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Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency

Guidance for Industry

January 2021

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

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-1137 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage 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>, the FDA webpage titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, and the FDA webpage titled "Biologics Guidances" *available at* <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>. You may also send an email to ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

Questions

For questions about this document, contact the Office of Communication, Outreach and Development (OCOD) by email at ocod@fda.hhs.gov or at 800-835-4709 or 240-402-8010.

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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 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 manufacturers of licensed and investigational cellular therapy and gene therapy (CGT) products with risk-based recommendations to minimize potential transmission of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This guidance is intended to supplement the recommendations to drug and biological product manufacturers provided in FDA's "Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing; Guidance for Industry" issued in June 2020 (Ref. 1) (June 2020 GMP Guidance). The recommendations in this guidance specifically consider the source material (cells and/or tissues) recovered from donors and how the CGT product will be manufactured (e.g., cell expansion in culture, viral reduction steps, formulation).

The scope of this guidance applies to CGT products regulated by FDA, Center for Biologics Evaluation and Research (CBER) as biological products under section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262) and as drugs under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355).¹ This guidance does not apply to those human cells, tissues, and cellular- or tissue-based products (HCT/Ps) regulated solely

¹ Many of the recommendations in this guidance may apply to combination products that are under the primary jurisdiction of CBER's Office of Tissues and Advanced Therapies (OTAT) (such combination products would consist of a biological product combined with a drug and/or a device).

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under section 361 of the PHS Act (42 U.S.C. 264), as described in Title 21 of the Code of Federal Regulations (CFR) Part 1271 (21 CFR Part 1271), or regulated as medical devices under the FD&C Act.

The recommendations in this guidance are intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the PHS Act (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 Related to Coronavirus Disease 2019,” available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the FD&C Act and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency’s good guidance practices.

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 guidances 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 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

Respiratory viruses, in general, are not known to be transmitted by implantation, transplantation, infusion, or transfer of HCT/Ps. FDA is not aware of any CGT products that have been contaminated with SARS-CoV-2 or of information indicating transmission of SARS-CoV-2 via these products. However, as noted in FDA’s June 2020 GMP Guidance, (Ref. 1), SARS-CoV-2 is a novel coronavirus and, to ensure compliance with current good manufacturing practice (CGMP) requirements, CGT manufacturers are expected to evaluate whether it poses new risks in the context of their specific products, facilities, processes, and manufacturing controls. FDA also

² Secretary of HHS Alex M. Azar, 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>.

³ President Donald J. Trump, 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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posted COVID-19 considerations for HCT/P establishments in general.⁴ Additional concerns specific to establishments that manufacture CGT products may involve the potential for the unintended expansion of SARS-CoV-2 in autologous or allogeneic infected cells or tissues during the manufacturing process (e.g., during cell culture) resulting in a final product with amplified SARS-CoV-2 viral load.

III. RISK ASSESSMENT AND MITIGATION IN PRODUCT MANUFACTURING

During this COVID-19 public health emergency, CGT manufacturers should review CGMP requirements and recommendations related to facility and equipment cleaning and sanitation and other controls that ensure materials, active pharmaceutical ingredients (APIs), components, in-process materials, drug product containers and closures, and drug products are safe and meet their quality requirements.⁵ In light of SARS-CoV-2, FDA recommends that CGT product manufacturers perform a risk assessment that identifies, evaluates, and mitigates factors that may allow for transmission of SARS-CoV-2 by CGT products. A description of the risk assessment and mitigation strategies should be included in the appropriate submission to FDA (e.g., investigational new drug application (IND), biologics license application (BLA), or master file).

In accordance with quality risk management principles,⁶ drug manufacturers are expected to prevent or mitigate potential adverse effects on the safety and quality of their products. To minimize the risk of SARS-CoV-2 transmission through CGT products, considerations include, but are not limited to, the assessment of donors, cellular and tissue source materials, manufacturing processes, manufacturing facility control, product testing, and the number of subjects that can be treated with the product. For example, an allogeneic product that is manufactured using a newly established cell bank and/or may be used to treat a large number of subjects or patients, would be associated with a higher infection risk than an autologous product.

A. Donor Assessment

Routine screening measures are already established for evaluating clinical evidence of infection in allogeneic HCT/P donors. Manufacturers of CGT products derived from HCT/Ps must determine and document the eligibility of a cell or tissue donor (21 CFR 1271.50). FDA recommends routine screening measures be considered for autologous HCT/P donors, due to the potential for expansion of SARS-CoV-2 during the manufacturing process. Based on limited information available at this time, we recommend that manufacturers consider whether, in the 28 days prior to HCT/P recovery, the allogeneic or autologous donor:

⁴ See section III.A of this guidance and [Updated Information for Human Cell, Tissue, or Cellular or Tissue-based Product \(HCT/P\) Establishments Regarding the COVID-19 Pandemic dated January 4, 2021](https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-human-cell-tissue-or-cellular-or-tissue-based-product-hctp-establishments) available at <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-human-cell-tissue-or-cellular-or-tissue-based-product-hctp-establishments>.

⁵ For example, other relevant CGMPs include but are not limited to 21 CFR 211.56, 21 CFR 211.67, 21 CFR 211.113, and 21 CFR 211.80. See also ICH Q7, section IV., Buildings and Facilities (4), section V.B., Equipment Maintenance and Cleaning (5.2), and section VII., Materials Management (7).

⁶ See the ICH guidance for industry Q9 Quality Risk Management (June 2006).

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1. cared for, lived with, or otherwise had close contact with individuals diagnosed with or suspected of having COVID-19 infection; or
2. had been diagnosed with or suspected of having COVID-19 infection; or
3. had a positive test result from a diagnostic test approved, cleared, or authorized by FDA for SARS-CoV-2 but never developed symptoms.

FDA does not recommend using laboratory tests to screen asymptomatic HCT/P donors for SARS-CoV-2 at this time because SARS-CoV-2 has not been declared a relevant communicable disease agent and disease under 21 CFR 1271.3(r). However, if a manufacturer is considering incorporating donor testing for SARS-CoV-2 as a risk mitigation strategy for manufacturing a CGT product, then viral tests (molecular or antigen) approved, cleared, or authorized by the FDA⁷ should be used to diagnose current infection. Additional information is available from the Centers for Disease Control and Prevention (CDC).⁸

At this time, FDA recommends that establishments not screen for or defer HCT/P donors who have been vaccinated against COVID-19 with non-replicating, inactivated, or RNA-based COVID-19 vaccines.

B. Cellular or Tissue Source Material

Manufacturers should consider the known characteristics of coronaviruses as well as the ability of SARS-CoV-2 to infect and replicate in the source cells and tissues, as documented in extensive and evolving literature regarding tissue tropism of SARS-CoV-2. In addition, manufacturers should consider whether SARS-CoV-2 can infect and propagate in cells or tissues during certain manufacturing processes (e.g., cell/tissue culture). Manufacturers should also consider the risk of infection of the specific organ system (e.g., respiratory system vs. central nervous system) from which the donor cells or tissues are derived. FDA recommends that manufacturers provide scientific justification and literature references to support their overall risk assessment and proposed risk mitigation strategy.

C. Manufacturing

In order to minimize the potential for contamination of CGT products with SARS-CoV-2, unintended expansion of SARS-CoV-2, and transmission of SARS-CoV-2 to facility personnel during manufacturing, manufacturers should consider starting materials, manufacturing processes used to control viral spread (e.g., cell expansion in culture, viral reduction steps, producer cell lines, controls for open systems), and contamination risk during manufacturing. Of note, SARS-CoV-2 has been shown to be capable of infecting and replicating in cells commonly used for vector production (e.g., HEK293 and Vero cells) (Refs. 2 and 3). Further, to ensure compliance with CGMP requirements, CGT product manufacturers must ensure that employees practice good sanitation and health habits, in accordance with 21 CFR 211.28(b), 21 CFR 600.10(c) and are expected to

⁷ See [Coronavirus Disease 2019 \(COVID-19\) Emergency Use Authorizations for Medical Devices - In Vitro Diagnostics EUAs](#).

⁸ See [CDC Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for COVID-19](#).

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prevent or mitigate potential adverse effects on the safety and quality of drugs from an infected or potentially infected employee engaged in drug manufacturing (Ref. 1).

D. Material Testing

At this time, FDA does not have specific recommendations for testing HCT/P source material, cell banks, in-process intermediates, final CGT products, or other relevant raw materials for SARS-CoV-2. However, manufacturers may include such testing as a risk mitigation strategy based on their assessment of potential risk.

To ensure compliance with CGMP requirements, CGT product manufacturers must ensure that all evaluations of the production controls (including risk assessments to determine if drug safety or quality were adversely affected), as well as any follow-up and changes, are approved by the manufacturer's quality unit and documented within the manufacturer's quality management system, in accordance with 21 CFR 211.22 and 21 CFR 211.100 (see also 21 CFR 211.113). CGT manufacturers should be aware that under section 501(a)(2) of the FD&C Act, a drug that is not manufactured, processed, packed, or held in conformity with CGMP to assure that the drug meets certain quality and purity standards is considered adulterated.

IV. ADDITIONAL RESOURCES

For further information, visit the following webpage:

- FDA: Coronavirus Disease 2019 (COVID-19) (<https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19>).

V. REFERENCES

1. Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing, Guidance for Industry, June 2020, <https://www.fda.gov/media/139299/download>.
2. Yamamoto, N., et al., Nelfinavir inhibits replication of severe acute respiratory syndrome coronavirus 2 in vitro. bioRxiv, 2020: p. 2020.04.06.026476.
3. Zang, R., et al., TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol, 2020. 5(47).