Recommendations for Investigational and Licensed COVID-19 Convalescent Plasma

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Guidance for Industry

This guidance is for immediate implementation.

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 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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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

This guidance provides FDA's recommendations to blood establishments for the submission of a Biologics License Application (BLA) for the manufacture of COVID-19 convalescent plasma for transfusion intended to treat patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting. The guidance also provides FDA's recommendations for Investigational New Drug applications (INDs) for investigational COVID-19 convalescent plasma for transfusion.

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see 21 CFR 10.115(g)(2) and (g)(3)). FDA made this determination because we recognize that SARS-CoV-2 continues to circulate and COVID-19 remains a serious health risk, especially for patients with immunosuppressive disease or receiving immunosuppressive therapy. FDA's recommendations on the development of drugs and biological products for treatment and prevention of COVID-19 is necessary to address an unmet public health need.

The recommendations in section III.A.2 of this guidance pertaining to investigational new drug applications for COVID-19 convalescent plasma supersede the recommendations in section III.C of the guidance, "Investigational COVID-19 Convalescent Plasma; Guidance for Industry," dated October 2023 (October 2023 guidance). All other recommendations in the October 2023, e.g., with respect to the collection of COVID-19 convalescent plasma under the emergency use authorization (EUA), remain in effect. We intend to withdraw the October 2023 guidance when COVID-19 convalescent plasma is no longer authorized for emergency use.

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. 360bbb-3), (85 FR 7316, February 7, 2020), and amended March 15, 2023 (88 FR 16644, March 20, 2023), the Secretary of HHS determined that there is a public health emergency, or significant potential for a public health emergency, that affects, or has a significant potential to affect national security or the health and security of United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.[1] 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, subject to the terms of any authorization issued under that section.

FDA first issued an EUA on August 23, 2020, for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions. Most recently, on December 28, 2021, FDA revised the EUA to limit authorization to the use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting.[2] At the time of the 2021 reissuance, the available studies in aggregate supported FDA's determination that that use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies may be effective in treating COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment.

Since the most recent reissuance of the EUA for COVID-19 convalescent plasma on December 28, 2021, the epidemiology of SARS-CoV-2, as well as available therapies and vaccines, have continued to evolve. Currently, a large majority of the U.S. population is expected to have detectable antibodies to SARS-CoV-2 by way of vaccination, infection, or both (Ref. 1). FDA has approved several therapeutic options for the treatment of COVID-19 in both the outpatient and inpatient settings (Ref. 2). As of April 2024, COVID-19 vaccines from three different manufacturers are authorized for emergency use or are FDA-approved (Ref. 3).

The COVID-19 pandemic has also seen the emergence of multiple variants of SARS-CoV-2 (Ref. 4). Consequently, we recognize the potential need for the continued availability of COVID-19 convalescent plasma for certain patient populations with COVID-19. Patients with immunosuppressive disease or receiving immunosuppressive treatments who are infected with

[1] https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[2] Denise M. Hinton, U.S. Food & Drug Admin., U.S. Dept of Health & Human Servs., Emergency Use Authorization for COVID-19 Convalescent Plasma (originally issued Aug. 23, 2020, and subsequently reissued with revisions) available at https://www.fda.gov/media/141477/download.

SARS-CoV-2 are at greater risk of poor responses to vaccination (Ref. 5), prolonged infection (Ref. 6), and severe COVID-19 (Ref. 7). Passive immune therapy, including COVID-19 convalescent plasma and monoclonal antibodies, can play a role in management of this patient population (Refs. 8-11). However, mutations in genomic regions encoding for viral proteins have been shown to negatively impact the expected therapeutic benefit of certain authorized drug products, particularly mAb products that bind to specific epitopes on the receptor binding domain of the SARS-CoV-2 spike protein (Ref. 12). Transfusion of COVID-19 convalescent plasma represents an approach to passive immune therapy in patients with immunosuppressive disease or receiving immunosuppressive treatments[3] that has the potential to retain activity against circulating SARS-CoV-2 variants when collected from donors with contemporaneous infection with SARS-CoV-2, including donors with a history of both infection and vaccination (Refs. 13 and 14). Data on the use of COVID-19 convalescent plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments were reviewed at the time of EUA reissuance in December 2021 (Ref. 15). Additional studies examining COVID-19 convalescent plasma in immunosuppressive disease or receiving immunosuppressive treatments have subsequently been published and were described in a recent meta-analysis (Ref. 9).

Under the current EUA for COVID-19 convalescent plasma, registered blood establishments can manufacture and provide COVID-19 convalescent plasma for transfusion without an approved BLA or IND in effect, provided they comply with the Conditions for Authorization in the EUA.[4] However, when the emergency use of COVID-19 convalescent plasma is no longer authorized, blood establishments can only manufacture and distribute COVID-19 convalescent plasma under an approved BLA or IND, as appropriate (21 CFR Part 601 and 21 CFR Part 312). Therefore, FDA is providing recommendations for the licensure of COVID-19 convalescent plasma, or the study of investigational COVID-19 convalescent plasma under an IND, as outlined in section III of this guidance.

III. RECOMMENDATIONS

A. Regulatory Pathways for COVID-19 Convalescent Plasma

COVID-19 convalescent plasma is plasma intended for transfusion that is collected from individuals who have recovered from COVID-19, which contains antibodies to SARS-CoV-2. COVID-19 convalescent plasma is a biological product subject to licensure under section 351(a) of the PHS Act. 42 U.S.C. 262(a). COVID-19 Convalescent Plasma is a blood component as defined in 21 CFR 630.3(b).

[3] Medical providers should use their medical judgment to identify patients with immunosuppressive disease or receiving immunosuppressive treatment. Examples include primary immunodeficiencies, hematologic malignancy, stem cell transplantation, solid organ transplants, and B-cell depleting therapies, among others. Additional information is available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-who-are-immunocompromised.html.

[4] The EUA Letter of Authorization also refers to the guidance entitled "Investigational COVID-19 Convalescent Plasma; Guidance for Industry" dated October 2023 available at https://www.fda.gov/media/136798/download.

FDA's recommendations for two regulatory pathways for COVID-19 Convalescent Plasma – licensure under a BLA and study under an IND – are provided below.

1. Biologics License Application

a. General Considerations for Licensure of COVID-19 Convalescent Plasma

In addition to the applicable regulations for blood components in 21 CFR 600 through 630 and the requirements for Plasma under 21 CFR 640 Subpart D, certain manufacturing steps are unique to COVID-19 convalescent plasma, such as donor selection and component suitability. Blood establishments that manufacture and distribute COVID-19 convalescent plasma for the treatment of COVID-19 must have an approved BLA (if they are not distributing under the EUA or IND pathways), in accordance with section 351 of the PHS Act (42 U.S.C. 262).

i. Blood establishments that manufacture licensed blood components for transfusion

Licensed blood establishments that are already approved to manufacture licensed blood and blood components must report major changes to their approved BLAs by submitting a Prior Approval Supplement (PAS) in accordance with 21 CFR 601.12(b): Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes). You must not distribute COVID-19 convalescent plasma until you have received FDA approval of your PAS (21 CFR 601.12(b)(3)).

ii. Registered-only blood establishments

Registered-only blood establishments must submit a BLA for COVID-19 convalescent plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments. A BLA is required to ensure consistent manufacturing of COVID-19 convalescent plasma for the defined intended use. COVID-19 convalescent plasma involves unique manufacturing considerations, including donor selection and component suitability (e.g., establishing antibody titer), and the indication for use of COVID-19 convalescent plasma is distinct.

b. Recommendations for Submissions of License Applications for COVID-19 Convalescent Plasma

COVID-19 convalescent plasma must be collected from individuals who meet all allogeneic donor eligibility requirements (21 CFR 630.10 and 21 CFR

630.15) and the additional donor eligibility described in your license application. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30). Testing for anti-SARS-CoV-2 is the scientifically supported method for confirming that the donation contains high-titers of anti-SARS-CoV-2 antibodies and is qualified as COVID-19 convalescent plasma. To mitigate the risk of transfusion-related acute lung injury, FDA recommends that COVID-19 convalescent plasma be collected from 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. Submissions for COVID-19 convalescent plasma license applications should include the following information:

i. Standard operating procedures that describe the processes used to establish donor eligibility, including:
    1. Criteria used to select donors with prior SARS-CoV-2 infection.
    2. Criteria used to define the period of donor eligibility after recovering from COVID-19, including:
        - The minimum required time after resolution of symptoms, and
        - The duration of eligibility after resolution of symptoms.
    3. Criteria for donor eligibility following receipt of COVID-19 therapy (e.g., monoclonal antibodies).
    4. Criteria used to select donors with respect to the donor's SARS-CoV-2 vaccination status.

ii. Standard operating procedures that describe processes for COVID-19 convalescent plasma unit qualification, including:
    1. A description of the test(s) used to establish that the COVID-19 convalescent plasma unit contains high-titers of anti-SARS-CoV-2 antibodies. Blood establishments should use tests cleared, approved, or authorized by FDA for the semi-quantitative or quantitative detection of anti-SARS-CoV-2 antibodies.
    2. A description of testing criteria or cut-offs used to qualify the COVID-19 convalescent plasma, including justification of why the criteria establish that the product contains high titers of anti-SARS-CoV-2 antibodies.

iii. Standard operating procedures that describe the process used to collect COVID-19 convalescent plasma including:
    1. The collection device(s) used to collect the plasma. Blood establishments must follow the manufacturer's instruction for use of the collection device for plasma (21 CFR 606.65(e)).

2. The processing and storage conditions of the plasma (e.g., time at room temperature before storage) and the dating period.
    - Considering the potential for emergence of genetic variants that may be less susceptible to antibodies in COVID-19 convalescent plasma, and based about what is known on the kinetics of SARS-CoV-2 viral evolution (Ref. 16), the dating period for COVID-19 convalescent plasma should be 6 months from the date of collection.

iv. Indications for use:
    1. Based on currently available clinical and scientific evidence, including that summarized in section II of this guidance, FDA recommends that the indication for use for licensed COVID-19 convalescent plasma should be the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments. Blood establishments should provide a summary of safety and effectiveness information supporting this indication in their BLA submission.

c. Labeling of COVID-19 Convalescent Plasma

i. Blood establishments must label COVID-19 convalescent plasma in accordance with 21 CFR 606.121. In particular, we recommend you use the International Society of Blood Transfusion (ISBT) 128 format specified in the U.S. Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128 for container labels.
    1. The name of the antibody test, as specified under the BLA, and corresponding result may be placed on the container label or on a tie tag.

ii. Blood establishments must provide adequate directions for use of COVID-19 convalescent plasma in the circular of information (COI) (21 CFR 606.122). You must include the following information in your COI:
    1. Indications for use
    2. Dosing
    3. A description of the product, including criteria used to qualify the donor and product
    4. You may refer to the relevant information on the transfusion of plasma already included in the COI recognized as acceptable by FDA that also applies to COVID-19 convalescent plasma (e.g., side effects and hazards) (Ref. 15).

d. Registration and Listing of COVID-19 Convalescent Plasma

Establishments that manufacture licensed COVID-19 convalescent plasma must update their blood product listing information to include COVID-19 convalescent plasma (see 21 CFR 607.30).

2. Investigational New Drug

a. General Considerations for Investigational COVID-19 Convalescent Plasma Under IND

At the time when the emergency use for COVID-19 convalescent plasma is no longer authorized under EUA, the distribution of COVID-19 convalescent plasma that is not covered in an approved BLA must be under an applicable IND (21 CFR 312). In addition, the current EUA only covers treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments, and provides for an approach to product manufacturing or qualification that is set forth in the Conditions of Authorization in the EUA. Therefore, even with this emergency use authorized, any other unlicensed uses of COVID-19 convalescent plasma are subject to the requirements of the IND regulatory pathway (21 CFR Part 312).

Under FDA's IND regulations, an IND (including an expanded access 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)).

Sponsors should include information in the IND submission that the investigational COVID-19 convalescent plasma will be obtained from an FDA-registered blood establishment. We recommend collection by a registered establishment to ensure that the blood and blood components are collected, processed, and tested, in accordance with the applicable regulations.

> **Note:** If collecting investigational COVID-19 convalescent plasma in accordance with an applicable IND held by a health care provider or other sponsor, registered and licensed blood establishments do not need to obtain their own IND, provided their activities are consistent with the IND (which may provide for 1) following their standard operating procedures for collecting plasma for allogeneic transfusion and all applicable regulations, 2) collecting plasma from individuals who meet the donor qualifications specified in the applicable IND(s), and 3) labeling investigational COVID-19 convalescent plasma as described in section III.A.2.c of this guidance).

b. Recommendations for IND Submissions for Investigational COVID-19 Convalescent Plasma

The IND must provide an introductory statement and general investigational plan that includes the rationale for the drug or the research study and the indication to be studied (21 CFR 312.23(a)(3)).

Investigational COVID-19 convalescent plasma must be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30).

We recommend IND submissions for investigational COVID-19 convalescent plasma include the information described in sections III.A.1.b.i, III.A.1.b.ii, and III.A.1.b.iii of this guidance.

c. Labeling of Investigational COVID-19 Convalescent Plasma

i. The container label of investigational 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)).
ii. 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.
iii. The investigational COVID-19 convalescent plasma container label must not indicate a license number.
iv. We recommend the use of a uniform container label for investigational COVID-19 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.
v. The label for investigational COVID-19 convalescent plasma should reflect its manufacturing process and should be the same as for other plasma products that are of the same type. For example, investigational COVID-19 convalescent plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18ºC or colder.
vi. The container label should include the dating period, as described in the applicable IND.
vii. Investigational COVID-19 convalescent plasma units may be labeled for anti-SARS-CoV-2 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. Expanded Access INDs

FDA recommends that physicians seeking to use convalescent plasma for treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment should do so under the EUA and not under single patient expanded access INDs. Therefore, FDA does not expect that blood establishments will manufacture COVID-19 convalescent plasma for use under expanded access INDs to treat COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments during the duration of the EUA. Even if the emergency use is no longer authorized and if COVID-19 convalescent plasma is licensed, FDA also generally does not expect that sponsors would submit requests for expanded access use of COVID-19 convalescent plasma (see 21 CFR 312.305(a)(1), providing that one criterion for expanded access is that no comparable or satisfactory alternative therapy exists).

IV. PLANNING FOR REVOCATION OF THE EMERGENCY USE AUTHORIZATION FOR COVID-19 CONVALESCENT PLASMA

Based on current knowledge and available evidence supporting efficacy and safety of COVID-19 convalescent plasma in the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, FDA expects that blood establishments intending to manufacture and market COVID-19 convalescent plasma will submit a BLA for licensure for the indication described in section III.A.1.b.iv of this guidance. If FDA determines that there are adequate, available, approved alternatives to the COVID-19 convalescent plasma provided through emergency use (or if FDA determines that other criteria for issuance of the EUA are no longer satisfied), FDA may determine that it is appropriate to revoke the EUA in accordance with section 564(g) of the FD&C Act. Absent an EUA, blood establishments must only manufacture and distribute COVID-19 convalescent plasma under an approved BLA or an IND in effect, as described in sections III.A.1 and III.A.2 of this guidance.

We recognize that blood establishments and transfusion services may have authorized COVID-19 convalescent plasma remaining in their inventory at the time of an EUA revocation. We do not intend to object to the distribution or use of this COVID-19 convalescent plasma; however, you should consider whether the products are likely to contain antibodies against the currently circulating strains of SARS-CoV-2 in your region based on the date of collection. We recommend units more than 6 months from the date of collection not be distributed as COVID-19 convalescent plasma. Such units should be relabeled as plasma for transfusion of the same product type (e.g., fresh frozen plasma), provided all manufacturing was performed in accordance with the applicable regulations and the establishment's standard operating procedure for the corresponding type of plasma for transfusion.

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