Recommendations for Investigational COVID-19 Convalescent Plasma

November 16, 2020

FDA issued an EUA for convalescent plasma (/media/141477/download) on August 23, 2020.

FDA has issued a new guidance (/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma)to provide recommendations to health care providers and investigators on the use of COVID-19 convalescent plasma under the EUA or investigational convalescent plasma under an IND during the public health emergency. The guidance also provides recommendations to blood establishments on collection. The guidance describes FDA's interim compliance and enforcement policy regarding the IND requirements for the use of investigational convalescent plasma to facilitate the availability of convalescent plasma to treat hospitalized patients with COVID-19. The guidance supersedes the guidance of the same title issued in April 2020 and updated in May and September 2020.

The guidance provides recommendations on the following:

- pathways for use of investigational convalescent plasma
- collection of convalescent plasma
- record keeping
- compliance and enforcement policy regarding investigational new drug requirements for use of convalescent plasma

Because convalescent plasma for the treatment of COVID-19 has not yet been approved for use by FDA, it is regulated as an investigational product. As such, its administration must be under the EUA or an IND. 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.

Excerpts from the guidance document are provided below.

Background

On August 23, 2020, FDA issued an emergency use authorization (EUA) (/media/141477/download) 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.

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, 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 (/media/141477/download), including the Scope of Authorization and Conditions of Authorization. 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.

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

1. Emergency Use Authorization

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 Sheet for Health Care Providers for information on the intended use and known and potential risks and benefits of COVID-19 convalescent plasma. The Fact Sheet (/media/141478/download)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 (/media/70676/download)" for recommendations on reporting fatalities related to blood transfusion to FDA.

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 (mailto: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 (mailto:CBERDCC_eMailSub@fda.hhs.gov).

A. Single Patient IND for Emergency Use

Given the public health emergency that the COVID-19 pandemic presents, FDA is continuing to facilitate access to investigational convalescent plasma through 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)).

Note: 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. FDA recommends that physicians seeking to use convalescent plasma for hospitalized COVID-19 patients should do so under the EUA and not under single patient INDs. Other options for the use of investigational convalescent plasma are listed above.

To obtain a single patient emergency IND, the requesting physician may contact FDA by completing **Form FDA 3926** (https://www.fda.gov/media/98616/download (https://www.fda.gov/media/98616/download)) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov (mailto:CBER_eIND_Covid-19@FDA.HHS.gov).

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. For more detailed instructions see the Form FDA 3926 Instructions (https://www.fda.gov/media/98627/download (https://www.fda.gov/media/98627/download)).

For requests when the provider is unable to complete and submit Form FDA 3926 due to extenuating circumstances, or in the case of a medical emergency during the hours of 8pm and 8am Eastern Time (ET), 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.

Collection of Convalescent Plasma

Registered or licensed blood establishments collecting authorized COVID-19 convalescent plasma under the EUA or investigational convalescent plasma under an IND should refer to the guidance (/media/136798/download) for recommendations on donor eligibility and qualification, testing plasma for anti-SARS-CoV2 antibodies, and labeling.

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)).

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 as a manufacturing step to determine suitability before release, using a test referenced in the EUA Letter of Authorization, 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.

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 the guidance (/media/136798/download).
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 the guidance. Please contact CBER OBRR Blood and Plasma Branch at CBEROBRRBPBInquiries@fda.hhs.gov (mailto: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 through February 28, 2021. 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 should not be amended because of

this enforcement discretion policy. Health care providers are encouraged to enroll patients and complete clinical trials.