# Current Submissions Expectations for Facility Information

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# Outline

1. Goals of Facility Review
2. Submission Expectations
3. Considerations for Risk-based Quality Assessment
4. Commonly Seen Deficiencies that may Impact Facility Review
5. Summary

# Goals of the Facility Review

- Identify manufacturing risks from a CGMP perspective
- Evaluate the compliance history of each facility related to the proposed operations
- Determine the need for an on-site pre-approval inspection (PAI) in collaboration with OPQ review team
- Ensure continuity in the review of the application and the assessment of operations on-site
- Recommend final approvability for each facility named in the application

# Submission Expectations

- 21 CFR 314.50(d)(1) and 314.54(a)(1)
  - Require the application contains the name and address of the commercial drug substance and drug product manufacturer(s)
  - **NOTE: 314.50(d)(1)(ii)(b) requires the same information for each contract facility involved in the manufacture, processing, packaging, or testing of the drug product submission batches and identification of the operation performed by each contract facility**
- *ANDA Submissions – Refuse-to-Receive Standards: Guidance for Industry, May 2015*:
  - An applicant should include all of the facility information that is listed in Modules 3.2.S.2 and 3.2.P.3.1 (drug substance and drug product, respectively) of the application in the 356h form. FDA will notify the applicant if there are any facilities listed that are not captured in the 356h form. If FDA does not receive a revised 356h form, FDA will refuse-to-receive the ANDA.

# Risk-based Quality Assessment

- Determine acceptability of each facility for its proposed operations
  - Final recommendation based on:
    - Relevant application facts (process development, control strategy, master batch records, etc.)
    - Manufacturing capability
    - Inspectional history (EIR review, quality defect data, etc.)
    - Collective analysis of factors listed above

# Common Review Deficiencies – Submission Expectations

- Inconsistencies between facility information in 356h form and Modules S.2 and P.3
- Inconsistencies in reported Facility Establishment Identifier
- Missing facilities used for submission batches
- Missing drug substance testing facilities listed in DMF
- Lack of detailed information regarding operations or tests to be conducted at each facility
- Sites not ready for inspection at time of submission

# Common Review Deficiencies – Before a Pre-Approval Inspection

- Facility headquarters site information provided
- Facility not performing listed function or unaware it was referenced in the ANDA
- Facility no longer in commercial operation

# Common Review Deficiencies – Pre-Approval Inspection Observations

- CPGM 52.832/46.832/52.832 Objective 1: Readiness for Commercial Manufacturing
  - Inadequate process design or justification for the commercial process/control strategy
  - Significant general CGMP issues observed
  - Commercial scale equipment not qualified
  - Analytical methods not transferred/verified/fully validated
  - Failure to adequately investigate unexpected deviations, discrepancies, trends, and OOS
  - Lack of CGMP training and/or understanding
    - Sites without FDA inspectional history
    - Sites converting from R&D to commercial operations

# Common Review Deficiencies – Pre-Approval Inspection Observations

- CPGM 52.832/46.832/52.832 Objective 2: Conformance to Application
  - Commercial scale equipment listed in the application not available on-site
  - Manufacturing process changes and/or in-process control revisions not reported after filing
  - Method updates not reported after filing
  - Implemented process/control strategy does not match that described in application

# Common Review Deficiencies – Pre-Approval Inspection Observations

- CPGM 52.832/46.832/52.832 Objective 3: Data Integrity Audit
  - Unknown impurities or failing stability results not submitted to application
  - Holding studies not representative of actual conditions
  - Retesting failing results until conformity achieved
  - Failing results routinely attributed to analyst error
  - Lack of audit trails in the laboratory data acquisition system
  - Use of trial injections
  - Data reported in application was average of test results including failing results

# Common Review Deficiencies – Post PAI Evaluation of Response

- Response identifies training and SOP updates as CAPA
  - Need assessment of impact on application and data supporting conclusions
- Response reveals need to provide updates to the application
  - Amendments should be submitted in timely fashion to allow for review
- Response indicates data integrity findings affect application
  - Impact of the data integrity findings on the veracity, accuracy and/or suitability of the application data should be assessed
  - Remediation plan should include detailed analysis of actions to correct the data
- Response identifies need for long term CAPAs
  - Proposed timeline should be provided for assessment to determine scheduling of additional PAIs as needed.

# Common Review Deficiencies – Site Change Amendments

- Withdrawal of facilities during review of the application may affect approvability
  - Factors to consider:
    - Data/information generated to support approval
    - CGMP status of facility being withdrawn
    - Completeness of the supply chain / manufacturing operations
- Helpful hints
  - Identify which existing facilities or new facilities will replace the withdrawn 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

# Common Review Deficiencies – Site Change Comparability Protocols

- New Draft FDA Guidance issued April 2016
  - *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, Guidance for Industry*
- Identify the facility name, address, and responsibility that is subject of the CP
- Facility proposed will be evaluated for CGMP compliance status at time of CP submission and during evaluation of the subsequent supplement
  - Facility's CGMP compliance status and history of related operations will impact approvability of the CP and the filing category

# 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
- Adhering to regulatory requirements and guidance by providing complete list of facilities in 356h and Sections S.2 and P.3 facilitates timely review of an application
- Ensuring clear and specific quality agreements with contract facilities will help minimize increasing number of withholds due to "firm not ready or doing function"

# Thank you for your attention!

Please evaluate this session:
**surveymonkey.com/r/PQS-D1S11**

Questions will be addressed during the Q&A Panel coming shortly.

Additional Questions: CDER-OPQ-Inquiries@fda.hhs.gov