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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Lisa Bercu at 240-402-6902.

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)

September 2020
Generics

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Failure to Respond to an ANDA Complete Response Letter Within the Regulatory Timeframe Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 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 (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] 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.[3]

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

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.[4] After receiving

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

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

[3] See 21 CFR 314.110(b)-(c).

[4] 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.

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),[5] (2) withdraw its ANDA, or (3) request the opportunity for a hearing.[6] 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.[7]

Under the Generic Drug User Fee Amendments 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 them 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.[8] 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

[5] 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). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[6] 21 CFR 314.110(b).

[7] 21 CFR 314.110(c)(1).

[8] 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).

actions prescribed by regulation), FDA may consider this failure to be a request by the applicant to withdraw the ANDA.[9] 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.[10] In order 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 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.[11]

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.[12] 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.[13] In order 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 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.[14]

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 as to why the applicant needs additional time to respond to the CRL. The justification should include:

[9] Ibid.

[10] 21 CFR 314.110(c)(2).

[11] Ibid.

[12] 21 CFR 314.110(c)(1).

[13] 21 CFR 314.110(c)(2).

[14] Ibid.

- 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

- 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

- 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.[15] 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 will consider in determining whether such requests are reasonable:[16]

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

- The number and types of deficiencies (e.g., whether the deficiencies were major or minor)[17] identified in the CRL

- 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 and has previously submitted an RLD access inquiry to FDA[18])

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[15] 21 CFR 314.110(c).

[16] 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.

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

[18] For information on RLD access inquiries, visit FDA's webpage at https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/reference-listed-drug-rld-access-inquiries. 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.

- Other public health reasons necessitating an extension

E. Withdrawal of an ANDA

If FDA determines, pursuant to 21 CFR 314.110(c), 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. 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. 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.[19] 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.[20] 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.[21]

[19] 21 C.F.R. 314.110(c)(2).

[20] Ibid.

[21] Ibid.