

POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Issuance of Information Requests and/or Discipline Review Letters for Abbreviated New Drug Applications

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PURPOSE

This Manual of Policies and Procedures (MAPP) describes how the Office of Generic Drugs (OGD) and the Office of Pharmaceutical Quality (OPQ) will issue information requests (IRs) and discipline review letters (DRLs) for abbreviated new drug applications (ANDAs) as contemplated in the Generic Drug User Fee Amendments (GDUFA) Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter).¹

BACKGROUND

In October 2012, with the implementation of Generic Drug User Fee Amendments (GDUFA I), FDA initiated a program to act on received ANDAs within agreed upon timeframes. As part of this undertaking, FDA instituted the use of multiple types of letters regarding the assessment² of an application, including complete response letters (CRLs), easily correctable deficiencies (ECDs),³ and IRs.⁴

¹ See References section, number 1.

² OGD and OPQ will generally use the term *assessment* in place of *review*. See References section, number 2.

³ ECDs are no longer issued after October 1, 2017, and have been replaced with IRs and DRLs.

⁴ See References section, number 3.

In the GDUFA III commitment letter, it was agreed that in the first assessment cycle by the mid-point of the assessment clock, FDA would (1) issue an IR to request clarification or further information that is needed or would be helpful to allow completion of a discipline assessment; and/or (2) issue a DRL, to convey preliminary thoughts on possible deficiencies found by a discipline assessor and/or assessment team for its portion of the pending application at the conclusion of a discipline assessment.⁵

In the GDUFA III commitment letter, it was also agreed that IRs and DRLs would identify major and minor deficiencies and all mid-cycle DRLs would include a due date for response. Additionally, to minimize the number of assessment cycles necessary for approval, FDA may extend the goal date for responses to any major deficiencies, or to minor deficiencies that include data and information that require comparable FDA assessment resources to those required for major deficiencies.⁶ It was also agreed that FDA will issue IRs and DRLs after the mid-point of the first assessment cycle and at any time in subsequent assessment cycles, when, in FDA's judgment, there are one or more minor deficiencies that, if resolved using an IR or DRL, could lead to approval or tentative approval in the current assessment cycle. In this scenario, FDA may extend the goal date for the responses to the minor deficiency(ies) (as explained below).⁷

POLICY

IR/DRL Content –

- An IR requests additional information or clarification that is needed or would be helpful to allow completion of a discipline assessment. An IR can include additional information or clarification that is needed or would be helpful to allow completion of a consulting discipline assessment or consult.
- A DRL conveys preliminary thoughts on possible deficiencies found by a discipline assessor and/or assessment team for its portion of the received ANDA at the conclusion of that discipline's assessment. An assessment has reached its "conclusion" when, at a minimum, the primary assessor of a discipline has read the relevant sections of the ANDA and developed preliminary thoughts on possible deficiencies.
- A DRL does not necessarily reflect input from all supervisory levels and a CRL, if issued, may contain additional or fewer deficiencies than were provided in

⁵ If a discipline has not found any deficiencies by the mid-point of the first assessment cycle, FDA will also issue a DRL that states that after preliminary assessment, that particular discipline has not identified deficiencies at the current time. See Policy section. FDA issues these DRLs to promote transparency and communication between FDA and ANDA applicants.

⁶ See References section, number 1.

⁷ See References section, number 1.

previously issued DRLs, depending on the final assessment and concurrence by the appropriate signatory authority.

- A discipline will strive to incorporate possible deficiencies identified via consults into a DRL; however, a discipline may issue a DRL when a consult request is outstanding.
- An IR or DRL generally will contain a requested response date; such a date will be determined by the discipline or consulting discipline, as appropriate, issuing the IR or DRL. It is normally expected that the applicant will respond by the requested response date or as quickly as possible to an IR or DRL.
- An IR or DRL will identify whether the IR or DRL contains major or minor deficiencies.⁸
- If an IR or DRL does not contain a requested response date, it generally indicates that the discipline does not anticipate assessing any response to the IR or DRL during the current assessment cycle due to the nature of the request or deficiency and likely signifies a forthcoming CRL.
- IRs and DRLs should clearly convey the requested information or preliminary thoughts on possible deficiencies and how that information or those thoughts relate to FDA's assessment.

IR/DRL Timing –

- An IR should be issued as early in the assessment cycle as possible (i.e., generally before the time during which a DRL or CRL is being prepared).
- With certain discrete exceptions,⁹ each discipline, as necessary, will issue a DRL at the conclusion of an assessment conducted by that discipline.
- In general, a discipline will reach the conclusion of their assessment and issue a DRL no later than by the mid-point of the assessment (i.e., mid-cycle date (MCD), meaning the mid-point of the GDUFA goal date plus 30 days).¹⁰
 - 8 month GDUFA clock – 5 month MCD (4 month mid-point + 30 days)
 - 10 month GDUFA clock – 6 month MCD (5 month mid-point + 30 days)

⁸ If a discipline identifies a significant major deficiency, that deficiency will be communicated in a CRL as soon as is feasible. See References section, number 1.

⁹ For example, a DRL will not be issued when a discipline assessment results in the ability to act on a received ANDA.

¹⁰ Exceptions that apply to the Labeling discipline are described in the GDUFA III commitment letter (see Section II(B)(2)(a)(ii)).

- If, upon initial submission, a standard or priority original ANDA contains a certification that a site/facility listed on the Form FDA 356h is not ready for inspection, FDA will not commence substantive assessment of the application until an amendment described in GDUFA III commitment letter subsection I(A)(3)(a) is submitted. The mid-point of the assessment cycle will be determined upon receipt of this amendment and IRs or DRLs will be issued accordingly. FDA will not issue a DRL until the mid-point of the period that begins with receipt of this amendment or the mid-point of the additional 15 months if the facility is still not ready after the initial 15-month period.¹¹
- For an ANDA for which a mid-cycle-review meeting or an enhanced mid-cycle-review meeting may be held, the DRLs will be issued before the mid-cycle-review meeting or enhanced mid-cycle-review meeting.¹²
- IRs and DRLs will continue to be issued after the mid-point of the first assessment cycle and at any time in subsequent assessment cycles, when, in FDA's judgment, there are one or more minor deficiencies in a discipline that, if resolved using an IR or DRL, could lead to approval or tentative approval of an ANDA in the current assessment cycle. FDA will issue the IR or DRL and provide a due date for the applicant's response before the goal date.
 - FDA will continue to issue IRs and/or DRLs late in the assessment cycle for original submissions and amendments) until it is no longer feasible within the current assessment cycle for the applicant to develop and FDA to assess a response to the IR and/or DRL.
 - For IRs and DRLs issued past the mid-point of the assessment cycle, the assessment discipline generally will assign a due date for the response and will identify whether the IR or DRL contains major or minor deficiencies.

IR/DRL Issuance –

- A DRL will be issued from a discipline. An IR may be issued from a discipline and/or consulting discipline.
- If a discipline has identified possible deficiencies at the conclusion of its assessment of its portion of the received ANDA, that discipline will issue a DRL. After assessment of a DRL response, if additional information or clarification is needed, such a request may be issued in a DRL or an IR.
- In the first assessment cycle, by the mid-point, if a discipline has not found any deficiencies by the completion of its assessment of its portion of the received

¹¹ See References section, number 1. See also References section, number 7.

¹² See References section, number 5.

ANDA, that particular discipline will issue a DRL that preliminarily indicates that no deficiencies have been identified at the current time.

- An IR or DRL may be issued using a teleconference, e-mail, facsimile, or letter. Issuance of an IR or DRL will be appropriately documented in an electronic document tracking and archiving system.

IR/DRL Response –

- If a full response to an IR or DRL is received, the assessment of such a response may be deferred to the next assessment cycle if an action letter is otherwise ready to be issued, the response is received later than the requested timeframe, the response contains information not requested by FDA, if FDA determines that it cannot assess the response before the goal date, or if FDA determines that adequate resolution of all deficiencies is not possible before the goal date or any possible goal date extension.¹³ If the assessment of a response is deferred to the next assessment cycle or no response or a partial response is received after the issuance of an IR or DRL, the content of the IR or DRL may be included in a newly issued DRL or CRL, as appropriate.
- An applicant may request a short extension of time to respond if the applicant is unable to respond by the requested response date in an IR or DRL. FDA will grant extensions in only exceptional circumstances and with the concurrence of the impacted assessment discipline supervisor.
- If a response to an IR or DRL contains information not requested by FDA or information that requires a more thorough assessment (e.g., the assessor issues a consult to another discipline as determined by FDA), FDA will classify the submission as an unsolicited minor or major amendment with a corresponding goal date that may or may not adjust the MCD.¹⁴
- In the first assessment cycle, if a response to a mid-cycle DRL is received by the due date (or any agreed-upon extension), FDA will assess a response to minor deficiencies within the originally assigned goal date for the submission. However, if responses to any major deficiencies or to minor deficiencies that also include data and information that require comparable FDA assessment resources to those required for major deficiencies (e.g., the assessor issues a consult to another discipline), FDA will extend the goal date consistent with the number of months needed to assess a comparable standard or priority Major Amendment.

¹³ For more on IR or DRL responses and possible goal date extensions, see References section, number 4.

¹⁴ See References section, number 6.

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- For late cycle¹⁵ IRs and DRLs, if the applicant responds to the minor deficiencies in the IR or DRL by the due date for the response, and FDA finds the amendment to satisfactorily address all of the issues identified in the IR or DRL, and the response does not contain unsolicited information, FDA may extend the goal date by 90 days from the date of the applicant's response.
 - If the applicant does not provide a complete response to an IR and/or DRL by the response due date (or any agreed-upon extension), FDA may include the same deficiencies from the IR or DRL in a CRL and assess the response during the next assessment cycle.
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RESPONSIBILITIES AND PROCEDURES

Assessors will:

1. Assess their section of an ANDA, assigned by an OGD consulting discipline project manager (PM) (OGD consulting discipline PM), OGD discipline PM, or OPQ Regulatory Business Process Manager (RBPM) before the Mid-cycle Review Date (MRD).¹⁶
2. Strive to identify and request required consults in conjunction with management, early in the first assessment cycle, as appropriate. Consults may be requested at any time during an assessment cycle at the discretion of the discipline assessor and/or assessment team. However, it is expected that the consultant be given enough time to provide a response, usually before the MRD.
3. Incorporate consults and consult responses into their assessment, as appropriate.
4. After an ANDA has been found acceptable for filing by OGD's Office of Regulatory Operations' (ORO) Division of Filing Review (DFR), on a rolling basis—
 - a. Identify discipline-related issues that need additional information or clarification or would be helpful to allow completion of a consulting discipline assessment or discipline assessment.
 - b. Request issuance of an IR by an OGD consulting discipline PM, OGD discipline PM, or OPQ RBPM.
 - c. Work with an OGD consulting discipline PM, OGD discipline PM, or OPQ RBPM to determine if a requested response date should be included and if so, identify an appropriate response date for such IR.
5. By the MRD—

¹⁵ "Late cycle" is defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment.

¹⁶ See the definition of "Mid-cycle Review Date."

- a. Identify (1) discipline-related issues that need additional information or clarification or would be helpful to allow completion of a consulting discipline or discipline assessment or (2) possible deficiencies in the ANDA submission.
 - If major deficiencies are identified, the assessor will include a justification statement in the IR or DRL explaining why the deficiencies are major.
 - b. Request issuance of a DRL (or an action letter, if appropriate) by an OGD discipline PM or OPQ RBPMs.
6. Work with the OGD consulting discipline PM, OGD discipline PM, or OPQ RBPM, as appropriate, to determine whether issues identified in the course of an assessment should be issued in an IR or a DRL.
 7. Promptly notify the OGD consulting discipline PM, OGD discipline PM, or OPQ RBPM if IR or DRL response contains information not requested by FDA or information that requires a more thorough assessment and classification (i.e., major or minor) of the submission as an amendment.

OGD Consulting Discipline PMs will:

1. Manage a consulting discipline assessment.
2. Work with a discipline assessor and/or assessment team, as appropriate, to determine whether issues identified in the course of an assessment should be issued in an IR or in a DRL.
3. Communicate with an OGD discipline PM if possible deficiencies have been identified to be included in a DRL.
4. Strive to ensure all consult responses relevant to the consulting discipline have been received before the MRD.
5. As appropriate, send an IR on behalf of a consulting discipline in accordance with any governing standard operating procedures after verifying the application has been found acceptable for filing.
 - If major deficiencies are identified, the OGD consulting discipline PM will include a justification statement in the IR explaining why the deficiencies are major.
6. As appropriate, confirm that an applicant (or the agent of an applicant) received an IR.
7. Promptly notify an OGD regulatory project manager (RPM) if an IR or DRL response contains information not requested by FDA or information that requires

a more thorough assessment and classification (i.e., major or minor) of the submission as an amendment.

- When applicable, coordinate with OGD discipline PMs, OPQ RBPMs, and the OGD RPM for the ANDA to determine if a goal date extension is appropriate.

OPQ RBPMs/OGD Discipline PMs will:

1. Verify an ANDA has been found acceptable for receipt for review by the OGD's ORO DFR.
2. Work with a discipline assessor and/or assessment team, as appropriate, to determine whether issues identified in the course of an assessment should be issued in an IR or a DRL.
3. Notify an OGD RPM if an assessor identifies a major deficiency.
4. Confirm the MRD for disciplines.
5. Strive to ensure all consult responses relevant to the discipline have been received before the MRD.
6. As appropriate, send an IR in accordance with any governing standard operating procedures after verifying the application has been found acceptable for filing.
 - If major deficiencies are identified, the RBPM or OGD discipline PM will include a justification statement in the IR explaining why the deficiencies are major.
7. Ensure that the DRL, at the conclusion of the discipline assessment, includes all issues identified by consulting discipline reviews.
8. Send a DRL on behalf of a discipline, generally no later than the MCD, after verifying the application has been found acceptable for filing.
 - a. If major deficiencies are identified, the RBPM or OGD discipline PM will include a justification statement in the DRL explaining why the deficiencies are major.
 - b. Include a response due date on MCD DRLs.
9. As appropriate, confirm that an applicant (or the agent of an applicant) received the IR or DRL.

10. Track any outstanding IRs and DRLs and any requests for extended response times.
11. Promptly notify the OGD RPM for the ANDA when an IR or DRL response may result in a goal date extension and, when applicable, coordinate with OGD discipline PMs and the OGD RPM to determine if a goal date extension is appropriate.

OGD Regulatory Project Managers (RPMs) will:

1. Notify all disciplines of any extension to a MCD or GDUFA goal date.
2. Notify all disciplines when a major deficiency has been identified.¹⁷
3. Adjust goal date (and possibly the MCD) when applicable if a response to an IR or DRL contains information not requested by FDA or information that requires a more thorough assessment and the submission is classified (i.e., minor or major) as an amendment.
 - When applicable, coordinate with OGD discipline PMs, OGD consulting discipline PMs, and OPQ RBPMs to determine if a goal date extension is appropriate.

REFERENCES

1. GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter)
2. Guidance for Industry: Good ANDA Submission Practices (January 2022)
3. Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA I commitment letter)
4. Guidance for Industry: Information Requests and Discipline Review Letters Under GDUFA Revision 1 (October 2022)
5. Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2022)
6. Guidance for Industry: ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018)

¹⁷ See footnote 8.

7. Draft Guidance for Industry: Facility Readiness: Goal Date Decisions Under GDUFA (October 2022)

DEFINITIONS

Action Letter – A complete response letter, an approval letter, a tentative approval letter.

Complete Response Letter (CRL) – A written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an ANDA that must be satisfactorily addressed before it can be approved. Issuance of a CRL completes the review cycle for an ANDA.

Days – means calendar days.

Discipline – An FDA office and/or division responsible for assessing a particular section of an ANDA. For the purposes of this MAPP, the relevant disciplines are the Office of Pharmaceutical Quality (responsible for the quality section), the Office of Generic Drugs’ Office of Bioequivalence (responsible for the bioequivalence section) and the Office of Generic Drug’s Office of Regulatory Operations’ Division of Labeling Review (responsible for the labeling section).

Discipline Review Letter (DRL) – A letter used to convey preliminary thoughts on possible deficiencies found by a discipline assessor and/or assessment team for its portion of the pending application at the conclusion of the discipline assessment. FDA does not consider a DRL to be a CRL because it does not represent a complete assessment of the entire submission (and, therefore, does not complete the assessment cycle for an ANDA).

Information Request (IR) – A letter that is sent to an applicant during an assessment to request further information or clarification that is needed or would be helpful to allow completion of the discipline assessment.

Mid-cycle Date (MCD) – The mid-point of the assessment cycle plus 30 days.

Mid-cycle Review Date (MRD) – The date before the MCD by which the discipline assessor and/or assessment team has read its section of the ANDA and provided preliminary thoughts on possible deficiencies to the appropriate project manager.

Consulting Discipline – An FDA office or division that is consulted by another discipline.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
12/15/2017	Initial	n/a
01/26/2022	1	Updated to revise responsibilities and procedures; modernize language.
10/5/2022	2	Revised for GDUFA III