

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

This guidance is intended to remain in effect until November 7, 2023. For further information, refer to 88 FR 15417, March 13, 2023, available at <https://www.federalregister.gov/documents/2023/03/13/2023-05094/guidance-documents-related-to-coronavirus-disease-2019-covid-19>.

*Contains Nonbinding Recommendations*

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

---

## **Guidance for Industry**

**August 2020**

**Updated on May 17, 2021**

**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](mailto:druginfo@fda.hhs.gov) or [ocod@fda.hhs.gov](mailto: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 the Center for Drug Evaluation and Research at [CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov) or the Center for Biologics Evaluation and Research at [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov).

## **Table of Contents**

|      |   |    |
|------|---|----|
| I.   | Introduction.....   | 1  |
| II.  | Background.....   | 2  |
| III. | Questions and Answers.....                                | 2  |
|      | A.    Inspections.....                                    | 3  |
|      | B.    Manufacturing and Supply Chain Change Requests..... | 8  |
| IV.  | For Additional Information.....                           | 10 |
| V.   | References.....   | 10 |

# **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.<sup>1</sup> This document updates the guidance of the same title issued in August 2020, and revised in January 2021.

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 (PHS) (42 U.S.C. 247d(a)(2)).

---

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

## ***Contains Nonbinding Recommendations***

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 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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA 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.<sup>2</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.<sup>3</sup>

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**

---

<sup>2</sup> Secretary of Health and Human Services 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>.

<sup>3</sup> Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>. On February 24, 2021, there was a Presidential Declaration continuing the national emergency concerning the COVID-19 pandemic beyond March 1, 2021. See Continuation of the National Emergency Concerning the Coronavirus Disease 2019 (COVID-19) Pandemic (February 24, 2021), available at <https://www.federalregister.gov/documents/2021/02/26/2021-04173/continuation-of-the-national-emergency-concerning-the-coronavirus-disease-2019-covid-19-pandemic>.

## *Contains Nonbinding Recommendations*

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.

### **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: During the COVID-19 pandemic, FDA has continued, on a case-by-case basis, to conduct mission-critical inspections and other activities to ensure that FDA-regulated pharmaceutical products are meeting applicable FDA requirements.

In the beginning of the COVID-19 pandemic, FDA announced 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.

Beginning the week of July 20, 2020, FDA resumed 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.<sup>4</sup> As explained in this statement, FDA uses its COVID-19 Advisory Rating system to determine what categories of regulatory activity can take place in a given geographic region. Based on this determination, FDA is either continuing, on a case-by-case basis, to conduct only “mission-critical” inspections,<sup>5</sup> or, where possible to do so safely, resuming prioritized domestic inspections, which generally include preapproval, pre-license, surveillance, and for-cause inspections. For the foreseeable future, prioritized domestic inspections will be pre-announced to FDA-regulated businesses.<sup>6</sup> 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.

---

<sup>4</sup> <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-prepares-resumption-domestic-inspections-new-risk-assessment-system>

<sup>5</sup> See Q2/A2 for a discussion of the types of inspections that would be deemed “mission-critical.”

<sup>6</sup> FDA follows the pre-announcement process outlined in FDA’s Investigations Operations Manual (IOM). Sections 5.2.1.1 and 5.2.1.1.1 of the IOM state that pre-announcements should generally be issued no less than 5 calendar days in advance of the plan day to start the inspection. For details visit <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual>.

## ***Contains Nonbinding Recommendations***

Currently, certain inspections (e.g., foreign preapproval, surveillance, and for-cause inspections that are not deemed mission-critical) remain temporarily postponed.

While inspections that can be conducted by FDA during the public health emergency are limited due to factors including travel restrictions, FDA intends to continue using alternative tools, when appropriate, to evaluate facilities. This includes requesting existing inspection reports from other trusted foreign regulatory partners through mutual recognition agreements and other confidentiality agreements,<sup>7</sup> requesting information from applicants, requesting records and other information directly from facilities and other inspected entities, and conducting remote interactive evaluations<sup>8</sup> where appropriate.

### **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 product has received breakthrough therapy designation, orphan-drug designation, or regenerative medicine advanced therapy designation; is included in the Drug Shortage or CBER-Regulated Products Shortage list; is used for critical care or as a medical countermeasure; is used to diagnose, treat, mitigate, cure, or prevent a serious disease or medical condition, including COVID-19, for which there is no other appropriate and available treatment. Therefore, for-cause (including follow-up and where a specific drug quality problem or facility issues come to FDA’s attention), preapproval, and pre-license inspections can be deemed mission-critical. When determining whether to conduct a mission-critical inspection, FDA also 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, FDA is expanding the use of other tools and approaches for assessing manufacturing facilities, when appropriate, to help ensure the quality of the 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 agreements and other confidentiality agreements, requesting

---

<sup>7</sup> For existing FDA mutual recognition agreements with the European Union and the United Kingdom, this includes the use of official inspection reports issued by a recognized authority for manufacturing facilities located inside and outside the territory of the issuing authority. For more information visit: <https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra>.

<sup>8</sup> See FDA guidance for industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 2021).



## *Contains Nonbinding Recommendations*

records directly from facilities “in advance of or in lieu of” certain drug inspections,<sup>9</sup> and conducting remote interactive evaluations where appropriate. 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.<sup>10</sup>

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 to use a risk-based analytics tool (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT)) to electronically screen regulated shipments imported or offered for import into the United States.<sup>11</sup> PREDICT uses automated data mining, pattern discovery, and automated queries of FDA databases to determine the potential risk of a shipment. It takes into consideration the inherent risk of a product and also information about the previous history of importers, manufacturers, and shippers.

### **Q5: How will travel restrictions resulting from the public health emergency 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<sup>12</sup> that include sites impacted by travel restrictions due to COVID-19. For example, FDA will continue the 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 alternative tools, where available, to determine or mitigate the need for an inspection and to support the application assessment. This includes reviewing a firm’s previous compliance history, using information sharing from trusted foreign regulatory partners through mutual recognition agreements and other confidentiality agreements, requesting records “in advance of or in lieu of” facility inspections<sup>13</sup> or voluntarily from facilities and sites, and conducting remote interactive evaluations where appropriate.

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 alternative tools mentioned above. FDA will continue to work directly with the applicants of those impacted applications.

FDA is also working directly with facilities to communicate any issues identified through a review of records or other information requested. For example, for both CDER- and CBER-regulated products, interim processes have been implemented to communicate with manufacturing facilities regarding issues identified following a review of records or other

---

<sup>9</sup> See section 704(a)(4) of the FD&C Act.

<sup>10</sup> See section 801(a) of the FD&C Act.

<sup>11</sup> For more details visit FDA’s Entry Screening Systems and Tools page at <https://www.fda.gov/industry/import-systems/entry-screening-systems-and-tools>.

<sup>12</sup> See 21 CFR 314.50(d), 314.94(a), and 601.20(d).

<sup>13</sup> See section 704(a)(4) of the FD&C Act.

## *Contains Nonbinding Recommendations*

information requested “in advance of or in lieu of” a preapproval or pre-license inspection. Responses from the facility regarding these issues will, as feasible, be considered before taking an action on a pending application.

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 resulting from the public health emergency will my application automatically receive a complete response letter?**

A6: No, FDA will **not** automatically issue a complete response (CR) letter if FDA cannot conduct an inspection because of travel restrictions resulting from the public health emergency.<sup>14</sup>

Decisions regarding applications will be based on the totality of the information available to FDA, including information obtained from use of the alternative tools as described in Q5/A5.

Based on an assessment of the product information provided in the application and based on available information about the facility or site, FDA will take one of the following actions:

- FDA plans to **approve** the application if
  - Available information, including information obtained from the use of alternate tools, supports the adequacy of the facilities and sites named in a pending application, no other deficiencies have been identified, and the application otherwise satisfies the requirements for approval.<sup>15</sup>
  - In this case, the need for an inspection could be sufficiently mitigated by the FDA’s use of alternate tools, including a firm’s responses to outstanding issues identified from the use of alternate tools (see Q5/A5).
- FDA plans to issue a **CR letter with facility- or site-related deficiencies** if
  - Available information from a prior FDA or mutual recognition agreement inspection or the use of alternate tools identifies concerns about the adequacy of a facility or site, and an inspection needed to address those concerns cannot be completed during the review cycle, or
  - Responses to outstanding issues identified from requested records and other alternate sources (see Q5/A5) are not sufficient to address the issues identified for a facility or site.
  - In this case, FDA intends to inform the applicant of the facility or site issues 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

---

<sup>14</sup> For mission-critical and prioritized domestic inspections needed to support application approval, FDA aims to conduct those inspections during the review of the application. However, in cases where travel restrictions due to the public health emergency prevent FDA from performing those inspections during the review clock, recommendations in Q6/A6 are applicable.

<sup>15</sup> See 21 CFR 314.50, 314.94, and 601.2.

### *Contains Nonbinding Recommendations*

and that the inspection may not be conducted before the action date due to restrictions on travel.

- FDA generally intends to issue a CR letter, including a deficiency related to the facility or site, if the inspection has not been conducted by the action date.
- FDA plans to issue a **CR letter without facility or site deficiencies** if
  - An inspection is necessary because there is insufficient information currently available to make a determination on the acceptability of a facility or site<sup>16,17</sup> and other deficiencies have been identified.
  - In this case, FDA will not include a facility or site deficiency in the CR letter if the needed inspection cannot be completed by the action date due to travel restrictions. Rather, in the CR letter FDA will list the other deficiencies and also include a non-deficiency facility or site comment stating that an inspection will be needed to support approval of the application because there is insufficient information available to make a determination on the acceptability of a facility or site.
  - During the review cycle, FDA intends to inform the applicant of the facility or site issues as soon as possible. Specifically, FDA intends to inform the applicant that the inspection may not be conducted before the action date due to restrictions on travel.
- FDA generally plans to **defer action (i.e., miss the goal date)** on an application if an inspection is necessary because there is insufficient information currently available to make a determination on the acceptability of a facility or site<sup>18</sup> and other deficiencies have not been identified.
  - FDA intends to inform the applicant of the facility or site issues as soon as possible during the review cycle. Specifically, FDA intends to inform the applicant that the inspection may not be conducted before the action date due to restrictions on travel.
  - If FDA defers action on the application, the project manager will contact the applicant to explain that FDA continues to monitor the public health situation, as well as travel restrictions, and that FDA will schedule the outstanding inspections once safe travel resumes. The scheduling will be based on public health need and other factors. In this case, therefore, there is no submission or communication needed by the applicant to ensure that an inspection will be scheduled to support application approval.

---

<sup>16</sup> An example of insufficient information includes, but is not limited to, the lack of relevant inspectional history by FDA or another regulatory agency with which FDA has a mutual recognition agreement.

<sup>17</sup> 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 PHS 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)).

<sup>18</sup> See footnotes 16 and 17.

## *Contains Nonbinding Recommendations*

### **Q7: How does FDA intend to prioritize inspections as travel restrictions are eased or lifted?**

A7: Where alternate tools are not available, insufficient, or otherwise will not satisfy the need for an inspection, FDA will use a risk-based approach to prioritize inspections, which includes consideration for (a) how product availability could impact public health; (b) investigator safety; and (c) travel restrictions and/or advisories associated with the location of the facility or site (e.g., country or region/state/province within the country, U.S. state, county, or territory). FDA will also seek to minimize, though not necessarily avoid, missing additional application goal dates due to travel restrictions during the COVID-19 public health emergency. These objectives will also be balanced with the effort to reduce any backlog of assigned inspections.

### **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.

### **Q8: How do I add or change a facility in my application in response to supply chain disruptions due to the COVID-19 pandemic?**

A8: Refer to the established guidance documents listed in section V. References, for changing or adding a facility to your application.

If your marketing application<sup>19</sup> relates to the treatment or prevention of COVID-19 or to a drug that is on FDA's drug shortage list,<sup>20</sup> the cover letter to the submission should clearly state "Priority Review Requested" and should include information to support your priority review designation request. If the product could enter, or is currently in drug shortage, also contact CDER DRUG SHORTAGES ([DRUGSHORTAGES@FDA.HHS.GOV](mailto: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](mailto: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).<sup>21</sup>

---

<sup>19</sup> The term *marketing application* in this guidance refers to an original or supplemental abbreviated new drug application (ANDA), new drug application (NDA), or biologics license application (BLA).

<sup>20</sup> <https://www.accessdata.fda.gov/scripts/drugshortages/><sup>21</sup> 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>).

<sup>21</sup> 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>).

## *Contains Nonbinding Recommendations*

### **Q9: What data are required to support manufacturing process or facility changes needed to address disruptions from the COVID-19 pandemic?**

A9: Refer to the Agency's existing guidance documents on making changes to an approved marketing application, 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](mailto:CDER-OPQ-Inquiries@fda.hhs.gov); for CBER-regulated products, contact the office responsible for the product's regulation for further assistance.

### **Q10: How can the implementation of postapproval manufacturing changes to an ANDA, NDA, or BLA for products needed during the COVID-19 pandemic be accelerated?**

A10: FDA is using multiple tools to facilitate implementation of manufacturing changes such as risk-based reduction in supplement reporting categories and flexible assessment practices.

Consistent with FDA's regulations for marketing applications 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 what otherwise would be most suitable (if such information and risk-mitigation approaches were not provided). 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 marketing applications related to products in shortage or intended to diagnose, treat, mitigate, cure, or prevent COVID-19.

- 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](mailto: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](mailto:DRUGSHORTAGES@FDA.HHS.GOV)) for products regulated by CDER and [cbershorteage@fda.hhs.gov](mailto:cbershorteage@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.

## *Contains Nonbinding Recommendations*

### **Q11: Can I submit an application if it includes facilities in regions that are impacted by COVID-19-related travel restrictions?**

A11: 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](mailto: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<sup>22,23,24</sup>**

### **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)<sup>25</sup>

---

<sup>22</sup> 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>.

<sup>23</sup> 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>.

<sup>24</sup> 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>.

<sup>25</sup> When final, this guidance will represent the FDA's current thinking on this topic.

### ***Contains Nonbinding Recommendations***

- *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)<sup>26</sup>
- *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 2021)

### **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)
- *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)*

---

<sup>26</sup> When final, this guidance will represent the FDA's current thinking on this topic.