# Best Practices for Abbreviated New Drug Applications (ANDAs) in GDUFA III: Office of Pharmaceutical Quality Perspective

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# Objectives

- Explain how to engage with the Office of Pharmaceutical Quality (OPQ) during the ANDA lifecycle
- Provide an overview of OPQ communications during and after the ANDA assessment cycles
- Review best practices

# OPQ Communications - POC

- Regulatory Business Process Manager (RBPM)
  - Primary point of contact (POC) for ALL OPQ-related communications internally and for industry
  - Works closely with OPQ assessment team and disciplines on your applications
  - Issues all communications related to the quality assessment during the assessment cycle

# OPQ Communications - IR

- Information Request (IR) Letter
  - Further information/clarification needed to complete assessment throughout the assessment cycle
  - Single Quality sub-discipline or multiple Quality sub-disciplines
  - Requested response date
  - Communicated by letter, e-mail, or phone

# OPQ Communications - DRL

- Discipline Review Letter (DRL)
  - Preliminary findings by the assessment team
    - May or may not represent management level assessment
  - Requested response date
  - Issued when Quality discipline has substantially completed assessments at around mid-point of the assessment cycle (Mid-Cycle Date)

# Responding to IR/DRLs

- Responses to IR/DRLs should be complete and timely.
  - Partial responses will not be accepted.
- Late responses will impact the goal date or could be deferred until the next assessment cycle.
- Responses should only include information related to the IR/DRL. Additional/gratuitous information could lead to goal date extensions.

# OPQ Communications - Meetings

- Mid-Cycle Review Meeting
  - Ask for rationale for any deficiency identified in mid-cycle DRL
  - Questions related to assessment of the data in the ANDA
  - No new data/information should be presented
- Enhanced Mid-Cycle Review Meeting
  - Questions related to proposed path (including new data) to address deficiencies in mid-cycle DRL
  - No substantive assessment of data at the meeting
- Post-CRL Teleconference
- Teleconference to Clarify First-Cycle DMF Deficiencies

# OPQ Controlled Correspondences GDUFA II

- During GDUFA II (FY19-FY22), OPQ received ~700 Controlled Correspondences annually
- Common themes included:
  - Amount of Stability Data
  - Container-closure changes
  - Bracketing or Matrixing of batches
  - Microbiology
  - Batch Size
  - Packaging

# OPQ Controlled Correspondences GDUFA III

- During an ANDA assessment cycle:
  - Can be submitted if an applicant seeks further feedback from FDA after a Product-Specific Guidance Teleconference or to seek a Covered Product Authorization.
- After an ANDA assessment cycle:
  - After issuance of CRL
  - After issuance of a tentative approval
  - After full approval

# DMF Unsolicited Amendment Issues

- Poorly timed unsolicited amendments continue to adversely impact application timelines
- Can result in goal date extensions or unnecessary CR letters to the DMF and applicant
- Frequently unsolicited amendments are not necessary to be submitted when they are sent.
- Communication between the applicant and DMF holder regarding the DMF submission and application timelines is the best solution

# Tips to avoid Unsolicited Amendment Issues

- DMF holders and applicants should share the following information in a timely way:
  - Plans to submit changes to the DMF
  - Key expected action dates and priorities for the referencing application(s)
  - Know the current status of your DMF – FA letters, NFC letters, real time updates from DMFOGD@FDA.HHS.GOV

- If it is not clear whether an unsolicited DMF submission will impact an application timeline do the following:
  - Reach out to your customers to get information on application timelines
  - Reach out to DMFOGD so we can provide helpful guidance on submission timing

- Understand the consequences of a poorly timed DMF amendment to your customer's ANDA
  - Goal date extension (extended from the date the DMF amendment is received)
  - Length of extension determined by nature of the amendment (major or minor)
  - Potential loss of an exclusivity (forfeiture date)
  - Withdrawal of a DMF amendment will not restore an already extended goal date

# GDUFA III DMF Enhancements

- DMF Prior Assessments
  - A DMF holder may submit a request for the assessment of an original DMF (previously unreviewed) six months prior to the planned submission date of a marketing application (original ANDA, ANDA amendment, or a prior approval supplement (PAS)
  - FDA will grant the request and review the DMF prior to ANDA submission when the planned application submission meets certain criteria
- FDA Assessment of Solicited DMF Amendments
  - FDA will assess certain solicited DMF amendments related to original ANDAs and PASs upon receipt even if the original ANDA or PAS in which the DMF is referenced is not currently under assessment.
  - Priority given to those amendments related to ANDAs for which acceptability of the DMF assessment may result in a full approval on the next application cycle
- Assessment comments issued to DMF holder at least in parallel with issuance of review comments relating to DMF for the ANDA.
- Teleconference to Clarify First-Cycle DMF Deficiencies

# Common Deficiencies in the DMFs

## Non-mutagenic Organic Impurity Controls

- A hazard assessment per ICH M7 is expected to support the impurity classifications (mutagenic vs. non-mutagenic) on control strategies.
- Some potential impurities are missed in the discussion.
- Degradation impurities should be included in the stability specification.
- Failure to demonstrate the method specificity for impurities which are controlled as any unspecified impurities.

*References: ICH Q3A, ICH M7, Guidance for Industry ANDAs: Impurities in Drug Substances*

# Common Deficiencies in the DMFs (cont.)

## Mutagenic Impurity Controls

- Failure to use (Q)SAR methodologies that are ICH M7 compliant in the hazard assessment.
- Insufficient data is provided when upstream controls are established at higher than acceptable limit.
  - Spike/purge study is recommended
- Incorrect threshold of toxicological concern (TTC) is proposed.
- Failure to limit total mutagenic impurities when multiple impurities are present.
- Failure to show the analytical method is suitable for its intended use.

*References: ICH M7*

# Drug Product Considerations

- Extractable/Leachable studies for key packaging components
  - Utilize correct Safety Concern Threshold and Analytical Evaluation Threshold from the beginning
  - Select studies conditions pertinent to specific attributes of the product of interest
- Impurity Qualification
  - Include sufficient studies to qualify impurities from the start, considering both ICH Q3A/B and M7

# Facility Assessment – What We Need

- Ensure that ALL current facilities (including all relevant DMF facilities) and responsibilities are clearly listed on the 356h Form
- Process development & bridge to commercial scale
- Commercial process descriptions, process flow diagrams, MBRs (sequence, equipment, process parameters, in process controls and tests)
- Sterilization validation package for sterile products

# Facility Assessment – Common Manufacturing Deficiencies

- New batches required due to significant failures with submitted batches; no root cause understanding provided
- Incomplete facility or facility responsibility listing on 356h form
- Process parameters and in process controls are not supported by process development knowledge in the application

# Cover Letter

- Use the draft guidance "Cover Letter Attachments for Controlled Correspondences and ANDA Submissions Guidance for Industry | FDA" when preparing submission cover letters.
- Be sure to identify all applicable disciplines for which you are submitting information
- Ensure your e-mail is secure so communications can be timely. Request for secure e-mail can be sent to SecureEmail@fda.hhs.gov

# Resources

- CDER Guidance Webpage: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
- GDUFA Webpage: https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
- Good ANDA Submission Practices Guidance for Industry: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-anda-submission-practices-guidance-industry

# Resources (cont.)

- Cover Letter Attachments for Controlled Correspondences and ANDA Submissions Draft Guidance for Industry : https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cover-letter-attachments-controlled-correspondences-and-anda-submissions-guidance-industry
- ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs Guidance for Industry: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/anda-submissions-amendments-and-requests-final-approval-tentatively-approved-andas

# Resources (cont.)

- Draft Guidance for Industry - Review of Drug Master Files in Advance of Certain ANDA Submissions Under GDUFA
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents
- Guidance for Industry: Information Requests and Discipline Review Letters Under GDUFA
  - https://www.fda.gov/media/109915/download
- MAPP 5220.5: Issuance of Information Request and/or Discipline Review Letters for ANDAs
  - https://www.fda.gov/media/109649/download
- MAPP 5015.6: Review of Grouped Product Quality Supplements
  - https://www.fda.gov/media/72531/download

# Summary

- Reach out to the RBPM for ALL Quality-related communications.
- Completely respond to all Quality IRs/DRLs by the requested response date.
- Be familiar with your ANDA assessment timeline and all possible communications.
- Actively and frequently communicate with your DMF holder
- Take advantage of the new ways to communicate with the Agency through GDUFA III enhancements!


THANK YOU!


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