Plasma Protein Therapeutics Association

May 12, 2009
Reference No.: FASC09026

The Honorable Anna G. Eshoo
U.S. House of Representatives
Washington, DC 20515

The Honorable Joe Barton
U.S. House of Representatives
Washington, DC 20515

The Honorable Jay Inslee
U.S. House of Representatives
Washington, DC 20515

RE: H.R. 1548, the Pathway for Biosimilars Act

Dear Representatives Eshoo, Barton, and Inslee:

On behalf of the Plasma Protein Therapeutics Association (PPTA), I am writing today to express the association's strong support for your legislation, H.R. 1548, the Pathway for Biosimilars Act.

PPTA is the association that represents human plasma collection centers and the manufacturers of medicinal therapies, including albumin, alpha$_1$-proteinase inhibitor, blood clotting factors, and immune globulin from this human plasma. Some of our members also use recombinant DNA technology to produce blood clotting factors. Collectively, these therapies – both plasma-derived and recombinant – are known as "plasma protein therapies."

We applaud your decision to emphasize patient safety in your legislation. Requiring the issuance of proposed product class specific guidance prior to Food and Drug Administration (FDA) consideration of an abbreviated biologics license application (BLA) and for the issuance of final product class specific guidance prior to FDA approval of an abbreviated BLA will provide important safeguards for the patient community. By providing criteria for the types of studies necessary to prove biosimilarity as well as criteria for assessing interchangeability and immunogenicity for particular biological products, the agency is establishing a framework that will allow FDA to ensure adequate consumer protection. Such protection is especially vital for patients that rely upon plasma protein therapies because their health is usually already severely compromised by rare, chronic, and debilitating diseases, disorders, and medical conditions.[1] Moreover, the language in H.R. 1548 requiring the issuance of final guidance on

[1] The National Institute of Health Office of Rare Diseases generally defines rare diseases as those having a "prevalence of fewer than 200,000 affected individuals in the United States." Among those diseases that meet this threshold, according to the agency's database, and are treated by plasma protein therapies are alpha1-antitrypsin deficiency, B-cell chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, hemophilia A, hemophilia B, hyperimmunoglobulinemia E syndrome, idiopathic thrombocytopenic purpura, Kawasaki syndrome, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, primary immune deficiency disease, staphylococcal toxic shock syndrome, and von Willebrand disease.. *See* OFFICE OF RARE DISEASES, U.S. DEP'T OF HEALTH & HUMAN SERVS., RARE DISEASE AND RELATED TERMS, *at* http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1 (last visited May 12, 2009).

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whether or not the product class to which the abbreviated BLA applicant belongs contains products that are interchangeable is essential when considering plasma protein therapies.

Plasma protein therapies are not interchangeable within their respective product classes – this is true for the four brands of alpha$_1$-proteinase inhibitor, the 11 brands of antihemophilic coagulation factor VIII (FVIII), the three brands of antihemophilic coagulation factor IX, the two brands of anti-inhibitor complex, the eight brands of immune globulin, and the three brands of prothrombin complex concentrate. This lack of interchangeability is due to documented patient tolerability and clinical response issues when certain patients use certain therapies; thus, FDA guidance required by H.R. 1548 would likely reflect that these therapies are not interchangeable within their respective product classes before the agency even considers an abbreviated BLA using a brand in one of these product classes as the reference product.

Patient tolerability of and their clinical response to these plasma protein therapies vary not only because each patient is unique, but also because each formulation within each therapy class available in the U.S. market is unique because each manufacturer uses different fractionation and manufacturing processes. For example, it is well-established that each step in the production of intravenous immune globulin (IVIG) can "affect the integrity and activity of the final protein and introduce [significant] differences" among the therapies in this product class.[2] A slight change in the pH during protein fractionation can result in plasminogen ending up in higher concentrations in IVIG, which "can have a devastating effect on the stability and efficacy of the immunoglobulins" as the enzyme attacks and degrades these proteins, especially immunoglobulin G, which is the active agent in IVIG.[3] Additionally, the type of excipients, as well as the stage in the manufacturing process during which they are used, will "influence the safety profiles of [IVIG therapies]."[4]

Immunogenicity is also an issue for certain classes of plasma protein therapies. For example, a major complication in the treatment of patients with hemophilia A is a poor control of bleeding linked to the development of an antibody (also called an inhibitor) against the FVIII protein. The development of FVIII inhibitors may be due to a patient commencing or changing treatment, or changes in the manufacturing process of a FVIII therapy. A study of previously untreated patients has demonstrated that those treated with recombinant FVIII (rFVIII) are 2.5 to 3 times more likely to develop inhibitors than patients treated with plasma-derived FVIII.[5] The European Medicines Agency (EMEA) recently concluded a study of rFVIII that revealed cases of recurring inhibitors are

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[2] Jerry Siegel, *The Product: All Intravenous Immunoglobulins Are Note Equivalent*, 25 PHARMACOTHERAPY 78S, 79S (2005); *see also* Ming-Han Tsai et al., *Clinical Responses of Patients with Kawasaki Disease to Different Brands of Intravenous Immunoglobulin*, 148 THE JOURNAL OF PEDIATRICS 38, 42 (Jan. 2006) (concluding that different formulations of IVIG may result in different clinical outcomes for children suffering from Kawasaki's syndrome).

[3] Basil Golding, MD, Dir. of Plasma Derivatives, U.S., Dep't of Health & Human Servs., Clinical Trial Endpoints for Immune Globulin Intravenous (IGIV), Address Before the Blood Products Advisory Committee (Mar. 26, 1999) (transcript available at http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3504t2.pdf.) [hereinafter "Golding Presentation"].

[4] *Id.*; *see also* Georg Lemm, MD, Ph D, *Composition and Properties of IVIg Preparations that Affect Tolerability and Therapeutic Efficacy*, 59 NEUROLOGY S28 (2002) (describing the affect of excipients, such as sugars (including the type of sugar) and salt, may have on the final formulation of an IVIG brand).

[5] *See* Jenny Goudemand, et al, *Influence of the Type of Factor VIII Concentrate on the Incidence of Factor VIII Inhibitors in Previously Untreated Patients with Severe Hemophilia A*, 107 BLOOD 46, 49 (2006).

especially prevalent after switching from one rFVIII therapy to another in previously treated patients. Because H.R. 1548 would require FDA to establish criteria in assessing immunogenicity for a product class like rFVIII, this guidance would not only protect patients, but also contain costs.

Treating hemophilia patients with inhibitors is both difficult and expensive. According to 2007 data, there are approximately 1,270 hemophilia patients with an inhibitor in what is a $909 million annual market in the U.S.[6] The treatment of inhibitor patients is difficult because each one reacts differently to the various treatments and therapies. Several therapeutic approaches may be required to control a bleed – patients are either infused at a high dose of FVIII in order to familiarize the immune system to recognize FVIII to the point that it stops producing antibodies, or they are treated with recombinant factor VIIa or activated prothrombin complex concentrate.[7] While many hemophilia patients with inhibitors achieve immune tolerance within six to nine months, 25 percent of the patients treated require expensive immune tolerance treatment regimens for the duration of their lives.[8] Approving an abbreviated BLA for a product claiming biosimilarity to a rFVIII brand without proper guidance on immunogenicity would significantly increase the risk of inhibitors, including recurring ones, in a patient that is switched to the biosimilar version of this therapy.

PPTA also supports the provision found in H.R. 1548 that allows FDA through guidance to indicate that the agency will not approve an abbreviated BLA for certain products or product class based on the current science and experience. In addition to the patient tolerability and immunogenicity issues surrounding these therapies, the molecules used as the active agents in these therapies are highly complex. For example, the human IgG molecule weighs about 150,000 daltons and is a quaternary structure consisting of two identical light polypeptide chains and two identical heavy polypeptide chains[9] and the FVIII molecule consists of a very large, single polypeptide chain protein with a tertiary domain structure and weighing 264,763 daltons.[10] The tertiary structure of the FVIII molecule includes a triplicated region of 330 amino acids (A-domains), a unique region of 980 amino acids (the B-domain), and a carboxy-terminal duplicated region of 150 amino acids (C-domains).[11] With regard to the rFVIII protein, it is considered one of the most complex therapeutic proteins ever developed by recombinant technology.[12]

It is also important to note that FDA has previously stated that all four alpha$_1$-proteinase inhibitor therapies in the market are "somewhat heterogeneous in terms of protein composition and chemical structures."[13] Specifically, the agency notes that although the alpha$_1$-proteinase inhibitor protein is the active agent in all four formulations in the marketplace, each formulation "contain[s] different amounts of other plasma proteins

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[6] *See* THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2007 152 (2008) [hereinafter "MRB Report"].
[7] *Id*. at 150.
[8] *Id*. at 151.
[9] *See* CHARLES A. JANEWAY, ET AL, IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE § 3.1 (5th ed. 2001).
[10] *See* Betty W. Shen, et al, *The Tertiary Structure and Domain Organization of Coagulation Factor VIII*, 111 BLOOD 1240, 1241, fig. 1 (2008).
[11] *See* Gordon A. Vehar, et al, *Structure of Human Factor VIII*, 312 NATURE 337 (1984).
[12] *See* Angelica Fatouros, et al, *Recombinant Factor VIII SQ – Influence of Oxygen, Metal Ions, pH and Ionic Strength on Its Stability in Aqueous Solution*, 155 INT'L J. OF PHARMACEUTICS 121, 122 (1997).
[13] CTR. FOR BIOLOGICS EVALUATION & RESEARCH, U.S. DEP'T OF HEALTH & HUMAN SERVS., HETEROGENEITY OF ALPHA-1 PROTEINASE INHIBITOR (HUMAN) PRODUCTS, *at* http://www.fda.gov/cber/infosheets/alph1pi.htm (last visited May 12, 2009).

and…chemical modifications which arise during manufacturing and occur at minor to substantial levels varying from [therapy] to [therapy]."[14] Moreover, a previous attempt at a *bona fide* technology transfer for this therapy nearly failed in recent years.[15]

Interestingly, the EMEA has exempted both plasma-derived therapies and recombinant blood clotting factor from a biosimilars process in the European Union. Specifically, the EMEA has stated that "[i]n view of the complex and variable physico-chemical, biological and functional characteristics of [immune globulin and both plasma-derived and recombinant blood clotting factors], it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described…for "new products"."[16] Although PPTA agrees with EMEA and does not believe the science and experience currently supports the use of an abbreviated FDA approval process for any plasma protein therapies (plasma-derived or recombinant), we recognize that H.R. 1548 would not allow FDA to issue similar guidance as it pertains to recombinant blood clotting factors. PPTA is, however, confident that FDA would issue guidance stating that it will not license any therapies derived from human plasma through abbreviated BLAs.

PPTA also supports the general rules, including those covering the number of reference products, the reviewing division, and the application of risk evaluation and mitigation strategies, for filing abbreviated BLAs under H.R. 1548. With regard to the reviewing division, plasma-derived therapies and recombinant blood clotting factors are licensed by the Center for Biological Evaluation and Research (CBER) at FDA. Because of the unique, complex nature of plasma protein therapies, we agree that it is imperative that CBER review any abbreviated BLAs using one of these therapies as a reference product.

Lastly, PPTA strongly supports the provision in H.R. 1548 that would extend up to 14 years a non-patent exclusivity period to innovator biologicals manufacturers. As you know, this language would afford the innovator with a period during which it may have the exclusive right to rely upon its clinical data to support an FDA determination of the safety and efficacy of the product. The underlying patents of the innovator product will generally not be sufficient to protect it against an abbreviated BLA under H.R. 1548 because such an applicant must only prove biosimilarity to the innovator product rather than sameness[17] and bioequivalence,[18] which are required for an abbreviated new drug application under Hatch-Waxman. Hatch-Waxman provides a total patent term of up to 14 years for the traditional, small molecule pharmaceuticals.[19] Although the actual manufacturing process is what distinguishes the various plasma-derived therapies in each plasma protein therapy class, a reasonable, non-patent data exclusivity period similar to the overall patent term under Hatch-Waxman is critical to preserve incentives

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[14] *Id.*
[15] *See* Golding Presentation, *supra* note 4 (demonstrating that an abbreviated BLA applicant using a plasma protein therapy as a reference product would not be able to precisely replicate the manufacturing process with less information).
[16] European Medicines Agency [EMEA], *Guideline on Similar Biological Medicinal Products*, at 7, CHMP/437/04 (Oct. 30, 2005).
[17] *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iii), and (v) (2008) (generally requiring "same": (1) conditions of use; (2) active ingredient; (3) route of administration; (4) dosage form; (5) dosage strength; and (6) labeling).
[18] *See* 21 U.S.C. § 355(j)(2)(A)(iv).
[19] 35 U.S.C. § 156(c) (2008).

for innovation for the manufacturers of lifesaving recombinant blood clotting factors. We greatly appreciate your recognition of the importance of providing similar protection for biologicals through this appropriate and necessary data exclusivity provision.

In conclusion, PPTA appreciates your recognition of the risk of immunogenicity reactions in biologicals in both the context of biosimilarity and interchangeability and your decision to require product class specific guidance, which is critical to ensure patient safety. Thank you again for your outstanding efforts on this important issue. If you would like to further discuss these comments, please contact Jay Greissing (jgreissing@pptaglobal.org) or Jon McKnight (jmcknight@pptaglobal.org) in our office at 202-789-3100.

Sincerely,

Julie Birkofer
Vice President
PPTA North America