



Advancing Transfusion and  
Cellular Therapies Worldwide

# Toolkit for COVID-19 Convalescent Plasma (CCP) under Emergency Use Authorization (EUA)

## The Toolkit has been updated based on new information from:

- FDA's November 30, 2020 Revised [EUA for Use of COVID-19 Convalescent Plasma](#)
- FDA's November 2020 [Investigational CCP Guidance for Industry](#),
- FDA's webpage, [Recommendations for Investigational COVID-19 Convalescent Plasma](#)
- FDA's comments on the AABB-FDA Zoom Call, September 2, 2020, and Live Session at AABB's Annual Meeting on October 5, 2020

## This Toolkit (dated 12/02/20) is intended to:

- supplement but not replace your review of the [Nov 30<sup>th</sup> EUA's conditions for use](#) and Nov 2020 [Investigational CCP Guidance](#) for Industry,
- provide an update on blood donor deferral following COVID-19 vaccine and CCP transfusion,
- help you identify new information by section in new guidance.

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## Change Table for Tracking New Information in the November 30, 2020 EUA

### TRACKING NEW INFORMATION IN THE

### November 30, 2020 Emergency Use Authorization for COVID-19 Convalescent Plasma

**Changes:**

- ✓ Key information added
- ✓ Red font indicates no change from the August EUA
- ✓ Strikeout shows information removed from the August EUA

**FDA’s November 30, 2020 EUA**

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).<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup>

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.

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

**FDA’s August 23, 2020 EUA**

Dear Dr. Kadlec:  
~~This letter is in response to your request that the Food and Drug Administration (FDA) issue an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma for the treatment of hospitalized patients with Coronavirus Disease 2019 (COVID-19), as described in the Scope of Authorization (Section II) of this letter, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3).~~

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, 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).<sup>1</sup> 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.<sup>2</sup>

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,<sup>4</sup> 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.<sup>5</sup>

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**

No change to this section.

**II. Scope of Authorization**

No change to this section.

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

~~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 ongoing National Convalescent Plasma Expanded Access Protocol (EAP) sponsored by the Mayo Clinic,<sup>3</sup> 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.<sup>4</sup>~~

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 ~~containing~~ antibodies to SARS-CoV-2 but not qualified as high-titer ~~by a test found acceptable for this purpose by FDA (see Section II)~~ 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**

No change to this section.

**II. Scope of Authorization**

No change to this section.

**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

o 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.

o 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

o Serum samples found to have an ELISA titer of 1:2880 or greater qualify the associated units as high titer COVID-19 convalescent plasma.

o 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

I am authorizing the use of COVID-19 convalescent plasma, a biologic 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. Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma. If a blood establishment is considering using an alternative test in manufacturing in order to qualify high 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 but not qualified as high titer by the test described above are considered low titer units and must be labeled accordingly.~~

The health care provider may assess whether units with a S/C value of less than 12 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.

<p>(CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA.</p> <p>Units containing anti-SARS-CoV-2 antibodies <b>must be labeled as high or low titer according to the results of the tests described above.</b> The health care provider may assess whether units with a <b>low titer</b> 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.</p> <p><b>No change to remainder of this section.</b></p>	<p><b>No change to remainder of this section.</b></p>
<p><b>III. Conditions of Authorization</b> <b>No change to this section</b></p>	<p><b>III. Conditions of Authorization</b> <b>No change to this section</b></p>
<p><b>ASPR</b> <b>No change to this section.</b></p>	<p><b>ASPR</b> <b>No change to this section.</b></p>
<p><b>Registered or Licensed Blood Establishments</b> <b>No change to this section.</b></p>	<p><b>Registered or Licensed Blood Establishments</b> <b>No change to this section.</b></p>
<p><b>Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma</b> <b>No change to this section.</b></p>	<p><b>Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma</b> <b>No change to this section.</b></p>
<p><b>Conditions Related to Printed Matter, Advertising, and Promotion</b></p> <p>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 <b>Section 502(a) and (n) of the Act</b> and FDA <b>implementing</b> regulations.</p> <p>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.</p> <p>Q. All descriptive printed matter, advertising, and promotional materials relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:</p> <ul style="list-style-type: none"> <li>• COVID-19 convalescent plasma has not been approved or licensed by FDA but has been authorized <b>for emergency use</b> by FDA under an EUA <b>for the treatment of hospitalized patients with COVID-19</b>; and</li> </ul>	<p><b>Conditions Related to Printed Matter, Advertising, and Promotion</b></p> <p>O. All descriptive printed matter, including advertising and promotional material, 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 the <b>applicable</b> requirements set forth in the Act and FDA regulations.</p> <p>P. No descriptive printed matter, including advertising or promotional material, relating to the use of COVID-19 convalescent plasma may represent or suggest that such product is safe or effective.</p> <p>Q. All descriptive printed matter, including advertising and promotional material, relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:</p> <ul style="list-style-type: none"> <li>• COVID-19 convalescent plasma has not been approved or licensed by FDA;</li> <li>• COVID-19 convalescent plasma has been authorized by FDA under an EUA;</li> </ul>

- **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.

- COVID-19 convalescent plasma is authorized only 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 authorization is terminated or revoked sooner.

**IV. Duration of Authorization**

**No change to this section.**

**IV. Duration of Authorization**

**No change to this section.**

## Change Table for Tracking New Information in FDA’s November 2020 CCP Guidance

<b>TRACKING NEW INFORMATION IN</b> <u><b>November 2020 FDA Guidance: Investigational COVID-19 Convalescent Plasma</b></u>	
<b>Changes:</b> <ul style="list-style-type: none"> <li>✓ <span style="background-color: #e0ffff;">Key information added</span></li> <li>✓ <span style="color: red;">Red font</span> indicates no change from September Guidance</li> <li>✓ <span style="text-decoration: line-through;">Strikeout</span> shows information removed from September Guidance</li> </ul>	
<b>FDA’s <u>November 2020 Investigational COVID-19 Convalescent Plasma Guidance</u></b>	<b>FDA’s September 2, 2020 Investigational COVID-19 Convalescent Plasma Guidance</b>
<b>I. INTRODUCTION</b> <span style="color: red;">No change to this section.</span>	<b>I. INTRODUCTION</b> <span style="color: red;">No change to this section.</span>
<b>II. BACKGROUND</b> <span style="color: red;">No change to this section.</span>	<b>II. BACKGROUND</b> <span style="color: red;">No change to this section.</span>
<b>III. RECOMMENDATIONS</b>  <b>A. Pathways for Use of Investigational Convalescent Plasma</b> <i>Clarification from FDA [page 3]:</i> 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. <span style="color: red;">No changes to these sections:</span> <b>III.A.1. Emergency Use Authorization</b> <b>2. Clinical Trials</b>	<b>III. RECOMMENDATIONS</b>  <b>A. Pathways for Use of Investigational Convalescent Plasma</b>  <span style="color: red;">No changes to these sections:</span> <b>1. Emergency Use Authorization</b> <b>2. Clinical Trials</b>
<b>III.A.3. Expanded Access</b> <span style="color: red;">No change to the introductory paragraph.</span>  <b>a. Single Patient IND for Emergency Use [page 4]</b>  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)).	<b>III.A.3. Expanded Access</b> <span style="color: red;">No change to the introductory paragraph.</span>  <b>a. Single Patient IND for Emergency Use</b>  <span style="color: red;"><del>For various reasons, COVID-19 convalescent plasma under the EUA or investigational convalescent plasma through participation in clinical trials may not be readily available to all patients in potential need.</del></span> Therefore, 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



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 IND for emergency use, the requesting physician may contact FDA by completing **Form FDA 3926** (<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>).

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.

No changes to these sections:  
**III.B. Collection of COVID-19 Convalescent Plasma under the EUA**

**III.B.1. Donor Eligibility**  
 Paragraph added to the end of this section [page 6]:

Note: You should not collect COVID-19 convalescent plasma from individuals who have received an investigational COVID-19 vaccine because of the uncertainty regarding the quality of the immune response produced by such investigational vaccines.

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)). 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.

**b. To Obtain a Single Patient IND for Emergency Use**

The detailed language in this section on obtaining a single patient IND for Emergency Use was condensed in the November 16 Guidance.

No changes to these sections:  
**III.B. Collection of COVID-19 Convalescent Plasma under the EUA**

**III.B.1. Donor Eligibility**

<p><b>III.B.2. Testing for anti-SARS-CoV2 Antibodies [page 7]</b></p> <p>a. Under the EUA, all 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, <b>using a test referenced in the EUA Letter of Authorization.</b><sup>9</sup></p> <p>b. <b>Plasma units that meet the specific testing requirements for SARS-CoV-2 antibodies described in the EUA</b> qualify as either high titer or low titer COVID-19 convalescent plasma. (See section III.B.3 of this guidance for labeling requirements.)</p> <p>c. <b>Blood establishments considering the use of a test not referenced in the EUA</b> to qualify COVID-19 convalescent plasma should <b>have the test developer</b> contact CBER OBRR to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA. FDA will consider data submitted to support such use in assessing the acceptability of other tests.</p> <p>Requests should be submitted to <a href="mailto:CBER-EUA-CCP-Assays@fda.hhs.gov">CBER-EUA-CCP-Assays@fda.hhs.gov</a></p>	<p><b>III.B.2. Testing for anti-SARS-CoV2 Antibodies</b></p> <p>a. Under the EUA, all 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.</p> <p>b. <del>Pursuant to the EUA, blood establishments must test units using the Ortho VITROS SARS-CoV-2 IgG. Units tested using Ortho VITROS SARS-CoV-2 IgG and found to have a signal-to-cutoff (S/C) value of 12 or greater</del> qualify as high titer COVID-19 convalescent plasma. <del>Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the Ortho VITROS SARS-CoV-2 IgG are considered low titer units.</del> (See section III.B.3 of this guidance for labeling requirements.)</p> <p>c. Blood establishments considering the use of a test <del>other than the Ortho VITROS SARS-CoV-2 IgG</del> to qualify COVID-19 convalescent plasma should contact the CBER OBRR to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA. FDA will consider data submitted to support such use in assessing the acceptability of other tests.</p> <p>Requests should be submitted to <a href="mailto:CBER-EUA-CCP-Assays@fda.hhs.gov">CBER-EUA-CCP-Assays@fda.hhs.gov</a>.</p>
<p><b>No changes to these sections:</b> <b>III.B.3. Labeling</b></p>	<p><b>No changes to these sections:</b> <b>III.B.3. Labeling</b></p>
<p><b>No changes to these sections:</b> <b>III.C. Collection of Convalescent Plasma Under an IND</b></p> <ol style="list-style-type: none"> <li>1. Donor Eligibility</li> <li>2. Testing for anti-SARS-CoV2 Antibodies</li> <li>3. Labeling</li> </ol>	<p><b>No changes to these sections:</b> <b>III.C. Collection of Convalescent Plasma Under an IND</b></p> <ol style="list-style-type: none"> <li>1. Donor Eligibility</li> <li>2. Testing for anti-SARS-CoV2 Antibodies</li> <li>3. Labeling</li> </ol>
<p><b>No changes to these sections:</b> <b>III.D. Recordkeeping</b></p>	<p><b>No changes to these sections:</b> <b>III.D. Recordkeeping</b></p>
<p><b>IV. COMPLIANCE AND ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF CONVALESCENT PLASMA</b></p>	<p><b>IV. COMPLIANCE AND ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF CONVALESCENT PLASMA</b></p>

**Changes were limited to two paragraphs of this section [page 10]:**

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.<sup>10</sup>

...

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.

**Changes were limited to two paragraphs of this section:**

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 **using the Ortho-VITROS SARS-CoV-2-IgG** as a manufacturing step to determine suitability before release, 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.<sup>9</sup>

...

FDA intends to exercise this discretion with respect to the IND requirements for the collection, shipment, and administration of investigational convalescent plasma **for a period of 90 days following the issuance of this guidance document**. 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.

**Flowcharts follow on pages 18-23**

## AABB SUMMARY: DONATION OF CCP AND BLOOD COMPONENTS FOLLOWING COVID-19 VACCINES OR CCP TRANSFUSION - Updated 12 15 2020

### DONOR DEFERRALS:

#### 1-Blood donor deferral following COVID-19 vaccines is not required. Consider the following:

- FDA does not have a policy requiring deferral of *routine* blood donors following COVID-19 vaccination.
- In response to questions from AABB, FDA:
  - Confirmed that it would be reasonable to have no donor deferral following mRNA COVID-19 vaccines.
  - Offered that a 14-day deferral is reasonable following a live-attenuated vaccine (we are expecting very few of those).
- Any decision to update policies for deferral following COVID vaccines is left to the discretion of the Medical Director.
- **For more information from AABB Standards and FDA – refer to the Resources Section below.**

#### 2-Donation following CCP transfusion requires deferral.

- CCP donors must meet all allogeneic blood donor criteria and deferral requirements, including the 3-month deferral from the date of CCP transfusion.

#### 3-Individuals receiving COVID-19 vaccines are not eligible to donate CCP – [FDA’s Nov 2020 CCP EUA guidance](#) (bottom of page 6) **FDA states:**

*Note: You should not collect COVID-19 convalescent plasma from individuals who have received an investigational COVID-19 vaccine because of the uncertainty regarding the quality of the immune response produced by such investigational vaccines.*

- FDA also shared information during the AABB Annual Meeting Session, [Live with FDA on the CCP Regulatory Landscape](#) - refer to slide 29 for CCP donation after vaccination and slides 27-28 for blood donation.

#### 4-Recovered COVID-19 patients who are eligible to donate CCP and also receive a COVID-19 vaccine after recovery are currently deferred from CCP donation per FDA Guidance, refer to #3 above.

However, FDA is actively looking at this donor eligibility issue and had the following response to an inquiry from AABB:

- *There will not be an immediate decision – it will take some weeks.*
- *The agency:*
  - *Is working internally with vaccine and vaccine review.*
  - *Appreciates those that have asked the question and understand it to be an important issue.*

#### 5-FDA confirmed that deferral following receipt of monoclonal antibodies is at the discretion of the physician oversight.

### RESOURCES:

- Aug 7<sup>th</sup> [REGULATORY UPDATE: Investigational Vaccines and Deferral for Donors of Blood and Convalescent Plasma](#)
- Nov 20<sup>th</sup> [REGULATORY UPDATE: Evaluating Donor Risk and Deferrals Following Vaccination](#)
- Oct 5<sup>th</sup> [Live with FDA on the CCP Regulatory Landscape](#) AABB Annual Meeting
- **AABB Standards** – Sept 2020 [Guidance for the Standards for Blood Banks and Transfusion Services, 32<sup>nd</sup> edition](#) - Deferral following COVID-19 vaccines

## FDA's Responses to Your Questions

### CCP Regulatory Landscape, October 5, 2020 and Sept 2, 2020

*AABB encourages clinicians and AABB members in transfusion services and blood establishments to **review the EUA\*** for all conditions for use, including Section III A-Q, and other requirements to ensure compliance.*

*\*On November 30, 2020 FDA revised the EUA for CCP to update testing options by adding the Mount Sinai COVID-19 ELISA Immunoglobulin G (IgG) Antibody Test (Mount Sinai Test), which was not available at the time of the Aug. 23 EUA.*

#### Testing Under the EUA

- 1) Please provide an update on the progress to qualify other antibody titer testing systems that can be used in manufacturing to label a CCP collection as high-titer or low-titer.
  - What tests are available now and will more tests be available soon?

- 2) The 90-day transition period cannot be considered adequate without antibody test systems in place now. At the time a test becomes available, is it possible for FDA to extend the period for temporary enforcement discretion to provide 90 days as a reasonable time frame to make significant operational changes and avoid discard of CCP?

**AABB Note:** The period of FDA's temporary enforcement discretion has been extended through February 28, 2021 in the [November 2020 guidance](#). [Section IV, page 11]

**\*FDA 10/5:** *In terms of the EUA, there is one test within the EUA currently that can be used to qualify convalescent plasma that is authorized under that EUA and that is the Ortho Vitros SARS-CoV-2 IgG test. We are certainly committed to adding additional assays to the EUA and that would be in the form of an amendment.*

- 3) Given the challenges in finding CCP donors, for CCP collections that meet all EUA criteria but were donated pre-EUA, is it possible to perform antibody titer testing on a retention sample and re-label such collections for use in the clinical setting?

**FDA 10/5:** *There are no prohibitions on retesting or relabeling if the product meets all of the EUA criteria. We are certainly open and allowing retesting and relabeling of units collected prior to the EUA as long as they meet the EUA criteria. In terms of units that qualify for shipment for National Surge Capacity Storage and prohibition on shipment – again, if the product meets the EUA criteria, it is not dependent when the actual unit was collected. If it meets the criteria of the EUA, you can use those units and you can certainly use them for the Surge Capacity Storage as well.*

**FDA 10/5:** *How can blood centers utilize a variance for retesting and relabeling to avoid the discard of CCP – a variance is not needed to avoid this discard. As long as the units are meeting all the EUA criteria, you do not need to contact us for that. I hope that answers those questions.*

- 4) Are there options to qualify CCP donations as high titer if the S/C is below high titer labeling threshold on the Ortho IgG or other future EUA binding Ab assays that receive approval (are PRNT, RVPNT or other nAb assays performed in GLP or CLIA labs acceptable)?

**\*FDA 10/5:** *No. I think that as we mentioned at the top of the hour, we are open and continuing to receive data, gather data, to add additional assays to the EUA specifically. If they don't meet the threshold of high titer they still need to be labeled as low titer CCP, and they still need to use assays that are found acceptable to qualify manufacturing of CCP through this EUA. The options, and some are using these options, are, if you would like to use an assay that is not in the EUA as an option, you can have an IND and gather information and use convalescent plasma that has been qualified by an alternative assay through the use of the IND. I think that's a good question because we have heard some confusion around the lower bar. If you have units that don't meet the high titer, they would be otherwise low titer. Can you just use any assay and then distribute those units? No, they still need to use assays that are found acceptable under the EUA.*

- 5) Does FDA require a CLIA lab to perform the Ortho testing?

**\*FDA 9/2:** *This antibody testing to determine titer does not have to be performed in a CLIA certified lab. This differs from other required testing - it is a test involved in the manufacturing of a biologic, not a test result given to a patient.*

6) Can our hospital donor room use an Ortho VITROS test system that is already setup and running (in another department's laboratory) to do the required testing?

**\*FDA 9/2:** *There is nothing to say you must use a dedicated system. You can use a system that is being used for other purposes. It does not have to be devoted to just this.*

7) The Ortho IgG assay EUA only allows for testing of serum, not plasma. Is approval pending for testing of sera, or is it acceptable to convert plasma to sera by clotting plasma samples prior to performing the Ortho IgG test?

**\*FDA 9/2:** *We can't comment on ongoing review and discussions specifically with Ortho. We recognize this is a limitation. Again, I know I keep repeating myself, but I just want to underscore that we really are committed to broadening the availability of additional assays and options for testing under the EUA. We look to do that as soon as possible.*

8) Is the Broad PRNT assay the only neutralization assay permissible for assay correlation for EUA "high/low titer" labeling?

**\*FDA 10/5:** *No. I hope we didn't confuse anyone. We used the Broad as a way of trying to get to, kind of a ground truth, for helping to sort out different titers. We did find it to be the most reliable when you looked at different methodologies. We compared it to either seven or eight other titering methodologies. It did seem to overall be the most reliable. What we are using obviously in the EUA is the Ortho Vitros IgG. The Broad is not being offered as a commercial assay.*

9) Will you consider amending the CCP EUA with an assay that is performed at a High Complexity Lab at a blood center if it meets requirements you set forth or will you only consider commercial assays to amend the EUA?

**FDA 9/2:** *Yes, FDA will consider laboratory-developed tests to qualify CCP; and if the test is found acceptable, to amend the CCP EUA. The test does not need to be a commercial assay.*

*As stated in the CCP guidance, such requests for alternative tests should be submitted to [CBER-EUA-CCP-Assays@fda.hhs.gov](mailto:CBER-EUA-CCP-Assays@fda.hhs.gov). Please let us know if you have additional questions.*

### **Titer Testing and Donor Qualification**

10) Does titer testing change how donor centers qualify CCP donors from the general population of whole blood donors?

For example, with the Ortho IgG test to confirm an antibody titer for SARS-CoV-2:

- With the high specificity of this test, is it still necessary to use prior symptoms or diagnosis of COVID-19 to qualify the donor?
- Given the confusing information around prior infection and variability in diagnostic COVID testing of the public, can the Ortho IgG test confirmation of antibody titer be used to qualify the CCP from a plasma donor?

**\*FDA 10/5:** *There are two distinctions here that I want to make. One is qualifying a unit of convalescent plasma – that is as a manufacturing step in the manufacturing of convalescent plasma and that is the use of the Ortho IgG test. The other is qualifying a donor. I just want to restate that donor eligibility can be determined based on either one: Symptoms of a COVID-19 and a positive test result from a diagnostic test that is approved/cleared or authorized by FDA OR having had reactive positive results on two different tests approved/cleared or authorized by FDA to detect SARS-CoV-2 antibodies. Those are the criteria for donor eligibility, and you have to meet those criteria to qualify a donor. That is independent of the specific use of the Ortho IgG test to qualify a unit. It is still necessary to use prior symptoms or diagnose the COVID to qualify a donor if you are using a donor who has had symptoms. We also have the option now, that I just mentioned, if someone does not necessarily have symptoms or symptomatic illness, that you can qualify them by using the two independent tests. If there are additional questions on this, please feel free to contact us.*

## Labeling

11) Please clarify if labeling requirements for EUA CCP:

**FDA 10/5, response to each question:**

- *Removal of license #? The container label does include a license number because convalescent plasma is not an approved product so that should be removed.*
- *Removing the IUO caution statement and adding an EUA statement? There is no EUA statement that is required so you don't need to add an EUA statement. Certainly, if you are using EUA CCP, you do not need an IUO caution statement.*
- *Addition of High Titer/Low Titer to the CCP name or include as labeling attributes? There is a requirement within the EUA to add specifically if the unit is high-titer or low-titer. You can include that in container label or the tie-tag.*
- *Obtaining two new ISBT128 pcodes? [see Q 15 for more on codes.]*
- *Registered (but not licensed) establishments can collect, label and distribute? Yes.*

12) Can centers relabel CCP collections as FFP, and similarly can you comment on units that were stockpiled before the EUA but are not distributed within the 90-day timeframe?

**AABB Note:** *Since this session, FDA's [Nov 2020 Guidance](#) states the period of FDA's temporary enforcement discretion extends through February 28, 2021. [Section IV, page 11]\*\**

**FDA 10/5:** *Yes, you can relabel units as FFP. That's fine as long as they meet the requirements for FFP.*

- *The second question is specifically about stockpile units. If those units are not distributed within the 90-day timeframe\*\*, after the temporary discretion period is completed, then those units should be consistent with the requirements that are outlined in the EUA to be distributed as EUA authorized CCP. Otherwise if they are not, they can be distributed, but would need to be distributed under an IND. That's after this temporary discretion period.\*\* During this 90-day temporary discretion period\*, no IND is needed to be able to distribute those units.*

13) Can product labeling include the signal to cutoff?

**FDA 10/5:** *The requirement, through the EUA, is to label them as either high titer or low titer. There is not enough knowledge at this point, based on, Dr Marks presented some of it and then a lot of it is in the EUA, to say specifically what the meaning of a specific S/C cutoff is outside of what we have put in place as either qualifying at this point high titer versus low titer. If someone put that on the label, a specific S/C cutoff, in terms of clinical applicability, I really don't know what that means based on the data that we have. I would recommend labeling it as we have outlined, which is either as high titer or low titer.*

14) After the discretion period, can units qualifying as CCP (prior to the EUA) but not able to be tested with Ortho Vitros, be simply be labeled as "low titer" under the EUA? In the absence of any Ortho Vitros IgG testing can they just be labeled as low titer?

**\*FDA 10/5:** *No, they cannot. Those units, specifically as you have outlined them, would need to be used in the setting of an IND. You can specifically contact FDA to talk to us a bit further about the context there. Units that are labeled under the EUA, whether they are high titer or low titer, need to be labeled after using an assay that is approved for use under that EUA. Right now that's the Ortho assay, but we anticipate there will be others. That's for low titer as well.*

## ISBT Codes

15) How do we know which ISBT codes are acceptable?

**AABB Note:** ICCBBA issued new codes on Nov 5, 2020, as projected.

**Also, from the October 2<sup>nd</sup> AABB Weekly Report, ICCBBA has shared the following:**

- ICCBBA is responding to FDA's CCP emergency use authorization (EUA) decision memorandum by introducing new product description codes to indicate high- and low-titer CCP.

- In order to implement the codes efficiently, ICCBBA will create two new product description codes—one for high-titer CCP and one for low-titer CCP—for all current U.S.-requested CCP codes (92). These codes will be available by the early November release of the PDC database.
- Additional codes can be requested via the normal code request process.
- The alternative practice of using special testing codes with current CCP product codes to designate the titer status of the product may still be used.

### Dosage

16) Does any of the data reviewed by FDA provide insight into the question of dosage, particularly whether two low titer units could be viewed as equivalent to one unit of high titer plasma?

**FDA 10/5:** *I think we can't say anything about that. I think we have to leave it to the discretion of the provider. There's just too many variables there including what are the actual titers of the low titer units. We don't really have a perfect handle on how that's going to work. I think it has to be left, at this point, to the discretion of the individual provider looking at the situation. If people want to try to study this, and try to understand it, we'd love to entertain INDs about this area, or talk about how it could be done, but I think for right now, we just have to leave it up to people to do their best.*

### Inventory Management

17) Can blood centers and transfusion services pool very high titer units with low titer units to achieve the minimum titer in more of the inventory?

**FDA 9/2:**

- *FDA has no data from a safety standpoint to support pooling at this point.*
- *Not recommended or permitted now under the EUA.*
- *Would welcome this in an IND or a study.*

18) Can we determine that it is necessary to keep thawed CCP beyond the 5-day expiration, if stored properly, to make it available for another patient? Can we keep CCP in our inventory longer than 1 year?

**FDA 10/5:** *Discuss this option with FDA if you would like to consider this change in your policy.*

### Surge Storage

19) We have been putting units in a Surge Center under BARDA direction. What happened to those units that do not meet EUA and cannot be retested as the Ortho IgG test requires a serum sample?

**\*FDA 10/5:** *I think that that's a tough question. Again, the temporary discretion period allows for the ability to continue to use those units. It sounds like what we are saying here is that we don't have a way to potentially retest those units, with the Ortho assay. During these next several months we are going to be working to add additional assays to the EUA as we obtain data that supports that. I do understand that the stockpile is an issue. I would welcome offline, to have some additional discussion around some of those issues specific to the stockpile. We understand that we do have though, the requirement that if units are going to be distributed under the guise of authorized EUA CCP that they really do need to be tested according to what is contained in the EUA.*

### Investigational Vaccines and Routine Blood Donation

**Questions 11-14:** To avoid an unnecessary deferrals that will have an adverse impact on the blood supply overall, what advice do you have for Medical Directors who will be making policy decisions on donor eligibility as many donors receive investigational COVID vaccines in the next year? **[also see Q 24-26 for specific information on CCP donation and deferral]**

And do we correctly understand that, based on infectious risk associated with the vaccines, FDA:



20) Does FDA require an automatic 12-month deferral for investigational vaccines?

**FDA 10/5:** *No, FDA does not have that requirement. We do recognize that AABB has specific policies around this that include a 12-month deferral, but FDA does not have that requirement.*

21) Would FDA consider 2 weeks as an acceptable deferral period after an individual receives a live attenuated vaccine?

- *Yes, that does seem reasonable. Again, this is not our policy per se.*

22) Would FDA consider a 2-week deferral as acceptable if a donor received an investigational COVID vaccine but does not recall which one?

**FDA 10/5:** *This should be in the hands of the responsible physician for that donor. We do not have a specific policy, as I said, on this.*

**AABB Note:** Refer to the “[Example Flowchart for Updated Deferral Policy for Vaccines](#)”, pages 23-24 of this Toolkit, for donor evaluation following COVID-19 vaccination.

23) Does FDA believe no deferral period is needed for non-replicating, inactivated or RNA-based vaccines?

**FDA 10/5:** *Again, this sounds reasonable, but consultation should really be with that responsible physician.*

### **CCP Donor Eligibility, Investigational Vaccines**

24) Under the EAP, FDA left the decision to collect CCP more frequently than every 28 days to the discretion of the medical director. Has FDA added any limitations on donation frequency for EUA CCP?

**FDA 10/5:** *No, we have not added any additional limitations at this time. If you would like to collect CCP more frequently again, please include the medical director and that is at their discretion. But there is no additional limitation.*

25) How long is a donor deferred from donation after receiving a CCP transfusion?

**AABB Note:**

- Donors who donate CCP must meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and qualifications. [Section III.B.1]
- There is a 3-month deferral from the date of CCP transfusion. Per the FDA August 2020 HIV Risk guidance, p 9, “Defer for 3 months from the most recent allogeneic transfusion, any individual who has a history of receiving an allogeneic transfusion of Whole Blood or blood components.”

26) How do investigational COVID vaccines effect the eligibility of CCP donors – if deferred, why and for how long?

**FDA 10/5:** *At this time, we don’t recommend the use of CCP donors who have received an investigational COVID vaccine.*

**AABB Note:** In the [November 16, 2020 guidance](#), Section III.B.1 page 6-7 FDA now states: “You should not collect COVID-19 convalescent plasma from individuals who have received an investigational COVID-19 vaccine because of the uncertainty regarding the quality of the immune response produced by such investigational vaccines.” **Refer to the “[Example Flowchart for Updated Deferral Policy for Vaccines](#)”, pages 23-24 of this Toolkit, for donor evaluation following COVID-19 vaccination.**

### **EUA versus IND for Reporting, Pediatrics, Continued Clinical Trials**

27) Does FDA have additional reporting requirements under the EUA that are similar to the EAP IND?

**FDA 9/2:** *No additional reporting requirement for the EUA other than adverse event reporting required for blood transfusion. Decreasing the administrative burden for reporting is one of the reasons for moving to the EUA.*

28) Please clarify that pediatric use of CCP is at the discretion of the healthcare provider **or** does FDA require an IND for pediatric use?

**FDA 10/5:** *Pediatric use is at the discretion of the healthcare provider who makes a benefit:risk determination in that pediatric patient. Under the EUA, we do allow for the use in pediatrics after that assessment is made. That is included in both our [healthcare provider fact sheet](#) and the [fact sheet for the recipient](#).*

29) How does the EUA impact FDA approved INDs, and where can we find a list of clinical trials?

**FDA 10/5:** *We are actually encouraging this, and have that specific language in the EUA approval, encouraging the continuation of INDs. We still need randomized controlled trials. We still need data in this space. So please, if you are interested in INDs in this space, we encourage it. We encourage those INDs that are already in place to continue. There is a list of clinical trials that are currently open on [clinicaltrials.gov](https://clinicaltrials.gov) and again we continue to encourage their enrollment.*

### **CCP Transfusion and Consent During the Period of Enforcement Discretion**

30) Are there restrictions on access or treatment if our blood supplier does not have EUA CCP ready OR Can we transfuse units that are **labeled as investigational CCP** until more EUA CCP can be provided?

**FDA 9/2:** *No relabeling or testing is required. [must transfuse CCP labeled as investigational CCP]*

**AABB Note:** Refer to Section IV, pages 11 & 12 of the CCP guidance and Flowchart 4 of this Toolkit for information on the use of investigational CCP during the transition period.

### **Fact Sheets and Consent Under the EUA**

31) Please confirm that FDA permits the use of the Fact Sheets required under the EUA to also be used with consent to receive a transfusion of pre-EUA investigational CCP during the transition period.

**FDA 10/5:** *In terms of using the Facts Sheets under the EUA during the transition period – I recognize the information that is contained in the Fact Sheets can be quite helpful not only to providers but also to recipients. The actual information- we are not opposed to you using that information but please understand that the Fact Sheets themselves have in them a section, “What is an EUA?”. The Fact Sheet at the top says Emergency Use Authorization for CCP. I don’t want it to be that these things are confused because during this transition period if you are not using convalescent plasma that qualifies under the EUA, it shouldn’t be billed as EUA authorized convalescent plasma. I recognize that to give that information to a patient might be helpful.*

32) If so, are there additional requirements for investigational CCP such as retesting and relabeling or patient consent?

**FDA 9/2:** *Consent is required for this investigational product. The EUA Fact Sheets should not be used in consent for CCP collected and transfused during this transition period because it [investigational CCP] does not meet the requirements of the EUA. [Section IV, pages 11 & 12 and Flowchart 4 of this Toolkit, p. 20.]*

33) Will research consent and IRB permission be needed for pre-EUA units?

**FDA 9/2:** *During the EUA there is not a specific research consent. During the enforcement discretion period, FDA is not requiring IRB oversight.*

34) Does FDA have Fact Sheets translated into Spanish available on their website? **Or** is the translation left to the discretion of the blood centers and hospitals?

**FDA 10/5:** *We have Fact Sheets in available on our website that are actually translated into 4 other languages, including Spanish. So, please go to our website and you can certainly use those.*

[Healthcare Providers](https://www.fda.gov/media/141478/download) OR <https://www.fda.gov/media/141478/download>

• [Chinese](#) / [Korean](#) / [Spanish](#)

• <https://www.fda.gov/media/141978/download>: [Tagalog](#) / [Vietnamese](#)

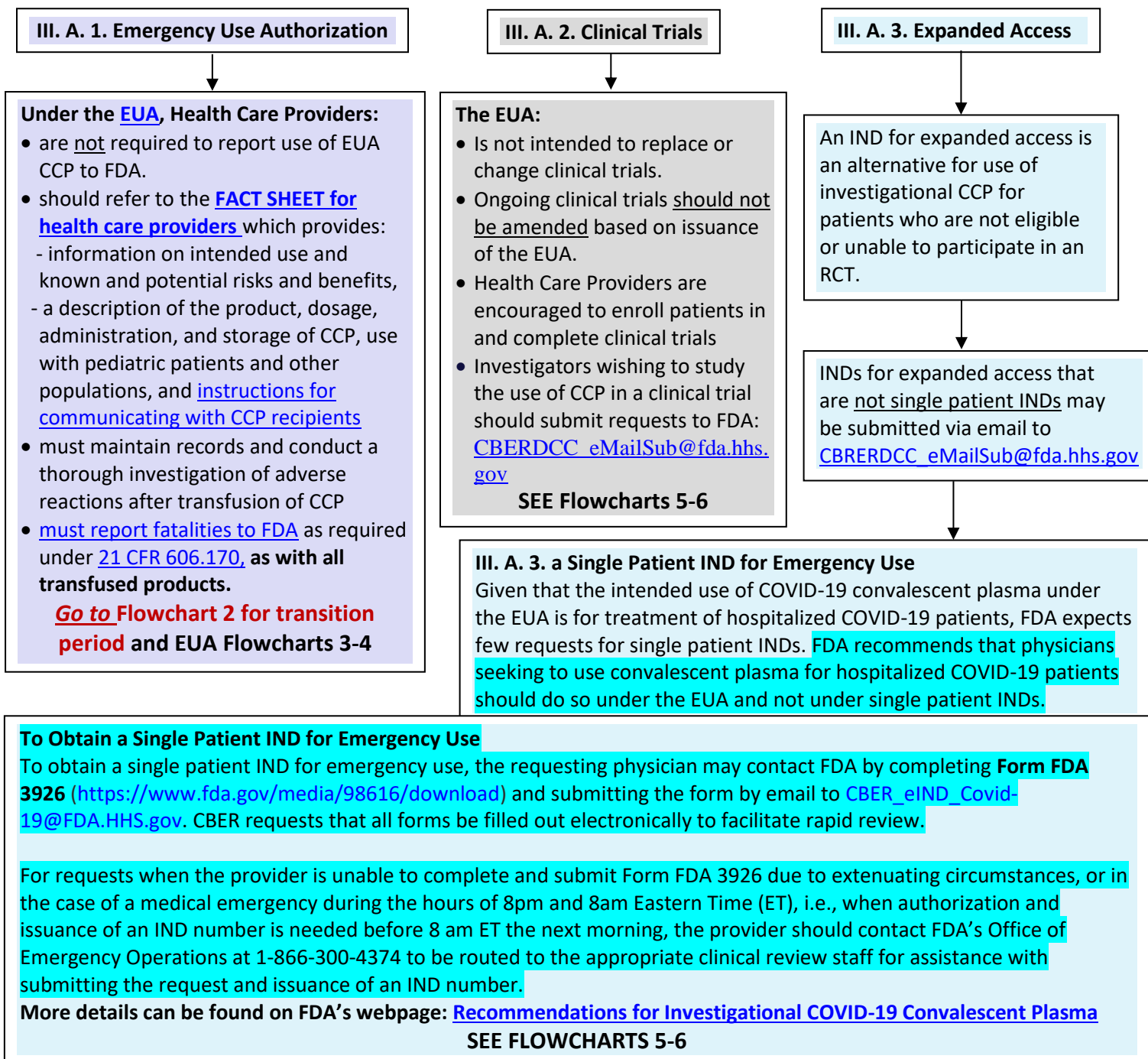
[Patients and Parents/ Caregivers](#) or <https://www.fda.gov/media/141479/download>

• [Chinese](#) / [Korean](#) / [Spanish](#) /

• <https://www.fda.gov/media/141984/download>: [Tagalog](#) / [Vietnamese](#) (103KB)

## Flowchart 1 – Two Pathways for Use of Investigational CCP, EUA and IND

- **Section III, Recommendations, states:** “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.*”
- **AABB encourages clinicians and AABB members in transfusion services and blood establishments to review the EUA for all conditions for use, including Section III A-Q, and other requirements to ensure compliance.**



## Flowchart 2 – Compliance and Interim Enforcement Policy for Investigational CCP

**November 2020 FDA guidance:** 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. [p11]

**Section IV. FDA’s decision to extend temporary enforcement discretion regarding the IND requirements for the use of investigational convalescent plasma will permit the collection, shipment, and administration of investigational products that:**

1- Were collected **prior to the EUA** *OR* collected **during the FDA defined period of enforcement discretion:**

- by registered or licensed blood establishments [Section IV, 3 on page 11]
- from donors who meet all eligibility requirements and qualifications in accordance with section III.C.1 of the guidance. [Section IV, 3 on page 11]
- is labeled as described in section III.C.3 of the guidance. Questions for FDA? Email FDA at [CBEROBRRBPBInquiries@fda.hhs.gov](mailto:CBEROBRRBPBInquiries@fda.hhs.gov) [Section IV, 4 on page 11]
- including the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use” (21 CFR 312.6(a)) [Section IV, 4 on page 11]

AND

2- Do not meet the EUA requirements [page 11] for SARS-CoV-2 antibody testing using a test referenced in the EUA **Letter of Authorization** and labeling the unit as high titer or low titer

Investigational CCP is transfused to hospitalized patients with COVID-19 **only if the health care provider obtains adequate informed consent** [Section IV, page 11]

- for the use of the investigational convalescent plasma.
- from the patient, legally authorized representative.
- which includes, at a minimum, a statement that the use of convalescent plasma is investigational and a discussion of its potential risks and benefits.

**FDA has clarified** (FDA Q&A, page 16 of this Toolkit, Q31 and Q32) that **Fact Sheet for Patients** intended for use with the EUA:

- **should NOT be used in the consent process for investigational CCP during this period of enforcement discretion**

The EUA **Fact Sheet for HCPs**, p.4: Report to FDA adverse reactions following transfusion as for any blood component. [21 CFR 606.170](#)

FDA recommends the measurement of neutralizing titers when available. [Section IV, page 11]

## Flowchart 3 – Collection of COVID-19 Convalescent Plasma Under the EUA

### Section III. B. 1. of the Guidance [pages 5-7]

**\*Section III. B. 1 CCP collected and distributed under the EUA must:**

- be collected by registered or licensed blood establishments from donors in the U.S. or its territories
- comply with the EUA Conditions for Authorization. Refer to Section III, p 4, in the [Letter of Authorization](#) for the Conditions of Authorization for registered and licensed blood establishments.

**AND you must [III. B, page 5]:**

- 1) follow your SOPs for plasma collection and all applicable regulations, and
- 2) collect plasma from individuals who meet all requirements for donor eligibility and testing (21 CFR 630.10, 630.15, 610.40) and found suitable (21 CFR 630.30).

**\*Establishments should review the [Letter of Authorization](#) for *all requirements of the EUA*, including details in Section III, Conditions on page 5**

**NOTE: Registered and licensed blood establishments do not need to contact FDA or request a supplement to their license, respectively, to collect and manufacture COVID-19 convalescent plasma for the authorized use under the EUA provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals who meet the donor qualifications specified below. Once manufactured, COVID-19 convalescent plasma may be distributed for use under the EUA. Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.121(a) [III. B, page 5-6]**



**III. B. 1. Donor Eligibility criteria for Collection under the EUA [III. B. 1, pages 6-7]:**

a.1. Individuals who had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA.

OR

a.2. Individuals who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have had reactive (positive) results in two different tests approved, cleared, or authorized by FDA to detect SARS-CoV-2 antibodies.

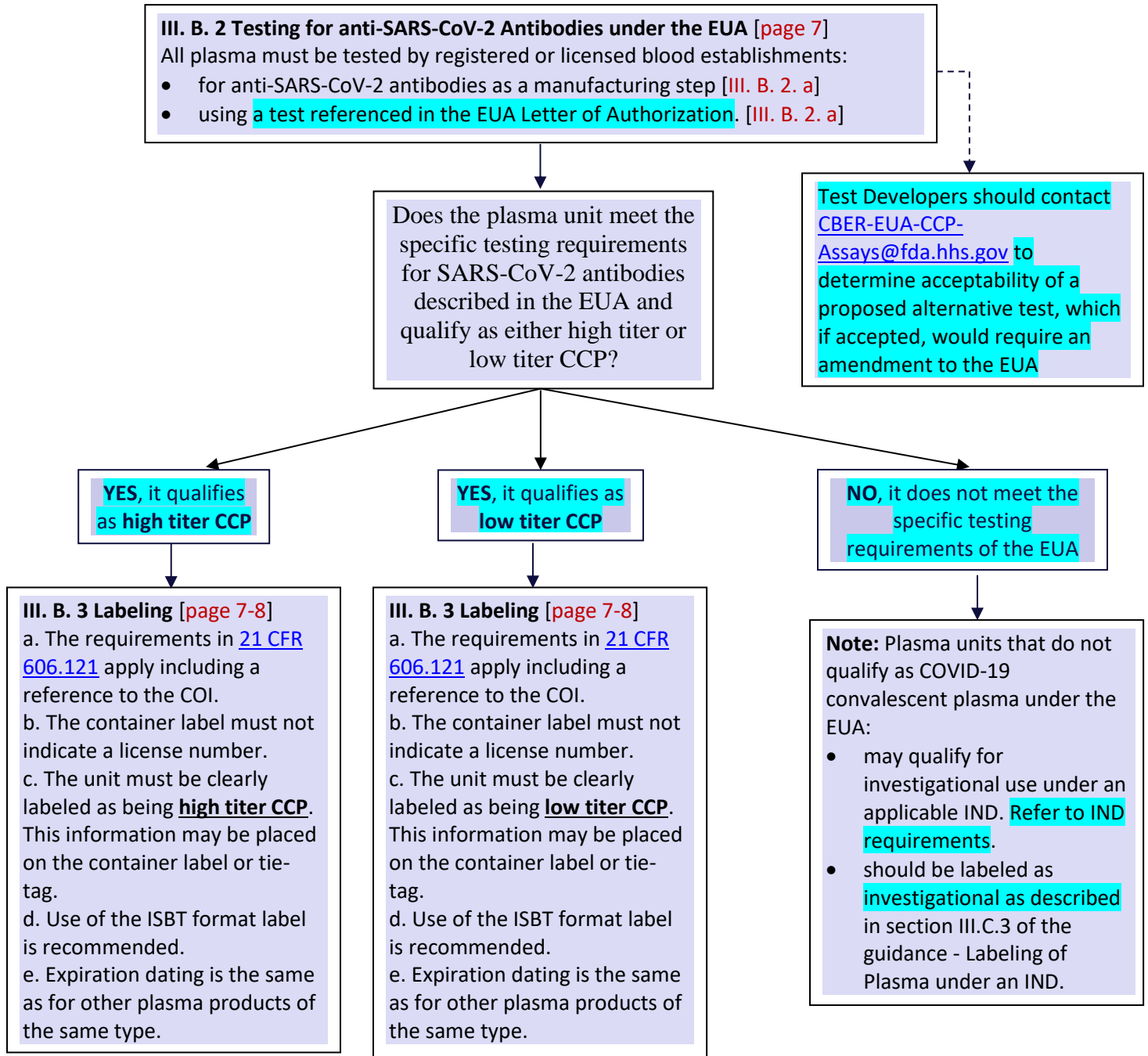
b. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

c. 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.

**Note from page 6-7: You should not collect COVID-19 convalescent plasma from individuals who have received an investigational COVID-19 vaccine because of the uncertainty regarding the quality of the immune response produced by such investigational vaccines.**

## Flowchart 4 – Testing and Labeling of COVID-19 Convalescent Plasma Under the EUA

### Section III. B. 2 of the Guidance [pages 7-8]



## Flowchart 5 – Collection of COVID-19 Convalescent Plasma under an IND

### Section III. C [pages 8-9]

**CCP collected and distributed under an IND (including an intermediate-size population expanded access or single patient IND) must [page 8]:**

- 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\(b\)\(2\)\(vi\)](#)).
- the IND should contain, among other things, adequate information to demonstrate that the plasma will contain SARS-CoV-2 neutralizing antibody titers, if available.
- Accordingly, health care providers or acute care facilities should include information in the IND submission that the investigational convalescent plasma will be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described in section III.C.1 of the guidance in collecting plasma from donors.



#### **III. C. 1 Donor Eligibility criteria for Collection under an IND [pages 8 & 9]:**

- a. Must be collected from individuals who meet all requirements for donor eligibility and testing ([21 CFR 630.10](#), [630.15](#), [610.40](#)) and found suitable ([21 CFR 630.30](#)).
- b. We recommend investigational convalescent plasma is collected from individuals who meet the following qualifications:
  - i. Evidence of COVID-19 documented by laboratory testing in either:
    - 1. Individuals who had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA.**
  - OR
  - 2. Individuals who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have had reactive (positive) results in two different tests approved, cleared, or authorized by FDA to detect SARS-CoV-2 antibodies.**
- ii. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.
- iii. 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.



#### **III. D Recordkeeping under an IND [page 10]**

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)).

## Flowchart 6 –Testing and Labeling of COVID-19 Convalescent Plasma under an IND

### Sections III. C. 2 & 3 of the Guidance [[pages 9-10](#)]

#### III. C. 2 Testing for anti-SARS-CoV-2 Antibodies under an IND [[page 9](#)]

- Plasma donations should be tested for anti-SARS-CoV-2 antibodies to determine suitability before release in accordance with an applicable IND.
- Note: Plasma units that do not qualify as COVID-19 convalescent plasma under the EUA may qualify for investigational use under an applicable IND. The units should be labeled as described in section III.C.3 below.



Registered and licensed blood establishments that collect plasma intended for transfusion do not need to contact FDA or request a supplement to their license, respectively, or obtain their own IND to collect and manufacture convalescent plasma for investigational use provided they:

- 1) follow their standard operating procedures for plasma collection and all applicable regulations, **AND**
- 2) collect plasma from individuals who meet the donor qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.



- Once manufactured, the convalescent plasma may be distributed for investigational use.
- Blood establishments do not need to request an alternative procedure or exception under [21 CFR 640.120\(a\)](#) to collect and distribute investigational convalescent plasma.



#### III. C. 3 Labeling [[pages 9 & 10](#)]

Investigational convalescent plasma must be appropriately labeled.

- a. The container label of investigational 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\(a\)](#)).
- b. 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. FDA recognizes that the current circular of information does not contain specific information about investigational convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.
- c. The investigational convalescent plasma container label must not indicate a license number.
- d. We recommend the use of a uniform container label for investigational 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.
- e. The manufacturing process used and the expiration date on the label for investigational convalescent plasma should be the same as for other plasma products that are of the same type. For example, Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18°C or colder and have an expiration date one year from the date of collection.
- f. Investigational 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.





## EXAMPLE FLOWCHART FOR UPDATED DEFERRAL POLICY FOR VACCINES

### EVALUATING DONOR RISK FOLLOWING VACCINATION:

1) FDA **DOES NOT** have a deferral requirement for vaccines, including investigational COVID-19 vaccines. Apart from the replication-competent small-pox vaccine, FDA leaves donor deferral decisions to the discretion of the responsible physician.

FDA provided the following during the [10/05/20 Live CCP Regulatory Landscape Session](#):

- Would FDA consider 2 weeks as an acceptable deferral period after an individual receives a **live attenuated vaccine**?  
“Yes, that does seem reasonable. Again, this is not our policy per se.”
- Would FDA consider a 2-week deferral as acceptable if a donor received an investigational COVID-19 vaccine but **does not recall which one**?  
“This should be in the hands of the responsible physician for that donor. We do not have a specific policy, as I said, on this.”
- Does FDA believe no deferral period is needed for **non-replicating, inactivated or RNA-based vaccines**?  
“Again, this sounds reasonable, but consultation should really be with that responsible physician.”

### 2) [AABB's Guidance to the Standards for Blood Banks and Transfusion Services, September 4, 2020](#)

- The standard remains at a deferral period of 12 months, unless otherwise indicated by the medical director. With that in mind, the medical director can consider a shorter deferral period for live attenuated vaccines (as short as 14 days).
- For donors who receive non-replicating, inactivated or RNA based vaccines, no deferral may be necessary.

### FLOWCHART FOR AABB's DHQ v2.1:

**Question: 8.** In the past 8 weeks, have you had any vaccinations or other shots?

**Donor Eligibility:** Certain vaccinations may contain live infectious agents. A person who has been exposed to a live infectious agent in a vaccination should not donate for a specified period of time.

**Note on 8alt flowchart:** Some blood centers may choose to use a simpler but stricter deferral scheme in which all donors who received the smallpox vaccination are deferred for a minimum of 56 days, regardless of when the scab fell off. Blood centers using these criteria should use alternative Flowchart 8alt.

