Plasma Protein Therapeutics Association

December 23, 2020

VIA Electronic Submission

The Honorable Alex Azar
Secretary
U.S. Department of Health & Human Services
200 Independence Avenue S.W.
Washington, D.C. 20201

RE: RFI Response: Regulatory Relief to Support Economic Recovery; Request for Information (FR Doc. 2020–25812)

Dear Secretary Azar:

The Plasma Protein Therapeutics Association (PPTA) appreciates this opportunity to provide comments to assist the Department of Health & Human Services (HHS) in identifying regulatory standards that may inhibit economic recovery and are candidates for rescission or suspension, including temporary deregulatory actions which should be made permanent. Source Plasma donation occurs at specialized blood establishments in the United States. The donations are subject to numerous federal statutes and regulations, as well as state and European laws. The comments we are providing should assist HHS meeting the objectives of Executive Order 13924, *Regulatory Relief To Support Economic Recovery,* 85 FR 31353 (May 19, 2020).

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.

There is an urgent need for source plasma donations. Reports vary, but plasma collectors experienced significant declines in collections due, in part, to the impacts of social distancing

[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.

measures and other mobility restrictions caused by the COVID-19 pandemic.[2] [3] Considering the complex manufacturing of plasma-derived therapies can take 7-12 months, any decline in plasma donations could impact patients' ability to access their lifesaving therapies.[4] [5] This sharp decline in plasma collections could cause more significant challenges in the months to come. These challenges are exasperated by certain federal regulations that limit source plasma donations without improving donor or product safety.

Therefore, we are grateful for this opportunity to share with you our ideas for agency action that would remove barriers that are inhibiting economic recovery. A few of our comments address temporary guidances that we believe need further attention. Our other comments address regulations that would improve public health.

TEMPORARY GUIDANCE

Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency

Time Limits for Obtaining Omitted Information from Donor Eligibility Records (21 CFR 630.10)

In this guidance, the FDA increased the time to obtain omitted information, under 21 CFR § 630.10(c)(2), from 24 hours to 72 hours, which is helpful. PPTA requests that FDA now review whether any time limit at all is necessary, as some omissions relate to medical history that does not change.

Donation Suitability (21 CFR 630.30)

In this guidance, the FDA allows an exception to certain requirements of 21 CFR 630.30(a)(2) and (b)(1). Under this exception, PPTA members may release blood components collected from certain ineligible donors without prior FDA approval. *See Alternative COVID-19 Procedures Guidance* at 3. The exception applies only when a blood establishment discovers — when reviewing records after a donation has occurred — that the donation was unsuitable under 630.30(a)(2) because of the failure to follow procedures to ensure that the donation would not adversely affect the health of the donor. *Id.* The guidance identifies the following four procedures as donor health provisions that qualify for the exception:

- Blood pressure: confirmation that it was in the range specified in 21 CFR 630.10(f)(2);
- Pulse: confirmation that it was regular, and in the range specified in 21 CFR 630.10(f)(4);
- Weight: confirmation that the donor met the 110 pound minimum specified in 21 CFR 630.10(f)(5); and

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[2]Cherney, Mike. "Coronavirus Pandemic Slashes Donations of Lifesaving Plasma." Wall Street Journal, August 19, 2020.
[3] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. (2020, April). Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency; Guidance for Industry.
[4] Hartmann J, Klein HG, "Supply and demand for plasma-derived medicinal products - A critical reassessment amid the COVID-19 pandemic." Transfusion. 2020 Aug 28:10.1111/trf.16078. doi: 10.1111/trf.16078.
[5] Prevot J, Jolles S, "Global immunoglobulin supply: steaming toward the iceberg?" Curr Opin Allergy Clin Immunol. 2020, 20:000–000 DOI:10.1097/ACI.0000000000000696

• Frequency: confirmation that the donor gave no more frequently than specified in 21 CFR 630.15(a)(1).

PPTA acknowledges and applauds the exceptions to sections 630.30(a)(2) and 630.30(b)(1) that FDA announced in this guidance. These exceptions are important steps toward protecting the source plasma supply at this critical time. But they do not go far enough, and they should continue after the pandemic.

FDA stated it issued this guidance to address challenges to the U.S. blood supply that the COVID-19 pandemic has created. FDA stressed that the pandemic has caused blood establishments and plasma collection centers across the nation to experience a dramatic reduction in collections. FDA acknowledged that it issued the guidance in response to blood establishments' urgent appeals for plasma donation and out of a concern about the nation's plasma supply during the pandemic. FDA designed these measures to improve availability of plasma while both maintaining a safe plasma supply for patients and helping to ensure adequate protections for donor health.

PPTA and our members care greatly about donor health, as donors are the lifeblood of our business. We believe that we have an alternate solution that will be acceptable to all parties, will further protect the availability of source plasma, and will save FDA resources. The solution uses this guidance as a conceptual starting point and builds on its approach.

First, we propose that under 21 CFR 640.120(a), FDA issues an exception to the prohibition in 21 CFR 630.30(b)(1) on releasing an unsuitable Source Plasma donation for further manufacturing. The exception would be limited to units that are unsuitable because they do not satisfy 21 CFR 630.30(a)(2), but which otherwise are suitable under 630.30(a). The exception would also be limited, like in the *Alternative COVID-19 Procedures Guidance,* to units collected before the blood establishment discovered the "unsuitability" based on these grounds. The exception may not be used to excuse "bad behavior" by blood establishment personnel if they actually knew that the deficiency existed before the donation but proceeded to collect the donation anyway.

Second, the exception should make clear that it is not limited to the four deficiencies listed as examples in the *Alternative COVID-19 Procedures Guidance,* namely, blood pressure, pulse, weight, and frequency of donation. The exception should cover all situations where a unit of Source Plasma might be considered unsuitable based on 630.30(a)(2), but where the establishment identified no concern about the safety, purity, potency, identity, strength, or quality of the units. The exception should also make clear that it is not needed for provisions like 640.65(b)(1) and (2) that cover only the forward-going eligibility of donors, and do not render any particular, already-donated units unsuitable; in those situations, 630.30(b)(1) does not apply.

Third, like in the *Alternative COVID-19 Procedures Guidance,* for units that satisfy the conditions for the exception, blood establishments may immediately release those units. We propose, however, that instead of requiring blood establishments to submit a CBE supplement concurrently with release, FDA should allow blood establishments to report all such exceptions in an annual report. This reporting will be sufficient to ensure that FDA has a means to monitor blood establishments' use of the exception. If a pattern emerges that indicates that an establishment habitually collects Source Plasma from ineligible donors, FDA will be able to rely on one of its many tools to bring that establishment into compliance, without wasting or delaying the availability of otherwise suitable Source Plasma.

Fourth, also like in the *Alternative COVID-19 Procedures Guidance,* for units that do not satisfy the conditions for the exception, the blood establishments will need to seek an exception under 640.120(a) as a prior approval supplement to seek approval to release such units. The burden would then be placed on the blood establishment to proffer evidence that the safety, purity, potency, identity, strength, or quality of the Source Plasma units is acceptable.

Finally, the exceptions should not be limited to the duration of the current pandemic. The alternative procedures announced in the *Alternative COVID-19 Procedures Guidance* do not reduce donor safety or Source Plasma quality. Thus, it is reasonable and appropriate to adopt these procedures permanently, rather than only during the pandemic.

PPTA wishes to note that per previous communication to FDA, we seek review of the Agency's opinion to deem units of Source Plasma adulterated and not releasable based solely on donor health protections when no concerns exist regarding the safety, purity, potency, identity, strength, or quality of the Source Plasma.

Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products.

In this revised guidance, the FDA updated donor deferrals for a number of behavioral risks. The FDA stated that these changes will continue after the pandemic and are permanent. PPTA applauds these changes that should have a positive impact on public health by increasing source plasma donations.

PPTA suggests that FDA continue the discussion with stakeholders through a workshop especially in view of the need to increase the availability of source plasma due to the COVID-19 pandemic and the absence of safety concerns for certain deferral criteria such as tattoos, piercings and males who have sex with males (MSM).

PPTA would also like to highlight the importance for global regulatory harmonization/ convergence for the plasma industry. Many U.S. fractionators have not implemented the revised FDA HIV Guidance for 'at risk behavior' due to stricter European Union (EU) donor deferrals. Currently, a working group at the European Medicines Agency (EMA) is conducting an assessment of EU donor deferrals. PPTA would encourage the FDA's participation, input and showcasing of own regulatory decisions; for instance, during the FDA-EMA Blood Cluster meetings.

PPTA believes the deferral/eligibility of donors based on information such as tattoos, piercings and MSMs warrants further deliberations. The eligibility criteria have only limited contribution to safety margins of plasma-derived medicinal products (PDMPs) but result in significant loss of plasma and administrative burden for the manufacturer and the FDA. Only nucleic acid amplification testing (NAT) non-reactive plasma pools enter the manufacturing process [as confirmed by the manufacturer and additional independent testing (OMCLs in Europe)], hence plasma products are considered safe after pooling.

The guidance was odd in that it did not address the 12-month hepatitis deferral for sexual contact "with" or "lived with" a person who has hepatitis, considering the FDA's own assessment of "surveillance information and the experience with a 3-month deferral in other countries" along with NAT detection of HIV, HBV, HCV which scientifically supported this update to a 3-month deferral period**.** On June 05, 2020 AABB, Plasma Protein Therapeutics Association (PPTA), America's Blood Centers (ABC) and the American Red Cross (ARC) jointly submitted comments the April

2020 HIV Guidance (replaced with August 2020 guidance) requesting clarification on deferral for "sexual contact with" or "lived with" a person who has hepatitis. No clarification was given in the updated August 2020 guidance.

REDUCE UNNECESSARY REGULATION TO INCREASE SOURCE PLASMA DONATIONS

The Order that prompted this RFI directs agencies to ''identify regulatory standards that may inhibit economic recovery'' and to take appropriate action such as rescission or suspension of regulations. PPTA would recommend the following changes to regulatory standards that would improve public health, and therefore would improve the economic recovery.

CLIA Moderate Complexity Personnel Regulations (42 CFR 493.1423)

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. The CLIA designation was made at a time when refractometers were analog devices, which required manual reading and subjective interpretation, and is now outdated. Plasma centers currently use digital refractometers that are simple to operate and do not require subjective interpretation. The device cannot be adjusted by the user and provides and direct read-out value or error code. An example of this test may be seen by visiting https://bit.ly/totalproteintest.

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 such as California and New York. These requirements exceed federal law and make operating plasma donation centers difficult in these states. The difficulty is shown by the number of plasma donation centers in each state. There are more than 930 plasma donation centers in the United States, yet only 28 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.

Even in states that follow the federal standard of high school diploma and total protein test training for testing personnel, 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.

Syphilis testing (21 CFR 640.65)

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.

Testing of Source Plasma Donations that will be Discarded (21 CFR 610.40)

Recently some PPTA members have been issued "advice" letters or other communications mandating that testing required in 21 CFR 610.40 be completed on donations that will not be released for manufacturing per requirements in 21 CFR 610.1. This is a major change from a long-standing, industry practice of eliminating testing on plasma units collected subsequent to a donation testing reactive for one or more relevant transfusion-transmitted infections (RTTIs).

21 CFR 610.40 (a) reads:

> *Human blood and blood components.* Except as specified in paragraphs (c) and (d) of this section, you, an establishment that collects blood and blood components for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device, must comply with the following requirements:
>
> > (1) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(i) through (iii) of this chapter (HIV, HBV, and HCV).

PPTA believes it is implied in this language that establishments must test each donation **intended for use in manufacturing** for HIV, HBV, and HCV. Regulations for the collection of Source Plasma allow for collection of Source Plasma twice in a 7-day period with at least 2 days between donations.[6] Current testing paradigms result in test turnaround times ranging from approximately 4 – 10 days. This results in donations being collected prior to the receipt of all test results for previous donations. The long-standing practice of the industry has been to stop processing subsequent plasma units/donations: to destroy subsequent units/donations and related samples once a reactive result has been found on a prior donation. Since these

[6] 21 CFR 640.65(b)(8)

subsequent donations **will not be used in manufacturing**, this complies with the intent of the regulation.

It is also consistent with the direction found in 21 CFR 610.1 which states, "No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product." Source plasma is the licensed product in this case. Since prior donations from the same donor have tested positive for HIV, HBV, or HCV, the subsequent donations will not be released for further manufacturing. The position of FDA that 21 CFR 610.40 requires the testing of these subsequent units that will not be used for further manufacturing is inconsistent with 21 CFR 610.1.

The reasons for discarding the unit include:

a. subsequent donations are no longer suitable for release for manufacturing use;

b. pulling subsequent units/donations from inventory removes risk of inadvertent release of unsuitable product;

c. ceasing subsequent unit/donation processing removes a potential exposure risk to plasma center personnel;

d. eliminating sending samples to the testing laboratory removes the exposure risk for laboratory personnel to a known positive RTTI sample;

e. removing known reactive samples from testing procedures eliminates possible cross- contamination of other test samples;

f. not adding known reactive samples to testing eliminates possibility of contaminating test runs;

g. not adding known reactive samples to testing pools allows expedited reporting of testing results since the positive testing pool does not have to be resolved;

h. delays result reporting for other donors' donations (i.e. NAT mini-pool resolution testing);

i. potential strain on test kit availability (e.g, RIBA, Anti-HIV2, Western Blot).

The rationale for requiring all RTTI testing on units/donations that are unsuitable for release into manufacturing is not clear:

a. there is no violative product unless released untested; and

b. the donor is managed based on results of positive test received on a prior donation—donor deferred and notified of reason based on the results of the further testing

It does not appear that there has been sufficient exploration into the risk of inadvertent adverse consequences of changing a long-standing practice in the midst of a global pandemic. The items listed above in the reasons for the practice of not testing subsequent reasons are real. Change adds risk to employees in the plasma collection centers and test laboratories, risk to samples and test runs, and risk of release of unsuitable units that are left in quarantine inventory until testing is completed. The perceived benefit to donors and donor health is not evident and does not appear to outweigh risks.

For the reasons stated above, PPTA recommends amending 610.40(a)(1) to read:

> (1) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(i) through (iii) of this chapter (HIV, HBV, and HCV). Testing does not need to be done if it is decided that the unit will not be used for further manufacturing.

Facility Licensing Requirements

FDA could engage in dialogue with stakeholders to reflect on lessons learned from the current pandemic and efficiencies or improvements that can be taken forward, e.g. desk audits, or hybrid of on-site and desk audits. Changes in facility licensing requirements for source plasma collection centers could expedite the process for site licensure now and in the future.

CONCLUSION

PPTA appreciates the opportunity to provide comments to this RFI. We are hopeful that HHS and its sub-agencies will receive suggestions that will improve economic recovery and promote public health. PPTA welcomes from HHS 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,

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