Plasma Protein Therapeutics Association

December 21, 2020

VIA EMAIL

Mr. Brian Harrison
Chief of Staff
U.S. Department of Health & Human Services
200 Independence Avenue S.W.
Washington, D.C. 20201
DuplicativeRegulations@hhs.gov.

RE: Request for Information (RFI) to assist the Department in identifying redundant, overlapping, or inconsistent regulations (FR Doc. 2020–26022)

Dear Mr. Harrison:

The Plasma Protein Therapeutics Association (PPTA) appreciates this opportunity to provide comments to assist the Department of Health & Human Services (HHS) in identifying redundant, overlapping, or inconsistent regulations. 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 in improving existing regulations, and eliminating unnecessary or duplicative regulations through future exercise of rulemaking authority.

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, albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions, and number of other therapies for rare diseases.

[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.

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 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 the regulations that are causing the limitations. Addressing these regulations would resolve issues that undermine agency and regulatory goals by injecting uncertainty, creating potentially conflicting regulatory regimes, and increasing transaction costs with no discernible benefit to the public.

REGULATION OF SOURCE PLASMA DONATIONS

The Food and Drug Administration (FDA) regulates the entire manufacturing process of plasma protein therapies in Subchapter F of Title 21 of the Code of Federal Regulations. This includes regulations governing the donation of source plasma. These regulations ensure, among other things, that the process is safe for donors.[6] Source plasma donation centers are also subject to the Clinical Laboratory Improvement Amendments (CLIA) regulations found in Title 42 of the Code of Federal Regulations due to the CLIA classification of the tests performed to determine hematocrit/hemoglobin and total protein levels as part of pre-donation screening required by 21 CFR 630.10 and 21 CFR 630.15.

REDUCE UNNECESSARY REGULATION TO INCREASE SOURCE PLASMA DONATIONS

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 a direct read-out value or error code. An example of this test may be seen by visiting https://bit.ly/totalproteintest.

Since PPTA members perform this one test, they must follow the hierarchy of medical director, technical consultant and other personnel required for moderate complexity testing laboratories.

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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
[6] Weinstein M. Regulation of plasma for fractionation in the United States. Ann Blood 2018;3:3.

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.

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.

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 donation centers.

The test for CLIA applicability is found in Guidance from December 10, 2014[7]. 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.[8] 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.

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[7] https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf
[8] 21 CFR 630.10 and 21 CFR 630.15

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.

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 (21 CFR 630.30)

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 informed 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, such as failing to record the donor's blood pressure pursuant to 21 CFR 630.10 (f)(2), 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) " The results in accordance with §§630.10 through 630.25 indicate that the donor is in good health and procedures were followed to ensure that the donation would not adversely affect the health of the donor;" 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 (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 the test is positive, the donor is 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.

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

FDA recently 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.

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.[9] 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. Once a reactive result has been found on a prior donation, the long-standing practice of the industry has been to stop processing subsequent plasma units/donations, destroy subsequent units/donations and related samples. Since these 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.

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[9] 21 CFR 640.65(b)(8)

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); and

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 of the index donation.

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 donations are real. Change adds risk to employees in the plasma collection centers and test laboratories, risk of contamination to negative 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 above mentioned 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). <u>Testing does not need to be done if it is decided that the unit will not be used for further manufacturing.</u>

Mutual Recognition Agreement (MRA)

PPTA would like to take this opportunity to encourage HHS to advocate for the inclusion of plasma derived pharmaceuticals within the product coverage of the amended Pharmaceutical Annex to the 1998 U.S.-European Union (EU) Mutual Recognition Agreement (MRA) that enables the United States (U.S.) and EU regulators to utilize each other's good manufacturing practice inspections of pharmaceutical manufacturing facilities. We believe including plasma derived pharmaceuticals in the MRA would benefit public health by allowing the U.S. and the EU to reallocate its inspection resources while improving the process for providing patients with much need plasma-derived pharmaceuticals.

According to Article 20 of the MRA, the Joint Sectoral Committee shall consider whether to include plasma derived pharmaceuticals within the product coverage by July 15, 2022. The purpose of the MRA is "to facilitate trade and benefit public health by allowing each Party to leverage and to reallocate its inspection resources, including by avoiding duplication of inspections, so as to improve oversight of manufacturing facilities and better address quality risk and prevent adverse health consequences." The inclusion of plasma derived pharmaceuticals would achieve that purpose.

In 1998, Plasma-derived pharmaceuticals were excluded from the Mutual Recognition agreement because the U.S. regulation of Plasma-derived pharmaceuticals had recently undergone intense scrutiny and regulatory change; therefore, the FDA did not believe it appropriate at this time to include plasma derived pharmaceuticals within the scope of the MRA.[10] A lot has changed since 1998. The safety of FDA-licensed plasma-derived pharmaceuticals is now well established. Many factors contributed to the increased safety, including PPTA's voluntary standards[11], FDA's regulations and guidances on good manufacturing practices for such products, and technological improvements in pathogen reduction measures employed during the manufacturing of these products. The MRA also excludes human plasma. Source plasma, which is intended for manufacturing use, should be included in the MRA within the umbrella of plasma-derived pharmaceuticals. The FDA and the EU regularly and rigorously inspect the source plasma donation centers that provide the source plasma that constitutes the drug substance for plasma derived pharmaceuticals. These source plasma centers are the first step in the manufacturing process for plasma derived pharmaceuticals.

There are more than 1,000 source plasma donation centers in the U.S. and the EU. Additional centers open every month. The source plasma donated at these centers is sent to manufacturing plants in the U.S. and the EU. Each additional center means a new inspection requirement for the EU and the FDA. We are aware of the administrative strain this puts on both agencies. The duplicate inspections have no additional benefit to donor, product or patient safety in the EU or U.S. Reducing duplication of inspections of plasma centers would allow to make better use of inspection resources.

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[10] Mutual Recognition of Pharmaceutical Good Manufacturing Practice Inspection Reports, Medical Device Quality System Audit Reports, and Certain Medical Device Product Evaluation Reports Between the United States and the European Community; 63 Fed. Reg. 60122, 60130(November 6, 1998)

[11] PPTA member companies have adopted voluntary standards that apply to the collection of Source Plasma (IQPP) and fractionation of plasma derived pharmaceuticals (See https://www.pptaglobal.org/safety-quality)

The MRA is the perfect vehicle to address the unnecessary duplicate inspections. This would be achieved by including plasma derived pharmaceuticals to the Annex would benefit public health by allowing the U.S. and the EU to reallocate its inspection resources to better address quality risk and prevent adverse health consequences.

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 (source and 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,

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Plasma Protein Therapeutics Association