Plasma Protein Therapeutics Association

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Reference No.: FDAA13015 **VIA EMAIL**

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Dear Dr. Golding,

We are writing on behalf of our members[1] to object to FDA's recent action to impose safety related labeling changes on human immune globulin products in the form of new boxed warnings regarding the risk of thrombosis. These changes are premature. As described more fully below, the Agency itself has stated that further evaluation is needed, and is on-going. If FDA has additional information relating to thrombosis risk, it has not been made known to industry nor has industry had the opportunity to evaluate the data upon which the decision for the new boxed warnings is based. Until FDA's on-going evaluation is complete, it is too early to conclude that existing labeling precautions on the risk of thrombosis are insufficient, that the proposed boxed warnings are necessary, or that the proposed boxed warnings recommend the proper risk mitigation strategies for the appropriate patients with the appropriate emphasis. For these reasons, we request that the agency:

- immediately withdraw its safety labeling change notifications to the sponsors of all human immune globulin products;

- withdraw or modify its corresponding Safety Communication on new boxed warnings for thrombosis related to human immune globulin products, dated June 10, 2013; and

- further and more fully analyze the data from the on-going data collection and make available the results of the evaluation prior to deciding whether boxed warnings or other safety labeling changes relating to the risk of thrombosis are needed and appropriate.

The Agency's Safety Communication on thrombosis risk, dated June 10, 2013 (the "Thrombosis Safety Communication") states that information from a retrospective

[1] Baxter, Biotest, CSL Behring, Grifols, Kedrion

analysis of data from a large health claims-related database, as well as from continued (emphasis added) postmarketing adverse event reports, necessitates a boxed warning for the entire class of human immune globulin products. The agency's own assessment, however, is that various factors might affect the risk of thrombosis and that the factors require further evaluation.

It is important to emphasize that thrombosis, the various associated risk factors and its mitigation are already a part of the Warnings and Precautions section (and other sections, including Patient Counseling) of the package insert for immune globulin products. FDA has not provided the rationale for the elevation of thrombosis to a boxed warning at this time; in particular FDA does not describe in detail the "new" evidence that presumably has strengthened the association between the use of immune globulin products and the risk of thrombosis. Until such evidence is put forth, the current wording in the Warnings and Precautions section is deemed adequate, with some additional changes to reflect that all patients are at risk, even those with no known risk factors, as FDA has pointed out. Further, the wording suggested by the agency for the boxed warning does not communicate any specifics related to the need for additional caution beyond what is already included in the package insert or anything new related to a change in the risk-benefit ratio as related to thrombosis.

FDA discussed the retrospective analysis in a published article entitled, "Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010." [2] As is clear from the title, the retrospective analysis did not include any data after 2010. That date is significant because FDA and industry did not identify activated Factor XI (FXIa) as a major cause of an increase in thromboembolic events until 2010. *Id.* at 2117-18. As you are aware, and as was discussed extensively in the May 2011 public workshop that we co-hosted, since 2010 our Members have instituted validated risk mitigation strategies to address the risk of FXIa in immune globulin products and to address the risk of harmful procoagulant activity in these products. Therefore, to know whether these products still have elevated thrombosis risks, not adequately addressed in current labeling, will require analyzing data collected since 2010. The Agency has implicitly conceded this point by engaging a Mini-Sentinel protocol to examine any on-going association between intravenous immunoglobulin and thromboembolic events.[3]

In addition, the Transfusion article acknowledges that a number of other observations of the study require further evaluation. For example, the article postulated that differences in rates of venous and arterial thromboembolic events (TEs) "could potentially be due to differences in predisposing risk factors for IG-exposed persons studied including but not

[2] Gregory W. Daniel, *et al., Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010,* Transfusion Oct 2012; 52:2113-2121 (the "Transfusion article").
[3] A description of the protocol is posted at: http://www.minisentinel.org/assessments/medical_events/details.aspx?ID=187.

limited to the demographic characteristics, underlying health conditions, indications for use, dose, rate of administration, or presence of elevated FXIa, which needs further investigation."[4] Similarly, the authors concluded that "identified age and sex-based differences in the effect of the IG products on occurrence of TEs need further epidemiologic investigation in clinical settings." *Id.* These are not the only limitations of the study. The Thrombosis Safety Communication does not provide citations to any more recent, post-2010 data, on which the agency could base more definitive conclusions. Furthermore, database studies similar to the one reported in the Transfusion article have been shown not to be predictive of the risks for thrombosis. In the article, "The validity of ICD-9-CM codes in identifying postoperative deep vein thrombosis and pulmonary embolism,"[5] authored by staff from the Department of Health and Human Services, the positive predictive value of ICD-9 codes in a large clinical database for DVT and PE is only 29%.

For the reasons stated above, any conclusions about the need for new boxed warnings about thrombosis risk for these products are premature. By FDA's own characterizations, the information the Agency has collected to date only amounts to a "signal of a serious risk," rather than "new safety information." In the provision of the Federal Food, Drug, and Cosmetic Act (the "FDCA") that covers safety labeling changes, the definition section distinguishes between "new safety information" and a "signal of a serious risk." [21 U.S.C. §505(o)(2)(C)] That distinction is important because the statute provides the Secretary with authority to request safety labeling changes only upon becoming "aware of new safety information" -- not upon becoming aware of a signal of a serious risk. [*Id.,* §505(o)(4)(A)]

In this case, the legal distinction is important for very practical reasons. Before representing that particular patient populations are at higher thrombosis risk from these products than the previously-recognized risk, and before recommending specific mitigation strategies for these patients, it is important to confirm these conclusions. If they turn out to be inaccurate, doctors are likely to decide against using immune globulin products for patients who could be helped by the products. FDA is well aware of the chilling effect that such premature warnings can have on products, such as when FDA previously issued Dear Doctor letters on albumin products. Such a chilling effect is even more likely in this case, where such a long period of time has passed since the observed increase in thromboembolic events in 2010 that many prescribers are likely to assume incorrectly that another increase in thromboembolic events has occurred since 2010 that has spurred the Agency into action.

Alternatively, other doctors may improperly rely on unvalidated mitigation strategies as sufficient to justify the risk of administering the products. Moreover, in this case where

[4] Transfusion article, at 2118 (emphasis added).
[5] Chunliu Zhan, *et al., The validity of ICD-9-CM codes in identifying postoperative deep vein thrombosis and pulmonary embolism,* The Joint Commission Journal of Quality and Patient Safety June 2007; 33:326-331.

the industry has worked collaboratively with FDA to address the only clearly-identified cause of elevated thrombosis rates – previously-undetected levels of FXIa in the products -- it may well turn out that post-2010 data show the thrombosis rates for these products to have returned to levels prior to 2010. In that case, it will be improper to have prioritized thrombosis warnings by placing them at the very top of the boxed warning, subjugating the other important warnings within the box. Moreover, no mechanism for correcting such an error is set forth in the safety labeling portion of the FDCA, and as a practical matter, the inertia against making a class-wide correction will make doing so extremely unlikely.

For those reasons, we request that the agency withdraw its safety labeling notices for these products, withdraw or modify the FDA Safety Communication on the agency website, and further and more fully analyze the data from the on-going evaluations to decide what boxed warnings for the class are needed and appropriate, if any. We also request that the Agency share with industry any additional safety analyses it may have done so industry can be informed and involved in the implementation of steps to further protect patients using human immune globulin products.

Sincerely,

Mary Gustafson
Vice President, Global Regulatory Policy
Plasma Protein Therapeutics Association

Cc: Dr. Jay Epstein
Dr. Dorothy Scott