Information Requests and Discipline Review Letters Under GDUFA

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Philip Bonforte 240-402-9871, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains how FDA will issue and use an information request (IR) and/or a discipline review letter (DRL) during the review of an original abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), as contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II).[2] This guidance does not apply to an amendment made in response to a Complete Response Letter (CRL), a supplement, or an amendment to a supplement.

Under the Generic Drug User Fee Amendments of 2012 (GDUFA I), FDA committed to performance goals for acting on received ANDAs.[3] In addition to these performance goals, FDA is now committed to provide applicants preliminary thoughts on possible deficiencies as each review discipline finishes its initial review of its portion of the received application (except when that review results in the ability to act on such application).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

GDUFA II was signed into law in order to facilitate timely access to quality, affordable generic medicines. Per the GDUFA Reauthorization Performance Goals and Program Enhancements

[1] This guidance has been prepared by the Office of Generic Drugs and the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] FDA Reauthorization Act of 2017 (FDARA), Pub. L. No. 115-52 (2017). FDARA includes GDUFA II, and by reference, the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter).

[3] Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), Pub. L. No. 112-144 (2012). FDASIA includes GDUFA I, and by reference, the Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA I Commitment Letter). Under 21 CFR 314.101(b)(1), an ANDA is *received* when "FDA has made a threshold determination that the abbreviated application is substantially complete."

Fiscal Years 2018-2022 (GDUFA II Commitment Letter or GDUFA II Goals)[4] that accompanied the legislation, FDA agreed to issue IRs and/or DRLs for all ANDAs.[5]

Under GDUFA I, beginning October 1, 2012, FDA agreed to act on received ANDAs within established time frames. As part of this undertaking, the Agency instituted the use of multiple forms of communicating with an applicant regarding the review of an application, including issuance of CRLs and IRs.

FDA issued a CRL after completing a review of an ANDA. The CRL described all the deficiencies identified in the ANDA that must be satisfactorily addressed before the ANDA can be approved. Issuance of a CRL also completed the ANDA's review cycle, with the next review cycle beginning when the applicant amended the ANDA by submitting a complete response to all deficiencies listed in the CRL.

FDA used IRs to ask for information that would assist reviewers during the course of the review or to convey deficiencies identified in the application in advance of a CRL. IRs did not stop the review clock, did not signal the completion of a review cycle, and were not always used consistently across divisions or offices.

In negotiations held for the reauthorization of GDUFA I, it was agreed that FDA will (1) issue an IR to request further information or clarification that is needed or would be helpful to allow completion of a discipline review and/or (2) issue a new type of letter for ANDAs, known as a DRL, to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its or their portion of the application under review at the conclusion of a discipline review.[6]

A *discipline review* refers to FDA's review of sections of the ANDA by its review staff with expertise in that particular discipline. These sections include, but are not limited to, the bioequivalence section, quality section, and labeling section of an ANDA.

At about the mid-point of the review clock, FDA will send either a IR or a DRL to the applicant, as described later in this guidance, except when a discipline review results in the ability to act on a received ANDA.[7]

The purpose behind IRs and DRLs is to improve FDA's predictability and transparency, promote the efficiency and effectiveness of FDA's review process, minimize the number of review cycles necessary for approval, increase FDA's overall rate of approval, and facilitate greater access to generic drug products. We strongly encourage applicants to submit high quality, complete submissions. Generally, the number and significance of deficiencies that FDA identifies in an

[4] The GDUFA II Commitment Letter is available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

[5] This commitment does not apply to an amendment made in response to a complete response letter (CRL), a supplement, or an amendment to a supplement.

[6] Please note that under GDUFA II, IRs and DRLs will replace Easily Correctable Deficiencies.

[7] FDA may issue an IR prior to the midpoint of the review clock. IRs and DRLs will, as appropriate, continue from each review discipline on a rolling basis.

application correlates to the number of review cycles. Application quality and applicant responsiveness are key factors in whether IRs and DRLs have maximized value for a particular application.

III. EXPLANATION OF TERMS AND PHRASES

Acting on a received ANDA means that FDA will issue a CRL, an approval, or a tentative approval. A CRL, an approval, or a tentative approval will be issued after the complete review of a received ANDA by all appropriate disciplines. If FDA issues a CRL, the CRL will set forth the deficiencies that must be satisfactorily addressed before the ANDA can be tentatively or fully approved. A CRL may contain additional or fewer deficiencies than were provided in previously issued DRLs, depending on the final review of the ANDA and concurrence by the appropriate signatory authority.[8] Acting on a received ANDA completes the review cycle for that ANDA, which is the benchmark by which the Agency's performance towards GDUFA ANDA review goals are measured.

As defined in section II of this guidance, a DRL is a letter used to convey FDA's early thoughts on possible deficiencies found by a discipline reviewer and/or review team for their portion of the received ANDA at the conclusion of that discipline's review. FDA does not consider DRLs to be CRLs because DRLs do not represent a complete review of the entire submission and therefore do not stop the review clock. In addition, a DRL does not necessarily reflect input from all supervisory levels.[9] A single DRL may or may not contain comments from multiple discipline reviews. If a discipline review team finds no deficiencies in its portion of the received ANDA, FDA will issue a DRL for that particular discipline that preliminarily indicates that no deficiencies have been identified at the time of that review.

Also as mentioned in section II of this guidance, an IR is a letter sent to an applicant during an application review to request further information or a clarification of the information already provided that is needed or would be helpful to allow completion of the discipline review. FDA does not consider IRs to be CRLs because IRs, like DRLs, do not represent a complete review of the submission and therefore do not stop the review clock. As with DRLs, an IR does not necessarily reflect input from all supervisory levels. However, unlike DRLs, FDA may issue IRs before the completion of a discipline review.

IV. ISSUANCE AND USE OF INFORMATION REQUESTS AND DISCIPLINE REVIEW LETTERS

A. General

FDA will use IRs to request further information or a clarification of the information that is needed or would be helpful to allow completion of a discipline review.

[8] *Signatory authority* means an agency employee with the power to commit the Agency to an action on a particular ANDA.

[9] The phrase *supervisory levels* includes, but is not limited to, the appropriate signatory authority for the CRL.

FDA will generally convey early thoughts on possible deficiencies to applicants in the form of a DRL as each discipline finishes the review of available information in its section of the pending application, except when the discipline review results in the ability to act on a received ANDA.

FDA will not issue a DRL if its issuance would delay or coincide with the issuance of a CRL. Applicants should not construe either the absence of a DRL for a particular discipline or a DRL for a particular discipline with no identified deficiencies to mean that the CRL will not contain any deficiencies for that discipline. Comments in a DRL will usually reflect the input of the review team but not the input from all supervisory levels.

The DRL will allow applicants to know as soon as possible the review team's early thoughts on possible deficiencies that have been identified within specific sections of the application. With this information, applicants can begin to assemble the needed data to address these deficiencies. A DRL will pertain to only items that the review team believes may require resolution prior to full (or tentative) approval of the application. A DRL is intended to convey early thoughts on possible deficiencies found during a discipline review whereas an IR is a request for further information or clarification that is needed or would be helpful to proceed with the discipline review.

Applicants should be aware that because the DRL will originate at the review team level, supervisors may modify the review in the course of their evaluation, resulting in more or fewer deficiencies in the subsequent CRL. In addition, as reviews from different disciplines (and internal consults) are integrated, additional concerns might arise or previously stated concerns may be resolved. Therefore, it is possible that applicants may spend time gathering information requested in the DRL that in the end may not be necessary for responding to a CRL.

DRLs and IRs may contain a requested response date; if so, the response date will be determined by the discipline review team issuing the DRL or IR. FDA generally expects that the applicant will respond to a DRL or IR by the requested response date or as quickly as possible. However, applicants may request a short extension of time if they are unable to respond by the requested response date.[10]

B. Applicant Response and Effect on the Review Cycle

FDA's issuance of an IR or a DRL will not affect the review clock for a given review cycle. Furthermore, an applicant's response to an IR or DRL generally will not be classified as a major or minor amendment and will not affect the review clock. However, if a response to an IR or a DRL contains either gratuitous information not requested by FDA or information that requires a

[10] Extensions will be granted in only exceptional circumstances. Applicants should make a request for an extension as soon as they become aware of the exceptional circumstance.

more thorough review as determined by FDA, FDA will classify the submission as an amendment and assign an appropriate new goal date for that amendment.[11]

FDA will strive to review a response to an IR or DRL during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review such a response before a goal date or if a CRL is otherwise ready to be issued, the review of the IR or DRL response may, in general, be deferred.[12] When FDA defers the review of a response to an IR or DRL, the response will be reviewed during the next review cycle for the application as part of the CRL amendment.

Deficiencies addressed by applicants in a response to an IR or a DRL may appear in a CRL if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has responded to some (or all) identified deficiencies in an IR or DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided IR or DRL response that renders its CRL amendment complete.

[11] See draft guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[12] FDA may continue to work through the goal date if, in FDA's judgment, that continued work would likely result either in an imminent tentative approval that could prevent forfeiture of 180-day exclusivity or in an imminent approval.