Association for the Advancement of Blood & Biotherapies

Toolkit to Support Implementation of Licensed COVID-19 Convalescent Plasma

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Association for the Advancement of Blood & Biotherapies

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Purpose and Overview

Note: This Toolkit is focused on information to support the submission of a Blood License Application (BLA) for COVID-19 convalescent plasma (CCP). Establishments interested in submitting an Investigational New Drug Application should refer to section III.A.2 of the guidance.

FDA's July 22 Guidance, Recommendations for Investigational and Licensed COVID-19 Convalescent Plasma provides recommendations for two regulatory pathways for manufacture and distribution of CCP – licensure under a BLA and study under an Investigational New Drug application (IND). The guidance was implemented without prior public comment to address an unmet public health need. FDA has determined that prior public comment is not feasible or appropriate. The agency recognizes that SARS-CoV-2:

- Continues to circulate and
- COVID-19 remains a serious health risk, especially to patients with immunosuppressive disease or receiving immunosuppressive therapy.

All recommendations in the October 2023 guidance, "Investigational COVID-19 Convalescent Plasma" with respect to the collection of CCP under the emergency use authorization (EUA), remain in effect with the exception that the recommendations pertaining to IND applications in section III.A.2 of the July 24, guidance supersede the recommendations of section III.C of the October 2023 guidance. FDA intends to withdraw the October 2023 guidance when CCP is no longer authorized for emergency use.

Highlights from the Guidance:

- Registered only blood establishments that wish to manufacture CCP must submit a BLA. This is to ensure consistency including unique manufacturing considerations such as donor selection and component suitability (e.g., establishing antibody titers). [Section III.A.1.a.ii, page 4]
- The dating period for COVID-19 convalescent plasma should be 6 months from the date of collection. [Section III.A.1.b.iii.2, page 6].

  NOTE: AABB has confirmed that FDA does "*not object if a facility relabels licensed CCP, **after expiration** (i.e., 6 months for CCP), 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. Blood establishments should establish procedures on how they will perform this process."

- Blood establishments must provide adequate directions for the use of CCP in the circular of information (COI). Information must include: [Section III.A.1.c.ii, page 6]
    1. Indications for use
    2. Dosing
    3. Description of the product including criteria used to qualify the donor and the 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 CCP. (e.g., side effects and hazards)
- Following the revocation of the EUA, FDA does not intend to object to the distribution or use of CCP manufactured under the EUA; however, manufacturers should consider whether the products are likely to contain antibodies against the currently circulating strains in the region based on the date of collection. "We recommend units more than 6 months from the date of collection not be distributed as CCP." [Section IV, page 9]

This Toolkit is intended to:

- Supplement but not replace your review of the July 2024 guidance.
- Support a comprehensive understanding of the regulatory responsibilities for the manufacture and licensing of CCP.

Background

The COVID-19 pandemic has seen the emergence of multiple variants of SARS-CoV-2 and mutations in the virus have negatively impacted the efficacy of some monoclonal antibody treatments approved by FDA. Consequently, FDA recognizes the need for the continued availability of CCP for patients with immunosuppressive disease or receiving immunosuppressive treatment who are infected with SARs-CoV-2 and at greater risk of poor responses to vaccination.

Transfusion of CCP collected from donors with a recent infection, including donors with a history of both a recent infection and vaccination has the potential to retain activity against circulating SARS-CoV-2 variants, represents an approach to passive immunity for patients with immunosuppressive diseases or receiving immunosuppressive treatments.

When the current EUA is no longer authorized, blood establishments can only manufacture and distribute CCP under an approved BLA or IND. Therefore, FDA is providing recommendations for submission of a BLA or IND in the July 2024 guidance.

Summary of the Guidance Recommendations

Biologics License Application [III.A.1, page 4]

a) General Considerations for CCP: [III.A.1.a, page 4]

- Regulations for blood components in 21 CFR 600 through 630 and for Plasma under 21 CFR 640 Subpart D apply.
- In addition, certain manufacturing steps, unique to CCP, such as donor selection and component suitability apply.

Licensed blood establishments: [III.A.1.a.i, page 4]

- Must report major changes to an approved BLA by submitting a Prior Approval Supplement (PAS) under 21 CFR 601.12(b).
    - The PAS must be submitted as Changes Requiring Supplement and Approval Prior to Distribution of Product Made Using the Change (Major Change)
- Must not distribute CCP until FDA approval of the PAS is received. (21 CFR 601.12(b)(3))

Registered only blood establishments: [III.A.1.a.ii, page 4]

- Must submit a BLA for CCP. A BLA is required to ensure consistent manufacturing for the defined intended use and:
    - CCP involves unique manufacturing considerations including donor selection and component suitability (e.g., establishing titer); and
    - The indication for use of COVID-19 convalescent plasma is distinct.

b) Submission of a BLA for CCP: [II.A.1.b, page 4]

- CCP must be collected from donors who meet all allogeneic donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and the additional donor eligibility described in the license application.
- Testing for relevant transfusion-transmitted infections (RTTIs) (21 CFR 610.40) must be performed and the donation found suitable (21 CFR 630.30).
- Testing for SARS-CoV-2 is the scientifically supported method for confirming that the donation contains high-titers of anti-SARS-CoV-2 antibodies and qualified as CCP.
- FDA recommends that CCP 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 CCP license applications should include the following:

    - Standard Operating Procedures (SOPs) that describe processes used to establish donor eligibility, including: [III.A.1.b. I, page 5]
        1. Criteria to select donors with prior SARs-CoV-2 infection.
        2. Criteria used to define the period of donor eligibility following recovery 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 their SARS-CoV-2 vaccination status.

    - SOPs that describe processes for CCP unit qualification, including: [III.A.1.b. ii, page 5]
        1. A description of test(s) used to establish that the CCP unit contains high-titers of anti-SARS-CoV-2 antibodies. Blood establishments should use tests cleared, approved, or authorized by FDA for the semiquantitative or quantitative detection of anti-SARS-CoV-2 antibodies.
        2. A description of testing criteria or cut-offs used to qualify the CCP, including justification of why the criteria establish that the product contains high titers of anti-SARS-CoV-2 antibodies.

    - SOPs that describe the process used to collect CCP including: [III.A.1.b.iii, page 5]
        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 CCP, and based about what is known on the kinetics of SARS-CoV-2 viral evolution, the dating period for CCP should be 6 months from the date of collection.

              NOTE: AABB has confirmed that FDA does "*not object if a facility relabels licensed CCP, after expiration (i.e., 6 months for CCP), 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. Blood establishments should establish procedures on how they will perform this process."

- Indications for use: [III.A.1.b.iv, page 5]
    1. Based on currently available clinical and scientific evidence, FDA recommends that the indication for use for licensed CCP 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 CCP [III.A.1.c, page 6]

NOTE: AABB has confirmed with FDA that because CCP manufacturing processes, including criteria used to qualify the donor and product (refer to section III.A.1.c.ii.3 of the guidance), may differ, FDA does not intend to provide or approve standard COI language to include in the AABB COI. FDA will review and approve the language within the context of each BLA.

- Blood establishments must label CCP in accordance with 21 CFR 606.121.
    - In particular, FDA recommends use of 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.
    - 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.
- Blood establishments must provide adequate directions for use of CCP in the COI (21 CFR 606.122). The following information must be included in the 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).

d) Registration and Listing [III.A.1.d, page 7]

- Establishments that manufacture licensed CCP must update their product listing information to include CCP (21 CFR 607.30).

Planning for Revocation of the EUA for CCP [IV, page 9]

- Based on current knowledge and evidence, FDA expects that blood establishments intending to manufacture CCP will submit a BLA for licensure for the specified indication described in Section III.A.b.iv of the guidance.
- FDA may revoke the EUA if there are adequate, available, approved alternatives to CCP provided under the EUA or other criteria for issuance of the EUA are no longer satisfied.
- Absent an EUA, CCP must be manufactured and distributed only under an approved BLA or an IND.
- FDA acknowledges that establishments may have authorized CCP remaining in inventory at the time of the EUA revocation.
- FDA does not intend to not intend to object to the distribution or use of this CCP; however, establishments 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.
- FDA recommends units more than 6 months from the date of collection not be distributed as COVID19 convalescent plasma.
- Units more than 6 months from the date of collection 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 SOP for the corresponding type of plasma for transfusion.

Checklist for BLA Submission

General:

_____ Establishments currently licensed to manufacture blood and blood components must report major changes to your BLA as a PAS.
  _____ Must be submitted as Changes Requiring Supplement Submission and Approval Prior to Distribution of Product Made Using the Change.
  _____ Must not distribute CCP until PAS approval has been received.

_____ Registered only blood establishments must submit a BLA for CCP for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.

_____ CCP must only be collected from donors who meet allogeneic criteria and any additional criteria described in your license application.

_____ RTTI testing must be performed, and the donation found to be suitable.
_____ Testing performed to confirm high-titers of anti-SARS-CoV-2 antibodies must be cleared, approved, or authorized by FDA.
_____ CCP should 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.

SOPs that Describe Donor Eligibility Must Include:

_____ The criteria used to select donors with prior SARS-CoV-2 infection.
_____ The criteria used to define the period of donor eligibility after recovery from COVID-19 including:
  _____ Minimum required time after resolution of symptoms, and
  _____ Duration of eligibility after resolution of symptoms
_____ The criteria for donor eligibility following receipt of COVID-19 therapy (e.g., monoclonal antibodies).
_____ The criteria sed to select donors with respect to the donor's SARS-CoV-2 vaccination status.

SOPs Describing Processes for CCP Unit Qualification Must Include:

_____ A description of the test(s) used to establish that CCP units contain high-titers of anti-SARS-CoV-2 antibodies.
  _____ Tests should be FDA cleared, approved, or authorized by FDA for the semiquantitative or quantitative detection of anti-SARS-CoV-2 antibodies.
_____ A description of testing criteria or cut-offs used to qualify the CCP, including a justification of why the criteria establish that the product contains high titers of anti-SARS-CoV-2 antibodies.

SOPs Describing the Process Used to Collect CCP Must Include:

_____ The collection device(s) used to collect the plasma.
  _____ SOPs must follow the manufacturer's instruction for use of the collection device.
_____ The processing and storage conditions of the plasma (e.g. time at room temperature before storage) and the dating period.
  _____ The dating period for CCP should be 6 months from the date of collection.

Indications for Use - Included in the Submission:

_____ Licensed CCP should be used for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.
_____ Establishments should provide a summary of safety and effectiveness information supporting this indication the BLA submission.

Labeling of CCP – Included in the Submission:

_____ Labeling of CCP must be in accordance with 21 CFR 606.121.

_____ FDA recommends the use of ISBT 128 format.
_____ 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.

_____ Establishments must provide adequate directions for the use of CCP. Information must include the following:
_____ Indications for Use
_____ Dosing
_____ A description of the Product, including criteria used to qualify the donor and product.
_____ You may refer to relevant information on the transfusion of plasma already included in the *Circular of Information* recognized as acceptable by FDA.

Registration and Listing of CCP:

_____ Establishments that manufacture CCP must update their blood product listing information to include CCP.