Overview of EUA for CCP
Updated 08 28 2020, 315 pm

This document is:
✓ intended to assist AABB members until an FDA guidance for the EUA is available.
✓ an overview of:
  o EUA Requirements from the Letter of Authorization.
  o Comments from FDA on August 26, 2020.

I. TRANSITION TO EUA – Based on the August 26th comments from FDA
AABB expects FDA to issue a formal communication in the very near future with more details on the timeline. The following is what we know to date:

A. Timeline for implementation of the EUA
FDA is comfortable that this product may be effective for the intended use and would like to help with operational aspect work.
FDA understands that the CCP EUA will require time to make significant changes in:
  • Antibody testing
  • Labeling
  • Inventory systems and BECS validation to handle new labeling requirements for high titer-low titer
FDA is providing a transition period of a few months to fully implement the EUA.

B. FDA’s plan to ensure continued patient access to CCP while the blood industry transitions to EUA CCP product.
During the transition period described in #1 above, FDA will allow for the use of unttitered investigational convalescent plasma at the same time centers will be using convalescent plasma under the EUA.
  • FDA is working on communications to provide Information regarding the transition period - and the agency’s expectations as you provide CCP to patients during the transition to the EUA.
  • FDA believes this is a reasonable path to:
    1. Address current CCP inventories collected under the EAP, without the need to “rework them.”
    2. Prevent a shutdown of the current system by permitting the use of the current inventory of unttitered investigational CCP with consenting patients.

C. Distribution of current inventory of investigational CCP, collected and labeled under the EAP
During the transition period, investigational convalescent plasma:
  • May be distributed without the titer.
  • Is still subject to the all donor eligibility criteria described in the May 1, 2020 guidance.
  • Can be transfused to patients if the hospital ensures the patients understand they are not receiving the EUA product and consent to receive a unit of unttitered plasma.
  • Hospitals may use the EUA Fact Sheet for Patients for some of this information but must make it clear that the patient is receiving an investigational product and not the EUA product.
  • FDA will provide more information on consent after discussions with FDA’s Chief Counsel.
    They are actively discussing the process of informed consent during the transition period.
FDA confirmed that an IND is not needed for investigational CCP collected under the EAP and transfused during the transition period to full implementation of the EUA.
This approach was used in the past with fecal microbiota transplant and FDA will consider a similar approach for CCP where use of an investigational product will be allowed without an IND.

FDA believes this is well justified during this public health emergency.

Other questions on investigational CCP and the EAP

Will results of samples sent to Mayo and Mount Sinai be reported back to blood centers and is there on-going data collection under the EAP?

FDA: They are in the process of getting that data together.

- There is ongoing data collection for the EAP.
- It is very important to continue to report data to the EAP in order to get to robust statistical significance.
- FDA noted the EAP is missing 7-day data on a number of patients and also data at 30 days. Getting those data in will be very helpful.
- FDA hopes that, with 100,000 patients in the Mayo Clinic EAP program, there will be more data on efficacy and correlation of the titers.

What should centers do with retention samples that have not been tested?

FDA: Mary Homer and BARDA will, through Mayo, contact centers that are still holding retention samples for titer testing.

Impact on FDA Approved INDs - Does the transitional pathway apply to a product collected under an RCT or a clinical trial or just to investigational CCP collected under the EAP?

FDA: The transitional pathway applies only to products collected under the EAP. Other products collected under a Randomized Controlled Trial (RCT) will continue to be used in an investigational way as provided by the RCT.

II. REQUIREMENTS OF THE EUA FOR CCP

A. 1-SARS-CoV-2 Antibody Testing under the EUA

EUA Section II. Scope of Authorization (Product Description) on page 3 states:

- 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.

Comments from FDA

Use of alternative testing such as Ortho Total IgG or another testing methodologies:

- FDA is performing some of this work using titer comparisons of different methodologies.
- Individual manufacturers may also contact the Office of Blood with data for a given system. FDA will provide the expectations for the “test in manufacturing.”
- The ultimate goal being to amend the EUA, before the period of transition ends, to expand the number of testing methodologies available for the test in manufacturing.
- These serologies tests are more complicated, possibly due to the complexity of the S protein, or other things.

Qualifying CCP donors from the general donor population without a documented history COVID infection

- FDA is comfortable with the use of two independent antibody assays, that have authorization through CDRH, as a pathway of collecting donors who do not have a documented history of COVID-19.
- Two separate tests are performed. The first is essentially the diagnostic test and the second is the confirmatory test.

Do orthogonal assays need to be directed toward different proteins/epitopes?:

FDA:

- You may do two orthogonal assays such as one toward S and one toward N.
- The titer is going to be driven off of the S protein.

What percentage of collections are likely to be labeled as high titer?
FDA: This is dependent on assay methodology but it seems to be about 60% high tier/40% low titer.

What is the titer of ORTHO IgG at a S/C of 12?

FDA: Somewhere in the 1:320 and 1:640 range. Many have extremely high titers.

B. Donor qualification and collections

EUA Introduction, 3rd paragraph on page 1 states:

- 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.

The same information is repeated as part of the product description in EUA Section II. Scope of Authorization (Product Description).

Comments from FDA

CCP Collection frequency?

FDA: Collection of CCP more frequently than every 28 days, such as weekly, is at the discretion of the medical director.

Eligibility as CCP donor after receiving CCP as a patient: Deferral is currently required.

FDA: Will discuss and get back to you.

Can CCP be collected from donors who have received an experimental CCP vaccine?

FDA: No. The Office of Blood and the Office of Vaccines are both in agreement on this.

*Refer to the August 7th Regulatory Update for more information of investigational vaccines and donation.

Does the qualification of the donor need to occur for each donation?

FDA: The collection center must keep on record the criteria that qualified the donor for CCP donation. If it is on record then they are qualified.

Is it necessary to perform a titer on each collection from the same donor?

FDA: Yes, every collection.

If a center plans to implement COVID-19 collections under the EUA and is not licensed for a specific apheresis technology, what is required?

FDA: Contact your CSO directly to see if additional approvals are needed to collect CCP. It may or may not be possible.

C. Requirements for Titer, Labeling, Storage, and Distribution under the EUA

EUA Section II. Scope of Authorization, Product Description, on page 3 states:

- 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.

AABB notes that the EUA:

- Only references testing necessary to qualify units as high-titer.
- Only references labeling units as “low-titer” if not qualified as high titer when tested, as quoted in the first bullet in this section, but the EUA does not mention a requirement to label high-titer units as mentioned during the call with FDA.

AABB expects an FDA guidance will clarify labeling and will seek additional information in the interim.

EUA Section III. G. states on page 5:

“G. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18℃ or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.”

Comments from FDA

- FDA will clarify in the future the labeling requirements under the EUA.
• The signal to cutoff (S/C) ratio may be included on a tie tag if desired, but in order to meet the labeling requirements of the EUA the component must be labeled as either high or low titer as described in the EUA. The S/C cannot be used to replace the titer.
• Reporting out a specific S/C value for a test that is considered part of the manufacturing process for CCP differs from a test that provides information to the donor. In terms of reporting out an S/C value, it may go on the unit but there is currently no approval to provide the S/C value to a donor. This is a very important distinction.
• CCP collected and manufactured by licensed and registered blood centers may be shipped across state lines.
• Export out of the U.S. and its territories: FDA believes there will be an export certificate issued.
• It is acceptable to convert CCP to FFP if the titer is too low.

ISBT Codes – what will be required?
• Yes, there will be additional ISBT 128 codes coming
• There will be separate codes for high titer and low titer

Can we default label as low titer until we have further detail on testing?
• No. Under the EUA the thought is that you need to use the EUA authorized test as part of manufacturing (Ortho IgG test). If you are not using this test, contact FDA to discuss alternative assays you are interested in using.

Pooling of CCP to increase high titer inventory?
• Pooling is not allowed at this time.
• This is a manufacturing step and there are concerns for contamination among other considerations.
• In the past, FDA has considered pooling and pathogen reduction to be manufacturing.

Extending the outdate of CCP beyond 12 months?
• This is not something that has not been discussed to date but will be taken under consideration.

D. Fact Sheets Required by the EUA

EUA Section II. Scope of Authorization, on page 4 states:
“COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:

EUA Section III. Conditions of Authorization, Registered or Licensed Blood Establishments, on page 5 states:
“F. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.”

EUA Section III. Conditions of Authorization, Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma on page 6 states:
“J. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.”

Comments from FDA
• The EUA Fact Sheets may be provided using electronic on-line printable versions.
• FDA will discuss Spanish translations of the Fact Sheets with BARDA. FDA is actively looking into way to make that happen.
• The hospital would be responsible for making the Fact Sheets available to Healthcare Providers and Patients after the information is provided by the blood establishment as required in the EUA.

E. Patient Criteria, Dosing, and Pediatric use of CCP

Section II of the EUA describes the scope and states:
The emergency use of the authorized COVID-19 convalescent plasma under this EUA must be consistent with,
and may not exceed, the terms of this letter, including the scope and the conditions of authorization set forth below.”

AND:

“Clinical dosing may first consider starting with one COVID-19 convalescent plasma unit (about 200 mL), with administration of additional COVID-19 convalescent plasma units based on the prescribing physician’s medical judgment and the patient’s clinical response.”

AABB encourages Healthcare Providers to carefully review the important information the Fact Sheet, including critical information on the intended use, dosing, patient populations, risks and benefits.

EUA Fact Sheet for Health Care Providers, Use in Specific populations on page 4 states:

“Pediatric Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population has not been evaluated. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.”

Comments from FDA

• Pediatric patients are not covered in the EUA – FDA cannot provide specific dosing recommendations for pediatric patients because there is no data from the EAP for pediatric use.
• FDA is allowing use of the EUA product for hospitalized patients and that can include pediatrics.
• FDA has added into the language in the EUA that there needs to be an additional benefit/risk determination made by the patient’s health care provider.
• Titered units can be used for pediatric patients.

Change in patient eligibility criteria?

• The May 2020 guidance criteria do not apply under the EUA.
• The EUA is for hospitalized patients with COVID-19 and the criteria are different from the indications outlined in the May 2020 guidance.

Considering an Outpatient EUA?

• This would require data to support the EUA.
• There are multiple studies and a large study at NHLBI. Pending the results of these studies FDA does not anticipate expanding to an outpatient EUA for convalescent plasma.

F. Reporting and Recordkeeping Required by the EUA

EUA Section III. Conditions of Authorization, Registered or Licensed Blood Establishments, H-I on page 5 states:

“H. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).
I. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.”

EUA Section III. Conditions of Authorization, Hospitals to Whom the Authorized COVID-19 Convalescent Plasma Is Distributed, and Health Care Providers Administering the Authorized COVID-19 Convalescent Plasma on page 6 states in L-N:

“L. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.
M. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).
N. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.”
Comments from FDA

- With the EUA, collection of additional efficacy data is no longer needed.
- Ongoing patient reporting is not required under the EUA beyond the usual serious adverse event reporting.
- Under the EUA, CCP would be treated as if it were any other blood product.
- Blood centers are not required to notify FDA of the implementation of a CCP collection program under the EUA.

G. Advertising and promotional material under the EUA

The EUA Section III, Conditions Related to Printed Matter, Advertising, and Promotion, page 6 states:

- 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 applicable requirements set forth in the Act and FDA regulations.
- 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.
- 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:
  - COVID-19 convalescent plasma has not been approved or licensed by FDA;
  - COVID-19 convalescent plasma has been authorized by FDA under an EUA;
  - 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.

Comments from FDA

Do flyers and social media need to include all of the language in the EUA?

Use your judgement and contact FDA with any questions.