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**Manufacturing, Supply Chain, and
Drug and Biological Product
Inspections During COVID-19 Public
Health Emergency
Questions and Answers**

Guidance for Industry

August 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)
Office of Regulatory Affairs (ORA)**

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 email request to druginfo@fda.hhs.gov or ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact the Center for Drug Evaluation and Research at CDER-OPQ-Inquiries@fda.hhs.gov or the Center for Biologics Evaluation and Research at ocod@fda.hhs.gov.

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Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

Guidance for Industry

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 answers to frequently asked questions about regulatory and policy issues related to inspections, pending drug applications, and changes in manufacturing facilities for approved pharmaceutical products.¹

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 Public Health Service Act (42 U.S.C. 247d(a)(2)).

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

¹ In this guidance, the terms *drug* and *pharmaceutical product* include biological products.

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because FDA 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.

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.² In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.³

FDA recognizes that the COVID-19 public health emergency is not only impacting public health, but also drug development programs, ongoing manufacturing operations, and FDA's ability to conduct inspections. FDA also recognizes that sponsors and applicants have many questions related to this impact. Therefore, FDA has developed this guidance to provide answers to a number of frequently asked questions.

III. Questions and Answers

FDA has issued guidance on how to implement manufacturing process and facility changes; relevant guidances that describe the process for reporting changes to an application can be found in section V., References. The Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA) remain fully capable of continuing daily activities, such as application assessments, including facility evaluation and certain inspection activities, while responding to public health needs related to the current COVID-19 pandemic. As this remains an evolving and very dynamic situation, FDA will continue to be flexible and as transparent as possible.

² Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020, and July 23, 2020), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

³ 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/>.

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A. Inspections

The following questions and answers are intended to provide information regarding common queries related to inspections for facilities manufacturing pharmaceutical products and sites involved in the conduct of clinical, analytical, and nonclinical studies.

Q1: How are inspections impacted by COVID-19?

A1: Due to the COVID-19 pandemic, FDA announced in March 2020 that it was temporarily postponing all domestic and foreign routine surveillance facility inspections. Similarly, routine surveillance inspections in support of the Bioresearch Monitoring (BIMO) program were postponed.

With respect to pre-approval inspections,⁴ FDA intends to continue using other tools and approaches where possible, including requesting existing inspection reports from other 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.

In response to the suspension of assignments during the public health emergency, beginning the week of July 20, 2020, FDA began to work toward resuming prioritized domestic inspections, as described in the FDA statement “Coronavirus (COVID-19) Update: FDA prepares for resumption of domestic inspections with new risk assessment system” issued on July 10, 2020.⁵ As explained in this statement, FDA is using its COVID-19 Advisory Rating system to determine what categories of regulatory activity can take place in a given geographic region and, based on this determination, FDA is either continuing, on a case-by-case basis, to conduct only “mission-critical” inspections,⁶ or, where possible to do so safely, resuming prioritized domestic inspections, which generally include pre-approval and surveillance inspections. Resumption of these domestic inspections is being done consistently with the National Guidelines for Opening Up America Again⁷ and those gating criteria that must be met before proceeding to the phased resumption of operations. In the July 10, 2020 statement, FDA also explained that, for the foreseeable future, prioritized domestic inspections would be pre-announced to FDA-regulated businesses. This helps ensure the safety of the investigator and the firm’s employees, providing the safest possible environment to accomplish FDA’s regulatory activities, while also ensuring the appropriate staff are on-site to assist FDA staff with inspection activities.

Foreign pre-approval and for-cause inspection assignments that are not deemed mission-critical remain temporarily postponed, while those deemed mission-critical will still be considered for inspection on a case-by-case basis.

⁴ See 21 CFR 314.50(d), 314.94(a), and 601.20(d).

⁵ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-prepares-resumption-domestic-inspections-new-risk-assessment-system>

⁶ See Q2/A2 for a discussion of the types of inspections that would be deemed “mission-critical.”

⁷ <https://www.whitehouse.gov/openingamerica/>

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Q2: What types of inspections would be deemed “mission-critical”?

A2: FDA’s assessment of whether an inspection is mission-critical considers many factors related to the public health benefit of U.S. patients having access to the product subject to inspection. These factors include, but are not limited to, whether the products have received breakthrough therapy designation or regenerative medicine advanced therapy designation, or are products used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute. Both for-cause and pre-approval inspections can be deemed mission-critical. When determining whether to conduct a mission-critical inspection, FDA takes into account concerns about the safety of its investigators, employees at a site or facility, and where applicable, clinical trial participants and other patients at investigator sites.

Q3: Does FDA determine what is “mission-critical” using the same factors for both domestic and foreign inspections?

A3: Yes, the determination is made considering the same factors regardless of whether the site is domestic or foreign.

Q4: How will FDA ensure the quality of imported products while inspections are limited?

A4: During this interim period, for manufacturing facilities, FDA is expanding the use of other tools and approaches, when possible, that have proven effective to help ensure the quality of drug products imported into the United States. These may include physical examinations of products arriving at U.S. borders or product sampling and testing before release into commerce, reviewing the compliance histories of facilities, using information shared by trusted foreign regulatory partners through mutual recognition and confidentiality agreements, and requesting records directly from facilities “in advance of or in lieu of” certain drug inspections.⁸ If a product appears not to meet applicable standards for safety, effectiveness, or quality based on these approaches, FDA has the authority to refuse admission of the product into the United States.⁹

In addition to records requests, FDA continues to work with U.S. Customs and Border Protection to target products intended for importation into the United States that violate applicable legal requirements for FDA-regulated products. FDA has the ability through its Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) import screening tool to focus its examinations and sample collections based on heightened concerns of specific products being entered into U.S. commerce. The PREDICT screening has continued to adjust product risk scores as necessary throughout the COVID-19 outbreak.

Q5: How will limited inspection activity affect my application?

A5: During the COVID-19 public health emergency, FDA is using all available tools and sources of information to support regulatory decisions on applications that include sites impacted by FDA’s ability to inspect due to COVID-19. For example, FDA will continue the quality

⁸ See section 704(a)(4) of the FD&C Act.

⁹ See section 801(a) of the FD&C Act.

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assessment of all applications per normal assessment operations for all disciplines, where all manufacturing facilities will be evaluated using a risk-based approach consistent with existing guidelines. Similarly, the need for and selection of sites for BIMO inspections will continue to be risk-based, considering application and site-specific factors. During this interim period, FDA is using additional tools, where available, to determine the need for an inspection and to support the application assessment, such as reviewing a firm's previous compliance history, using information sharing from trusted foreign regulatory partners through mutual recognition and confidentiality agreements, and requesting records "in advance of or in lieu of" facility inspections¹⁰ or voluntarily from facilities and sites.

CDER and CBER are continuing to evaluate applications, strategically applying a holistic approach in the decision-making process to determine if an inspection is warranted or if an inspection is no longer needed due to information gained through the use of the additional tools mentioned above. FDA will continue to work directly with the applicants of those impacted applications. The Agency encourages applicants to be in communication with all their facilities and sites to ensure timely responses to any inquiries to support application assessment.

Q6: If my application includes sites that cannot be inspected because of travel restrictions, will my application automatically receive a complete response letter?

A6: Applications will not automatically receive a complete response letter if FDA cannot conduct an inspection. Decisions regarding applications will be based on the totality of the information available to FDA, including information obtained from use of the tools as described in Q5/A5. If, based on a benefit-risk assessment of the product and based on available information about the facility or site, it is determined that an inspection is needed before approval of the application, FDA would communicate this to the applicant and would generally follow one of the following pathways:

- If FDA determines that an inspection is necessary for approval because available information raises concerns about the adequacy of the facility or site, and the inspection cannot be completed during the review cycle, FDA intends to inform the applicant of this issue as soon as possible during the review cycle. Specifically, FDA intends to inform the applicant that an inspection will be needed before the application can be approved, but due to restrictions on travel, the inspection may not be conducted before the action date. If the inspection of a facility that raises such concerns has not been completed by the action date, FDA generally intends to issue a complete response.
- If there is inadequate information to make a determination on the acceptability of a facility,¹¹ FDA may defer action on the application until an inspection can be completed. In such cases, the project manager will contact the applicant.

¹⁰ See section 704(a)(4) of the FD&C Act.

¹¹ A biological product manufacturing facility must meet applicable requirements to ensure continued safety, purity, and potency of the product (section 351(a)(2)(A) and 351(a)(2)(C)(i)(II) of the Public Health Service Act; 21 CFR 601.2(d) and 21 CFR 601.20(d)). Similarly, an application for a drug product submitted under section 505 of the FD&C Act will not be approved if the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity (section 505(d)(3) and 505(j)(4)(A) of the FD&C Act; 21 CFR 314.125(b)(1) and 21 CFR 314.127(a)(1)).

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B. Manufacturing and Supply Chain Change Requests

The following questions and answers are intended to provide information regarding common queries related to changes in manufacturing facilities for approved pharmaceutical products.

Q7: How do I add or change a facility in my application in response to supply chain disruptions due to the COVID-19 pandemic?

A7: Refer to the established guidance documents listed in section V., References, for changing or adding a facility to your application.

If your drug application or biologics license application (BLA) relates to the treatment or prevention of COVID-19 or to a drug that is on FDA's drug shortage list,¹² the cover letter to the submission should clearly state "Priority Review Requested" and include supporting information for the request. If the product could enter, or is currently in, drug shortage, also contact CDER DRUG SHORTAGES (DRUGSHORTAGES@FDA.HHS.GOV). See <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages> for more information. For products regulated by CBER, contact cbershortage@fda.hhs.gov. Except as described above, FDA intends to continue following the procedures outlined in relevant Manuals of Policies and Procedures (MAPPs) and Standard Operating Procedures and Policies (SOPPs).¹³

Q8: What data are required to support manufacturing process or facility changes needed to address disruptions from the COVID-19 pandemic?

A8: Refer to the Agency's existing guidance documents on making changes to an approved abbreviated new drug application (ANDA), new drug application (NDA), or BLA, as well as scale-up and postapproval change guidance documents for specific dosage forms (see section V., References). Should circumstances resulting from the COVID-19 pandemic warrant atypical or flexible submission strategies, for CDER-regulated products, contact CDER-OPQ-Inquiries@fda.hhs.gov; for CBER-regulated products, contact the office responsible for the product's regulation for further assistance.

Q9: How can the implementation of manufacturing changes to an ANDA, NDA, or BLA for drugs or biological products needed during the COVID-19 pandemic be accelerated?

A9: FDA is using multiple tools to facilitate implementation of manufacturing changes such as risk-based reduction in supplement reporting categories and flexible assessment practices.

¹² <https://www.accessdata.fda.gov/scripts/drugshortages/>

¹³ See MAPP 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* and MAPP 5310.3 Rev. 1 *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes* (available at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>); and SOPP 8401 *Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)* (available at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps>).

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Consistent with FDA’s regulations for drug applications and BLAs related to postapproval chemistry, manufacturing, and controls changes, FDA may consider available information and approaches to mitigate the risk to product quality associated with the change to support a reporting category for certain supplements that is lower than would otherwise be most suitable (without the benefit of such information and risk-mitigation approaches). During this public health emergency, FDA is willing to consider requests from applicants to submit certain changes using a lower reporting category based on such risk-mitigation information **for drug applications or BLAs related to the treatment or prevention of COVID-19 or drugs/biologics in shortage**.

- Before submitting a supplement with a lower reporting category, applicants should contact FDA for feedback and concurrence. For CDER-regulated products, applicants should contact CDER-OPQ-Inquiries@fda.hhs.gov. For CBER-regulated products, applicants should contact the office responsible for the product’s regulation.
 - If the product could enter, or is currently in, drug shortage, include CDER DRUG SHORTAGES (DRUGSHORTAGES@FDA.HHS.GOV) for products regulated by CDER and cbershortage@fda.hhs.gov for products regulated by CBER.
- Applicants wishing to request a lower supplement reporting category should clearly provide (1) their rationale, (2) supporting information, and (3) risk-mitigation approaches, because this information is needed to consider a reduction in reporting category.

FDA may additionally implement flexible assessment practices such as expediting assessment of supplements, adjusting submission data requirements as part of a risk-benefit assessment, and using additional tools when determining the need for inspections.

Q10: Can I submit an application if it includes facilities in regions that are impacted by COVID-19-related travel restrictions?

A10: Yes, reference in an application to a facility in a region impacted by COVID-19 travel restrictions does not preclude submission to FDA.

IV. For Additional Information

For additional questions about manufacturing and supply chain changes, contact CDER-OPQ-Inquiries@fda.hhs.gov, or for CBER, contact the office responsible for the product’s regulation. Include “COVID-19 inquiry” in the subject line of the email.

V. References^{14,15,16}

Draft and Final Guidances

- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
- *Changes to an Approved Application: Biological Products* (July 1997)
- *Changes to an Approved NDA or ANDA; Questions and Answers* (January 2001)
- *Changes to an Approved NDA or ANDA* (April 2004)
- *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)
- *Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture* (December 2014)
- *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)¹⁷
- *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)¹⁸

Scale-Up and Postapproval Changes Guidances

- *Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- *SUPAC-IR: Questions and Answers about SUPAC-IR Guidance* (February 1997)
- *Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)

¹⁴ 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>.

¹⁵ MAPPs can be found on the CDER Manual of Policies & Procedures web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>.

¹⁶ SOPPs can be found on the Biologics Procedures (SOPPs) web page at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps>.

¹⁷ When final, this guidance will represent the FDA's current thinking on this topic.

¹⁸ Ibid.

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- *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997)
- *SUPAC: Manufacturing Equipment Addendum* (December 2014)

Manual of Policies and Procedures

- MAPP 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*
- MAPP 5310.3 Rev. 1 *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes*

Standard Operating Procedures and Policies

- SOPP 8401 *Administrative Processing of Original Biologics License Applications (BLA) and New Drug Applications (NDA)*