

Investigational COVID-19 Convalescent Plasma

Guidance for Industry

Document issued on September 2, 2020.

**This document supersedes the guidance of the same title issued in April 2020
and updated in May 2020.**

**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) 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-1825 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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Investigational COVID-19 Convalescent Plasma

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

FDA plays a critical role in protecting the United States (U.S.) 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.

On August 23, 2020, FDA issued an Emergency Use Authorization (EUA)¹ for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.² FDA recognizes that while COVID-19 convalescent plasma may be used under an EUA consistent with the authorization, COVID-19 convalescent plasma may also be used under an investigational new drug application (IND). For the purposes of this guidance, the term “COVID-19 convalescent plasma” refers to the convalescent plasma authorized under the EUA, while the term “investigational convalescent plasma” refers to convalescent plasma that does not meet all the conditions of the EUA and/or is being used under an IND.

¹ On February 4, 2020, pursuant to section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3), the Secretary of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19. On the basis of such determination, the Secretary then declared, on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564 of the FD&C Act. Under section 564 of the FD&C Act, the Commissioner of Food and Drugs may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, and nuclear agents, including emerging infectious disease threats when the product may be effective for its intended use, the known and potential benefits of the product outweigh the known and potential risks, and there are no adequate, approved, and available alternatives to the product. Additional information on Emergency Use Authorization and a list of all current EUAs are available at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

² Denise M. Hinton, U.S. Food & Drug Admin., U.S. Dep’t of Health & Human Servs., Emergency Use Authorization for COVID-19 Convalescent Plasma (Aug. 23, 2020) available at <https://www.fda.gov/media/141477/download>.

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FDA is issuing this guidance to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma or investigational convalescent plasma during the public health emergency. The guidance also provides recommendations to blood establishments on collection. We also describe FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma. This document supersedes the guidance of the same title issued in April 2020 and updated in May 2020.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by 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 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) of the FD&C Act (21 U.S.C. 371(h)(1)(C)) 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.

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.³ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁴

One investigational treatment for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19 which contains antibodies to SARS-CoV-2

³ 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. (Accessible at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>).

⁴ 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/>).

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(Refs. 1-4). Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic (Refs. 5-7).

On August 23, 2020, FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. However, adequate and well-controlled randomized trials remain necessary for a definitive demonstration of COVID-19 convalescent plasma efficacy and to determine the optimal product attributes and appropriate patient populations for its use. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials. The ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA; health care providers are encouraged to enroll patients in those trials.

III. RECOMMENDATIONS

A. Pathways for Use of Investigational Convalescent Plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA,⁵ it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. The emergency use of COVID-19 convalescent plasma is not authorized under the EUA unless it is consistent with, and does not exceed, the terms of the Letter of Authorization, including the Scope of Authorization and Conditions of Authorization.⁶ Alternatively, investigational convalescent plasma may be administered under the traditional IND regulatory pathway, a single-patient IND for emergency use, or an intermediate-size population expanded access IND (section 351(a)(3) of the PHS Act (42 U.S.C. 262(a)(3)); section 505(i) of the FD&C Act (21 U.S.C. 355(i)); 21 CFR 601.21; and 21 CFR Part 312).

FDA does not collect convalescent plasma or provide convalescent plasma. Health care providers or acute care facilities should obtain convalescent plasma from an FDA-registered or licensed blood establishment.

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

1. Emergency Use Authorization

On August 23, 2020, FDA issued an EUA for COVID-19 Convalescent Plasma for the treatment of hospitalized patients with COVID-19.

Health care providers intending to administer COVID-19 convalescent plasma under the EUA are not required to report its use to FDA. Providers should refer to the Fact

⁵ Convalescent plasma is a biological product subject to the licensure requirement under section 351 of the PHS Act. 42 U.S.C. 262(a).

⁶ See <https://www.fda.gov/media/141477/download>.

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Sheet for Health Care Providers⁷ for information on the intended use and known and potential risks and benefits of COVID-19 convalescent plasma. The Fact Sheet also provides a description of the product, information on the dosage, administration and storage of COVID-19 convalescent plasma, use in specific populations, and instructions for communicating with recipients.

As described in the Fact Sheet, health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of COVID-19 convalescent plasma, and must report fatalities to FDA as required in 21 CFR 606.170. Refer to FDA's guidance entitled "Notifying FDA of Fatalities Related to Blood Collection or Transfusion" for recommendations on reporting fatalities related to blood transfusion to FDA (Ref. 8).

2. Clinical Trials

The EUA is not intended to replace clinical trials that are critically important for the definitive demonstration of safety and efficacy of investigational convalescent plasma. Ongoing clinical trials of investigational convalescent plasma should not be amended based on the issuance of the EUA. Health care providers are encouraged to enroll patients in those trials and complete clinical trials to fully answer the questions about the effectiveness of convalescent plasma for the treatment of COVID-19.

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). The Center for Biologics Evaluation and Research (CBER) Office of Blood Research and Review (OBRR) is committed to engaging with sponsors and reviewing such requests expeditiously. During the COVID-19 pandemic, INDs may be submitted via email to CBERDCC_eMailSub@fda.hhs.gov.

3. Expanded Access

An IND application for expanded access is an alternative for use of investigational 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). During the COVID-19 pandemic, INDs for expanded access, that are not single patient INDs, may be submitted via email to CBERDCC_eMailSub@fda.hhs.gov.

a. Single Patient IND for Emergency Use

For various reasons, COVID-19 convalescent plasma under the EUA or investigational convalescent plasma through participation in clinical trials may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, FDA is continuing to facilitate access to investigational convalescent plasma through

⁷ See <https://www.fda.gov/media/141478/download>.

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the process of a physician requesting a single patient IND for an individual patient with serious or life-threatening COVID-19 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 cases, a licensed physician seeking to administer investigational convalescent plasma to an individual patient must request the IND (see 21 CFR 312.310(b)). Given that the intended use of COVID-19 convalescent plasma under the EUA is for treatment of hospitalized COVID-19 patients, FDA expects few requests for single patient INDs.

b. To Obtain a Single Patient IND for Emergency Use

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.

NOTE: To enable electronic completion of the form, download it from your internet browser, save locally, close, and re-open. Do NOT ATTEMPT to fill out this form after opening it from your internet browser; the form will not be fillable until downloaded, saved, and opened locally. Check either box 3a or 3b to enable form logic and the appropriate fields. For more detailed instructions see the **Form FDA 3926 Instructions** (<https://www.fda.gov/media/98627/download>).

CBER requests that all forms be filled out electronically to facilitate rapid review. Hand written forms are often hard to read and may delay the processing of the request. Please pay special attention to the following:

- The completed form should include a brief clinical history of the patient, including: age, gender, 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 312.310.
- The form should include the name of the blood establishment collecting the investigational convalescent plasma.
- Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.

For requests between 8am ET and 8pm ET (Mon-Sun): FDA will respond within four hours. For requests between 8am ET and 8pm ET when the provider is unable to complete and submit **Form FDA 3926** due to extenuating circumstances, the provider may contact FDA's Office of Emergency Operations at 1-866-300-4374 to be routed to the appropriate clinical review staff for assistance with submitting the request.

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For requests that are made overnight between 8pm ET and 8am ET (Mon-Sun):

- In case of a medical emergency, i.e., when authorization and issuance of an IND number is needed before 8 am ET the next morning, the provider should contact FDA's Office of Emergency Operations at 1-866-300-4374 to be routed to the appropriate clinical review staff for assistance with submitting the request and issuance of an IND number.
- In case of a non-critical overnight request, the Form FDA 3926 should be **submitted by email to CBER_eIND_Covid-19@FDA.HHS.gov** for review, and the IND number will be issued by 8 am ET the next morning.

In situations when the provider is unable to complete and submit **Form FDA 3926** due to extenuating circumstances, the requestor must agree to submit an expanded access application (i.e., **Form FDA 3926**) within 15 working days of FDA's authorization of the use (21 CFR 312.310(d)(2)). When submitting the expanded access application form, the requestor is advised to indicate that the application is a follow-up to a previously granted IND for emergency use, and to provide the IND number.

B. Collection of COVID-19 Convalescent Plasma under the EUA

Blood establishments collecting authorized COVID-19 convalescent plasma must comply with the Conditions for Authorization in the EUA. Please refer to the Letter of Authorization for the Conditions of Authorization for registered and licensed blood establishments.⁸

NOTE: Registered and licensed blood establishments do not need to contact FDA or request a supplement to their license, respectively, to collect and manufacture COVID-19 convalescent plasma for the authorized use under the EUA provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals who meet the donor qualifications specified below. Once manufactured, COVID-19 convalescent plasma may be distributed for use under the EUA. Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect and distribute COVID-19 convalescent plasma.

1. Donor Eligibility

As described in the authorization letter, COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains anti-SARS-CoV-2 antibodies and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. Under the EUA, authorized COVID-19

⁸ See <https://www.fda.gov/media/141477/download>.

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convalescent plasma must be collected by registered or licensed blood establishments from donors in the U.S. or its territories in accordance with applicable regulations, policies, and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30).

COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:

- a. Evidence of COVID-19 documented by laboratory testing in either:
 1. Individuals who had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA.

OR

2. Individuals who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have had reactive (positive) results in two different tests approved, cleared, or authorized by FDA to detect SARS-CoV-2 antibodies.

A list of all current EUA COVID-19 in vitro diagnostics is available at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidinvitrodev>.

- b. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.
- c. Male donors, female donors who have never been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

2. Testing for anti-SARS-CoV2 Antibodies

- a. Under the EUA, all plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release.
- b. Pursuant to the EUA, blood establishments must test units using the Ortho VITROS SARS-CoV-2 IgG. Units tested using Ortho VITROS SARS-CoV-2 IgG and found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma. Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the Ortho VITROS SARS-

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CoV-2 IgG are considered low titer units. (See section III.B.3 of this guidance for labeling requirements.)

- c. Blood establishments considering the use of a test other than the Ortho VITROS SARS-CoV-2 IgG to qualify COVID-19 convalescent plasma should contact the CBER OBRR to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA. FDA will consider data submitted to support such use in assessing the acceptability of other tests.

Requests should be submitted to CBER-EUA-CCP-Assays@fda.hhs.gov.

3. Labeling

COVID-19 convalescent plasma must be appropriately labeled.

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

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. COVID-19 convalescent plasma is not an approved product. The container label must not indicate a license number.
- c. COVID-19 convalescent plasma units must be clearly labeled, based on the test results that are used as part of manufacturing, as being high titer COVID-19 convalescent plasma or low titer COVID-19 convalescent plasma based on the level of anti-SARS-CoV-2 antibodies. This information may be placed on the container label or on a tie tag.
- d. 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 U.S. Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.
- e. 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, stored at -18°C or colder and have an expiration date one year from the date of collection.

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C. Collection of Convalescent Plasma Under an IND

Under FDA's IND regulations, an IND (including an intermediate-size population expanded access or single patient IND) must provide information with respect to the investigational drug, chemistry, manufacturing, and controls 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 investigational convalescent plasma, the IND should contain, among other things, adequate information to demonstrate that the plasma will contain SARS-CoV-2 neutralizing antibody titers, if available. Accordingly, health care providers or acute care facilities should include information in the IND submission that the investigational 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.

1. Donor Eligibility

- a. Investigational convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). 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. We recommend investigational convalescent plasma is collected from individuals who meet the following qualifications:
 - i. Evidence of COVID-19 documented by laboratory testing in either:
 1. Individuals who had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA.

OR

2. Individuals who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have had reactive (positive) results in two different tests approved, cleared, or authorized by FDA to detect SARS-CoV-2 antibodies.

A list of all current COVID-19 in vitro diagnostics is available at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidinvitrodev>.

- ii. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

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- iii. Male donors, female donors who have never been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

2. Testing for anti-SARS-CoV2 Antibodies

Plasma donations should be tested for anti-SARS-CoV-2 antibodies to determine suitability before release in accordance with an applicable IND.

Note: Plasma units that do not qualify as COVID-19 convalescent plasma under the EUA may qualify for investigational use under an applicable IND. The units should be labeled as described in section III.C.3 below.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to contact FDA or request a supplement to their license, respectively, or obtain their own IND to collect and manufacture convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals who 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 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 and distribute investigational convalescent plasma.

3. Labeling

Investigational convalescent plasma must be appropriately labeled.

- a. The container label of investigational 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)).
- b. 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.

FDA recognizes that the current circular of information does not contain specific information about investigational convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.

- c. The investigational convalescent plasma container label must not indicate a license number.

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- d. We recommend the use of a uniform container label for investigational convalescent plasma. In particular, we recommend the use of the ISBT format specified in the U.S. Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.
- e. The manufacturing process used and the expiration date on the label for investigational convalescent plasma should be the same as for other plasma products that are of the same type. For example, Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18°C or colder and have an expiration date one year from the date of collection.
- f. Investigational convalescent plasma units may be labeled for anti-SARS-CoV2 antibodies based on the test results as specified under the applicable IND. This information may be placed on the container label or on a tie tag.

D. Recordkeeping

A health care provider who is participating in an IND, including an expanded access IND or single patient IND for emergency use, must maintain records for the investigational 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)).

IV. COMPLIANCE AND ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF CONVALESCENT PLASMA

Following issuance of the EUA for COVID-19 convalescent plasma on August 23, 2020, FDA has received numerous inquiries from blood establishments and health care providers regarding investigational convalescent plasma that was collected prior to the EUA and remains in inventory and the need to continue to collect investigational convalescent plasma while operational changes are being made to meet the requirements in the EUA. The Agency understands that investigational convalescent plasma collected prior to the EUA may not meet the Conditions of Authorization, specifically the requirement for testing plasma donations for anti-SARS-CoV-2 antibodies using the Ortho VITROS SARS-CoV-2 IgG as a manufacturing step to determine suitability before release, as well as qualifying the unit as high titer or low titer COVID-19 convalescent plasma, based on the results of this testing. FDA also understands that it will take time for blood establishments to develop the necessary operating procedures to manufacture COVID-19 convalescent plasma pursuant to the Conditions of Authorization set forth in the EUA. In addition, the Agency is aware that the National Expanded Access Treatment Protocol has been discontinued as of August 28, 2020.⁹

⁹ See <https://www.uscovidplasma.org/>.

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Considering these issues and recognizing the immediate need for convalescent plasma to treat hospitalized patients with COVID-19, we intend to exercise temporary enforcement discretion regarding the IND requirements for the use of investigational convalescent plasma. FDA intends to exercise this temporary enforcement discretion provided the following circumstances are present:

- 1) The investigational convalescent plasma is intended for the treatment of hospitalized patients with COVID-19.
- 2) The treating health care provider obtains adequate informed consent from the patient or his or her legally authorized representative for the use of the investigational convalescent plasma. Informed consent should include, at a minimum, a statement that the use of convalescent plasma is investigational and a discussion of its potential risks and benefits.
- 3) The investigational convalescent plasma is collected by registered blood establishments from donors who meet all eligibility requirements and qualifications in accordance with section III.C.1 of this guidance.
- 4) The container label of investigational convalescent plasma includes the following statement, “Caution: New Drug—Limited by Federal (or United States) law to investigational use” (21 CFR 312.6(a)) and is labeled as described in section III.C.3 of this guidance. Please contact CBER OBRR Blood and Plasma Branch at CBEROBRRBPBInquiries@fda.hhs.gov with any questions regarding labeling the investigational product.

In addition, we recommend the measurement of neutralizing antibody titers when available.

FDA intends to exercise this discretion with respect to the IND requirements for the collection, shipment, and administration of investigational convalescent plasma for a period of 90 days following the issuance of this guidance document. This should provide blood establishments adequate time to develop the necessary procedures to manufacture COVID-19 convalescent plasma under the conditions of the EUA, and if unable to develop such procedures, only administer investigational convalescent plasma under an IND.

This enforcement discretion policy does not extend to convalescent plasma that is not collected and administered as described above.

During this period of enforcement discretion and beyond, FDA will continue to work with any investigators who wish to submit INDs for the study of investigational convalescent plasma. Ongoing clinical trials of investigational convalescent plasma

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should not be amended because of this enforcement discretion policy. Health care providers are encouraged to enroll patients and complete clinical trials.

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V. REFERENCES

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