Plasma Protein Therapeutics Association

June 17, 2020 **VIA EMAIL**: ACBTSA@hhs.gov

Mr. James Berger
Designated Federal Officer
Office of Infectious Disease and HIV/AIDS Policy
U.S. Department of Health and Human Services
Mary E. Switzer Building
330 C Street SW, Room L600
Washington, DC 20024
Attn: ACBTSA-PAHPAIA Sec. 209

RE: RFI RESPONSE: ACBTSA – PAHPAIA Sec. 209

Dear Mr. Berger:

The Plasma Protein Therapeutics Association (PPTA) appreciates this opportunity to provide comments related to maintaining an adequate national blood supply. PPTA applauds the HHS for working through its stakeholders to develop recommendations that will be included in the report to Congress mandated by the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 (PAHPAI). Source Plasma donation occurs at specialized blood establishments in the United States. The current pandemic has shown any challenges the blood supply will face, the plasma supply will face as well, and both are important in assuring that patients receive the life-saving treatments they need.

PPTA is the standards-setting and global advocacy organization that represents the private sector manufacturers of plasma-derived and recombinant analog therapies, collectively known as plasma protein therapies, and the collectors of Source Plasma[1] used for manufacturing of plasma protein therapies. Our membership accounts for approximately 90 percent of plasma-derived therapies in the United States.

Plasma protein therapies are primarily used in the treatment of genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies include blood clotting factors for individuals with bleeding disorders, immunoglobulins (Ig) to treat a complex of diseases in persons with antibody deficiencies and severe autoimmune disorders, and albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions.

Without continued Source Plasma donations, thousands of individuals who rely on plasma protein therapies may have difficulty accessing their life-saving pharmaceuticals. Clinical need for plasma protein therapies has been steadily

[1] 21 CFR 640.60 defines Source Plasma as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use.

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increasing for many years[2]. This need, which necessitates a high level of Source Plasma collections, has not gone away or diminished due to the COVID-19 situation. Patients reported serious Ig access issues as recently as Summer 2019 when plasma donations were at their highest level.[3] According to the FDA, "As the COVID-19 pandemic affects communities, … plasma donation centers across the nation have experienced a dramatic reduction in collections.[4]" We are hopeful that the comments we provide will help remedy the reduction in collections resulting from the COVID-19 pandemic, restore and enhance collections, and ensure patients have access to the plasma protein therapies they need.

Challenges associated with the continuous recruitment of blood donors (including those newly eligible to donate)

The manufacturing of plasma protein therapies is dependent on donations from committed, repeat donors. PPTA members make tremendous efforts to attract plasma donors. Despite these efforts, less than 5% of persons eligible to donate, do. We need more research on what motivates donors and a national data system that captures not only data on donor recruitment and retention but is comprehensive in capturing data that will enhance knowledge and inform decision making about donor health and safety, blood component quality, and the blood and plasma supply chain.

Ensuring the adequacy of the blood supply in the case of public health emergencies

In order to ensure patient access to plasma protein therapies, we must maintain adequate supplies of Source Plasma at all times, even during public health emergencies. We have found that the current pandemic has highlighted a few key points.

Messaging

At the beginning of the current pandemic, there was some difficulty with local authorities' interpretation of The President's Coronavirus Guidelines for America (the 15-day plan) with respect to the continued operation of plasma collection centers. We viewed the message as clear and applicable "critical infrastructure industry. . .pharmaceutical. . , you have a special responsibility to maintain your normal work schedule." However, our member companies in several states were challenged by local health, fire department and police to close as they have more than 10 people in the buildings.

We suggest that in the future governing officials make clear that plasma donation centers are part of this country's essential infrastructure. All government messaging should clearly identify that plasma centers and associated infrastructure (labs, warehouses, transportation, corporate offices, manufacturing) are critical infrastructure. The message should clearly state "Plasma". Without this clear message, "blood banks"

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[2] Grabowski, H., & Manning, R. (2018). *Key economic and value considerations in the U.S. market for plasma protein therapies*. Washington, DC: Bates White at 31.

[3] https://www.pptaglobal.org/images/Data/Plasma_Collection/Total_Yearly_Collections_2008-2019.pdf

[4] Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency, Guidance for Industry, April 2020.

or “blood centers” can be easily construed by local authorities to not include plasma centers.

We also suggest providing separate clear messaging immediately that **plasma center employees** and **donors** are critical infrastructure and should be allowed movement to/from plasma centers. Our members experienced situations where both groups were afraid to venture from their homes and are concerned that center employees may be challenged to defend their movement to authorities.

Access to supplies
A continuing difficulty with access to supplies has impacted PPTA members’ ability to collect plasma. Evolving policies concerning PPE, specifically mask-wearing, social distancing and other hygiene issues, led to employees and donors adopting their own perceptions of what should have been done. It would be helpful if HHS could assist plasma companies through a centralized procurement process when critical supplies are in short supply. Supplies include PPE, donor center supplies (general medical supplies and specific plasmapheresis supplies), testing supplies, and manufacturing supplies.

We suggest in advance of future pandemics, HHS could identify and then designate supplies necessary for plasma procurement and manufacturing (see above general supply list) as critical infrastructure and consider the impact of any pandemic on these supplies immediately and direct supply manufacturers to implement increased manufacturing and inventory immediately.

Response to Industry
Generally, FDA was responsive to requests for guidance and assistance. However, in a few instances, it seems they were trying to set guidance in a general manner to industry when in fact individual companies were asking similar, but not the same questions. This appears to have led to delay in responsiveness and in fact, caused additional conversations to receive clarifications. As an alternative, we suggest that FDA understand that industry members often have unique requests and must be dealt with individually, even though it may be difficult, resource stretching, and to them, the same question.

CLIA Personnel
Source plasma donation centers are held to moderate complexity CLIA standards because they use a moderate complexity test (refractometer) to perform the total protein level determination as part of the plasma donor’s pre-donation screening. PPTA members are having difficulty obtaining and retaining CLIA personnel. This difficulty is exacerbated by the COVID-19 crisis. Members are especially hard hit in states that require licensed personnel to perform the total protein test (CA and NY) because state licensed registered nurses, technicians and technologists are being pulled away for COVID-19 related testing and health care. Even in states where the actual testing personnel standard is a high school diploma and total protein test training, members are having difficulty in hiring new staff since schools are closed for the pandemic. In addition, PPTA Members must follow the hierarchy of medical director, technical

consultant and other personnel required for moderate complexity testing laboratories. These personnel are in short supply during the current pandemic.

A solution to the CLIA personnel issue for source plasma donation centers would be to amend the list of waived tests found in 42 CFR §493.15 to add the total protein test performed at source plasma donation centers for source donor screening purposes. This would allow PPTA members to collect more plasma since they will be able to operate more centers with other personnel. They would still be held to the personnel standards found in Title 21 of the CFR.

Implementation of the transfusion transmission monitoring system
Donations of Source Plasma are not covered by the transfusion transmission monitoring system (TTIMS). PPTA has a set of voluntary industry standards that comprise certification programs for Source Plasma (International Quality Plasma Program—IQPP) and for plasma protein therapies (Quality Standards of Excellence, Assurance and Leadership—QSEAL). PPTA's Viral Marker Standard and Donor Adverse Event Recording Standard are used to monitor viral and non-viral risks to plasma and donors. Besides those mentioned, there are numerous other private or public data programs within the blood and plasma industry, e.g., Recipient Epidemiology and Donor Evaluation Study (REDS), the hemovigilance module of the National Healthcare Safety Network (NHSN), the National Blood Collection and Utilization Survey (NBCUS) and the Biologics Effectiveness and Safety (BEST) Sentinel Initiative. All of these efforts could be of enhanced use to the community if HHS and its stakeholders could work to develop a comprehensive data system that would build on the successes of each program.

Other measures to promote safety and innovation, such as the development, use, or implementation of new technologies, processes, and procedures to improve the safety and reliability of the blood supply.
There are a few areas where HHS could make changes that would improve the reliability of the plasma supply. Some of the changes we recommend would also meet the Administration's goal of reducing the regulatory burden on businesses. PPTA agrees with the FDA in revisiting and updating some existing policies to help ensure the plasma supply while still protecting the safety of the nation's plasma supply. With that in mind, we suggest the following updates to improve plasma supply while protecting the safety of the nation's plasma supply.

CLIA
As mentioned above, plasma supply could be improved if HHS were to amend the list of CLIA waived-tests to include the total protein test performed at source plasma donation centers for source donor screening purposes. This change would help also during non-pandemic times, especially in states that require licensed individuals to perform the moderate complexity tests. California and New York are two states that require operators performing moderate complexity tests to be licensed. These requirements exceed federal law and make operating plasma donation centers difficult in California and New York. The difficulty is shown by the number of plasma donation centers in

each state. There are more than 840 plasma donation centers in the United States, yet only 27 in California and 12 in New York.

The licensed individuals, such as registered nurses and clinical laboratory technologists are needed in other settings like hospitals, doctor's offices, and large laboratories. Their duties at these settings are often more in line with their training. Given that both these professions are said to be in shortage and their job satisfaction is likely higher when performing tasks to the highest degree of their training, finding and retaining such professionals is difficult for plasma donation centers. If the regulation were changed to make the total protein test a waived test as we suggest, plasma donation centers would no longer have to struggle to find staff to perform such an easy test. This would likely lead to more centers in those states. This would lead to an increase in plasma supply.

Additionally, HHS could choose to exempt source plasma donation centers from CLIA. The question has arisen within our membership about the applicability of CLIA to Source Plasma[5] donation centers.

The test for CLIA applicability is found in Guidance from December 10, 2014[6]. CLIA applies when: (1) patient-specific results are reported from the laboratory to another entity; and (2) the results are made available "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." Therefore, if a facility performs tests for the above-stated purposes, it is considered a laboratory under CLIA and must obtain a certificate from the CLIA program that corresponds to the highest complexity of tests performed.

The FDA regulations require source plasma donation centers to determine the eligibility of a prospective donor to donate on a specific day based on a few measurements[7]. The prospective donor is weighed. They have their temperature, blood pressure and pulse taken. They have their hematocrit or hemoglobin, and total protein level determined. The individual's weight must be at least 110 pounds to donate source plasma. The other five measurements must be within ranges established in FDA regulation based on those of a normal adult to be eligible to donate on the date of the measurement. The results of these measurements are entered into the donor management system of the source plasma donation center. Source plasma donation centers do not provide the prospective results to another entity.

Plasma donors are not patients. In addition, the second element of the first prong of the test for CLIA applicability is whether the laboratory reports the results to another entity? The results of the eligibility measurements are not reported to another entity. The second prong of the test is "results are made available…". The results are not made available.

[5] 21 CFR 640.60
[6] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf
[7] 21 CFR 630.10 and 21 CFR 630.15

Since the eligibility determinations at a source plasma donation center are not performed on patients, are not reported to another entity, nor are they made available to others, the measurements to determine a prospective plasma donor's eligibility should not be subject to CLIA.

Donation Suitability
In 2015, as part of a large regulatory re-write, the FDA created 21 CFR 630.30(a) to define when a donation of blood and blood components, including plasma, is suitable. In the case of Source Plasma, the question is whether the donation is suitable for further manufacturing? The regulation states that if donors are not eligible to donate, then a donation is not suitable. The inappropriateness of this regulation is being shown by the way it is being enforced which hurts the supply of plasma in this country. For example, FDA personnel have told our members that when a plasma donation center discovers, after collecting a unit of Source Plasma, that the donor did not meet certain donor eligibility requirements, the donated plasma unit is unsuitable and may not be released. They are saying this even though there is nothing wrong with the unit of plasma and it could be safely used to make plasma protein therapies.

Specifically, FDA now appears to be relying on donor health protection provisions in 21 CFR 630.30(a)(2) to deem units of Source Plasma to be unsuitable for further manufacture and to be in violation of current Good Manufacturing Practice (cGMP) even when no concerns exist regarding the safety, purity, potency, identity, strength, or quality of the Source Plasma. This appears to exceed the authority granted to FDA in statute. It certainly is a policy that fails to improve the safety and reliability of the plasma supply. We recommend changing the policy.

Syphilis testing
According to 21 CFR 640.65, source plasma donation centers must draw a sample of blood from each donor on the day of the initial physical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter. A serologic test for syphilis shall be performed on the sample. If a donor's syphilis test is positive, they are deferred from future donations, but the units they have already donated are allowed to be used for further manufacturing.

The already donated units are allowed to be used because the bacterium that causes syphilis can't survive the manufacturing process. This shows the FDA agrees syphilis poses no concern regarding the safety, purity, potency, identity, strength, or quality of the Source Plasma, or the finished product provided to patients. It is a policy that fails to improve the safety and reliability of the plasma supply. We recommend eliminating the syphilis test requirement for Source Plasma donors.

Global Regulatory Convergence
As a final comment, PPTA encourages HHS, specifically FDA, to continue its work to seek global convergence of regulatory requirements that affect our industry. While blood for transfusion has been thought to be a local responsibility, plasma (including recovered from blood collected for transfusion) for manufacturing plasma protein

therapies is global. To facilitate efficient operations and to provide therapies for patients who rely on them throughout the world, it is important that regulatory policies be seamless region to region. We encourage continued participation at international forums such as the International Council for Harmonization (ICH) and the Blood Regulators Network (BRN). It is through cooperative efforts that progress is made.

In conclusion, PPTA appreciates the opportunity to comment. PPTA welcomes from FDA any questions regarding these comments. Should you have any questions or require additional information please do not hesitate to contact me at: mgustafson@pptaglobal.org.

Respectfully submitted,

Mary Gustafson
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Plasma Protein Therapeutics Association