# 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)**

**October 2022**
**Generic Drugs**

**Revision 1**

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*Contains Nonbinding Recommendations*

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# Information Requests and Discipline Review Letters Under GDUFA Guidance for Industry[1]

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 GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter).[3] This guidance does not apply to 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 in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II commitment letter) and the GDUFA III commitment letter. In addition to these performance goals, FDA committed in the GDUFA II commitment letter and the GDUFA III commitment letter 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).

This guidance revises the guidance of the same title issued in January 2022. This revision is being issued to incorporate information on IRs and DRLs included in the GDUFA III

[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. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6752 (available at https://www.regulations.gov/docket/FDA-2017-D-6752).

[2] The Office of Generic Drugs and the Office of Pharmaceutical Quality will generally use the term *assessment* in place of *review*. See guidance for industry *Good ANDA Submission Practices* (January 2022). 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] The GDUFA III commitment letter is available at: https://www.fda.gov/media/153631/download.

[4] Title III of the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144. 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."

commitment letter, including FDA's issuance and use of IRs and DRLs and identification of major and minor deficiencies.

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 guidance means that something is suggested or recommended, but not required.

## II. BACKGROUND

The Generic Drug User Fee Amendments of 2012 (GDUFA I)[5] amended the FD&C Act to authorize FDA to assess and collect user fees to provide FDA with resources[6] to help ensure patients have access to quality, affordable, safe, and effective generic drugs. GDUFA fee resources bring greater predictability and timeliness to the review of generic drug applications. GDUFA has been reauthorized every 5 years to continue FDA's ability to assess and collect GDUFA fees, and this user fee program has been reauthorized two times since GDUFA I, most recently in the Generic Drug User Fee Amendments of 2022. As described in the GDUFA III commitment letter applicable to this latest reauthorization, FDA has agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program that build on previous authorizations of GDUFA. New enhancements to the program are designed to maximize the efficiency and utility of each assessment cycle, with the intent of reducing the number of assessment cycles for ANDAs and facilitating timely access to generic medicines for American patients.

Under the GDUFA III commitment letter, FDA agreed to issue IRs and/or DRLs for all ANDAs.[7] As described in the GDUFA III commitment letter, FDA agreed to (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 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.[8]

FDA strongly encourages applicants to submit high quality, complete applications. Generally, the number and magnitude of deficiencies that FDA identifies in an application correlate 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.

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[5] See footnote 4.
[6] User fees are available for obligation in accordance with appropriations acts.
[7] See the GDUFA III commitment letter at 12. 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.
[8] See GDUFA III commitment letter at 47. 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 after preliminary assessment, that particular discipline has not identified deficiencies at the current time. FDA issues these DRLs to promote transparency and communication between FDA and ANDA applicants.

## 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.[9] 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.[10] 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.

A *discipline assessment* refers to FDA's assessment of the section of the ANDA pertaining to a certain discipline 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.

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.[11] 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 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.

[9] See GDUFA III commitment letter at 45.
[10] *Signatory authority* means an agency employee with the power to commit the Agency to an action on a particular ANDA.
[11] The phrase *supervisory levels* includes, but is not limited to, the appropriate signatory authority for the CRL.

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

### A. General Information

By the mid-point of the assessment clock of the first assessment cycle, FDA agreed to send an IR and/or a DRL to the applicant,[12] except when a discipline assessment results in the ability to act on a received ANDA.[13,14] The IR or DRL will identify whether the IR or DRL contains minor or major deficiencies.[15]

FDA generally 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,

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[12] This commitment does not apply to IRs and DRLs issued by the labeling discipline, as described in Section II(B)(2)(a)(ii) of the GDUFA III commitment letter.

[13] 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, and 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 (see the GDUFA III commitment letter at 5).

[14] FDA may issue an IR prior to the mid-point of the assessment clock.

[15] GDUFA III commitment letter at 12. Identification of major or minor deficiencies will be determined as noted in the guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

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 generally will 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.[16] 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.[17]

Applicants that are eligible to request a mid-cycle review meeting (MCRM) or an enhanced mid-cycle review meeting (EMCRM) may, within 7 days of receiving the last mid-cycle DRL (the latter of the quality DRL and the bioequivalence or clinical bioequivalence DRL), submit a request for either an MCRM or an EMCRM.[18]

### B. Information Request and Discipline Review Letters and Applicant Responses

In the first assessment cycle, FDA's issuance of an IR or a DRL and the applicant's response may affect the goal date. For an IR or DRL issued by the mid-point of the assessment, if the applicant responds by the response due date, FDA agreed to assess a response to minor deficiencies within the originally assigned goal date for the submission.[19] However, applicant responses to an IR or DRL issued by the mid-point of the assessment containing any major deficiencies, or minor deficiencies if the responses include data and information that require comparable FDA assessment resources to those require for major deficiencies (e.g., consults), will be considered major amendments. FDA will extend the goal date consistent with the number of months needed to assess a comparable standard or priority Major Amendment.[20]

For IRs and DRLs issued after the mid-point of the first assessment cycle, the assessment discipline generally will assign a due date for the response and identify whether the IR or DRL contains minor or major deficiencies.[21]

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[16] 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.
[17] GDUFA III commitment letter at 13.
[18] For more information on MCRMs and EMCRMs, see the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022).
[19] GDUFA III commitment letter at 12. Exceptions that apply to the Labeling discipline are described in Section II(B)(1)(iii) of the GDUFA III commitment letter.
[20] GDUFA III commitment letter at 13. FDA's decision to extend the goal date will be communicated in an amendment acknowledgement letter.
[21] GDUFA III commitment letter at 13.

FDA agreed to 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 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.[22] FDA agreed to issue the IR or DRL and provide a due date for the applicant's response before the goal date.[23] If the applicant responds to the minor deficiencies in the IR or DRL by the due date (or any agreed-upon extension), 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.[24]

FDA agreed to 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.[25]

If a response to an IR or a DRL contains either 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 amendment and assign an appropriate new goal date for that amendment.[26]

Furthermore, if the Agency determines that it cannot assess 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.[27] 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.

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.[28]

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

[22] Ibid.
[23] Ibid.
[24] Ibid. See also footnote 20.
[25] GDUFA III commitment letter at 13.
[26] See the guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).
[27] FDA will continue assessment of an ANDA past the goal date if, in FDA's judgment, it may be possible to approve or tentatively approve an ANDA within 60 days after the goal date (GDUFA III commitment letter at 14).
[28] GDUFA III commitment letter at 13.

clearly identify the previously provided IR or DRL response that renders its CRL amendment complete.