Advancing Transfusion and Cellular Therapies Worldwide

03 10 2021

Toolkit for COVID-19 Convalescent Plasma (CCP) Under Emergency Use Authorization Issued 03 10 21

The Toolkit has been updated to reflect the new information from:

- FDA's February 4, 2021, February 23, 2021 and March 9, 2021 Revised EUA for Use of COVID-19 Convalescent Plasma
- FDA's February 11, 2021 Investigational CCP Guidance for Industry,
- FDA's webpage, updated February 11, 2021 Recommendations for Investigational COVID-19 Convalescent Plasma

This Toolkit (dated 03/10/21) is intended to:

- supplement but not replace your review of the three documents listed above,
- provide an update on blood donor deferral following COVID-19 vaccine and transfusion,
- help you identify new information in guidance.

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1- FDA's February 11, 2021 Guidance: Investigational COVID-19 Convalescent Plasma and the Impact of the February 4 and 23, 2021 CCP EUA

Changes are identified:

- ✓ Updated information in the February 11, 2021 Guidance
- ✓ Recommendations impacted by the revised CCP EUA March 9, 2020

February 11, 2021 CCP Guidance	• **Key changes in the revised CCP EUA (Feb 4, 2021) - FDA recommendations impacted by the EUA are highlighted at left.** • **Additional test authorized in the revised Feb 23, 2021 EUA. No additional significant changes.**	• **Revisions in the March 9, 2021 revised CCP EUA**
I. INTRODUCTION **Updated information is highlighted below** Page 1: On August 23, 2020, FDA issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued this EUA with revisions. … 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 January 2021 (previous versions November 2020, September 2020,	**Revised CCP EUA** page 1-2: 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 again reissuing the Letter of Authorization in its entirety with revisions to: (1) include updates based on data from additional clinical trials; (2) clarify that the authorization **is limited to use of only high titer** COVID-19 convalescent plasma in hospitalized patients **early in the course of disease and those hospitalized with impaired humoral immunity;** Following the August 23, 2020 authorization, additional studies, including randomized, controlled trials, have provided data to further inform the safety and efficacy of COVID-19 convalescent plasma, and further characterize product attributes and patient populations for its use. Based on assessment of these data, potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with **high titer**	**Revised CCP EUA page 2:** FDA is again reissuing the Letter of Authorization in its entirety with revisions to: • add the Abbott AdviseDx SARS-CoV- 2 IgG II test as an acceptable test to be used for the purpose of qualifying high titer COVID-19 convalescent plasma in the manufacture of COVID-19 convalescent plasma • move the list of appropriate tests, including name and date of listing, to Appendix A for ease of reference, • revise the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets.

May 2020, and April 2020). We have revised the recommendations in section III.B.1 of this guidance pertaining to convalescent plasma donors. The revisions address when individuals who have received an investigational COVID-19 monoclonal antibody therapy as a participant in a clinical trial, or received an authorized or licensed COVID-19 **monoclonal antibody therapy**, qualify as convalescent plasma donors. We also revised the recommendations in section III.B.2 and 3 of the guidance pertaining to the **qualification and labeling of high titer COVID-19 convalescent plasma** under the EUA. In addition, we updated section IV of the guidance to note that FDA intends to exercise **enforcement discretion** related to the investigational new drug requirements for use of convalescent plasma including when, among other circumstances, the donor meets the qualifications for individuals who have received a COVID-19 vaccine or COVID-19 monoclonal antibody therapy in accordance with section III.B.1 of this guidance.	**units administered early in the course of disease**.[6] [6]Based on what is known about the typical course of illness and kinetics of the humoral immune response in COVID-19, for most hospitalized patients, early in the course of disease likely represents **prior to** respiratory failure requiring intubation and mechanical ventilation. The therapeutic window may be longer when CCP is administered to patients with clinical or laboratory evidence of impaired humoral immunity.	
III. RECOMMENDATIONS **A. Pathways for Use of Investigational Convalescent Plasma** **1. Emergency Use Authorization,** page 4 On August 23, 2020, FDA issued an EUA for COVID-19 Convalescent Plasma for the treatment of hospitalized patients with COVID-19. FDA has subsequently reissued the EUA with revisions. **2. Clinical Trials** **3. Expanded Access**	**Refer to the Revised CCP EUA** page 1-2 (above)	
B. Collection of COVID-19 Convalescent Plasma under the EUA **1. Donor Eligibility,** page 7		

New information is highlighted below **NOTE:** III.B.1.d was added to address CCP donor eligibility criteria after COVID-19 vaccination and a new 3-month deferral recommendation following monoclonal antibody therapy: d. To ensure that COVID-19 convalescent plasma collected from donors contains antibodies directly related to their immune responses to SARS-CoV-2 infection, you should not collect COVID-19 convalescent plasma from: i. Individuals who have received an investigational COVID-19 vaccine as a participant in a clinical trial, or received an authorized or licensed COVID-19 vaccine, **unless they**: 1) had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA (i.e., individuals who meet the qualification for evidence of COVID-19 described in section III.B.1.a.1 above), AND 2) received the COVID-19 vaccine after diagnosis of COVID-19, AND 3) are within 6 months after complete resolution of COVID-19 symptoms. Administration of COVID-19 vaccines for the purpose of boosting immunity of convalescent plasma donors would need to be conducted within a clinical trial under IND [21 CFR Part 312]. ***or***		

ii. Individuals who received an investigational COVID-19 monoclonal antibody therapy as a participant in a clinical trial, or received an authorized or licensed COVID-19 monoclonal antibody therapy, until at least three months after receipt of the therapy.

2. Testing for anti-SARS-CoV2 Antibodies page 8

b. Plasma units that meet the specific testing requirements for SARS-CoV-2 antibodies described in the EUA qualify as high titer COVID-19 convalescent plasma. (See section III.B.3 of this guidance for labeling requirements.)

Revised CCP EUA page 2:

Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course. The related fact sheets are revised accordingly. **The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA**.

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma

Manufacturer (listed alphabetically)	Assay	Qualifying Result
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinityi)	Index (S/C) ≥ 4.5
Beckman Coulter	Access SARS-CoV-2 IgG	S/CO ≥ 3.3
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5

Revised CCP EUA moves this Table to Appendix A:

Tests Acceptable for Use in the Manufacture of High Titer COVID-19 Convalescent Plasma

Manufacturer (listed alphabetically)	Assay	Qualifying Result
Abbott	SARS-CoV-2 IgG (ARCHITECT and Alinity i)	Index (S/C) ≥ 4.5
Abbott	AdviseDx SARS-CoV-2 IgG II (ARCHITECT and Alinity i)	≥ 840 AU/mL
Beckman Coulter	Access SARS-	S/CO ≥ 3.3

GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer ≥ 1:2880
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C ≥ 9.5
Roche	Elecsys Anti-SARS-CoV-2	COI ≥ 109
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index ≥ 4.8

	CoV-2 IgG	
EUROIMMUN	Anti-SARS-CoV-2 ELISA (IgG)	Ratio ≥ 3.5
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 68%
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 47 AU/mL
Mount Sinai	COVID-19 ELISA IgG	Spike ELISA titer ≥ 1:2880
Ortho	VITROS Anti-SARS-CoV-2 IgG	S/C ≥ 9.5
Roche	Elecsys Anti-SARS-CoV-2	COI ≥ 109
Roche	Elecsys Anti-SARS-CoV-2 S	≥ 132 U/mL
Siemens	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Index ≥ 4.8

3. Labeling page 8 c. COVID-19 convalescent plasma units must be clearly	**Revised CCP EUA** page 5: To be labeled as COVID-19 convalescent plasma under this EUA,	

labeled as high titer COVID-19 convalescent plasma based on the results of the SARS-CoV-2 antibody test used as part of manufacturing. This information may be placed on the container label or on a tie tag.	units containing anti-SARS-CoV-2 antibodies **must be labeled as high titer** according to the results of the tests described above. **Low titer units are no longer authorized** for use under the conditions of this EUA.	
C. Collection of Convalescent Plasma Under an IND **No change to this section.**		
IV. COMPLIANCE AND ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF CONVALESCENT PLASMA Reference to "qualifying the unit as low titer" has been removed. **New information is highlighted below** **…** FDA intends to exercise this temporary enforcement discretion provided the following circumstances are present: 3) The investigational convalescent plasma is collected by registered blood establishments from donors who meet a) all eligibility requirements and qualifications in accordance with section III.C.1 of this guidance, **and b) the qualifications for individuals who have received a COVID-19 vaccine or COVID-19 monoclonal antibody therapy, in accordance with section III.B.1 of this guidance.** **NOTE: FDA HAS INDICATED THAT THE AGENCY DOES NOT PLAN TO EXTEND THIS DEADLINE:** FDA intends to exercise this discretion with respect to the IND requirements for the collection,	**Revised CCP EUA** page 2: Therefore, this EUA is being revised to authorize only the use of high titer COVID-19 convalescent plasma, for the treatment of hospitalized patients with COVID-19, early in the disease course. The related fact sheets are revised accordingly. The use of low titer COVID-19 convalescent plasma is no longer authorized under this EUA.	

shipment, and administration of investigational convalescent plasma through **May 31, 2021**.		

2- FDA's RESPONSES TO YOUR QUESTIONS-Hot Topic Discussion: FDA Updates EUA for CCP in Response to New Data

Officials from the Food and Drug Administration answered a series of questions from the blood community during AABB's 02/09/21 Hot Topic Discussion on the updated emergency use authorization for CCP. In the hour-long event, Peter Marks, MD, PhD, director of the Center for Biologics Evaluation and Research CBER; and Nicole Verdun, MD, director of CBER's Office of Blood Research and Review, clarified questions on implementation of the EUA, use of high-titer CCP and the eligibility of CCP donors following vaccination for COVID-19. **This session is available ON-DEMAND. FDA's responses can also be found in the slide presentation.**

3-UPDATED INFORMATION ON DONATION OF CCP, BLOOD COMPONENTS and HCT/Ps During the COVID-19 Pandemic Updated 02 12 2021, includes:

1) HCT/P DONOR ELIGIBILITY
2) CCP and ROUTINE BLOOD DONOR ELIGIBILITY

- 2-1. Blood donor eligibility following COVID-19 vaccine
- 2-2. Blood donor eligibility following CCP transfusion
- 2-3. CCP donor eligibility following vaccination if never infected
- 2-4. CCP donor eligibility if recovered patient later receives a COVID-19 vaccine
- 2-5. CCP donor eligibility after treatment with monoclonals

4-EXAMPLE FLOWCHART: ELIGIBILITY FOR CCP DONATION AFTER COVID-19 VACCINATION/MONOCLONAL ANTIBODY THERAPY *based on recommendation III.B.1.d.*

"To ensure that COVID-19 convalescent plasma collected from donors contains antibodies directly related to their immune responses to SARS-CoV-2 infection," you should: