Failure to Respond to an ANDA Complete Response Letter Within the Regulatory Timeframe

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)

December 2022
Generic Drugs

Revision 1

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Failure to Respond to an ANDA Complete Response Letter Within the Regulatory Timeframe 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 is intended to assist applicants of abbreviated new drug applications (ANDAs), which were submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), in responding to complete response letters (CRLs) from FDA. As described in regulation, ANDA applicants are required to take action after receiving a CRL.[2] The guidance revises the guidance of the same title issued in July 2022. This revision is being issued to incorporate the performance goals outlined in the Generic Drug User Fee Amendments Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (GDUFA III commitment letter).[3] This guidance provides information and recommendations regarding potential courses of action for an ANDA applicant after issuance of a CRL, as well as the actions that FDA may take if the applicant fails to respond to that CRL.[4]

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.

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[1] This guidance has been prepared by the Division of Policy Development in the Office of Generic Drug Policy in the Center for Drug Evaluation and Research, in cooperation with 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-2020-D-1548 (available at https://www.regulations.gov/docket/FDA-2020-D-1548).

[2] 21 C.F.R. 314.110(b).

[3] The GDUFA III commitment letter is available at https://www.fda.gov/media/153631/download.

[4] See 21 CFR 314.110(b)-(c). This guidance applies to applications which the agency has acted upon by issuing a CRL. A CRL may contain major and/or minor deficiencies. See FDA's guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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 the Agency with resources[6] to help ensure patients have access to quality, affordable, safe, and effective generic drugs. Generic Drug User Fee Amendments (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 Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023[7] (GDUFA III). 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.

Once an ANDA has been received for review, FDA performs a substantive assessment to determine if the ANDA meets the regulatory requirements for approval. FDA communicates any deficiencies identified during this assessment in a CRL to the ANDA applicant.[8] After receiving a CRL, as described in 21 CFR 314.110 an applicant must (1) resubmit its ANDA (i.e., submit all materials needed to fully address all deficiencies identified in the CRL),[9] (2) withdraw its ANDA, or (3) request the opportunity for a hearing.[10] If an applicant fails to take one of these three actions within 1 year after issuance of a CRL, FDA may consider this failure to be a request to withdraw the ANDA unless the applicant has requested an extension of time to address all deficiencies identified in the CRL.[11] In addition, as described in the GDUFA III commitment letter, FDA agreed to reclassify a minor amendment as a major amendment if the amendment is submitted more than 1 year after the date FDA issued the CRL, unless the ANDA falls under one of three exceptions that are further described in section III.A of this guidance.[12]

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[5] Title III of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144.

[6] User fees are available for obligation in accordance with appropriations acts.

[7] See Division F, Title III, of the Continuing Appropriations and Ukraine Supplemental Appropriations Act, 2023 (Public Law 117-180).

[8] 21 CFR 314.110. A *CRL* is a written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an NDA or ANDA that must be satisfactorily addressed before it can be approved. 21 CFR 314.3(b). See also 21 CFR 314.102.

[9] See 21 CFR 314.3(b) (defining *resubmission*). Applicants may address the deficiencies identified in a CRL by submitting an amendment to their application. See FDA's guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018).

[10] 21 CFR 314.110(b).

[11] 21 CFR 314.110(c)(1).

[12] GDUFA III commitment letter at 17.

Under the GDUFA program, FDA has seen a steady increase of ANDAs pending with industry for more than a year. Historically, FDA, in its discretion, has liberally granted requests for multiple extensions to respond to an individual CRL to the detriment of the ANDA assessment process. Lengthy response times because of multiple extensions, which can result in applicants submitting an amendment addressing deficiencies years after the initial assessment of the ANDA and issuance of the CRL, are disruptive to the assessment process and can create additional assessment cycles. Over time, information submitted in the original ANDA can become obsolete because of changes such as new or revised United States Pharmacopeia requirements, labeling changes to the reference listed drug (RLD), or other events such as a facility evaluation becoming outdated. In addition, over time, FDA assessment staff may have changed, and it may take time for another assessor(s) to familiarize themselves with the original ANDA. For these reasons, assessing an amendment submitted years after the initial ANDA assessment and issuance of the CRL diverts the Agency's limited resources from the review of other applications.

III. DISCUSSION

As described above, FDA's regulations provide that if an applicant wishes to continue pursuing approval of its ANDA, an applicant should submit all materials needed to fully address all deficiencies identified in the CRL within 1 year of issuance of the CRL.[13] If an applicant wishes to continue to seek approval in this manner and determines it will be unable to address the deficiencies within 1 year of issuance of the CRL, the applicant should submit an amendment to its ANDA requesting an extension of time to address those deficiencies. The applicant should submit its request for an extension on or before the date the response to the CRL is due.

A. Failure to Respond to a CRL Within 1 Year

If an applicant fails to submit to FDA all materials needed to fully address all deficiencies identified in the CRL within 1 year after issuance of the CRL (or take either of the other two actions prescribed by regulation and that are described above), FDA may consider this failure to be a request by the applicant to withdraw the ANDA.[14] FDA will notify the applicant in writing and the applicant will have 30 days from the date of that notification to (1) explain why the ANDA should not be withdrawn and (2) request an extension of time to address all deficiencies identified in the CRL.[15] To best facilitate FDA's consideration of the reasonableness of the request under 21 CFR 314.110(c), we recommend that the applicant provide the information described in section III.C of this guidance, and FDA will evaluate that request for an extension of time by considering, among other relevant information, the factors identified in section III.D of

[13] FDA regulations also provide that an applicant can request an opportunity for a hearing on the question of whether there are grounds for denying approval of the ANDA. 21 CFR 314.110(b).

[14] 21 CFR 314.110(b)-(c).

[15] 21 CFR 314.110(c)(2).

this guidance. If the applicant does not respond to the notification within 30 days, FDA will deem the ANDA withdrawn and will notify the applicant of the withdrawal in writing.[16]

In addition, as described in the GDUFA III commitment letter, FDA will reclassify a minor amendment as a major amendment if the amendment is submitted more than 1 year after the date FDA issued the CRL, unless the ANDA is for a product on the drug shortage list under section 506E of the FD&C Act (21 U.S.C. 356e), or is the subject of a response to a Public Health Emergency as declared by the Secretary of the U.S. Department of Health and Human Services under section 319 of the Public Health Service Act (42 U.S.C. 247d), or is anticipated to be subject to the same criteria as apply to such a declaration, at the time of submission.[17]

B. Failure to Respond to a CRL Within the Extended Time Period Granted by FDA

If FDA grants the applicant's request for an extension to respond to a CRL but the applicant fails to submit an amendment which addresses all the deficiencies identified in the CRL within the extended time period granted by FDA or to request an additional extension, FDA may consider this failure to be a request by the applicant to withdraw the ANDA.[18] FDA will notify the applicant in writing and the applicant will have 30 days from the date of that notification to (1) explain why the ANDA should not be withdrawn and (2) request another extension of time to address all deficiencies identified in the CRL.[19] To best facilitate FDA's consideration of the reasonableness of the request under 21 CFR 314.110(c), we recommend that the applicant provide the information described in section III.C of this guidance. If the applicant does not respond to the notification within 30 days, FDA will deem the ANDA withdrawn and notify the applicant of the withdrawal in writing.[20]

C. Submission of a Request for an Extension to Respond to a CRL

Applicants should submit a request for an extension to respond to a CRL via an amendment to their ANDA. We recommend that a request address the following issues:

- A justification or reason as to why the applicant needs additional time to respond to the CRL. The justification should include:
    - For an applicant submitting a request for a first extension, the reason why it was unable to respond to the deficiencies identified in the CRL within 1 year

[16] Ibid.

[17] GDUFA III commitment letter at 17.

[18] 21 CFR 314.110(c)(1).

[19] 21 CFR 314.110(c)(2).

[20] Ibid.

  - For an applicant submitting a request for an additional extension, the reason why it was unable to respond to the deficiencies identified in the CRL within the time period FDA granted in the previous extension

  - Information about the additional work that needs to be performed before the applicant can respond to the CRL

- Evidence of progress being made toward the completion of work needed to respond to the deficiencies in the CRL (e.g., information demonstrating that the ANDA applicant is working to address the deficiencies)

- The amount of additional time the applicant is requesting

D. Evaluation of a Request for an Extension to Respond to a CRL

FDA will evaluate requests for an extension of time to respond to a CRL and will grant any requests that FDA determines are reasonable.[21] In addition to the information provided by the applicant when submitting a request for an extension, below is a non-exhaustive list of factors that FDA generally intends to consider in determining whether such requests are reasonable:[22]

- The number of, length, and reason(s) for any previously granted extension(s) for the ANDA

- The number and types of deficiencies identified in the CRL (e.g., whether the deficiencies were originally classified as major or minor in the CRL)[23]

- Extenuating factors that are outside of the control of the applicant that impact the applicant's ability to respond to the CRL (e.g., if the applicant is unable to obtain the RLD[24] and is attempting to procure the product samples under CREATES[25])

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[21] 21 CFR 314.110(c).

[22] The factors identified in this guidance are specific to evaluating requests for an extension to respond to a complete response letter for an ANDA and were developed in consideration of the Office of Generic Drug's program needs. Other offices within CDER may consider different factors in determining whether an extension request is reasonable.

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

[24] As used here, the term "RLD" may also refer to the reference standard (RS) in cases where the RLD is no longer marketed. The RS is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting any bioequivalence study in humans for approval of the ANDA. 21 CFR 314.3(b). Ordinarily, the RS selected by FDA will be the RLD. Where the RLD has been withdrawn from sale (for reasons other than safety and effectiveness), FDA generally will select a previously approved ANDA that referred to the RLD as the RS.

[25] See Public Law 116-94 (*Further Consolidated Appropriations Act*, 2020, enacting Division N, Title I, Subtitle F, Section 610—Actions for Delays of Generic Drugs and Biosimilar Biological Products (Dec. 20, 2019)). The provisions of this law related to access to product samples were codified at 21 U.S.C. 355-2 and 355-1(l). For information on access to product samples, see the draft guidance for industry *How To Obtain a Covered Product Authorization* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

- Other public health reasons necessitating an extension

See Appendix A for examples of factors that FDA could consider as the basis for concluding that an applicant's request for an extension of time to respond to a CRL is reasonable.

E. Withdrawal of an ANDA

Under 21 CFR 314.110(c), "FDA will grant any reasonable request" for an extension of time to respond to a CRL. If FDA determines that a request for an extension of time (i.e., a first or subsequent extension of time) to respond to a CRL is not reasonable, FDA will notify the applicant in writing of that determination.[26] The applicant will have 30 days from the date of the notification denying the extension request to respond in writing explaining why the ANDA should not be withdrawn.[27] If the applicant does not respond to FDA's denial of the extension request within 30 days, and the time for responding to the CRL has elapsed, FDA will deem the ANDA withdrawn and notify the applicant of the withdrawal in writing.[28] If the applicant responds to that notification within 30 days and requests an extension of time that includes information not previously considered by the Agency, FDA will evaluate that request with the new information and will grant any reasonable request for an extension.[29] However, if FDA determines that the request for an extension is not reasonable, FDA will deem the ANDA withdrawn and notify the applicant of the withdrawal in writing.[30]

[26] See 21 CFR 314.110(c).

[27] 21 CFR 314.110(c)(2).

[28] 21 CFR 314.110(c)(2).

[29] Ibid.

[30] Ibid.

Appendix A

This Appendix provides examples of factors that FDA could consider as the basis for concluding that an applicant's request for an extension of time to respond to a CRL is reasonable. This is a non-exhaustive list. FDA will make such determinations based on the facts and circumstances of each individual case and will grant any reasonable request for an extension.

- A national or global public health emergency (e.g., COVID-19) delayed the initiation of studies needed to address deficiencies identified in the CRL.
- The ANDA applicant and/or active pharmaceutical ingredient (API) manufacturer are conducting an ongoing risk assessment for impurities in the drug product and/or API.
- The ANDA applicant is conducting an ongoing analytical assessment of extractables/leachables.
- The ANDA applicant is unable to procure the API from the API manufacturer.
- The ANDA applicant is unable to obtain the RLD and is attempting to procure the product samples under CREATES.
- The RLD has reformulated and the ANDA applicant needs to conduct new bioequivalence (BE) studies.
- The ANDA applicant chooses to conduct new BE studies based on the deficiencies identified in the CRL and needs to manufacture one or more new test product batches to conduct the BE studies.
- The ANDA applicant is transferring production to a new manufacturing facility.
- The ANDA applicant is continuing to address deficiencies identified during a recent facility inspection.