



November 30, 2020

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Assistant Secretary for Preparedness and Response
Office of the Assistant Secretary for Preparedness and Response
Office of the Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Dr. Kadlec:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), the Secretary of the Department 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 United States citizens living abroad, and that involves the virus that causes COVID-19 (the virus was later named SARS-CoV-2).¹ On March 27, 2020, on the basis of such determination, the Secretary of HHS declared 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 Act, subject to the terms of any authorization issued under that section.²

On August 23, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), pursuant to Section 564 of the Act.³

Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2)(C) of the Act (21 U.S.C. § 360bbb-3(g)(2)(C)), FDA is reissuing the August 23, 2020, Letter of Authorization in its entirety with revisions to add the Mount Sinai COVID-19 ELISA IgG Antibody Test as an acceptable test to be used for the purpose of qualifying high and low titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma.

¹ U.S. Department of Health and Human Services (HHS). *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act*, 21 U.S.C. § 360bbb-3. February 4, 2020.

² HHS. *Emergency Use Authorization Declaration*. 85 FR 18250 (April 1, 2020).
<https://www.govinfo.gov/content/pkg/FR-2020-04-01/pdf/2020-06905.pdf>.

³ Additional information about this EUA can be found on the FDA website at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs>.

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. It is an investigational product and is not currently approved or licensed for any indication. Based on review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current outbreak, and data obtained from the National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic,⁴ it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks of the drug for the treatment of patients hospitalized with COVID-19.⁵

Current data suggest the largest clinical benefit is associated with high-titer units administered early in the course of disease. COVID-19 convalescent plasma units shown to contain antibodies to SARS-CoV-2 by a test listed in Section II of this letter but not qualified as high-titer are considered low titer units and are acceptable for use based on an individualized assessment of patient benefit-risk. 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. Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Additional data will be forthcoming from other analyses and ongoing, well-controlled clinical trials in the coming months. These ongoing clinical trials of COVID-19 convalescent plasma should not be amended based on the issuance of this EUA; providers are encouraged to enroll patients in those trials.

Having concluded that the criteria for issuance of this authorization under 564(c) of the Act are met, I am authorizing the emergency use of COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization (Section II) meet the criteria for issuance of an authorization under Section 564(c) of the Act, because:

⁴ A national expanded access protocol (EAP) sponsored by the Mayo Clinic was established in April 2020 and enrolled >100,000 subjects. The EAP discontinued enrollment in August 2020, following the issuance of the EUA for the emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The goal of this uncontrolled, single-arms study was to provide access to COVID-19 convalescent plasma in hospitalized subjects with severe or life-threatening COVID-19 or judged by the treating provider to be at high risk of progression to severe or life-threatening disease.

⁵ Information derived from ongoing clinical trials of COVID-19 convalescent plasma (particularly randomized controlled trials), as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform the risk-benefit assessment for this EUA.

1. SARS-CoV-2 can cause COVID-19, a serious or life-threatening disease or condition, including severe respiratory illness, in humans infected by this virus;
2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that COVID-19 convalescent plasma may be effective in treating COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of COVID-19 convalescent plasma when used to treat COVID-19 outweigh the known and potential risks of such products; and
3. There is no adequate, approved, and available alternative to the emergency use of COVID-19 convalescent plasma for the treatment of COVID-19.^{6,7}

II. Scope of Authorization

I have concluded, pursuant to section 564(d)(1) of the Act, that the scope of this authorization is limited to the use of the authorized COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The emergency use of the authorized COVID-19 convalescent plasma under this EUA must be consistent with, and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.

The Authorized COVID-19 Convalescent Plasma (Product Description):

I am authorizing the use of COVID-19 convalescent plasma, a biological product to be used for the treatment of hospitalized patients with COVID-19.

COVID-19 convalescent plasma is human plasma collected from individuals whose plasma contains SARS-CoV-2 antibodies and who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. Under this EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States 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).

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, using one of the tests listed below, as follows:

1. Ortho VITROS SARS-CoV-2 IgG Test
 - Serum samples found to have a signal-to-cutoff (S/C) value of 12 or greater qualify the associated units as high titer COVID-19 convalescent plasma.

⁶ At the time of reissuance of this letter of authorization, one drug had been approved by FDA for the treatment of certain hospitalized patients with COVID-19 and was available. However, the adequacy criterion was not met.

⁷ No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

- Serum samples found to contain anti-SARS-CoV-2 antibodies with an S/C value below 12 qualify the associated units as low titer COVID-19 convalescent plasma.

2. Mount Sinai COVID-19 ELISA IgG Antibody Test

- Serum samples found to have an ELISA titer of 1:2880 or greater qualify the associated units as high titer COVID-19 convalescent plasma.
- Serum samples found to contain anti-SARS-CoV-2 antibodies with an ELISA titer below 1:2880 qualify the associated units as low titer COVID-19 convalescent plasma.

If a blood establishment is considering using a different test in manufacturing in order to qualify high titer and low titer COVID-19 convalescent plasma, they should contact the FDA Center for Biologics Evaluation and Research (CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA.

Units containing anti-SARS-CoV-2 antibodies must be labeled as high or low titer according to the results of the tests described above. The health care provider may assess whether units with a low titer are acceptable for use based on an individualized assessment of benefit-risk. FDA will continue to evaluate this recommendation based on additional data that become available.

Health care providers will administer the authorized COVID-19 convalescent plasma with anti-SARS-CoV-2 antibodies according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one COVID-19 convalescent plasma unit (about 200 mL), with administration of additional COVID-19 convalescent plasma units based on the prescribing physician's medical judgment and the patient's clinical response.

COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients
- Fact Sheet for Patients and Parents/Caregivers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.

Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and are authorized to be made in consultation with, and with concurrence of, the Office of Blood Research and Review (OBRR)/Center for Biologics Evaluation and Research (CBER), Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER, and Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS)/Office of the Commissioner (OC), as appropriate.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma, when used for the treatment of hospitalized patients with COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that COVID-19 convalescent plasma may be effective for the treatment of hospitalized patients with COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that COVID-19 convalescent plasma (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), COVID-19 convalescent plasma is authorized for the treatment of hospitalized patients with COVID-19 as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to section 564 of the Act, I am establishing the following conditions on this authorization:

ASPR

- A. ASPR will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, registered or licensed blood establishments, hospitals, health care providers) involved in distributing or receiving authorized COVID-19 convalescent plasma. ASPR will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).
- B. ASPR may request changes to this authorization, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, PREP/OD/CBER, and OCET/OCS/OC.

- C. ASPR may request changes to the authorized Fact Sheets for COVID-19 convalescent plasma, and such changes may be permitted without amendment of this EUA upon concurrence of OBRR/CBER, PREP/OD/CBER, and OCET/OCS/OC.
- D. ASPR will report to FDA serious adverse events and all medication errors associated with the use of the authorized COVID-19 convalescent plasma that are reported to ASPR, or of which ASPR otherwise becomes aware, during the pandemic.
- E. ASPR will make available to FDA upon request any records maintained in connection with this EUA.

Registered or Licensed Blood Establishments

- F. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.
- G. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.
- H. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).
- I. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma

- J. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.
- K. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.
- L. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records

and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.

- M. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).
- N. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

- O. All descriptive printed matter, advertising, and promotional materials relating to the use of the authorized COVID-19 convalescent plasma shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the Act and FDA implementing regulations.
- P. No descriptive printed matter, advertising, or promotional material relating to the use of COVID-19 convalescent plasma may represent or suggest that such product is safe or effective.
- Q. All descriptive printed matter, advertising, and promotional materials relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:
 - COVID-19 convalescent plasma has not been approved or licensed by FDA but has been authorized for emergency use by FDA under an EUA for the treatment of hospitalized patients with COVID-19; and
 - The emergency use of COVID-19 convalescent plasma is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures