Contains Nonbinding Recommendations

Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency

Guidance for Industry

December 2020

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)

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and the FDA web page titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an e-mail request to druginfo@fda.hhs.gov or ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the document number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact CDER at CDER-OPQ-Inquiries@fda.hhs.gov, or CBER at ocod@fda.hhs.gov.

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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 staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide information pertaining to review timelines that FDA will use during the COVID-19 public health emergency for the following applicant responses to complete response (CR) letters when a facility assessment is necessary before FDA can take action on a marketing application:

- Amendments to original and supplemental abbreviated new drug applications (ANDAs) submitted to FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

- Resubmissions of original and supplemental biologics license applications (BLAs) submitted to FDA under sections 351(a) and (k) of the Public Health Service (PHS) Act.[2]

[1] This guidance has been prepared by the Office of Pharmaceutical Quality 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] These include devices licensed under section 351 of the PHS Act (42 U.S.C. 262). The term *resubmission* is as defined in 21 CFR 314.3(b) and 600.3(mm).

- Resubmissions of original and supplemental new drug applications (NDAs) submitted to FDA under sections 505(b)(1) and (2) of the FD&C Act.

Specifically, the guidance explains how FDA will determine review timelines following issuance of a CR letter when a facility assessment is necessary for FDA's regulatory decision on an original or supplemental application.[3] This guidance applies to inspections of manufacturing facilities and also bioresearch monitoring (BIMO) program sites conducting clinical, analytical, and nonclinical studies.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the PHS Act.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the FD&C Act and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents, including this guidance, 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

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[4] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[5]

[3] In this guidance, the term *facility* also means *establishment*.

[4] Secretary of Health and Human Services Alex M. Azar II, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[5] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

As a result of the COVID-19 public health emergency, FDA is facing difficulties in conducting facility assessments that are necessary before regulatory decisions can be made on marketing applications. FDA conducts facility assessments through inspections or the use of alternative tools, which include requesting existing inspection reports from trusted foreign regulatory partners through mutual recognition and confidentiality agreements, requesting information from applicants, and requesting records and other information directly from facilities and other inspected entities.[6]

During the emergency, inspections may not be possible because of multiple factors, including travel restrictions between and within countries, limited access to facilities, and health risks for inspectors and facility employees. Although FDA is using all available tools to conduct facility assessments, these alternative tools can be as resource intensive as inspections, if not more. FDA recognizes that applicants have many regulatory questions related to the COVID-19 public health emergency's effects on application approval and has therefore developed this guidance to provide increased transparency and clarity. The review timelines described below are intended to promote an efficient use of FDA resources and facilitate timely application and supplement decisions.

III. Discussion

This temporary policy clarifies the review timelines—new and established—that FDA will observe for applicant responses to CR letters when the Agency determines that a regulatory decision on an original or supplemental application:

- Requires an inspection that cannot be conducted in a timely manner because of COVID-19; or
- Involves the use of time- and resource-intensive alternative tools to assess a facility or BIMO site.

During the COVID-19 public health emergency, if FDA has communicated to an applicant (e.g., in the CR letter) that either of the above are applicable:

- Amendments to original ANDAs and amendments to prior approval supplements to approved ANDAs submitted under section 505(j) of the FD&C Act will be received as a major amendment and will be reviewed per the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018), regardless of whether the CR letter contains a major deficiency.

- Resubmissions of original applications and efficacy supplements for NDAs under sections 505(b)(1) and (2) of the FD&C Act and for BLAs under section 351(a) of the PHS Act will be subject to a Class 2 review timeline of 6 months.[7] This timeline is consistent with existing

[6] See guidance for industry *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers* (August 2020). 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.

[7] See 21 CFR 600.21 and 601.20(d); PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022 (PDUFA VI commitment letter), *available at* https://www.fda.gov/media/99140/download; and MAPP

policies and practices when a facility inspection is required and will also be followed under this temporary policy if FDA uses alternative tools for its facility assessment.

There will be no changes in the timelines used for the following regardless of whether FDA conducts an inspection or uses alternative tools for its facility assessment:

- Resubmissions of original applications, supplements with clinical data, and manufacturing supplements for BLAs under section 351(k) of the PHS Act. These submissions will continue to be subject to existing user fee timelines[8]:
    - Resubmitted manufacturing prior approval supplements will be subject to a 4-month timeline.
    - All other resubmitted applications and supplements in this category will be subject to a 6-month timeline.
- Resubmissions of manufacturing supplements for NDAs under sections 505(b)(1) and (2) of the FD&C Act and for BLAs under section 351(a) of the PHS Act. These submissions will continue to be subject to existing user fee timelines[9]:
    - Resubmitted manufacturing prior approval supplements will be subject to a 4-month timeline.
    - All other resubmitted manufacturing supplements in this category will be subject to a 6-month timeline.

IV. Additional Resources

For further information, drug manufacturers are encouraged to visit the following FDA web page:

Manufacturing, Supply Chain, and Drug Inspections: COVID-19, *available at* https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19

6020.4 Rev. 2 *Classifying Resubmissions of Original NDAs, BLAs, and Efficacy Supplements in Response to Complete Response Letters*.

[8] See Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, *available at* https://www.fda.gov/media/100573/download.

[9] See the PDUFA VI commitment letter.