Request for Reconsideration Under GDUFA III – Overview and Experience from a Bioequivalence Perspective

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Learning Objectives

- To define a Request for Reconsideration (RfR)
- To differentiate what it means to Accept vs. Not Accept and Grant vs. Deny for RfRs
- To understand FDA's process for reviewing/responding to RfRs
- To understand Office of Bioequivalence (OB)'s current perspective and experience when reviewing RfRs

Disclaimer:

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

What is a Request for Reconsideration (RfR) and why it is needed?

A procedure between FDA and ANDA applicants to resolve scientific and/or regulatory issues or matters.

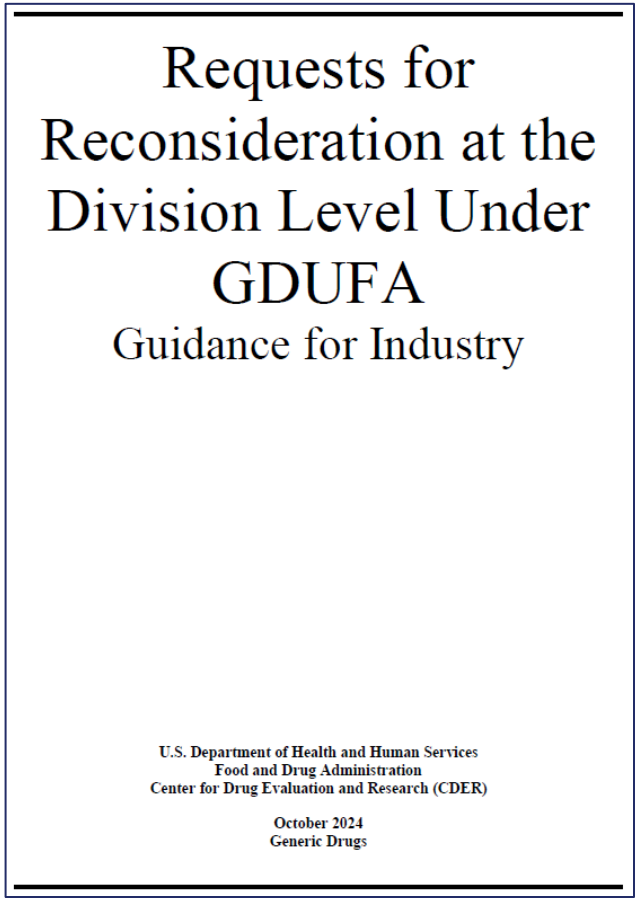
- *Guidance for Industry: RfR at the Division Level Under GDUFA (Finalized 10/2024)*

GDUFA III Commitment Letter:

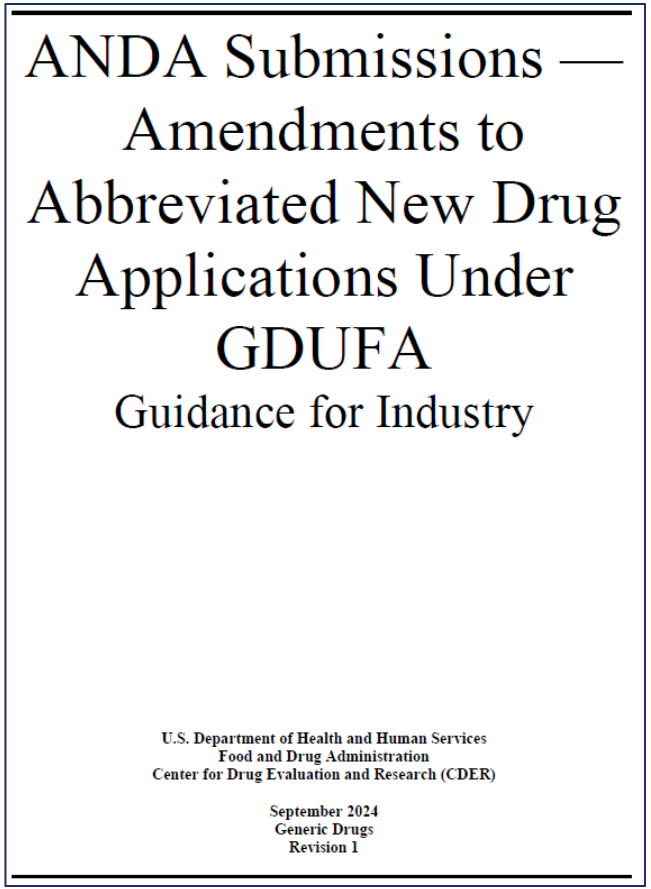
- The applicant may pursue a request for reconsideration (RfR) within the assessment discipline at the division level or original signatory authority, as needed.

Related Guidance:

- **Two FDA guidance related to RfR published in 2024:**
  - *Guidance for Industry: ANDA Submissions – Amendments to Abbreviated New Drug Applications under GDUFA (Finalized 9/2024).*
  - *Guidance for Industry: Requests for Reconsideration at the Division Level Under GDUFA (Finalized 10/2024).*

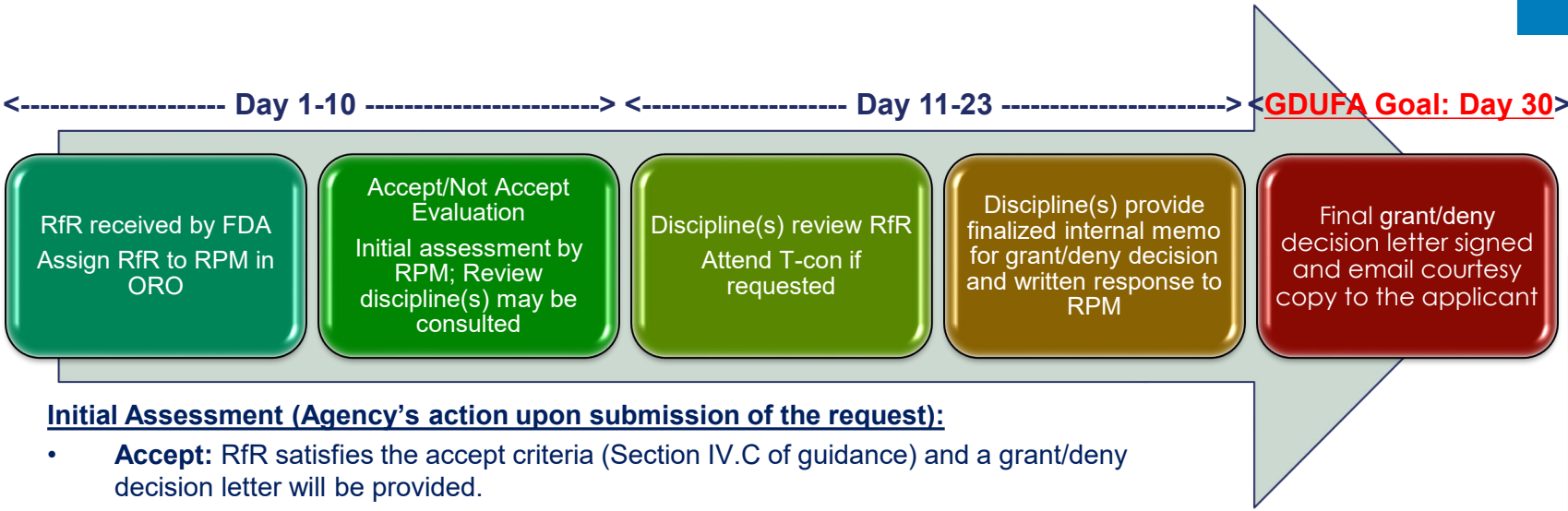


- Initially published in 2017
- Current version to reflect GDUFA III updates
- Recommendations to ANDA applicants on pursuing a RfR within the review discipline.
- Appropriate matters for RfRs.
- FDA's timelines and procedures for reviewing and responding to RfRs.



- Section VII. RfR of major amendment classification
- Other related information:
  - How to classify ANDA amendments as major vs minor, and corresponding assessment Goal dates under GDUFA III?
  - Examples of “Potential Major Deficiencies” across different review disciplines [e.g., Pharmaceutical Quality, Bioequivalence (BE), Labeling, et al.]

FDA's Process for Reviewing/Responding to a RfR:



Initial Assessment (Agency's action upon submission of the request):

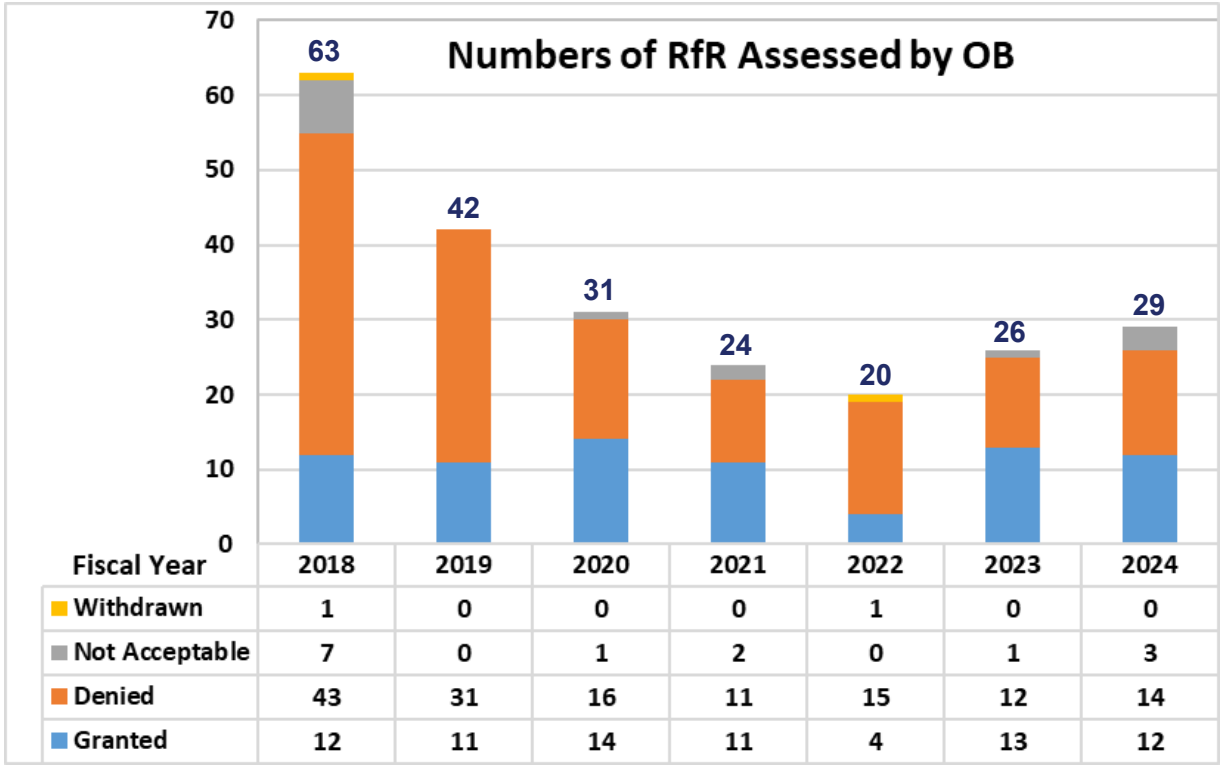
- **Accept:** RfR satisfies the accept criteria (Section IV.C of guidance) and a grant/deny decision letter will be provided.
- **Not Accept:** RfR does not satisfy the accept criteria (Section IV.C of guidance) and does not receive a grant/deny decision letter [Applicant will be informed with reason(s)].

A grant/deny decision letter (Agency's action after acceptance and review of the request)

- **Grant:** The signatory authority agrees with the applicant's proposal for the reconsideration request (Applicable shortened goal dates may apply).
- **Deny:** The signatory authority does not agree with the applicant's proposal for the reconsideration request and the reason(s) will be provided.

- Per Guidance for Industry: RfR at the Division Level Under GDUFA

RfRs Triaged to Office of Bioequivalence (OB) and Outcomes



Fiscal Year	2018	2019	2020	2021	2022	2023	2024
Withdrawn	1	0	0	0	1	0	0
Not Acceptable	7	0	1	2	0	1	3
Denied	43	31	16	11	15	12	14
Granted	12	11	14	11	4	13	12

- Survey data collected based on Fiscal Year for GDUFA II (10/2017-9/2022) and GDUFA III (10/2022-9/2024).
- Total # of RfR reviewed by OB per year from FY18 to FY24.
- Outcome / Subcategory of RfR: Accept vs. Not Accept (to review by OB); Grant vs. Deny (after accepted and reviewed by OB).

RfRs Triaged to OB and Outcomes

FY 2018 - 2024	Total #	Not Acceptable	Granted	Denied	Withdrawn
# of RfR Assessed by OB (%Percentage)	235 (100%)	14 (6%)	77 (33%)	142 (60%)	2 (< 1%)

- Accumulative data for RfRs reviewed by OB (FY18 - FY24) and overall outcomes.
- **Appeal Reasons:** Of 235 RfRs reviewed by OB,
  - **Requests for reclassification from major to minor, 96%** of RfRs.

    [i.e., Reclassification of a major CRL (complete response letter); Reclassification of a major amendment]
  - **Requests to reconsider BE deficiency** (<4%) and **others** (<1%; e.g., Downgrade "TE" code from A* to B*)**, 4%** of RfRs.

Potential Major BE Deficiencies

Guidance for Industry: ANDA Submissions – Amendments to ANDAs under GDUFA (9/2024).

APPENDIX A: Potential Major Deficiencies:

- **B1. BE**

a. Inadequate or insufficient in vivo or in vitro BE studies requiring submission of new studies
b. Inadequate physicochemical data
c. Deficiencies related to device comparability for nasal/inhalation products that require consult to other offices within the Agency or require additional BE studies
d. Insufficient validation data that would require extensive review of resubmitted data and/or development of new analytical procedures with full validation data
e. Reintegration of chromatograms that may result in method revalidation
f. Reanalysis of samples required due to contract/clinical research organization issue, site issue, analytical issue, inadequate justification for reanalysis of samples, or other significant issues
g. Insufficient justification for protocol deviations that could impact the BE determination
h. Submission contains an in vivo study with a serious adverse event(s) or death(s) possibly related to test product
i. Inadequate in vitro dissolution testing or in vitro alcohol dose dumping study data resulting from, for example, the use of aged or expired batches or inadequate study methodology
j. Information needed to address the impact of significant Office of Study Integrity and Surveillance inspectional or review findings
k. Inadequate formulation and/or recommendation to reformulate
l. Deficiencies identified during the technical review related to excipient intake above the limit in the Inactive Ingredient Database without adequate justification
m. Deficiencies related to sugar alcohol content in a drug product formulation in cases where an in vivo comparative study is not conducted, or adequate justification is not provided
n. Consult-related deficiencies found including, but not limited to: insufficient information submitted to address safety issues; insufficient information to address tablet size, or a change in device/container closure; and insufficient information to support alternative study designs in relation to the product-specific guidance
o. Deficiencies related to changes in FDA's guidances for industry that result in inadequate in vivo and/or in vitro BE studies
p. Inadequate information to support that the alternate method is acceptable for demonstrating BE between products
q. Unacceptable study data due to a concern about study conduct or data integrity

- **Majority of RfRs reviewed by OB are Reclassification Requests (major to minor) for either major CRL or major amendment.**
- **A non-exhaustive list of examples of major BE deficiencies.**
- **The determination of a major or minor deficiency will be in the judgment of the relevant assessment discipline.**
- **FDA attempts to resolve possible deficiencies identified during the assessment cycle through information requests (IRs) and discipline review letters (DRLs) prior to sending them in a CRL.**
- **In general, a CRL classification will advise the applicant whether a CRL response will be classified as a major or minor amendment. However, FDA may change its classification of the CRL response based on the content of the amendment.**

Case Studies

- RfRs Reviewed by Office of Bioequivalence (OB)

Case #1: RfR Not Acceptable

- BE deficiency in CRL classified as major due to a failed in vitro BE study and a new BE study was requested.
- RfR requesting reclassification of CRL deficiency major to minor with reanalysis of previously submitted BE data in the RfR.
- OB's assessment:
  - Reanalysis of previously submitted data using a different approach is considered as new information.
  - RfR is not acceptable (Recommended to submit new information as CRL amendment).

❖ ***Key Considerations:***

- Applicant should not submit new information as part of a RfR because FDA's decision must be based on the same information that was used to make the original decision (i.e., information already in the ANDA file).
- FDA considers new analyses of previously reviewed data submitted by the applicant to be new information.

Case #2: RfR Denied

- BE deficiency in CRL classified as major due to an inadequate in vivo BE study and a new BE study was requested.
- CRL amendment submitted along with a RfR requesting reclassification of amendment major to minor. Additional information/data submitted to justify the acceptability of original BE study.
- OB's assessment:
  - Major CRL classification aligning with FDA Guidance, *ANDA Submissions - Amendments to ANDAs Under GDUFA*.
  - Significant new information/data (including modeling data) submitted in CRL amendment requiring a substantial assessment, including potential consultation to other office.
- FDA uphold the initial decision, and no change to be made to the classification of CRL amendment.

❖ ***Key Considerations:***

- The major classification of an amendment is based on a determination by FDA that the content of the information or data provided will require extensive assessment.

Case #3 RfR Granted

- CRL classified as major due to inadequate in vivo BE study related to quality concerns of test product (including bio-bath) identified by Office of Pharmaceutical Quality (OPQ), and a new BE study was requested.
- CRL amendment submitted along with a RfR requesting reclassification of amendment major to minor. Applicant stated that new BE study is not warranted as the quality concerns had been resolved with additional supportive information/data submitted to OPQ.
- OB's assessment:
  - OB agrees that no substantial information/data or unsolicited information is provided in this amendment.
  - RfR is granted (GDUFA goal date will be revised accordingly if applicable).

❖ ***Key Considerations:***

- OB may grant a RfR (major to minor) provided that no substantial information is submitted in the amendment that requires extensive assessment by OB.
- Acceptability of justification will be evaluated during the scientific assessment of amendment.

Challenge Question #1

If the BE deficiencies are issued as major in a discipline review letter (DRL), can the applicant submit a RfR to request reclassification of this DRL from major to minor?

A. Yes

B. No

Challenge Question #1

- Advice communicated during meetings or in meeting minutes, and in other correspondence (e.g., information requests, discipline review letters) is not a regulatory action taken by FDA; therefore, such advice would not be an appropriate subject for a request for reconsideration by an applicant.

  - *Guidance for Industry: RfR at the Division Level Under GDUFA (Finalized 10/2024)*

Challenge Question #2

Which of the following statements is NOT true?

A. FDA will schedule and conduct the teleconference and decide 90% of such reclassification requests within 30 days of the receipt date, when request for reconsideration submitted within 7 calendar days from the date of the regulatory action taken by FDA.

B. An applicant may request a change in the assessment classification at any time during the assessment.

C. The major BE deficiency must be listed in "APPENDIX A: Potential Major Deficiencies" of *Guidance for Industry: ANDA Submissions – Amendments to ANDAs under GDUFA*.

D. If the eligible request cannot be resolved through the request for reconsideration process at the division level or original signatory authority, the applicant may pursue formal dispute resolution above the division level.

Summary

- RfR is a procedure between FDA and ANDA applicants to resolve scientific and/or regulatory issues or matters.
- Most RfRs received and reviewed by OB are reclassification requests (major to minor) for either major CRLs or major amendments.
- A non-exhaustive list of potential major BE deficiencies has been updated in the *Guidance for Industry: ANDA Submissions – Amendments to ANDAs under GDUFA (9/2024)*.
- All initial amendment classifications and any changes to those classifications will be made at FDA's discretion. Typically, a CRL classification will advise whether a CRL amendment is major or minor. However, FDA may change its classification based on the content of the amendment reviewed on a case-by-case basis.
- FDA will inform the applicant of the reason(s) if a RfR is not accepted (to review) or denied.

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