DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

October 9, 2015

Mr. Jan M. Bult
President & CEO
Plasma Protein Therapeutics Association
147 Old Solomons Island Road
Suite 100
Annapolis, MD 21401

Dear Mr. Bult,

Thank you for your letter of July 29, 2015, in which you expressed concern regarding FDA's Final Rule on **Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule** (Federal Register Volume 80, Number 99, 29842 – 29906, Friday, May 22, 2015). In your letter, you expressed concern about the impact of the inventory hold provision (§640.69(f)) of the final rule on PPTA members and burdens that it would impose. In particular, you raised concerns that the inventory hold as finalized in §640.69(f) would not be consistent with industry practice because it imposes a burden for the inventory hold on the Source Plasma collectors and not the plasma fractionators. You stated: "Changing the responsibility for the "hold" from the fractionator to the collector will represent a major disruption in the operations of both collectors and fractionators." We respectfully disagree with your interpretation of the requirements of §640.69(f) and your assessment of the impact of the final rule on existing operations of PPTA members, fractionators, and Source Plasma collectors.

Final section 640.69 states:

(f) *Hold.* Source Plasma donated by paid donors determined to be suitable for further manufacturing into injectable products must be held in quarantine for a minimum of 60 calendar days before it is released for further manufacturing. If, after placing a donation in quarantine under this section, the donor is subsequently deferred under §610.41 of this chapter, or you subsequently determine a donor to be ineligible under §630.10 of this chapter due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection, you must not distribute quarantined donations from that donor for further manufacturing use to make an injectable product.

As we noted in response to PPTA's comment in the final rule (see 80 FR 29884, Response to Comment 121), we stated:

"The language of the proposed rule would not have required that Source Plasma be stored at the collection site, nor did it require establishments to label individual collections of Source Plasma as "Quarantined." Rather the proposed rule simply required that the product be "held in quarantine." The final rule requires that Source Plasma be held for a minimum of 60 days and prohibits distribution of certain units "after placing a donation in quarantine." Final §640.69(f) does not specify where an establishment must store the product. The establishment is not required to store the product at the collection site, and an establishment may store the product at an appropriate off site facility during the 60-day Inventory Hold. Nor does this provision require individual labeling of units. Instead, it simply requires that the establishment be able to identify any units that may not be distributed because of post-

donation information received during the 60-day hold, and to identify when the 60-day hold has expired for a unit. We believe that establishments can meet these requirements by employing a variety of methods, including physical segregation, labeling (units, cases, or other packing units), or by electronic means (such as by computerized inventory). Finally, we disagree that the use of the term "quarantine" in this context suggests that the product subject to the Inventory Hold is violative. Rather, the term merely implies that the establishment is restricted from distributing the quarantined product while it is subject to the Inventory Hold."

Final §640.69(f) allows Source Plasma collected by establishments that are part of a larger corporate entity that includes a fractionation facility to store the plasma that they collect either at the collection establishment or at the fractionation facility. The responsibility for the inventory hold required under §640.69(f) for these "vertically integrated" corporations lies with both the collection facility and the parent corporation. Final §640.69(f) does not prevent the fractionation facility that is part of the same corporate entity as the collection facility from managing the inventory hold in conjunction with the collection. The fractionation facility would act on information provided by the collection facility to not release any donation for further manufacture if the donor was subsequently deferred under §610.41, or was subsequently determined to be ineligible under §630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection. Responsibilities for management of the inventory hold (quarantine mechanism, data transfer, culling and disposition, record keeping, etc.) should be specified in written agreements and related SOPs.

With regard to independent Source Plasma collectors, we believe that the provisions of the final §640.69(f) can be met through contractual agreement with the fractionator not to use the Source Plasma for 60 days pending further information from the collection facility that the donor was subsequently deferred under §610.41, or was subsequently determined to be ineligible under §630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection. Current practice by plasma fractionators should already include provisions to not release donations during the 60 day hold in the event that information is received from the Source Plasma collector that the donor has been deferred under §610.41.

You also raised concern about the lack of a scientific rationale for including the inventory hold in the regulations. As you are aware, there have been concerns about the safety of plasma collected from paid donors. Data from the 1970s and from the 1998 GAO report (Plasma Product Risks Are Low if Good Manufacturing Practices Are Followed HEHS-98-205: Published: Sep 9, 1998) indicate that paid plasma donors are at a higher risk of infectious disease than volunteer donors. The GAO found that incidence rates for qualified donors were about 24 times higher for HIV (61.80/100,000 person-years vs 2.59), about 40 times higher for HBV (245.50 vs. 6.25), and about 6 times higher for HCV (63.50 vs 11.65). The GAO also found that voluntary industry standards such as the qualified donor standard and inventory hold "greatly reduce the chances of these units being pooled for manufacturing". As you know, Source Plasma donors can donate up to 2 times per week. Some donors donate at this frequency each week for 52 weeks. This means that a donor who seroconverted could have donated multiple window period donations before he/she is detected. The inventory hold serves to intercept these donations from entering the manufacturing pools. For these reasons, FDA decided to incorporate these standards into regulation. We welcome a comprehensive review of current data and we invite PPTA or PPTA member firms to provide FDA with well-characterized contemporary information on Relevant Transfusion Transmitted Infections prevalence and incidence rates in Source Plasma donors. We note that Source Plasma collectors have for some time provided such information to European regulatory authorities.

At a recent PPTA/FDA Liaison Meeting on September 16, 2015, you also verbally raised the issue of Source Plasma that is exported to non-US licensed fractionators. We believe that licensed Source Plasma collectors who ship Source Plasma outside the US to non-licensed fractionators would still be responsible for notifying the fractionator if the donor was subsequently deferred under §610.41, or was subsequently determined to be ineligible under §630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection.

We respectfully decline your suggestion to reconsider the inventory hold provision as finalized in §640.69(f).

Sincerely,

Jay Epstein, M.D.
Director, Office of Blood Research and Review
Center for Biologics Evaluation and Research