



Advancing Transfusion and
Cellular Therapies Worldwide

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

Updated: September 4, 2020

The Toolkit has been updated based on new information from:

- FDA's September 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

[This Toolkit will be updated as new information is available.](#)

TABLE OF CONTENTS

The flowcharts are intended to:

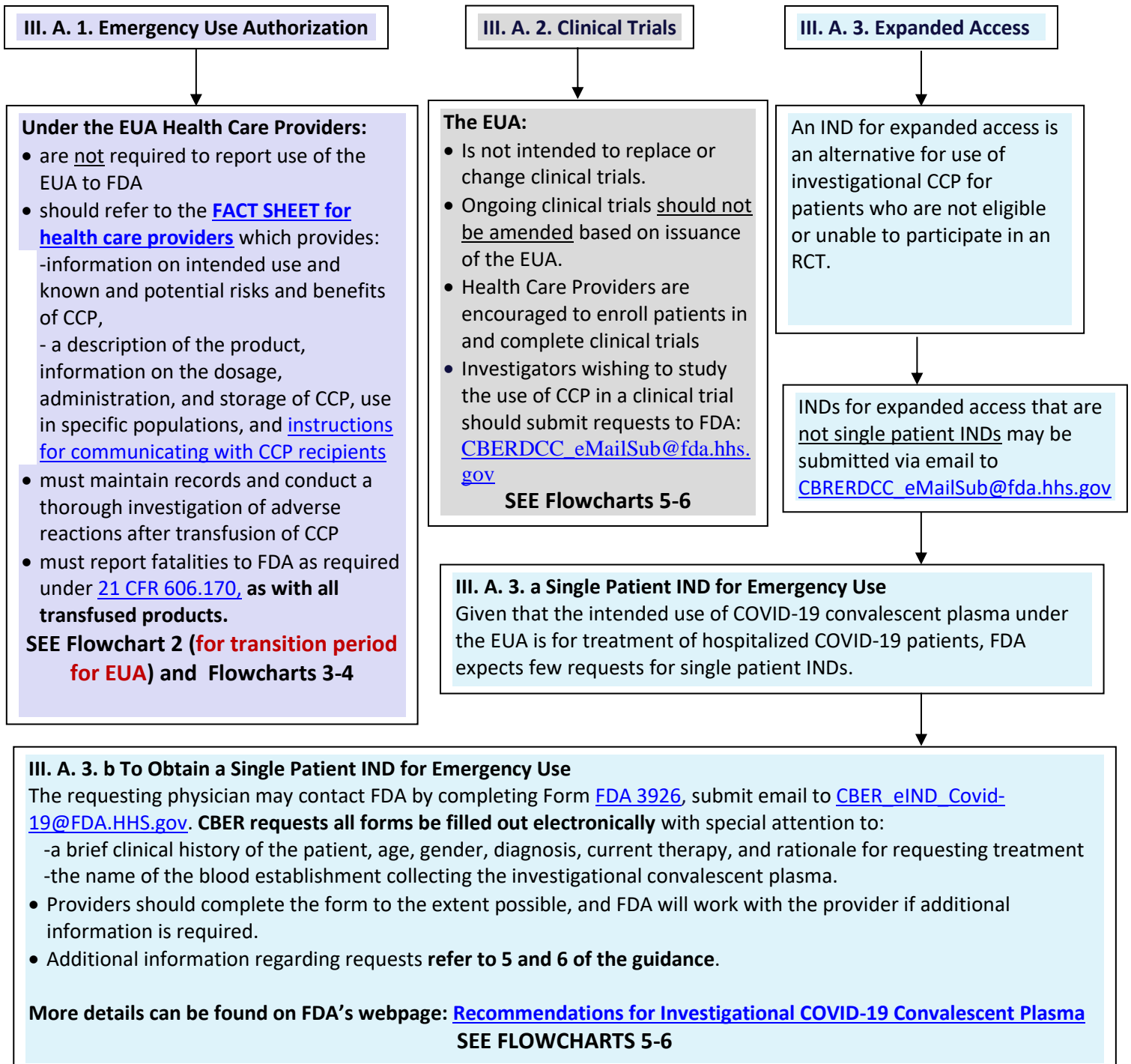
- **supplement but not replace** your review of the [EUA's conditions for use](#) and Sept 2020 [Investigational CCP Guidance](#) for Industry,
- **organize the information on pathways** for use of CCP, and
- **reference the related sections** of the guidance to assist you in finding the details necessary to understand the recommendations from FDA.

Flowchart 1 –Pathways for Use of Investigational CCP Under the EUA	2
Flowchart 2 – 90 Day Transition Period with Temporary Enforcement Discretion	3
Flowchart 3 –Collection of COVID-19 Convalescent Plasma under the EUA	4
Flowchart 4 –Testing and Labeling of COVID-19 Convalescent Plasma under the EUA	5
Flowchart 5 – Collection of COVID-19 Convalescent Plasma under an IND	6
Flowchart 6 –Testing and Labeling of COVID-19 Convalescent Plasma under an IND	7
Questions for FDA on CCP and the EUA from Clinicians and Hospitals, September 2, 2020	8

Flowchart 1 –Pathways for Use of Investigational CCP Under the EUA

Section III of the Guidance

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 – 90 Day Transition Period with Temporary Enforcement Discretion Section IV of Guidance, p11

An IND is not required to collect, distribute, or administer investigational CCP during the 90-day temporary enforcement discretion period. [p11]

Section IV. FDA has decided to exercise enforcement discretion during the next 90 days to permit the collection, shipment, and administration of investigational products that:

1- Were collected **prior to the EUA** OR collected **during the 90-day** enforcement discretion period:

- by registered or licensed blood establishments [Section IV, 3 on page 12]
- from donors who meet all eligibility requirements and qualifications in accordance with section III.C.1 of the guidance. [Section IV, 3 on page 12]
- is labeled as described in section III.C.3 of the guidance. Questions for FDA? Email FDA at CBEROBRRBPBInquiries@fda.hhs.gov [Section IV, 4 on page 12]
- including the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use” ([21 CFR 312.6\(a\)](https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-312/subpart-312.6/section-312.6(a))) [Section IV, 4 on page 12]

AND

2- Do not meet the EUA requirements for [page 11]:

- SARS-CoV-2 antibody testing by Ortho IgG
- Qualifying and labeling the unit as high titer or low titer

For the treatment of hospitalized patients with COVID-19
(There are no additional patient eligibility criteria) [Section IV, 1 on page 12]

Investigational CCP is transfused to hospitalized patients with COVID-19 **only if the health care provider obtains adequate informed consent** [Section IV, 2 on page 12]

- 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 (page 8 of this Toolkit, Q6 and Q20 on the FDA Q&A) that Fact Sheets provided in the EUA:

- are NOT intended for use during this 90-day period and
- are only intended for use with the EUA CCP.

Report adverse reactions following transfusion as for any blood component.

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

Section III. B. 1. of the Guidance

Section III. B. 1 CFP 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 Conditions for Authorization in the EUA. Refer to Section III which begins on page 4 in the [Letter of Authorization*](#) for the Conditions of Authorization for registered and licensed blood establishments.

AND you must [III. B, page 6]:

- 1) follow your standard operating procedures 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

DO NOT NEED TO:

Contact FDA or request an alternative procedure or exception under 21 CFR 640.120(a) to collect and distribute COVID-19 convalescent plasma for authorized use under the EUA. [III. B, page 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

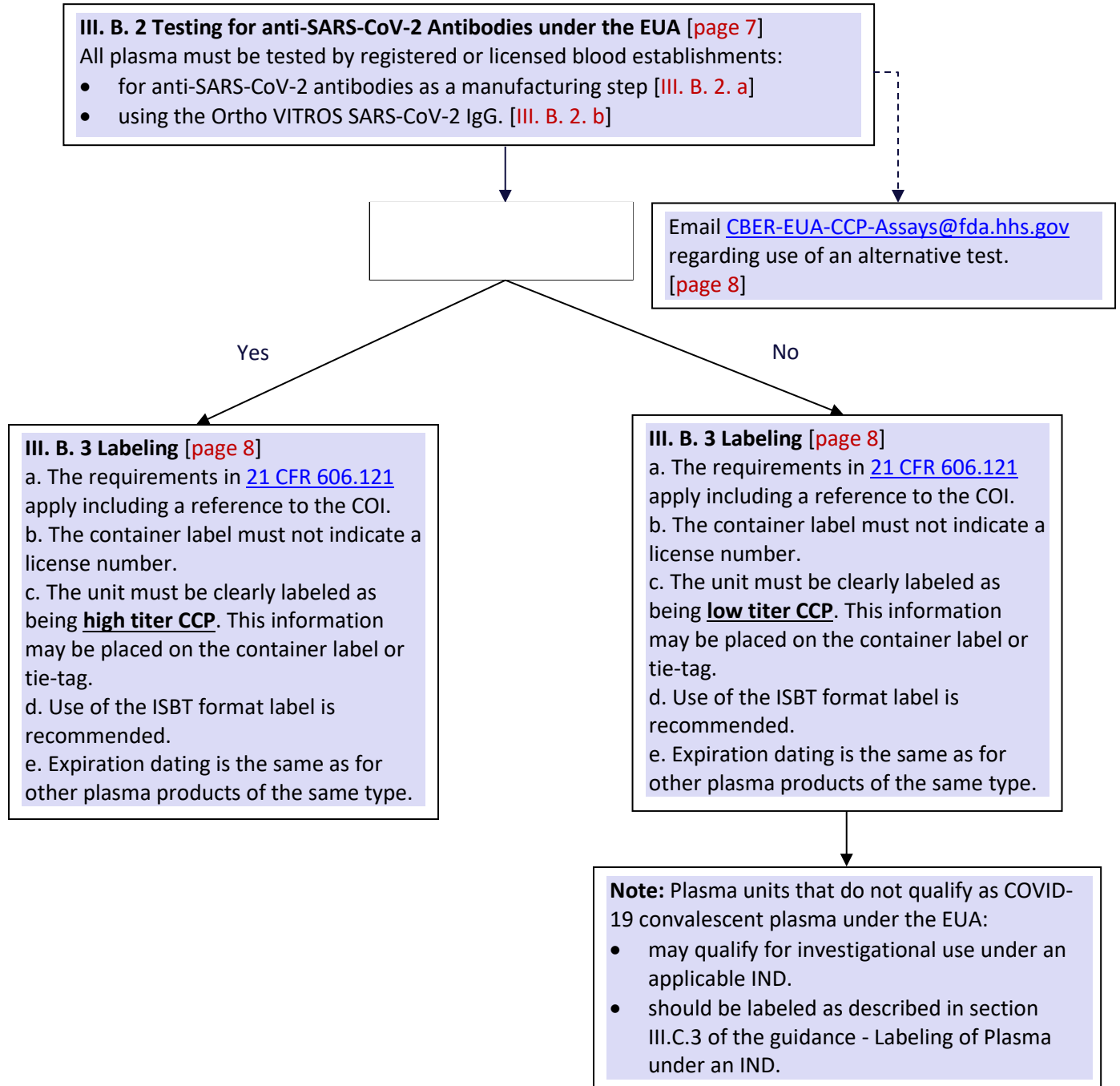
a.2. Individuals who did not have a prior positive diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have had reactive (positive) results in two different tests approved, cleared, or authorized by FDA to detect SARS-Cov-2 antibodies.

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.

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

Section III. B. 2 of the Guidance



Flowchart 5 – Collection of COVID-19 Convalescent Plasma under an IND Section III. C of the Guidance

CCP collected and distributed under an IND (including an intermediate-size population expanded access or single patient IND) must [page 9]:

- 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 9 & 10]:

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 11]

A health care provider who is participating in an IND, including an expanded 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

III. C. 2 Testing for anti-SARS-CoV-2 Antibodies under an IND [page 10]

- 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 10 & 11]

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.

Questions for FDA on CCP and the EUA from Clinicians and Hospitals, September 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-going analysis of data, efficacy, and reporting under the EUA

- 1) The EUA Fact Sheet for health care providers mentions a risk-benefit assessment - Is FDA still reviewing data on efficacy and will there be more information for physicians treating COVID patients?
 - *The standard that is required for FDA to use an EUA requires that a product “may be effective” for its intended use.*
 - *As additional data comes in, FDA will continue to look at the risk-benefit assessment.*
 - *FDA will consider amending the EUA if new data is substantially different.*
- 2) What patients can receive these units? (Hospitalized and COVID+ test, I assume) and how early should CCP be given?
 - *FDA does not have data on non-hospitalized patients.*
 - *There are several clinical trials ongoing.*
 - *Did not exclude intubated patients in the EUA from being treated.*
 - *FDA cannot make recommendations because institutions have different bars set for intubation hospital admissions.*
- 3) When should hospitals and physicians provide information to recovered patients to suggest they consider donating? What donor information would be given to a patient?
 - *Based on information from New York City, at the time of discharge is the best time to provide information about donating convalescent plasma to a patient who is doing well.*
 - *The same would be true when discharged from outpatient care.*
- 4) Does FDA have reporting requirements under the EUA that are similar to the EAP?
 - *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.*

Special Considerations during the transition to full implementation of the EUA

- 5) 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 for investigational CCP until more EUA CCP can be provided?
 - *No relabeling or testing is required.*
 - *Refer to Section IV, pages 11 & 12 and Flowchart 4 of this Toolkit.*
- 6) If so, are there additional requirements for investigational CCP such as retesting and relabeling or patient consent?
 - *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 does not meet the requirements of the EUA.*
 - *Refer to Section IV, pages 11 & 12 and Flowchart 4 of this Toolkit.*
- 7) Will research consent and IRB permission be needed for pre-EUA units?
 - *During the EUA there is not a specific research consent.*
 - *During the enforcement discretion period, FDA is not requiring IRB oversight.*
- 8) During the 90-day transition period, can an untitered unit still be transfused?
 - *Answer as regulators: This is the reason for having a period of enforcement discretion when you can use untitered units while you get titring in place. Work to use that inventory in the next 90 days.*

- *After 90 days, those investigational units could be used under an IND, but FDA is giving this enforcement discretion period, so they do not have to be under an IND.*

Testing

- 9) Why does FDA require the Ortho VITROS IgG test for the titer?
- *Had to use a methodology that could adequately distinguish high titer vs. low titer.*
 - *And had to use available data - the Ortho IgG. Not wedded to it.*
 - *This test is involved in manufacturing but not reported to patients, FDA has a little latitude in how it's conducted.*
- 10) Does FDA require a CLIA lab to perform the Ortho testing?
- *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.*
- 11) 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?
- *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.*
- 12) One institution that is using the Ortho Total – Does it correlate with the Ortho IgG test required by the EUA?
- *Not perfectly. Not the same titer cut off. It's one of the first ones FDA is looking at.*
 - *Trying to determine a titer cut off that correlates with the current one. Expect to hear more in the coming weeks.*

Other comments from FDA on Testing

- *If validating your own assay, FDA will require validation data.*
- *Rather than validate your own assay, it might be easier than if you can use Ortho VITROS test or use one of the larger labs.*
- *FDA may have a list of assays that meet the EUA criteria – check with FDA to see if your test is on the list.*
- *If not on the list, you will have to decide if you want to go through the validation process for your assay.*

Labeling, Titer and Dosing

- 13) Do we need the actual result from the Ortho assay on the label or will it simply say “high titer” or “low titer”?
- *For labeling, actual result from the ortho assay do not need to be on the label. Label as high titer or low titer.*
- 14) Once we have units labeled under the EUA, are two low-titer units equivalent to one high-titer unit? If administering two low titer units, what should be the timing of the two transfusions? Is there a recommended dose/kg? Should we consider patient EBV when working with an inventory of both low titer and high titer units to maximize the benefit to the patient? Under what circumstances should we order more than one high titer unit per patient?
- *FDA does not have those specific recommendations.*
 - *If you are giving two low titer units to achieve a higher titer, it's probably reasonable to give both units at the same time to try to accomplish that because giving CCP sooner is better than giving later.*
- 15) Is there any word on the additional E codes for the titered products?
- *Yes – FDA has received news that the high titer and low titer codes are up on the ICCBBA web site.*

Inventory Management

- 16) 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 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.*
- 17) 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?

- *Discuss this option with FDA if you would like to consider this change in your policy.*

Treating other patient populations

- 18) Can the EUA be used for pediatric patients? For pregnant women? Where can we find data to guide our decisions?
- *There is language in the EUA and health care provider letter to allow for treatment of pediatric patients, pregnant patients.*
 - *EUA says individual health care provider must make the decision based on a risk-benefit determination for each patient.*

Consent during the Transition Period and under the EUA

- 19) If the hospital uses the EAP consent form during affirmation of informed consent will that be a problem?
- *Would not recommend using a specific EAP consent form.*
- 20) Is it acceptable to use our standard transfusion consent form that we would use for FFP and add COVID-19 Convalescent Plasma?
- *Yes, during the transition period, add to the consent form that the patient will be receiving an investigational product.*
 - *The EUA Fact Sheets should not be used in consent for CCP collected and transfused during the transition period because it does not meet the requirements of the EUA.*
- 21) Does FDA have Spanish language Fact Sheets available?
- *Not yet but FDA is in the process of reaching out – may be available soon.*

Randomized Clinical Trials

- 22) Use of EUA or support RCT?
- *The hospital makes the choice about what to do for its patients including how to use the EUA and alternative treatment.*
 - *Check with your IRB.*
- 23) How can we find more information on current trials?
- *Go to www.clinicaltrials.gov and COVID-19 convalescent plasma*

Reimbursement and billing

- 24) Is there a price difference between high and low titer plasma?
- *Not anticipating that.*
- 25) Does FDA anticipate any disruptions to supply as a result of the changing reimbursement picture?
- *No, BARDA has committed to work through this.*