

Investigational COVID-19 Convalescent Plasma

Guidance for Industry

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

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 Stakeholder," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and from the FDA webpage titled "Search for FDA Guidance Documents" available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

Additional copies of this guidance are also available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>.

Questions

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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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 responsible for this guidance as listed on the title page.

I. INTRODUCTION

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, such as 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 recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

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 Department of Health and Human Services (HHS), including any renewals made by the Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act).

Given this public health emergency, and as discussed in the Notice published 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)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21 of the Code of Federal Regulations (CFR) 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.

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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.¹ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.²

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19 (Refs. 1-4). Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic (Refs. 5-7).

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials. This guidance provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. This guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

III. RECOMMENDATIONS

A. Pathways for Use of Investigational COVID-19 Convalescent Plasma

Because COVID-19 convalescent plasma has not yet been approved for use by FDA,³ it is regulated as an investigational product. As such, administration of COVID-19 convalescent plasma by a health care provider must be under an investigation new drug application (IND) under the traditional IND regulatory pathway, an expanded access IND, or a single-patient emergency investigational new drug application (eIND) (42

¹ Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>).

² President Donald J. Trump, Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>).

³ Convalescent plasma is a biological product subject to licensure under section 351 of the PHS Act. 42 USC 262(a).

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U.S.C. 262(a)(3); 21 U.S.C. 355(i); 21 CFR 601.21; and 21 CFR 312.1). FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Health care providers or acute care facilities would instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.

The following pathways are available for administering or studying the use of COVID-19 convalescent plasma:

1. Clinical Trials

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). CBER's Office of Blood Research and Review is committed to engaging with sponsors and reviewing such requests expeditiously.

2. Expanded Access

An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). FDA has worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma across the nation. For patients with serious or immediately life-threatening COVID-19 who are not eligible for or who are unable to participate in randomized clinical trials, access to this investigational product may be available through participation of acute care facilities in an investigational expanded access protocol under an IND that is already in place. Currently, the following protocol is in place: [National Expanded Access Treatment Protocol](#).

3. Single Patient Emergency IND

Although participation in clinical trials or an expanded access program are ways for patients to obtain access to convalescent plasma, for various reasons these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, while clinical trials are being conducted and an expanded access protocol is available, FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient's physician requesting a single patient eIND for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such case, a licensed physician seeking to administer COVID-19 convalescent plasma to an individual patient must request the eIND (see 21 CFR 312.310(b)).

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a. To Obtain a Single Patient Emergency IND

To obtain a single patient eIND, the provider must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition 21 CFR 312.310(a).

- For requests between 8am EST and 8pm EST (Mon-Sun), the requesting physician may contact FDA by completing Form FDA 3926 (<https://www.fda.gov/media/98616/download>) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov. For eIND requests submitted via email during this time frame, FDA will respond within 4 hours.
 - The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements in 21 CFR 312.305 and 21 CFR 312.310.
 - The form should include information regarding where the COVID-19 convalescent plasma will be obtained.
 - Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required. Providers are strongly encouraged to fill out the form electronically whenever possible.
 - FDA will review the request and, upon authorization, send the requesting physician a confirmatory email that includes the emergency IND number.
- For requests between 8am EST and 8pm EST where the provider is unable to complete and submit Form 3926 due to extenuating circumstances, the provider can contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
- For requests that are **overnight** between 8pm EST and 8am EST, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
 - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15

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working days of FDA's authorization of the use (21 CFR 312.310(d)(2)).

B. Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol, discussed in section III.A. of this guidance. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,
 - Severe disease is defined as one or more of the following:
 - shortness of breath (dyspnea),
 - respiratory frequency ≥ 30 /min,
 - blood oxygen saturation $\leq 93\%$,
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 ,
 - lung infiltrates $> 50\%$ within 24 to 48 hours
 - Life-threatening disease is defined as one or more of the following:
 - respiratory failure,
 - septic shock,
 - multiple organ dysfunction or failure
- Informed consent provided by the patient or healthcare proxy.

C. Collection of COVID-19 Convalescent Plasma

Under FDA's IND regulations, an IND (including an expanded access or eIND) must provide information with respect to the investigational drug, chemistry, manufacturing, and controls that is adequate to ensure the proper identification, quality, purity, and strength of the investigational drug (21 CFR 312.23(a)(7) and 21 CFR 312.305(b)(2)(vi)). For INDs for use of COVID-19 convalescent plasma, the IND would therefore need to contain, among other things, adequate information to demonstrate that the plasma will contain defined SARS-CoV-2 neutralizing antibody titers. Accordingly, health care providers or acute care facilities seeking to use COVID-19 convalescent plasma should include information in the IND submission that the COVID-19 convalescent plasma will be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described in section III.C.1. of this guidance in collecting plasma from donors.

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1. Donor Eligibility

- a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15(b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).
- b. COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:
 - Evidence of COVID-19 documented by a laboratory test either by:
 1. A diagnostic test (e.g., nasopharyngeal swab) at the time of illnessOR
 2. a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.
 - Either one of the following:
 1. Complete resolution of symptoms at least 28 days prior to donationOR
 2. Complete resolution of symptoms at least 14 days prior to donation, AND

Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood.
 - Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.
 - Defined SARS-CoV-2 neutralizing antibody titers
 - We recommend neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

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- NOTE: If neutralizing antibody titers cannot be obtained in advance, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license or obtain their own IND to collect and manufacture COVID-19 convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulation, and 2) collect plasma from individuals that meet the donor qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.

Once manufactured, the COVID-19 convalescent plasma may be distributed for investigational use.

Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

2. Labeling

- a. The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug--Limited by Federal (or United States) law to investigational use” (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

- i. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.
- b. We recommend the use of a uniform container label for COVID-19 convalescent plasma. In particular, we recommend the use of the International Society of Blood Transfusion (ISBT) format specified in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.
- c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection,

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stored at -18C or colder and have an expiration date one year from the date of collection.

D. Recordkeeping

A health care provider who is participating in an IND, including an expanded access IND or eIND, must maintain records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patient (21 CFR 312.62). Such records should include the unique identification number(s) (e.g., the ISBT donation identification number(s)) of the unit(s).

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IV. REFERENCES

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