Information Requests and Discipline Review Letters Under GDUFA

Guidance for Industry

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)

January 2022
Generics

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This guidance represents 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 office 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 assessment[2] 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).[3] 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.[4] FDA also committed to performance goals for acting on received ANDAs under GDUFA II. In addition to these performance goals, FDA is now committed to provide applicants preliminary thoughts on possible deficiencies as each assessment discipline finishes its initial assessment of its portion of the received application (except when that assessment results in the ability to act on such application).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations,

[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 and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] The Office of Generic Drugs and the Office of Pharmaceutical Quality will generally use the term *assessment* in place of *review*. See draft guidance for industry *Good ANDA Submission Practices* (January 2018). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] 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).

[4] 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."

unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance 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 Fiscal Years 2018-2022 (GDUFA II Commitment Letter or GDUFA II Goals)[5] that accompanied the legislation, FDA agreed to issue IRs and/or DRLs for all ANDAs.[6]

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 assessment of an application, including issuance of CRLs, easily correctable deficiencies (ECDs), and IRs.

Under GDUFA I, FDA could issue a CRL after completing an assessment of an ANDA, describing 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 original ANDA's assessment cycle, with the next assessment cycle beginning when the applicant amended the original ANDA by submitting a complete response to all deficiencies listed in the CRL.

Under GDUFA I, FDA used IRs to ask for information that would assist assessors during the course of the assessment or to convey possible deficiencies identified in the application in advance of a CRL. IRs did not stop the assessment clock, did not signal the completion of an assessment 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 assessment 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 assessor and/or assessment team for its portion of the application under assessment at the conclusion of a discipline assessment.[7]

A *discipline assessment* refers to FDA's assessment of sections of the ANDA by its assessment staff (i.e. assessors) 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 assessment clock of the first assessment cycle, FDA will send either an IR or a DRL to the applicant, as described later in this guidance, except when a discipline assessment results in the ability to act on a received ANDA.[8]

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

[6] 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.

[7] Please note that under GDUFA II, IRs and DRLs replaced ECDs.

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

The purpose behind IRs and DRLs is to improve FDA's predictability and transparency, promote the efficiency and effectiveness of FDA's assessment process, minimize the number of assessment cycles necessary for approval, increase FDA's overall rate of approval, and facilitate greater access to generic drug products. FDA strongly encourages applicants to submit high quality, complete applications. Generally, the number and magnitude of deficiencies that FDA identifies in an application correlates to the number of assessment 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 the issuance by FDA of a CRL, an approval, or a tentative approval. A CRL, an approval, or a tentative approval will be issued after the complete assessment of a received ANDA by all appropriate disciplines. If FDA issues a CRL, the CRL will set forth the deficiencies that an applicant must satisfactorily address before the ANDA can be tentatively approved or approved. A CRL may contain additional or fewer deficiencies than were provided in previously issued DRLs, depending on the final assessment of the ANDA and concurrence by the appropriate signatory authority.[9] Acting on a received ANDA completes the assessment cycle for that ANDA, which is the benchmark by which the Agency's performance towards GDUFA ANDA assessment goals is measured.

As defined in section II of this guidance, a DRL is a letter used to convey FDA's 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" for these purposes 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.

FDA does not consider DRLs to be CRLs because DRLs do not represent a complete assessment of the entire application and therefore do not stop the assessment clock. In addition, a DRL does not necessarily reflect input from all supervisory levels.[10] A single DRL may or may not contain comments from multiple discipline assessors. If a discipline assessment 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 completion of that assessment.

Also as mentioned in section II of this guidance, an IR is a letter sent to an applicant during an application assessment 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 assessment. FDA does not consider IRs to be CRLs because IRs, like DRLs, do not represent a complete assessment of the entire application and therefore do not stop the assessment clock. As with

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

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

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 assessment.

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 assessment. FDA will generally convey preliminary thoughts on possible deficiencies to applicants in the form of a DRL as each discipline finishes the assessment of available information in its section of the pending application, except when the discipline assessment 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 assessment team but not the input from all supervisory levels.

The DRL will allow applicants to know as soon as possible the assessment team's preliminary 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 assessment team believes may require resolution prior to full (or tentative) approval of the application. A DRL is intended to convey preliminary thoughts on possible deficiencies found during a discipline assessment, whereas an IR is a request for further information or clarification that is needed or would be helpful to proceed with the discipline assessment.

Applicants should be aware that because the DRL will originate at the discipline assessment team level and does not necessarily reflect input from all supervisory levels, a subsequent CRL, if issued, may contain more or fewer deficiencies than were provided in previously issued DRLs, depending on the final assessment and concurrence by the appropriate signatory authority. In addition, as assessments from different disciplines (and internal consults) are integrated, additional concerns might arise or previously stated concerns may be resolved. Therefore, it is possible that information requested in the DRL may be gathered by an applicant, but that in the end, such information may not be necessary for responding to a CRL, if issued.

DRLs and IRs may contain a requested response date; if so, the response date will be determined by the discipline assessment 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.[11] If an IR or DRL does not contain a requested response date, it

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

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.

B. Applicant Response and Effect on the Assessment Cycle

FDA's issuance of an IR or a DRL will not affect the assessment clock for a given assessment 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 assessment clock. However, if a response to an IR or a DRL contains either information not requested by FDA or information that requires a more thorough assessment as determined by FDA, FDA will classify the submission as an amendment and assign an appropriate new goal date for that amendment.[12]

FDA will strive to assess a response to an IR or DRL during the assessment cycle in which it is received if such assessment can be completed during such assessment cycle. However, if the Agency determines that it cannot assess such a response before the goal date or if a CRL is otherwise ready to be issued, the assessment of the IR or DRL response may, in general, be deferred.[13] When FDA defers the assessment of a response to an IR or DRL, the response will be assessed during the next assessment cycle for the application as part of the CRL amendment and this will be communicated in the CRL.

Deficiencies addressed by applicants in a response to an IR or a DRL may appear in a CRL if FDA's assessment of the response has been deferred or if FDA has outstanding concerns after assessment 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.

[12] See the guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

[13] FDA should 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.