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) in accordance with commitments made under the Generic Drug User Fee Amendments of 2017 (GDUFA II).[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 assessment[2] 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 GDUFA II, it was agreed that at about 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.

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 sub-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 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 may contain a requested response date; such a date will be determined by the discipline or sub-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.

- 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.

IR/DRL Timing –

- An IR should be issued as early in the assessment cycle as possible (i.e., generally prior to the time during which a DRL or CRL is being prepared).

- With certain discrete exceptions,[5] 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 about the mid-point of the assessment (i.e., mid-cycle date (MCD), meaning the mid-point of the GDUFA goal date plus 30 days).

    - 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)

- For an ANDA that was the subject of a prior product development meeting or a pre-submission meeting, a mid-review-cycle meeting may be held. A DRL will be issued prior to the mid-review-cycle meeting (and before the agenda is issued for such meeting).[6]

- After the MCD, IRs and DRLs may continue to be issued on a rolling basis during the first assessment cycle of an original ANDA submission, as appropriate (until it is no longer feasible, within the current assessment cycle, for the applicant to develop and FDA to assess a complete response to the IR and/or DRL).

- In response to submissions received after the first assessment cycle of an original ANDA submission (e.g., an amendment in response to a CRL, a supplement, or an amendment to a supplement), IRs and DRLs may continue to be issued at the discretion of a discipline or sub-discipline.

IR/DRL Issuance –

- A DRL will be issued from a discipline. An IR may be issued from a discipline and/or sub-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.

- If a discipline has not found any deficiencies by the completion of its assessment of its portion of the received ANDA, that particular discipline will issue a DRL that states no deficiencies are 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.

[5] For example, a DRL will not be issued when a discipline assessment results in the ability to act on a received ANDA.
[6] See References section, number 5.

IR/DRL Response –

- If a full response of 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 being prepared, the response is received later than the requested timeframe, the response contains information not requested by FDA, or if FDA determines that it cannot assess the response before the goal date. 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 assessment team's supervisor.

- If a response to an IR or DRL contains information not requested by FDA or information that requires a more thorough assessment 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.[7]

RESPONSIBILITIES AND PROCEDURES

Assessors will:

1. Assess their section of an ANDA, assigned by an OGD sub-discipline project manager (PM), OGD discipline PM, or OPQ Regulatory Business Process Manager (RBPM) prior to the Mid-cycle Review Date (MRD).[8]

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—

[7] See References section, number 6.
[8] See the definition of "Mid-cycle Review Date."

a. Identify discipline-related issues that need additional information or clarification or would be helpful to allow completion of a sub-discipline assessment or discipline assessment.
b. Request issuance of an IR by a OGD sub-discipline PM, OGD discipline PM, or OPQ RBPM.
c. Work with a OGD sub-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—
   a. Identify (1) discipline-related issues that need additional information or clarification or would be helpful to allow completion of a sub-discipline or discipline assessment or (2) possible deficiencies in the ANDA submission.
   b. Request issuance of a DRL (or an action letter, if appropriate) by a OGD discipline PM or OPQ RBPMs.
   c. Work with OGD discipline PM or OPQ RBPMs to determine if a requested response date should be included and if so, identify an appropriate requested response date for such DRL.

6. Work with the OGD sub-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 sub-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 Sub-Discipline PMs will:

1. Verify an ANDA has been found acceptable for receipt for review by OGD's ORO DFR.

2. Manage a sub-discipline assessment.

3. 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.

4. Communicate with an OGD discipline PM if possible deficiencies have been identified to be included in a DRL.

5. Strive to ensure all consult responses relevant to the sub-discipline have been received before the MRD.

6. As appropriate, send an IR on behalf of a sub-discipline in accordance with any governing standard operating procedures after verifying the application has been found acceptable for filing.

7. As appropriate, confirm that an applicant (or the agent of an applicant) received an IR.

8. 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.

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 a assessment should be issued in an IR or a DRL.

3. Notify an OGD RPM if an assessor identifies a major deficiency.

4. Sets 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.

7. Ensure that the DRL, at the conclusion of the discipline assessment, includes all issues identified by sub-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.

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 OGD RPM if IR or DRL response contains information not requested by FDA or information that requires a more thorough assessment and classification (i.e., minor or major) of the submission as an amendment.

OGD Regulatory Project Managers (RPMs) will:

1. Notify all disciplines of an extension to a MCD or GDUFA goal date (due to an amendment).

2. Notify all disciplines when a major deficiency has been identified.

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 whether the submission is classified (i.e., minor or major) as an amendment.

REFERENCES

1. GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter)

2. Draft Guidance for Industry Good ANDA Submission Practices (January 2018)

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 (January 2022)

5. Guidance for Industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (November 2020)

6. Guidance for Industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018)

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.

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 prior to 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.

Sub-Discipline – An FDA office or division that is component of a 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
1/26/2022	1	Updated to revise responsibilities and procedures; modernize language.