Overview of Major Quality Deficiencies and Approaches Available in GDUFA III

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Learning Objectives

- Identifying deficiency themes that may be considered major for the Quality discipline
- Understanding how major deficiencies may be communicated to applicants
- Identifying new approaches in GDUFA III to address questions related to major deficiencies

Disclaimers

- The major deficiency themes discussed in this presentation are not an exhaustive list of all potential major themes for the Quality discipline
- Not all approaches discussed for questions related to major deficiencies are available for all abbreviated new drug applications (ANDAs)

Major Quality Deficiency Themes

Drug Substance

- Major issues with referenced Drug Master File (DMF) for the active pharmaceutical ingredient (API)
- Demonstration of API sameness, such as for a peptide product
- Toxicological studies are needed to qualify an unqualified impurity

Drug Product

- Toxicological studies are needed to qualify an unqualified impurity
- Assessment of extractables and leachables
- Unacceptable analytical methods: Need substantial revision to proposed analytical procedures

Manufacturing

- Inadequate facilities due to pre-approval or surveillance inspection
- Inadequate control of critical process parameters for important unit operations
- Inadequate justifications for the scale-up strategy of processes and equipment
- New batches need to be manufactured due to observed stability failures

Microbiology

- Missing or inadequate validation for product release and/or stability test method
- Absence of sterilization validation data to support the terminal sterilization of the drug product
- For aseptically filled products, failure to provide validation data to support the sterilization of the equipment and/or components utilized in production of the drug product
- For multi-dose products, absence of antimicrobial effectiveness test results

Biopharmaceutics

- New in vitro dissolution (release) analytical method, including development report and validation, is needed because the proposed method is inadequate
- Data supporting the proposed in vitro release acceptance criteria (e.g., in vitro in vivo correlation (IVIVC), data or in silico physiologically based pharmacokinetics (PBPK) modeling) is inadequate.
- Upon review, the post-approval change is determined to a level requiring an in vivo bioequivalence study that is not included within the submission

Challenge Question

- FDA will tell an ANDA applicant why their referenced type II DMF is considered Major

  A. True

  B. False

How Will Major Deficiencies Be Communicated?

Information Request

- Generally, Quality will not issue Major Information Requests (IR)
  - Applicants may see Major IRs from the Clinical discipline for combination products at the mid-point of the first review cycle
- If a Major IR is issued from Quality with no due date, that may indicate a forthcoming Complete Response Letter (CRL)

Discipline Review Letter

- Major Quality deficiencies will be sent in the Quality Discipline Review Letter (DRL)
  - Excluding facility deficiencies
- If applicants respond by the due date, the goal date will be extended to allow time for review of the DRL response

Complete Response Letter

- Major Quality deficiencies will be sent in CRLs, including facility deficiencies
- Any remaining deficiencies from consults that were not sent in a DRL will be communicated in this letter

Challenge Question

- Which letter type is when an applicant with an unapproved ANDA most likely will first learn of a major deficiency for Microbiology?

A. Information Request

B. Discipline Review Letter

C. Complete Response Letter

Discussing Major Quality Deficiencies with FDA

Meetings

- Clarifying Questions
  - Mid-Cycle Review Meeting (MCRM) *‡
  - Post-CRL Teleconferences
- Scientific Questions (New in GDUFA III)
  - Enhanced MCRM ‡
  - Post-CRL Scientific Meeting ‡

* Competitive Generic Therapy (CGT) drug products
‡ Complex drug products

Controlled Correspondences

- Post-CRL questions for major deficiencies can be submitted via a Controlled Correspondence (CC)
- CC may be considered Level 1 or Level 2 depending on the complexity of the major deficiency and the offices involved

Challenge Question

- Which category of ANDA drug products are eligible for meetings to address scientific questions regarding major deficiencies?

  A. All drug products

  B. CGT drug products

  C. Complex drug products

Summary

- Major deficiencies can span any of the Quality sub-disciplines
- Quality major deficiencies will most likely be communicated either in a DRL or CRL
- Applicants now have new avenues to address their questions regarding major deficiencies in GDUFA III

Resources

Guidance for Industry

- ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA
- Information Requests and Discipline Review Letters Under the Generic Drug User Fee Amendments
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA
- Post-Complete Response Letter Clarification Meetings Between FDA and ANDA Applicants Under GDUFA
- Controlled Correspondence Related to Generic Drug Development

Other Resources

- GDUFA III Commitment Letter
- MAPP 5220.5 Rev. 2: Issuance of Information Requests and/or Discipline Review Letters for Abbreviated New Drug Applications

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