

*Contains Nonbinding Recommendations*

# **Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency**

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## **Guidance for Industry**

**September 2020**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Center for Biologics Evaluation and Research  
Center for Veterinary Medicine**

# 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](mailto:druginfo@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 (CDER) [CDER-OPQ-Inquiries@fda.hhs.gov](mailto:CDER-OPQ-Inquiries@fda.hhs.gov), (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010, or (CVM) [AskCVM@fda.hhs.gov](mailto:AskCVM@fda.hhs.gov).

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# Resuming Normal Drug and Biologics Manufacturing During the COVID-19 Public Health Emergency

## 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 help drug and biological product manufacturers<sup>1</sup> during the COVID-19 public health emergency plan and prioritize current good manufacturing practice (CGMP) activities as they transition from operations impacted by the public health emergency to normal manufacturing operations. This guidance describes how to evaluate and prioritize the remediation of CGMP activities that were necessarily delayed, reduced, or otherwise modified during the public health emergency in order to maintain production and the drug supply.

Except as noted in this guidance, 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 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 (85 FR 16949), titled “Process for Making Available Guidance Documents

<sup>1</sup>For purposes of this guidance, the term *drug manufacturer* refers to entities that manufacture human or animal active pharmaceutical ingredients, prescription drugs, over-the-counter drugs, and biological products regulated under section 351 of the Public Health Service Act (42 U.S.C. 262), as well as drugs prepared by outsourcing facilities registered with FDA under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).

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) 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.<sup>2</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.<sup>3</sup>

Under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)), a drug, including an active pharmaceutical ingredient (API), is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with CGMP to ensure that such drug is safe and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.<sup>4</sup> CGMP regulations for finished pharmaceuticals are found in 21 CFR Parts 210 and 211. Guidance regarding CGMP for APIs is described in the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).<sup>5</sup>

During the COVID-19 public health emergency, drug<sup>6</sup> manufacturers may face unusual challenges such as employee illness and absenteeism, travel restrictions, site closures, and supply chain disruptions. Measures to prevent COVID-19 transmission, such as quarantines and social

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<sup>2</sup>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>.

<sup>3</sup>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/>.

<sup>4</sup>The provision also applies to a drug contained in a medicated feed. See 21 CFR 225.1(a).

<sup>5</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>6</sup>The term *drug* or *drugs* as used throughout this guidance includes biological products regulated under section 351 of the PHS Act (42 U.S.C. 262).

distancing, may have been implemented across the company. These challenges may impact normal manufacturing operations and CGMP activities.

While the scope of this guidance includes all drugs, FDA recognizes that the risk of a shortage of particular categories of drugs is an important consideration when determining whether certain manufacturing and quality assurance activities may be reduced in frequency, delayed, or handled differently than prescribed in established procedures. These categories include, for example, human drugs that are life-supporting, life-sustaining, intended for use in the prevention or treatment of a debilitating disease or condition (including any such drug used in emergency medical care or during surgery), or any such drug that is critical to the public health during a public health emergency declared by the Secretary.<sup>7</sup> Categories of animal drugs of particular concern with respect to a risk of shortage include those that are used to treat or prevent serious animal diseases or conditions or that are needed to ensure the availability of safe food products of animal origin, and for which no other available source of that product or adequate alternative drug substitute exists.<sup>8</sup>

The guidance for industry *Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* (March 2011) (the High Absenteeism guidance) recommends a risk-based approach to determine which products should be prioritized for manufacturing and which CGMP activities could be delayed, reduced, or otherwise modified during an emergency. The High Absenteeism guidance recommends prioritizing production of certain products, described as medically necessary products.<sup>9</sup> For these products, the High Absenteeism guidance recommends modifying CGMP activities not connected with any specific batch, and if the modification of additional activities is warranted, the drug manufacturer may modify non-critical, batch-specific CGMP activities provided the drug manufacturer has a documented rationale or risk assessment to show that the proposed changes will not unacceptably reduce assurance of product quality.<sup>10</sup>

The High Absenteeism guidance describes high-level considerations for resuming normal operations. The current guidance, however, provides more detailed considerations and is specific to the COVID-19 public health emergency. This guidance makes recommendations to help drug manufacturers who have delayed, reduced, or otherwise modified CGMP activities impacted by the COVID-19 public health emergency prioritize products and remediation activities when returning to normal operations using a quality risk-management approach (e.g., prioritizing activities related to the production of drugs at risk of shortage). Recommendations in this guidance may also be useful for drug manufacturers who have already resumed normal CGMP operations. Unlike the High Absenteeism guidance, the scope of this guidance is not limited to medically necessary drug products.

A drug manufacturer whose manufacturing operations have been disrupted by the COVID-19 public health emergency should follow an established plan, which includes returning to normal

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<sup>7</sup> See section 506C(a) of the FD&C Act, 21 CFR. 314.81(b)(3)(iii)(f), and 21 CFR 600.82(f).

<sup>8</sup> See “What Is a Medically Necessary Drug Product?” at <https://www.fda.gov/animal-veterinary/product-safety-information/animal-drug-shortage-information>.

<sup>9</sup> See sections I and III(B) of the guidance for industry *Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* (March 2011) (the High Absenteeism guidance).

<sup>10</sup> See section III(D) of the High Absenteeism guidance.

CGMP operations, with consideration given to when there is a reasonable expectation that normal operations will be maintainable for an extended period of time. Although examples of delayed, reduced, or otherwise modified CGMP activities are described in this guidance, CGMP requirements remain in effect during the COVID-19 public health emergency and this guidance is not intended to describe FDA's enforcement priorities.

### **III. Recommendations**

Drug manufacturers should assess the impact of the COVID-19 public health emergency on CGMP activities that were necessarily delayed, reduced, or otherwise modified in order to maintain production and the drug supply, and they should identify necessary remediations that ensure drug quality while endeavoring to return to normal manufacturing operations. FDA recognizes that in some cases, remediation activities that a manufacturer started during the public health emergency may not be completed until after the duration of the public health emergency. In such cases, the manufacturer should continue to follow the recommendations in this guidance with respect to such activities after termination of the public health emergency.

If a drug manufacturer departed from established CGMP activities impacted by the COVID-19 public health emergency, the drug manufacturer should identify these deviations and any necessary remediation actions (see section III(A) below). The drug manufacturer should evaluate these actions as part of their risk management approach (see section III(B)). The results of the evaluation will help the drug manufacturer prioritize resumption activities (see section III(C)).

#### **A. Addressing Deviations From Established CGMP Activities**

Remediation may be necessary for activities impacted by the COVID-19 public health emergency that were delayed, interrupted, or reduced in frequency. Remediation could include a modification to an activity, a new activity, or a more comprehensive program change that mitigates the risk of a drug quality issue due to the deviation from normal operation. Where critical CGMP activities were delayed, interrupted, or reduced in frequency, the batch should be quarantined and the decision to approve the batch delayed until remediation activities ensuring drug quality are completed. Such activities include, for example, critical quality attribute testing, investigations of critical deviations,<sup>11</sup> and evaluation of unapproved changes to critical operations or materials. Drugs not manufactured in a manner that ensures their quality must not be distributed.<sup>12</sup>

As part of the effort to identify areas in need of remediation, drug manufacturers should proactively seek out and obtain information about changes (e.g., to services or materials) that occurred outside of their control.

The list below includes examples of areas where remediation may be needed. The questions below are intended to help drug manufacturers identify the need for, and type of, remediation for their specific operations.

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<sup>11</sup> Completing investigations into critical deviations should continue to be a priority during the COVID-19 public health emergency to ensure that drugs that are released to the market are of high quality.

<sup>12</sup> See section 501(a)(2) of the FD&C Act.

- If investigations into non-critical product or process discrepancies and deviations that occurred before or during the COVID-19 public health emergency remain unresolved, the following questions may be helpful in determining how to appropriately complete and document the investigation:
  - Should the scope of the investigation be expanded to supplement information lost because staff were not present to fully observe or gather information about the incident, or because the extent of the problem increased due to a delay in response?
  - Were short-term changes to normal operations implemented that may have increased the risk to product quality (e.g., change in material flow or personnel flow)?
  - Are the procedures that govern investigations covering discrepancies, deviations, and non-conformances suitable during this public health emergency, or should they be updated?
  
- A decision to delay or reduce testing less directly associated with a batch or not associated with a batch should have been made based on a risk assessment that included evaluation of available data, the significance of the test to the quality of the drug product, and whether the drug is in shortage.<sup>13</sup> If, during the COVID-19 public health emergency, testing was incomplete or was accomplished under conditions that may have compromised the accuracy of the test results, the following questions may be helpful in assessing whether additional measures are needed for a batch to determine suitability for release:
  - For delayed or reduced testing that indirectly measures a batch operation (e.g., certain types of in-process tests), what was the impact on drug quality?
  - For delayed or reduced testing not associated with a batch (e.g., microbiological testing of environmental monitoring plates from low-criticality clean areas or routine stability testing supporting a marketed drug with robust history of minimal degradation), should additional testing be performed to ensure that the facility is appropriate to manufacture quality drugs?
  - Were operations or materials<sup>14</sup> used in the production of drugs changed in any way that could impact the quality or availability of the finished drug product? If so, was the change evaluated and implemented under the drug manufacturer's change management program? Is an investigation necessary to determine if an associated batch is suitable for release? Should the testing program or other monitoring program be modified to evaluate any long-term adverse effects on the quality of the drug product (e.g., additional stability testing)?

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<sup>13</sup>A decision to delay or reduce testing directly connected with batch manufacturing or a product accept or reject decision (e.g., testing associated with a critical quality attribute) should generally be avoided.

<sup>14</sup>For purposes of this guidance, *materials* include components (e.g., APIs and inactive ingredients) used in making drug products, raw materials (e.g., starting materials, reagents, solvents), and any other materials (e.g., intermediates, process aids, and packaging and labeling materials).



- Drug manufacturers should proactively obtain information from suppliers about the impact of the COVID-19 public health emergency on their operations. If there are changes to, or difficulties in obtaining, materials used in drug manufacturing, the following questions may be helpful in assessing whether additional measures are needed:
  - Are you aware of any changes to the operations or materials that could impact the quality of the finished product (e.g., a change in starting material for an API or interruptions in the supplier's supply chain)?
  - Has the higher demand for certain materials led to doubts about the quality or authenticity of those materials (e.g., economically motivated adulteration, potential for increased impurities)?
  - Are there observable differences about a material's shipment that give reason to question the integrity or source (e.g., broken tamper-evident seals, unexpected changes to packaging or labeling)?
  - If an on-site audit of a new or existing supplier is not possible due to travel restrictions related to the COVID-19 public health emergency, what measures can be taken to ensure the quality of the materials (e.g., a remote supplier audit, reassessment or revision of a quality agreement, additional testing to verify a certificate of analysis)? Should the supplier qualification program be updated?
  - Were there any changes from established logistics or transportation systems (e.g., excursions from temperature or humidity parameters during transport) that you rely upon for movement of materials or supplies that could have affected the quality of materials or drugs shipped?
- If facilities and equipment have been changed or have not been maintained on schedule, or if operations were interrupted during the COVID-19 public health emergency, the following questions may be helpful in assessing whether additional measures are needed:
  - Did a disruption or change to water, gas, electricity, or sewage removal utilities pose a challenge to operational capabilities (e.g., the water purification system was not operated according to established procedures, putting it at greater risk of objectionable microbiological contamination)?
  - If the use of equipment changed (e.g., if equipment was reconfigured or barriers were added for operator safety) and was not qualified prior to use, should there be a retrospective evaluation of equipment performance and the type of remediation necessary to continue using the equipment?
  - Was there a change in the frequency of cleaning/disinfection, or to the type of cleaning agent or disinfectant (e.g., to increase appropriate control of bioburden) used that warrants a reassessment of cleaning procedures?

- If equipment servicing requires a technician with special expertise and that individual is unable to be on-site, are there alternative means to ensure that the equipment is suitable for use (e.g., when service that is normally performed on-site but was conducted with remote assistance)?
- Did a delay in preventive maintenance or calibration activities for facilities or equipment impact the function (e.g., adequacy for use) of facilities or equipment?

## **B. Risk Management and Other Important Elements of a Plan To Resume Normal Drug Manufacturing**

A plan to resume manufacturing and CGMP activities is normally part of an emergency plan.<sup>15,16</sup> Drug manufacturers who have not established a resumption plan prior to this public health emergency may find themselves in the suboptimal position of having to quickly develop and execute a plan at the same time; this can lead to errors and poor decisions. We encourage drug manufacturers to develop a resumption plan, in conjunction with an emergency plan, if one is lacking especially due to the possibility of additional waves of COVID-19. Drug manufacturers should develop a comprehensive resumption plan that is specific to their operations and organizational needs.

Once the drug manufacturer has identified the appropriate remediations, these activities should be incorporated into their resumption plan. The plan should state that the risk management approach prioritizes the manufacture of drugs at risk of shortage and activities related to restarting batch production (e.g., performance of equipment maintenance prior to restarting production lines) in addition to activities that were delayed, reduced in frequency, or otherwise modified.

The following elements are considerations for developing a plan to resume normal drug manufacturing:

- The drug manufacturer's plan should include using a risk management approach that identifies, evaluates, and mitigates factors that may impact product quality, including those described in section III(A) of this guidance.<sup>17</sup> These factors include activities performed, not performed, delayed, interrupted, or performed remotely; changes to procedures, processes, or programs; and associated outcomes. For effective mitigation, it may be sufficient to conduct additional activities (e.g., increased testing for a specific API). However, in some cases, effective mitigation may require more extensive program changes (e.g., a more in-depth supplier qualification program, enhanced change management activities) with a strong emphasis on risk reduction. The findings and conclusions drawn from the risk management process should be used to plan and prioritize remediation activities implemented when production activities resume.
- Management leadership is important to successful execution of the resumption plan.

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<sup>15</sup>See the High Absenteeism guidance for a description of *emergency plan*.

<sup>16</sup>Drug manufacturers may refer to an emergency plan by a different name, such as *business continuity plan*.

<sup>17</sup>See the ICH guidance for industry *Q9 Quality Risk Management* (June 2006).

- The plan should include a timeline for implementing priorities.
- The plan should specify that all changes be reviewed and approved by the drug manufacturer's quality unit. It is the drug manufacturer's responsibility<sup>18</sup> to document CGMP activities and to include a justification when a drug manufacturer deviates from established procedures.
- The plan should specify that drug manufacturers submit the required Field Alert Reports (FARs),<sup>19</sup> Biological Product Deviation Reports (BPDRs),<sup>20</sup> and animal drug product/manufacturing defect and adverse drug experience reports.<sup>21</sup>
- The plan should specify that if a drug manufacturer decides that a recall is needed, they should notify FDA as recommended in the guidance for industry *Product Recall, Including Removals and Corrections* (March 2020).
- The plan should specify that applicants and drug manufacturers notify FDA of a permanent discontinuance in the manufacture of certain products or an interruption in the manufacture of certain products that is likely to lead to a meaningful disruption in supply of that product in the United States.<sup>22</sup>
  - For products regulated by the Center for Drug Evaluation and Research (CDER), this notification is required for certain, specified drugs according to section 506C of the FD&C Act and 21 CFR 314.81(b)(3)(iii). Initial notifications should be submitted either via email at [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov) or through the CDER Direct NextGen Portal at <https://edm.fda.gov/wps/portal>. All additional updates should be submitted by email at [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov), not through the NextGen Portal.
  - For products regulated by the Center for Biologics Evaluation and Research, this notification is required according to section 506C of the FD&C Act and 21 CFR 600.82. Initial and additional notifications should be submitted via email at [cbershortage@fda.hhs.gov](mailto:cbershortage@fda.hhs.gov).
  - For products regulated by the Center for Veterinary Medicine, FDA encourages voluntary reporting of potential animal drug shortages as recommended in the guidance for industry *Reporting and Mitigating Animal Drug Shortages During the COVID-19 Public Health Emergency* (May 2020). Notifications may be submitted to FDA via email at [animaldrugshortages@fda.hhs.gov](mailto:animaldrugshortages@fda.hhs.gov).
- The plan should be updated based on new information, as appropriate. An update to a plan may result in a reprioritization of activities.

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<sup>18</sup>21 CFR 211.100(b); 21 CFR 211.160(a)

<sup>19</sup>21 CFR 314.81(b)(1) (human drugs); 21 CFR 514.80(b)(1) (animal drugs)

<sup>20</sup>21 CFR 600.14

<sup>21</sup>21 CFR 514.80(b)(4)(iv)(A)

<sup>22</sup>See the guidance for industry *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act* (March 2020).

## C. Prioritizing Activities To Resume Normal Drug Manufacturing

Drug manufacturers should use the findings and conclusions drawn from the risk management approach to plan and prioritize resumption activities. High priority should be given to drugs that are in shortage or at risk of shortage.<sup>23</sup>

Some activities must be conducted prior to the restarting of a production line and therefore should be prioritized ahead of normal batch production (e.g., resolution of deviations related to a specific production line, confirmation that the supply of API is reliable). Other activities may be accomplished in tandem with batch production (e.g., restart activities for a different product).

Returning to normal operations is often a fluid process. When production priorities change or new information impacting priorities is obtained the drug manufacturer should update the resumption plan and reprioritize activities, as appropriate.

## IV. Additional Resources

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

- Coronavirus Disease 2019 (COVID-19) (<https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19>)
- Manufacturing, Supply Chain, and Drug Inspections | COVID-19 (<https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19>)

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<sup>23</sup>Changes in supply and demand of drugs may affect their categorization as drugs at risk of shortage. See the FDA Drug Shortages web page, available at <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>.