GDUFA-III Implementation – Facility related updates

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GDUFA III

- Generic Drug User Fee Amendments III (GDUFA-III or G-III) signed in 2022
- New enhancements to the program maximize the efficiency and utility of each assessment cycle.
  - Reducing the number of assessment cycles for ANDAs
  - Facilitating timely access to generic medicines for American patients.
- Facility related updates:
  - Updated: Presubmission facility correspondence (PFC)
  - New: Reclassification of facility-based major complete response letter amendments to minor (M2m)
  - New: Submissions with facilities not ready for inspection (FNR)

PFC- What has changed?

GDUFA-II	GDUFA-III
• All eCTD sections related to manufacturing and bioequivalence (clinical and analytical) • Final bioequivalence report required • No changes allowed between PFC and ANDA	• Limited eCTD sections containing information needed for FDA to determine the need for a preapproval inspection • Final bioequivalence report may be submitted but not required* • Changes between PFC and ANDA allowed if not “significant”

*If information in the final BE study report submitted with the ANDA leads FDA to determine that an inspection is needed, the 10-month goal date will apply.

PFC case study

Case 1: A PFC submitted 2 months prior to original ANDA submission.

Background

- The PFC was submitted on 11/29/2023
  - CMC and facilities information was submitted to support initial manufacturing facility assessment.
  - No BE report submitted.
- Original ANDA application submitted on 1/30/24
  - No changes made to information submitted in support of initial manufacturing facility assessment
  - BE report did not result in a need for inspection

Decision: Priority application status granted with a goal date of 8 months

Rationale: The applicant submitted PFC request in accordance with G-III

Tips for submitting a PFC

- Submit PFC electronically in eCTD format
- Certify that all information in the PFC is complete and accurate
- Confirm that all facilities are ready for inspection
- Submit ANDA application no earlier than 60 days of submitting PFC
- Notify FDA of any significant changes during ANDA submission

Major to Minor (M2m)

- The request for reclassification must be made at the same time as submitting the response to the CRL. The reclassification request must include supporting information detailing why the facility deficiency has been resolved and no additional facility assessment is needed.
- The facility is the only major deficiency.
- The facility deficiency was issued after observations were made as part of a surveillance inspection.
- FDA determines that the facility issues have been addressed and there is no need for an inspection or use of an alternative tool.
- The reclassification request is easily identified in the cover letter for the amendment submitted in response to the CR letter.
- The CR letter is less than 1 year old (from the date the CR letter was signed).*

*The CR letter can be more than 1 year old for drug shortage or public health emergency products.

M2m case study

Case 2: Deficiency in CRL: Following surveillance inspection of the Rockville manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this ANDA may be approved.

Background

- The application was submitted on 6/10/2018
- A Surveillance Inspection occurred on 6/15/2018
- A complete response letter was sent on 10/16/2022
- Rockville received no observations after the most recent surveillance inspection on 11/22/2022
- The M2m request was received on 12/22/2022
- The facility manufactures immediate-release tablets by granulation and application product is also using similar manufacturing process

Decision: M2m request will be granted

Rationale: The surveillance inspection deficiencies were resolved and the applicant submitted M2m request in accordance with G-III

Tips for submitting a M2m request

- Prominently identify in bold that there is a Facility Only Reclassification Request at the top of the Cover Letter while citing MAPP 5021.5
- Include a Cover Letter Attachment and indicate there is a Facility Only Reclassification Request
- Requests must be submitted within a year of issuance of CRL with a CRL response to be considered
- Requests must include one of the following:
  - FDA Issued VAI or NAI cGMP classification letter to the facility referenced in the CRL

    OR

  - Withdrawn statement of the facility reference in the CRL <u>AND</u> that the withdrawn facility/ facilities did not generate data to support a regulatory action (e.g., exhibit batches, stability batches)

Facility Not Ready (FNR) for inspection

- If any site is indicated as not ready for inspection on 356h form, the goal date will be set at 15 months.
- FDA will conduct a filing review of the application; however, substantive assessment of the application will not begin until all facilities are ready for inspection
- If the applicant submits an amendment with Form FDA 356h indicating all facilities are ready for inspection while goal date is 15 months after original submission
  - Goal date will be reset based on date of the amendment submission (8 months for priority/ 10 months for standard amendments)
  - Substantive assessment will begin.
- If no amendment indicating all facilities are ready for inspection is received by 30 days before the 15 month goal date
  - Goal date will be changed to 30 months after the original submission
  - FDA will assess and act on 90% of applications by the 30 month goal date

FNR case study

Case 3: Bethesda Pharmaceuticals submits a standard-review application with 1 facility marked as not ready for inspection on 10/30/2022

Background

- The goal date is set as 3/30/2024 which is 15 months after submission.
- On 2/22/2024, Bethesda Pharmaceuticals submits an amendment indicating on Form FDA 356h that all facilities are ready for inspection

Decision

The goal date will be reset to 12/22/2024.

Rationale

The goal date is set as 10 months after submission of the amendment indicating all facilities are ready for inspection as it is a standard review and the amendment was submitted within the first 15 month goal date.

Tips for submitting a complete ANDA application

- All manufacturing and testing sites are ready for inspection at the time of submission & clearly note this on 356h form
- Compliance with CGMPs
- Operations match those in application
- Data in the submission is an accurate representation of data generated at the facility
- Manufacturing operations - Fit for Purpose

Resources

- GDUFA III Commitment Letter: https://www.fda.gov/media/153631/download
- GDUFA III information, including guidance: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii
- Guidance: ANDAs: Pre-Submission Facility Correspondence Related to Prioritized Generic Drug Submissions, 2022
- MAPP 5021.5 Assessment of Facility-Based Deficiency Major-to-Minor Reclassification Request
- Draft guidance: Facility Readiness: Goal Date Decisions Under GDUFA Guidance for Industry, 2022