the applicant.

* RAI and IR can be used in tandem to ensure proper control strategy in the application and appropriate implementation at the facility

# Analysis of PAI Results

- PAI EIR packages are reviewed to determine:
  - Adequate coverage
  - Initial risks identified have been addressed
  - Additional items uncovered during the inspection
- Domestic Facility
  - District Pre-Approval Manager
  - OPF involvement with inspectional concerns/initial WH recommendations
- International Facility
  - OPF determines final outcome

# Wrapping up Facility Review

- Interaction with IQA review team
  - Communication of PAI findings (this is done throughout review)
  - Pending facility compliance issues (this could change for any facility during review cycle)
- Review Documentation:
  - The manufacturing risks identified in the application and applying the reviewer's understanding and critical thinking to the described processes.
  - Description of the Risk Assessment (Facility, Process, Product) and the rationale for a PAI recommendation;
    - includes elements of the compliance history, manufacturing risks, and product specific concerns.
  - For any PAIs, the risks communicated to the inspection team, the corresponding findings from the inspection with respect to these concerns, and any additional information found on-site that is pertinent to the assessment of the facility;
  - Justification for the final Facility Recommendation.

# Overall Facility Recommendation

- Recommend Approve:
  - There are no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities.
- Recommend Withhold:
  - If any one site is unacceptable:
    - If any enforcement action is pending or has occurred; or
    - If recent surveillance inspection provides initial evidence of concerns with currently marketed product; or
    - If a product-specific issues are identified and concerns not adequately addressed

***Facility recommendations in pending applications are dependent on both Surveillance status (CGMP) and product specific (PAI) findings. Overall Approvability may be affected by either one, or both***

# Site Changes During Review

- Facility Withdrawals
  - Factors OPF considers:
    - CGMP status of the facility being withdrawn
    - Completeness of the supply chain/ manufacturing operations
    - Data / information generated to support approval

- Considerations when Withdrawing a facility:
  - Identify an existing facility or new facility that will replace all the previous functions of the WD facility
  - Assess impact of data/information provided by site and ensure additional data is available as appropriate to support the new facility and the submission
  - Provide comparison of manufacturing process/equipment as appropriate

# SUMMARY

- Facility assessment considers risks from a CGMP perspective and a review perspective, incorporating the OPQ review team's findings to ensure a holistic assessment

- Goals of the Division of Inspectional Assessment & Facility Reviews:
  - Identify CGMP manufacturing risks on the proposed process and control strategy
  - Evaluate the compliance history of each facility while considering its ability to perform the proposed operations
  - Determine whether an on-site PAI should be conducted at each of the facilities named using risk-based decision criteria (collaboration with other members of the OPQ review team)
  - Make a decision on the final commercial acceptability for each facility named in the application
    - What degree of confidence is established the facility can perform its outlined responsibilities and functions within a state of control over the lifecycle of product.

# Thank you!

Please complete the session survey:
**surveymonkey.com/r/GDF-D2S14**