POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS AND OFFICE OF PHARMACEUTICAL QUALITY

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 review of an application, including complete response letters (CRLs) and IRs. [2]

[1] See References section, number 2.
[2] See References section, number 1.

While negotiating the reauthorization of GDUFA, it was proposed that applicants be notified of possible deficiencies in an ANDA as early as possible after a discipline review has been completed. It was agreed that at about the mid-point of the review 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 review; and/or (2) issue a DRL, to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of a discipline review.

POLICY

IR/DRL Content –

- An IR requests additional information or clarification that is needed or would be helpful to allow completion of a discipline review. This includes additional information or clarification that is needed or would be helpful to allow completion of a sub-discipline review.

- A DRL conveys preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the received ANDA at the conclusion of that discipline's review.

- 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 as quickly as possible to an IR or DRL.

IR/DRL Timing –

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

- With certain discrete exceptions,[3] a DRL will be issued at the conclusion of a review conducted by a discipline.

- A discipline will reach the conclusion of their review and issue a DRL no later than about the mid-point of the review (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)

[3] For example, a DRL will not be issued when a discipline review results in the ability to act on a received ANDA.

A review has reached its "conclusion" when, at a minimum, the primary reviewer of a discipline has read her/his section of the ANDA and developed preliminary thoughts on possible deficiencies. A discipline will strive to include consult responses in a DRL.

- 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).[4]

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

- In response to submissions received after the first review 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, at the conclusion of a review, additional information or clarification is needed or would be helpful to allow completion of a discipline review, such a request for additional information or clarification will be issued in a DRL and not an IR since the conclusion of a review occurred.

- If a discipline finds no deficiencies in his or her portion of the received ANDA after the discipline has completed their review, 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.

- Easily Correctable Deficiencies will no longer be issued after October 1, 2017, and will be replaced with IRs and DRLs.

[4] See References section, number 5.

IR/DRL Response –

- If a full response is received after the issuance of an IR or DRL, the review of such a response may be deferred to the next review cycle if an action letter is being prepared or the response is received later than the requested timeframe. If 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 for consideration if they are unable to respond by the requested response date in an IR or DRL.

- If a response to an IR or DRL contains gratuitous information not requested by FDA, or information that requires a more thorough review, 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.[5]

RESPONSIBILITIES AND PROCEDURES

Reviewers will:

1. Review their section of an ANDA, assigned by either a sub-discipline project manager (PM) or Discipline PM (DPM), prior to the Mid-cycle Review Date (MRD).[6]

2. Strive to identify and request required consults in conjunction with management, as appropriate. Consults may be requested at any time during a review cycle at the discretion of the discipline reviewer and/or review team. However, it is expected that the consultant be given enough time to provide a response, usually before the MRD.

3. Incorporate consult responses into their review, as appropriate.

4. After filing of an ANDA, on a rolling basis—
    a. Identify additional information or clarification that is needed or would be helpful to allow completion of a sub-discipline review or discipline review;
    b. Request issuance of an IR by a sub-discipline PM or discipline PM; and

[5] See References section, number 4.
[6] See the definition of "Mid-cycle Review Date."

c. Work with a sub-Discipline PM or discipline PM to identify an appropriate response time for such IR.

5. By the MRD—
   a. Identify additional information or clarification that is needed or would be helpful or possible deficiencies in the ANDA submission;
   b. Request issuance of a DRL (or an action letter, if appropriate) by a DPM; and
   c. Work with DPM to identify an appropriate response time for such DRL.

6. Notify the sub-discipline PM or discipline PM as early as possible if a potential major deficiency is identified during a review.

7. Work with the sub-discipline PM or discipline PM, as appropriate, to determine whether issues identified in the course of a review should be issued in an IR or a DRL.

8. Notify the sub-discipline PM or discipline PM if IR or DRL response contains gratuitous information not requested by FDA or information that requires a more thorough review resulting in reclassification of the amendment.

Sub-Discipline PMs will:

1. Manage a sub-discipline review.

2. Work with a discipline reviewer and/or review team, as appropriate, to determine whether issues identified in the course of a review should be issued in an IR or included in a DRL.

3. Communicate with a DPM if possible deficiencies have been identified to be included in a DRL.

4. Notify a DPM as early as possible if a reviewer identifies a possible major deficiency.

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

6. Verify an ANDA has been found acceptable for filing by the Office of Generic Drugs' Office of Regulatory Operations' Division of Filing Review.

7. 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.

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

9. Notify an OGD regulatory project manager (RPM) if IR or DRL response contains gratuitous information not requested by FDA or information that requires a more thorough review and minor or major classification of the amendment.

Discipline PMs will:

1. Work with a discipline reviewer and/or review team, as appropriate, to determine whether issues identified in the course of a review should be issued in an IR or a DRL.

2. Notify a sub-discipline PM, if appropriate, and an OGD RPM if a reviewer identifies a major deficiency.

3. Sets the MRD for disciplines.

4. Strive to ensure all consult responses relevant to the discipline have been received by the MRD.

5. Ensure that the DRL, at the conclusion of the discipline review, includes all issues identified by sub-discipline reviews.

6. Verify an ANDA has been found acceptable for filing by the Office of Generic Drugs' Office of Regulatory Operations' Division of Filing Review.

7. Send a DRL on behalf of a discipline no later than the MCD after verifying the application has been found acceptable for filing.

8. Send an IR in accordance with any governing standard operating procedures 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. Notify RPM if IR or DRL response contains gratuitous information not requested by FDA or information that requires a more thorough review and minor or major classification of the amendment.

OGD Regulatory Project Managers (RPMs) will:

1. Verify whether all disciplines issued a DRL by the MCD.

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

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

4. Adjust goal date (possibly MCD) when applicable if a response to an IR or DRL contains gratuitous information not requested by FDA or information that requires a more thorough review and whether it is classified as minor or major.

REFERENCES

1. Generic Drug User Fee Act Program Performance Goals and Procedures

2. GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022

3. Draft Guidance for Industry – Information Requests and Discipline Review Letters Under GDUFA (December 2017)

4. Draft Guidance for Industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA (October 2017)

5. Draft Guidance for Industry – Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2017)

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 – FDA Office and/or Division responsible for reviewing 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 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 reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review. FDA does not consider a DRL to be a CRL because it does not represent a complete review of the entire submission (and, therefore, does not complete the review cycle for an ANDA).

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

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

Mid-cycle Review Date (MRD) – The date prior to the MCD by which the discipline reviewer and/or review team has read their section of the ANDA and provided a preliminary conclusion to the appropriate project manager.

Sub-Discipline – An FDA office and/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