PPTA
Plasma Protein Therapeutics Association

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Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA E-Mail & USPS

SUBJECT: Draft Guidance for Industry, "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency."
Docket No.: 2005D-0438

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Food and Drug Administration's (FDA) Draft Guidance for Industry "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency" [hereinafter, "Draft Guidance Document" or "Draft Guidance"]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

We appreciate the opportunity to comment on this Draft Guidance Document. We note that the approach for this Draft Guidance Document was presented at a March 1999 Blood Products Advisory Committee (BPAC) meeting. Furthermore, the essence of the current document was then discussed the following year at the spring BPAC meeting and, as far as, we know, has been the licensing policy since that time. For that reason, PPTA would like to take this opportunity to comment on the process for guidance development and its use. PPTA commends FDA for publishing the Draft Guidance Document, which allows public comment on FDA review criteria. PPTA believes it is important for FDA to develop draft guidance documents when considering new biologics license application (BLA) review criteria that are not implicitly delineated in regulations. It is critical that new criteria be published by FDA for public and industry comment,

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rather than those criteria being imposed on a single manufacturer in the process of reviewing an individual BLA.

While PPTA appreciates FDA's willingness to discuss "current thinking" with regard to new criteria in advisory committee meetings and other settings, it is only through the Good Guidance Practices process of developing guidance documents that industry and others have the opportunity to provide comments on the Agency's "current thinking." Although we appreciate being able to comment on the guidance for intravenously administered immune globulins, we note that licensing criteria for subcutaneously administered immune globulins were presented in April 2005 at FDA's workshop, Intravenous Immune Globulins in the 21st Century: Progress and Challenges in Efficacy, Safety, and Paths to Licensure, and the current Draft Guidance Document does not include the licensing policy for the subcutaneous product that was presented at the workshop. Our members request the opportunity to comment on those criteria and encourage FDA to either expand the current document's scope or publish an additional draft guidance covering subcutaneous administration.

One of PPTA's goals is to encourage international harmonization whenever possible. On June 29, 2000, the European Medicines Agency (EMEA) issued a "Note for Guidance on the Clinical Investigation of Human Immunoglobulin for Intravenous Administration (IVIG)" [hereinafter, "Note for Guidance"]. A copy is enclosed for your convenience. This document describes the information that should be included when an application for marketing authorization for IVIG is made, including biological data, clinical trials, and patient follow-up. There are several differences between the data elements between FDA and EMEA. The greatest divergence can be found in the number of patients needed to validate efficacy, pharmacokinetic (pK), and safety studies. For instance the EMEA recommends pK parameters be studied in 15 patients, 10 of which should have primary immunodeficiency. Yet, FDA recommends at least 20 primary immunodeficiency patients. Furthermore, EMEA states that the 15 patients included in the pK study should be followed over 6 months to validate efficacy requirements. FDA, on the other hand, recommends 40 to 50 patients and a year time-frame to satisfy efficacy guidelines. For guidance regarding the evaluation of safety, FDA recommends approximately 40 patients and EMEA advises at least 30 patients or 180 infusions. Even though, we appreciate FDA providing definitive guidance regarding sample size, such disparities with EMEA lead to the duplication of clinical studies which often subject the same patients to redundant trials. In addition, it increases the cost of development, prolongs the approval process, and the products availability. We encourage FDA, in developing its final guidance, to consider harmonizing criteria with EMEA. This will facilitate development, instead of hindering it, which will bring life-saving therapies more quickly to those who need them.

In addition to the above comments regarding the process for guidance development and international harmonization, PPTA has the following specific comments regarding the Draft Guidance Document:

- As a general comment, the Draft Guidance does not specifically address pediatric use and testing in pediatric populations. It would be helpful if FDA's expectations and criteria for fulfilling the requirements of the Pediatric Rule were clarified in this Draft Guidance Document. Among issues that need clarification are the parameters for testing in a pediatric population vis-à-vis in an adult population. Are pK studies adequate or are separate clinical trials needed? May pediatric testing be conducted as a post-marketing commitment? If so, what labeling is required at the time of licensing?

- In the section on Safety, Adverse Experience (AE) rates should be more clearly defined according to the concentration level of the product being infused. For example, much of the experience with IGIV is with 5 % products. At this level, AE's are generally low but are not standardized. Consequently, due to the absence of a standardized algorithm to measure AEs, some investigators may count them wrong, which would disproportionately skew the numbers. Furthermore, AE rates change with 10% products. Much of the data assumes that doubling the concentration level would double the AEs. However, the 10% product may be infused at a quicker rate, which might result in a more exponential, rather than arithmetic, increase in AEs. Therefore, it is recommended that FDA reconsider the upper limit of a 95% confidence interval (defined as .40 for AEs) for 10% products. Furthermore, FDA should provide guidance on whether maximum infusion rates apply and whether then the AE endpoints listed within this document would apply.

- Additionally, in this section, FDA states that explanations regarding discrepancies between patient diary data and case report forms (CRF) data must be included. Is it FDA's expectation that the explanation will include resolution of the discrepancies?

- In the section on Efficacy, FDA recommends comparing the rate of serious bacterial infections against relevant historical data. However, it is then recommended that a statistical demonstration of a serious infection rate of less than 1 be achieved to provide substantial evidence of efficacy. The comparison to relevant historical data would be redundant, if the end goal was to compare to infection rate of less than 1.

- In the Guidance for Pharmacokinetic (pK) studies of IGIV, FDA recommends pK parameters be compared to 3 versus 4 week dosing schedules. However, this comparison would be inconclusive because irrespective of schedule, once a patient is in a steady state and a detailed pK is completed, no differences should be expected. Therefore, this recommendation would not offer any relevant information on the merits of the pK study. Additionally, the pK parameters require the measurement of specific antibodies, however including this

information could alter pK values. For instance, if a patient has a cold, the Hemophilus titers may be consumed and confused. Further Guidance from FDA regarding the necessity of such measurements and how such factors should be evaluated may be appropriate to help clarify this requirement.

- Additionally, in the Pharmacokinetic section, the Draft Guidance recommends that the sponsor identify and justify a minimum acceptable trough level. Is it FDA's intention to allow a case-by-case approach to trough levels or does FDA have predetermined targets?

PPTA appreciates the opportunity to comment on the Draft Guidance. Should you have any questions regarding these comments or would like additional information, please contact PPTA.

Respectfully submitted,

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Plasma Protein Therapeutics Association

Attachment: FDAA06005a_EMEA Note for Guidance