Facility Related Updates in GDUFA III

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Facility related updates in GDUFA III

- Reclassification of facility-based major complete response letter (CRL) amendments
- Submissions with facilities not ready for inspection

Reclassification of Facility-Based Major CRL Amendments

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What is reclassification?

Upon submission of a Facility-Based Major CRL Amendment, an applicant can request that FDA reclassify the Major Amendment to Minor (M2m) when applicable criteria are met.

Overview of Reclassification Request

- A MAPP with instructions on requesting reclassification and providing supportive information will be available soon
- In general, request with the submission of the CRL response amendment
  - Request must be made at the time of CRL response amendment submission
    - Request for reclassification in subsequent amendments will be denied
  - CRL should be less than 1 year old
    - Exceptions can be made for drug shortage or public health emergency
- Include supportive information in CRL response amendment to demonstrate
  - Why the facility deficiency is resolved
  - Why no additional facility assessment is needed

When will reclassification be granted?

- If the FDA determines that for assessment of the amendment, the following criteria apply
  - No facility inspection is needed
    - Facility is no longer under an Official Action Indicated (OAI) or facility alert
    - No Pre-Approval Inspection (PAI) is necessary
  - No use of alternate tools for facility inspection are needed
    - 704(a)(4) evaluation
    - Remote Interactive Evaluation (RIE)
  - No continued assessment of inspection deficiency responses are needed
    - Facility deficiency was sent after the observations were issued to the facility.
    - Facility deficiency was not sent as a result of a PAI
  - No additional major deficiencies

Pre-Approval Inspection Facility Deficiencies

- CRL Facility deficiencies will specifically state if the deficiency is based on observations from a surveillance inspection or pre-approval inspection (PAI).
- A PAI facility deficiency will require continued assessment of inspection deficiency responses and reclassification will be denied
  - Unresolved inspection deficiencies from pre-approval inspections are sent to the site in the post action letter (PAL) after the CRL is sent to the applicant
  - Responses to the PAL are assessed along with the CRL response

Timeline – Original ANDA's

Submission Type	FDA Response Regarding Major to Minor Reclassification	New ANDA Goal Date if Reclassification Granted	ANDA Goal Date if Reclassification Denied
Standard Major Amendment	Within 60 days of submission date	Within 5 months of submission date	Within 8 months of submission date if preapproval inspection is not required
			Within 10 months of submission date if preapproval inspection is required
Priority Major Amendment	Within 30 days of submission date	Within 4 months of submission date	Within 6 months of submission date if preapproval inspection is not required
			Within 8 months of submission date if preapproval inspection required and applicant meets the requirements under section I(A)(5)(b)
			Within 10 months of submission date if preapproval inspection required and applicant meets any limitations as described under section I(A)(6)

Will this Facility-based Major CRL be reclassified?

- Scenario 1
  - Deficiency in CRL: Following pre-approval inspection of the White Oak 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
  - A Pre-Approval Inspection occurred on 10/13/2022
    - 4 observations were noted at the end of the inspection
    - A post action letter with 2 deficiencies was delivered to the site
  - Complete response letter was sent on 12/13/2022
  - White Oak received no observations after the most recent surveillance inspection on 1/01/2023

Will this Facility-based Major CRL be reclassified?

- Scenario 1 - Answer
  - Reclassification is denied
- Rationale
  - An adequate surveillance inspection does not indicate that product specific issues have been resolved.
  - There would be continued assessment of inspection deficiency responses to resolve the issues indicated on the post action letter.

Will this Facility-based Major CRL be reclassified?

- Scenario 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 which resulted in a Warning Letter
  - 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 facility manufactures immediate-release tablets by direct compression for on market products
  - The application is for a capsule filled with extended-release pellets made using fluidized bed coating which was not covered in either surveillance inspection

Will this Facility-based Major CRL be reclassified?

- Scenario 2 - Answer
  - Reclassification is denied
- Rationale
  - A Pre-Approval Inspection would need to be scheduled for the application

Will this Facility-based Major CRL be reclassified?

- Scenario 3
  - Deficiency in CRL: Following surveillance inspection of the Silver Spring 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 originally submitted on 5/16/2021
  - A Surveillance Inspection occurred on 3/18/2022 which resulted in an OAI classification
  - A complete response letter was sent on 12/16/2022
    - 1 Facility-based major deficiency
    - 4 minor deficiencies
  - Silver Spring received no observations after the most recent surveillance inspection on 01/23/2023
  - The facility manufactures immediate-release tablets by direct compression for on market products
  - The application is for an immediate-release tablets made by direct compression

Will this Facility-based Major CRL be reclassified?

- Scenario 3 - Answer
  - Yes, reclassification should be granted if there are no additional concerns
- Rationale
  - The CGMP issues identified during the initial surveillance inspection were resolved per the second surveillance inspection.
  - Reclassification may be granted even if there are additional minor deficiencies.

Submissions with facilities not ready for inspection

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Draft Guidance - Facility Readiness: Goal Date Decisions Under GDUFA

Is the site ready for inspection?

- Prior to GDUFA III, if any site was not ready for inspection, the agency would refuse to receive the application at the filing stage.
- Under GDUFA III, if any site is indicated as not ready for inspection, the goal date will be set at 15 months.

Initial 15 Month Goal Date

- FDA will conduct a filing review of the application
- Substantive assessment of the application will not begin until all facilities are ready for inspection.

Initial 15 Month Goal Date

- 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 amendments
    - 10 months for standard amendments
  - Substantive assessment will begin.

Goal Date Extension

- 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

What is the Goal Date?

- Scenario 5
  - 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

What is the Goal Date?

- Scenario 5 - Answer
  - 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 because it is a standard review and the amendment was submitted within the first 15 month goal date.

What is the Goal Date?

- Scenario 6
  - Potomac Pharma submits a standard application with 1 facility marked as not ready for inspection on 11/29/2022
- Background
  - The goal date is set as 2/29/2024
  - On 1/30/2024, the goal date is reset to 5/29/2025
  - On 3/15/2024, Potomac Pharma submits an amendment indicating on Form FDA 356h that all facilities are ready for inspection

What is the Goal Date?

- Scenario - Answer
  - The goal date remains 5/29/2025
- Rationale
  - The goal date has already been reset to 30 months after the original submission.

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Thank You for Your Attention