

The background of the slide features a stylized world map in shades of blue and green. A network of thin grey lines connects various geographical locations across the map, with several nodes highlighted by red starburst icons. The map is partially obscured by a green horizontal band at the bottom.

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COVID-19 Convalescent Plasma

The Regulatory Landscape

October 5, 2020

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Faculty Disclosure

We have no financial disclosures:

*In compliance with ACCME policy,
AABB requires the following
disclosures to the session audience*

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Objectives

- Describe the approach to the regulation of CCP under the Emergency Use Authorization (EUA)
- Describe FDA's current recommendations for antibody titer testing, labeling, and inventory management
- Describe FDA's use of temporary enforcement discretion during the transition to the EUA

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LIVE PRESENTATION WITH Q & A

We invite you to add questions to the CHAT



CCP Regulatory Landscape

By the numbers...

- **46** Traditional INDs
 - 53 Protocols, 3 pediatric
 - Approval time for most 48 hours
- **14** Expanded Access Programs
 - Mayo EAP largest. At time of discontinuation over 105,000 patients were enrolled from over 2,700 sites.
- **6000+** eINDs

*And now...**EUA** approved on August 23, 2020*

Dr. Verdun:

Thank you everyone. I just would like to start by saying thanking you for the partnership throughout this pandemic. FDA clearly appreciates the partnership. I going to go through the CCP regulatory landscape by the numbers because it has been quite a time since this pandemic started.

In general, by the numbers, we have approved 46 traditional INDs. Within those 46 INDs, we have 53 protocols that we have approved, and 3 that include pediatric patients. There's one trial that goes up to age 22 but, of those 53 protocols, I thought it was prudent to point out that 3 are in pediatrics.

The approval time for most of these INDs as been 48 hours. We have really tried to step up and to respond to this pandemic and to the acuity of things going on. As you know with traditional INDs normally we have a 30 day clock, and we have been able to turn these around in 2 days.



Dr. Verdun continued:

In addition, we have had 14 expanded access programs. And as many of you know, the Mayo Expanded Access programs has been the largest. At the time of discontinuation and in conjunction with the approval of the EUA, in terms of timing, over 105,000 patients were enrolled from over 2,700 sites. This expanded access program allowed for the use and distribution of convalescent plasma considering the acuity of this pandemic. I just want to underscore the amount of sites we were able to have access to products and we thank you all for that partnership.

In addition to this heavy lift, we approved 6000+ emergency INDs and many of those were approved within an hour, and most of them. That was again a heavy lift for our team, but partnership with you it provided access to convalescent plasma for the United States at a time when there are not a lot of therapeutics available.

Now we have an EUA for CP which was approved on August 23, 2020.

We will move to the questions (slide 20) and come back to these slides when Dr. Marks arrives.



Emergency Use Authorization (EUA)

- Put in place after 9/11 to ensure that potentially lifesaving medical products could be available to people in medical need when there is not an approved and available alternative
- The standard used is that the product “may be effective” and its “known and potential benefits outweigh the known and potential risks”

Dr. Marks:

[Dr Marks comments below start at approximately 27 minutes into the program – please skip to slide 20 now.]

We recently did a relook at the EUA. Part of the law for the Emergency Use Authorization is that at intervals FDA goes back and looks at the data to make sure there is continuing data supporting an emergency use authorization. We did that and that has been posted on our website. The same site that has the information for the EUA for convalescent plasma. There's an update that's dated September 23rd where you can find additional information. I'll just summarize that for you here.

The EUA was put in place as a pathway. For those of you who aren't familiar, Emergency Use Authorization was put in place after the terrorist attacks of 9/11 to ensure that potentially lifesaving medical products in the chemical, biological, radio nuclear area would be available to people in medical need when there is not an approved and available alternative. It was assumed that for some of these you might have products that had been not fully developed because they would be difficult to develop in the absence of those emergencies.

The standard that was used, rather than our conventional standard, which is substantial evidence of effectiveness from adequate and well controlled trials, is a lower standard. It is the standard that



Dr. Marks continued:

the product “may be effective” and it’s “known and potential benefits outweigh the known and potential risks.” That gives us a fair amount of latitude. In fact, we will use that latitude because for treating patients who are sick with a disease, “may be effective” on the lower end of things, in terms of evidence, might be very reasonable, but when you are using a prophylactic vaccine you might want something more than just getting over the bar. So it does give us some latitude here which is helpful. But lets stick with convalescent plasma for the moment. If we go to the next slide...



Expanded Access Program Data

	7-day			28-day		
	Overall (N=4330)	Not Intub (N=2488)	Not intub, ≤80 y, ≤72 h (N=932)	Overall (N=2817)	Not Intub (N=1238)	Not intub, ≤80 y, ≤72 h (N=485)
Deaths Lower Titer	14.97%	13.99%	11.29%	49.57%	49.43%	46.63%
Deaths Higher Titer	13.61%	11.00%	6.27%	46.21%	41.48%	33.23%
Absolute Improvement	1.36%	2.99%	5.02%	3.36%	7.95%	13.40%
Relative Improvement	9%	21%	44%	7%	16%	29%
Statistical Significance	Not significant	Significant p=0.03	Significant p=0.008	Not significant	Significant p=0.004	Significant p=0.004

Dr. Marks continued:

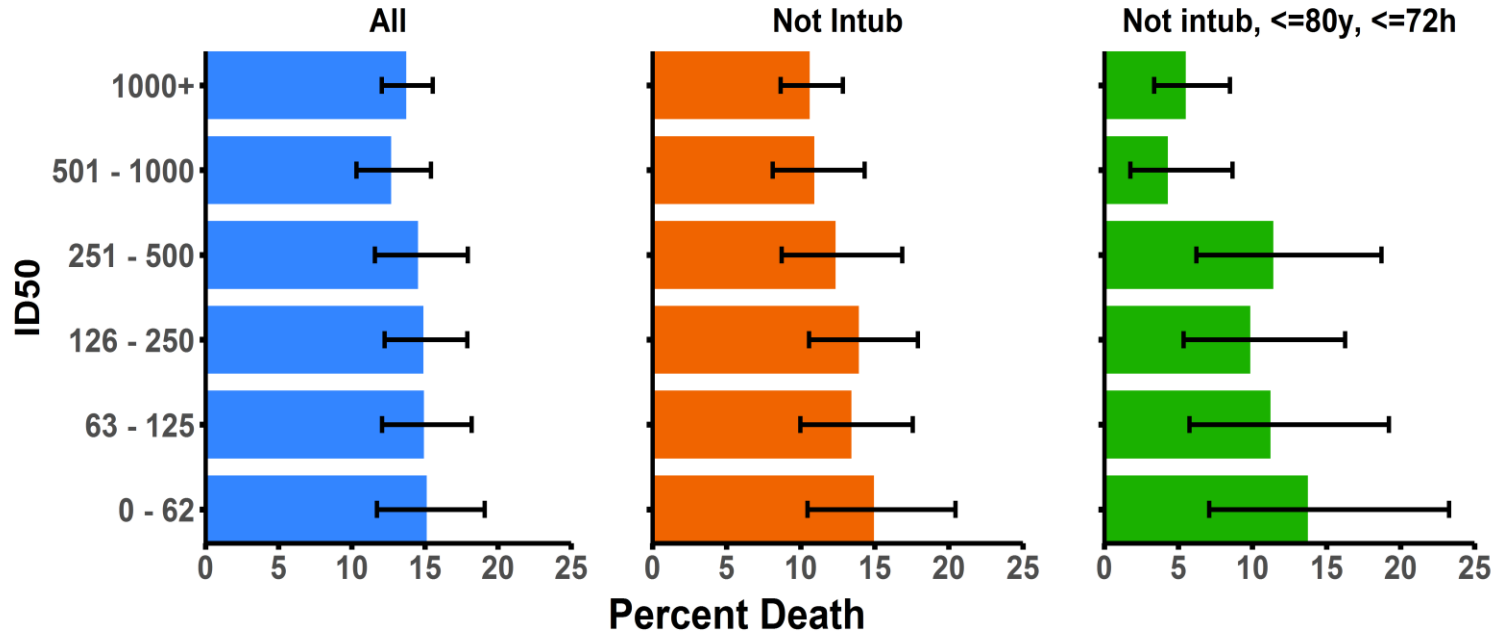
The data, just looking at the expanded access program data, we cleaned up the data. Using data from a titer methodology that we have reasonable confidence in, which is a neutralization assay that was performed in a BSL 3 lab using live virus, where we think this is kind of a gold standard assay, if you look at the data from over 4000 patients, and you look at the various subsets including the planned subset that we looked at of patients who were non-intubated, and a group that we looked at essentially with a post hoc analysis of non-intubated patients, less than or equal to 80 years of age, who were treated within 72 hours, you can see that those are kind of subsets of one another. If you look at the overall population of 4330 patients treated at 7 days, there was not a statistically significant difference in the survival or improvement and survival at 7 days, nor at 28 days in the subset of patients who were still hospitalized at 28 days. By the way, just to make it clear, the numbers you are seeing here are patients who were remaining in the hospital at 7 days and at 28 days. Because of the way the study was done, we have a very limited amount of information on patients who were not in the hospital and that's not included in these numbers here. If you look at 7 days and 28 days for the overall population, no significant differences. But, in the non-intubated patients, either at 7 days or at 28 days, there were statistically significant improvements in 7-day and 28-day survival. This is



Dr. Marks continued:

kind of interesting because if you were treated early on, you still seemed to have some benefit out late. If you look in terms of absolute improvement, obviously absolute improvement number is small. At 7 days it's about 3%, 28 days it's close to 8%. If you look at the relative values it's 21% at 7 days and 16% at 28 days. If you look at this subset of patients who were treated with higher titer plasma versus lower titer plasma, and that's what the difference is here, I should have mentioned that, if you look at the difference between higher titer plasma and lower titer plasma, in the non-intubated patients, there you start to see a more significant difference. At 7 days you have a 5% absolute improvement in survival, which translates into a 44% relative improvement. Relatively statistically significant and that holds out even at 28 days. So in patients who were obviously much sicker, probably, because they're still in the hospital at 28 days, you have 13% absolute improvement and a 29% relative improvement. Again, showing that at least here, although we don't have a randomized trial comparing high titer plasma to no plasma, if you compare high titer plasma to low titer plasma, you saw these apparent benefits. We'll go to the next slide which actually does give you something closer to that...

Hospitalized Patient Outcome at 7d

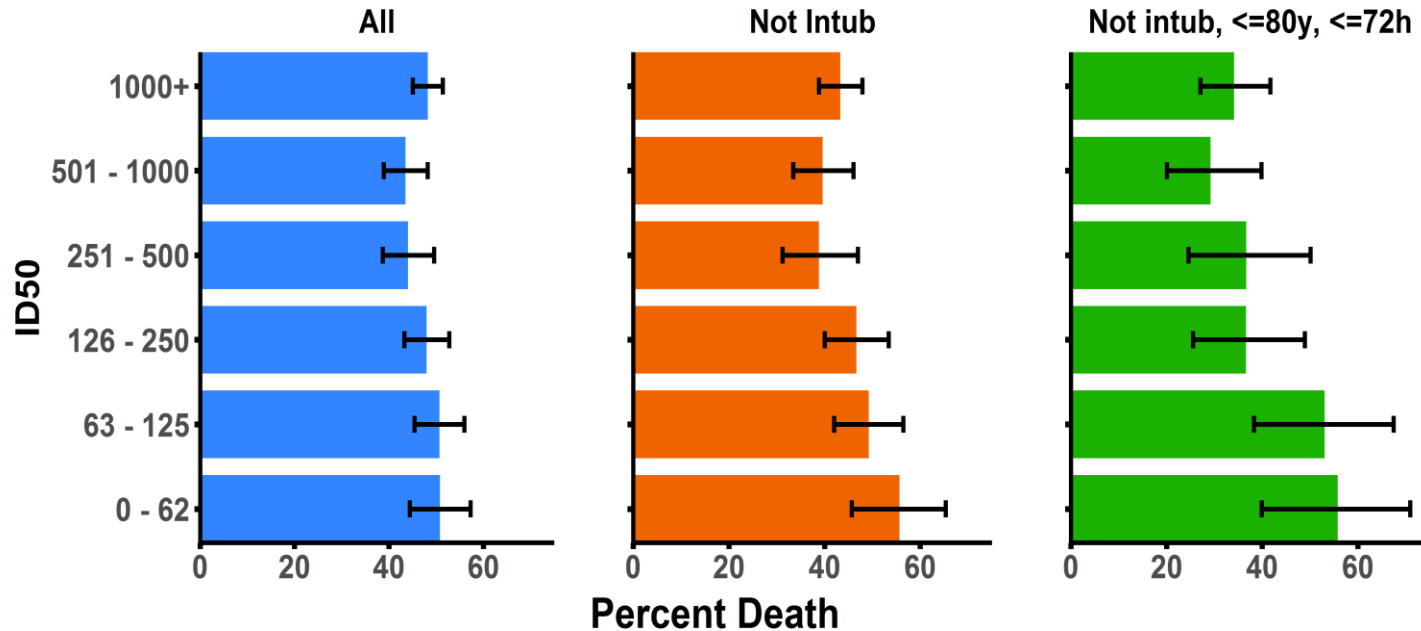




Dr. Marks continued:

Using the Broad assay, although 0 to 62 is not nothing, those are the lowest titers and 1000+ at the top, those are the highest titers. If you break down the titer ranges here onto buckets, you can see that there doesn't seem to be any major dose response. It's trending in the right direction but there's no major dose response in the overall population at 7 days in terms of going to higher titers. There is a dose response apparent at 7 days in the non-intubated patients. That dose response is more marked when you look at this group of patients who were non-intubated, less than or equal to 80 years of age and treated within 3 days of presentation. If you go to the next slide just to show that that holds at 28 days.

Hospitalized Patient Outcome at 28d





Dr. Marks continued:

You see that same trend, that's not statistically significant in the overall patient population, but the trend becomes statistically significant in the non-intubated and in the non-intubated patients less than or equal to 80 years of age and are treated within 3 days. Again, just to graphically show you this. I find these graphs reassuring in some ways because dose response is one of the things that we do consider at FDA to be an element of a well controlled trial. To me, it indicates that what we are looking at is a real effect here. Next slide...



Summary of Exploratory Efficacy Data

- Data suggest modest survival benefit of COVID-19 convalescent plasma at 7 and 28 days
 - Higher titers more effective (at least 1:320)
 - Early administration optimal (≤ 72 hrs after diagnosis)
- To be confirmed by prospective analysis of titers and outcomes in ongoing randomized clinical trials

Dr. Marks continued:

Summarizing here, data suggests that there is a modest survival benefit of COVID-19 convalescent plasma at 7 and 28 days. We know that higher titers are more effective. If you look at the traditional titering methodology it's at least 1:320, probably more like 1:640 or higher is best. Early administration seems to be optimal, less than 72 hours after diagnosis. We do realize though, that it really would be helpful to have a prospective analysis of titers and outcomes in ongoing randomized clinical trials. Those outcomes will be really helpful.

What I will just say here is that if you take everything together, when you look at the data here, we feel that the known and potential benefits still outweigh the known and potential risks. So the EUA continues at this time. We will have additional data analysis performed in the next month, with a larger number of samples. Something I know has been an issue is that blood donor centers have wanted to get their results. Not necessarily the outcomes, but at least know the range of titers that they collected from the donors. We are working on getting a list of donor identification numbers and titers that can be distributed back to the collection facilities. It's taking a little longer than originally expected. They are working on it and having to go through the database and make that happen.

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?

Testing under the EUA

FDA Response to Q1 & 2 - Dr. Verdun: Thank you for those two questions. We do hear those a lot so I appreciate you starting with those. 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. The process is that if there are centers interested in using other assays for use in this EUA to determine and qualify convalescent plasma, please contact FDA. We do have several manufacturers that are interested and currently going through that process. We are committed to, once we have the data in house, reviewing that data and making a determination about whether those can be added.

To answer the question specifically, there is one test now, however we anticipate there will be several more tests available as the data comes into FDA and as it is reviewed.

Testing under the EUA

FDA Response to Q1 & 2 - Dr. Verdun continued: We do understand the transition period is 90 days and we understand that several people feel that is might not be adequate. We will continue to reevaluate the status of things and where we are. As you know we have been very flexible throughout this entire process and will continue to do so. We certainly not want to have the discard of convalescent plasma and recognize the operational changes that are involved for coming into compliance with the EUA. And potentially if we add additional tests that will also require some additional changes in operations.

To this question, I say we remain flexible and if you have additional questions as this transition period moves on, please contact us.

Testing under the EUA

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?
- What would prohibit retesting and relabeling if the product meets all EUA criteria?
 - The same questions apply for CCP that qualifies for shipment to the National Surge Capacity Storage and what would prohibit the shipment?
 - How can a blood collection center utilize a variance for retesting and relabeling to avoid the discard of CCP that would qualify when antibody titer testing is in place?

Testing under the EUA

FDA Response to Q3 - Dr. Verdun: 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.

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.

Titer Testing and Donor Eligibility

4. 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?

Titer Testing and Donor Eligibility

FDA Response to Q4 - Dr. Verdun:

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 systems 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. I know this piece and the separation for qualifying the donor and qualifying the unit can be a bit difficult.

INVESTIGATIONAL VACCINES AND BLOOD DONATION

5. 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?

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

- Does not require an automatic 12-month deferral for investigational vaccines?
- Would consider 2 weeks as an acceptable deferral period after an individual receives a live attenuated vaccine?
- Would consider a 2 week deferral as acceptable if a donor received an investigational COVID vaccine but does not recall which one?
- And FDA believes no deferral period is needed for non-replicating, inactivated or RNA-based vaccines?

INVESTIGATIONAL VACCINES AND BLOOD DONATION

FDA Response to Q5 - Dr. Verdun: It sounds like this first question [Q5] is for the routine blood donor and our next question [Q6] is specifically for investigational COVID vaccines.

Does not require an automatic 12-month deferral for investigational vaccines? 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.

Would 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 perse.

Would consider a 2 week deferral as acceptable if a donor received an investigational COVID 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.

And FDA believes 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.

INVESTIGATIONAL VACCINES AND BLOOD DONATION

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

FDA Response to Q6 - Dr. Verdun: At this time, we don't recommend the use of CCP donors who have received an investigational COVID vaccine. Dr Marks, I will let you jump in here if you want to add anything as to the why.

Dr. Marks: I think at this point we really are not sure – we have the data right now from people who have had COVID-19 who have developed antibodies. They have developed antibodies against the full surface complement of proteins and other molecules that are on COVID-19 that they see, specifically not just the S-proteins but probably also N-proteins but we don't know what component of this is most important. Since some of the investigational COVID-19 vaccines in the development don't even cover the entire S-protein, although some do but most don't, it seems unwise at this point to try to use vaccines in the same way to immunize people to get antibodies to fight COVID-19 as the normal infection does. We also don't know exactly all the levels. Obviously, we could test for those but we don't know exactly how those would compare. For right now, our Office of Vaccines, when consulted, feel most comfortable and I would support that we do not use vaccination as a way to get to donation. That could be a question for the future and it could be investigated in a clinical trial.

GUIDANCE RECOMMENDATIONS

EUA vs IND

7. 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 Response to Q7 - Dr. Verdun: 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.

GUIDANCE RECOMMENDATIONS

EUA vs IND

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

FDA Response to Q8 - Dr. Verdun: 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 and again we continue to encourage their enrollment.

GUIDANCE RECOMMENDATIONS

Fact Sheets and Consent

9. 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 Response to Q9 - Dr. Verdun: 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.

LINKS ON NEXT SLIDE

GUIDANCE RECOMMENDATIONS

Fact Sheets and Consent

TRANSLATED CCP EUA FACT SHEETS ON FDA WEBSITE:

[Healthcare Providers](#) 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)

GUIDANCE RECOMMENDATIONS

Fact Sheets and Consent

10. 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 Response to Q10 - Dr. Verdun: 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. I don’t want you to pass it off as EUA convalescent plasma, if that makes sense.

MORE QUESTIONS

Donation Frequency, Labeling

11. 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 Response to Q11 - Dr. Verdun: 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.

MORE QUESTIONS

Donation Frequency, Labeling

12. Please clarify if labeling requirements for EUA CCP include:

- Removal of license #?
- Removing the IUO caution statement and adding an EUA statement?
- Addition of High Titer/Low Titer to the CCP name or include as labeling attributes?
- Obtaining two new ISBT128 pcodes?
- Registered (but not licensed) establishments can collect, label and distribute?

FDA Response to Q12 - Dr. Verdun:

- Removal of license #? The container label does include a license number because convalescent plasma is not an approved product so that should be removed.

MORE QUESTIONS

Donation Frequency, Labeling

FDA Response to Q12 - Dr. Verdun continued:

- 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? Sharon is sharing this information in Q 13.
- Registered (but not licensed) establishments can collect, label and distribute? Yes.

MORE QUESTIONS - ISBT codes

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13. How do we know which ISBT codes are acceptable?

From the October 2nd 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.

***Live Questions
from our Audience
for
Dr. Verdun and Dr. Marks***

Audience Questions - Live Session

Question 14: 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?

FDA Response to Q 14 - Dr. Verdun: 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.

Audience Questions - Live Session

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Question 15: Only about 50% of CCP units in the Mayo EUA program exceeded the S/C threshold of 12 on the Ortho IgG test. Of units with S/C <12 a significant proportion would meet the PRNT titer of 250 on the Broad or other PRNT, a pseudo virus RVPNT assay or a neutralizing Ab proxy assay such as RBD-ACE-2 blocking assays, but to my knowledge none of these have EUA claims for quantitation of neutralizing Abs or release of CCP. 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 Response to Q15 - Dr. Verdun: 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

Audience Questions - Live Session

FDA Response to Q15 – Dr. Verdun continued: 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.

Audience Questions - Live Session

Question 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 Response to Q16 - Dr. Marks: 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.

Audience Questions - Live Session

Question 17: 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 Response to Q17 - Dr. Verdun: 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.

Audience Questions - Live Session

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Question 18: Can product labeling include the signal to cutoff?

FDA Response to Q 18 - Dr. Verdun: They were saying a specific S/C cutoff for that unit? (Sharon: Yes)

Response continued: 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.

Dr. Marks: I don't really have much to add. I think there have been people who have wanted to keep some track of this. People want to keep a tie-tag on the label with that, so they keep track of it for themselves as they move along. I don't think that's a problem. It can create issues otherwise. Some facilities that have had INDs have kept track of this but that's been under protocol.

Audience Questions - Live Session

Question 19: 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 Response to Q19 - Dr. Verdun: 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.

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Question 20: We hear questions periodically about the next therapeutic options that would be available because CCP was seen as a bridge therapy until additional therapeutic options were available. Is it possible for you to comment on the progress with any of those?

FDA Response to Q 20 - Dr. Marks: What I can say is that the hyperimmune globulins are in investigation but more so the monoclonal antibodies, as you've probably heard, there are results starting to come in and I think we will start to hear more results in the coming weeks and few months about the results. Instead of just single monoclonals we are starting to hear about cocktails of monoclonals which may be the way to go. Initial results from the monoclonals, despite this issue of possibly starting to lead to single monoclonals leading to some potential resistance, what could be resistance, growing out although we don't know for sure yet, I think we are kind of optimistic here, that we'll see some development here of some very promising products in the not too distant future. There are enough different combinations out there. Those are obviously handled in the Center for Drug Evaluation and Research and we'll stay posted for what's going on there.

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Question 21: 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 Response to Q21 - Dr. Verdun: 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.

Audience Questions - Live Session

Question 22: Given the lack of clarity around dosage, does giving two low titer units change the risk profile of the CCP approval?

FDA Response to Q22 - Dr. Verdun: Not to our knowledge. We do have some data within the expanded access program, the Mayo expanded access program, from those that did receive two units and it does not seem to change the risk profile in general. We cannot comment specifically on the use of two low titer units and its equivalence to a high titer unit. We just don't have that data. But from a safety standpoint, we do have some data around the use of two units in general.

Audience Questions - Live Session

Question 23: Can Peter or Nicole comment on the status of monoclonal antibody trials?

FDA Response to Q23 - Dr. Marks: They are enrolling. There are plenty open from multiple companies. We would suggest, when possible, that patients get enrolled in those trials because obviously there is a lot of hope that they will provide a fair amount of help both in the more advanced setting, as well as early on after people are infected. I don't have any magic updates except to say that obviously some of the initial results with these seem to be promising there's hope that the class will have promising efficacy.

Audience Questions - Live Session

Question 24: Is the Broad PRNT assay the only neutralization assay permissible for assay correlation for EUA "high/low titer" labeling?

FDA Response to Q24 - Dr. Marks: 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 titrating 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.

Audience Questions - Live Session

Question 25: This is for EUAs. Has the agency stopped evaluating EUAs for screening and surveillance testing not intended to be licensed for diagnostic testing? For example, an EUA request for pooled samples testing using a device or kit under EUA for singlet PCR testing.

FDA Response to Q25 - Dr. Marks: I don't know the answer to that one. That's a CDRH question, I think. **Dr. Verdun:** Yes. I think that's a question that would need to be discussed in conjunction with our device colleagues.

Audience Questions - Live Session

Question 26: Could you comment on the difference between CBER and CDRH with respect to testing and how that all works? I think sometimes that's not well understood.

FDA Response to Q26 - Dr. Marks: CBER will handle tests if they are used for screening the actual blood supply. On the other hand, CDRH is involved in tests where the laboratory result will be given back to a patient and/or will determine a clinical outcome for that individual patient. That includes if that patient is being told they are antibody positive as part of, they are going to do something else like donate blood. That is why CDRH regulates testing and a lot of the tests that we are talking about here, because ultimately the results are given back to the patient and could potentially influence clinical care or the choice that a patient might make.

Dr. Verdun: I would just add that in the context of convalescent plasma, which we are discussing today, I want to add the distinction there. The tests that are reviewed by CDRH are specifically to, as Peter eluded to, give information or provide information

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FDA Response to Q26 – Dr. Marks continued: to a patient or to a person. Specifically, the antibody assays, as they are EUA approved by CDRH, are to give someone information about the presence or absence of antibodies for that particular person that's getting that test. We are reviewing similar assays. There is some overlap, there are some assays that are EUA approved, as I just outlined. We are specifically looking at assays as part of a manufacturing step to qualify convalescent plasma units not as assays that will be used to inform decision making for a patient or for a person who is receiving that test. There is a distinction there. The review that we are doing to qualify these assays in terms of manufacturing of a unit, will not result in an EUA for that particular assay. If the assay developer is interested in a specific EUA for the assay in order to be used for patients and to provide information to those patients then they would need to contact CDRH. If there are any questions, please contact us because I know that the distinctions can sometimes be a bit confusing.

Audience Questions - Live Session

Question 27 – *we were unable to answer this question before the Live session ended:*

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 Response provided to AABB via email:

“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 .

Please let us know if you have additional questions.”

IF YOU HAVE QUESTIONS:

**Please contact
AABB Regulatory Affairs
at:**

REGULATORY@AABB.ORG

Thank you

On behalf of the AABB team, we have all been humbled by the response of the blood community to this pandemic. Thank you for your remarkable efforts to respond swiftly to unexpected challenges; for meeting needs of patients around the world during this unprecedented time; and for continuing to provide the bridge to more advanced therapeutic options for far longer than expected. Our community is extraordinary, and it's an honor to serve you.