PPTA
Plasma Protein Therapeutics Association

March 2, 2009
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The Honorable Max Baucus
United States Senate
Washington, DC 20510

The Honorable Kent Conrad
United States Senate
Washington, DC 20510

RE: Comparative Clinical Effectiveness Research – Comments on S. 3408 from the 110th Congress

Dear Chairman Baucus and Chairman Conrad:

On behalf of the Plasma Protein Therapeutics Association ("PPTA"), I am writing today to underscore a few specific issues related to the evaluation of medical treatments, services, and items for the treatment of rare diseases.[1] As you move toward reintroduction of the Comparative Effectiveness Research Act, we would respectfully ask for your consideration of recommendations we have put forth in the Appendix.

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."

As the leading voice of the plasma protein therapeutics industry, we are very familiar with the various issues facing the patients that require plasma protein therapies in the treatment of their rare, chronic, and debilitating diseases, disorders, and medical conditions. From issues ranging from safety to access, PPTA maintains an open dialogue with all consumers of plasma protein therapies. For many of the diseases treated by plasma protein therapies, the patients who are afflicted lack vital proteins. For example, a patient suffering from alpha1-antitrypsin deficiency

[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 qualifying for this status, according to the agency, are alpha1-antitrypsin deficiency, B-cell chronic lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, hemophilia A, hemophilia B, idiopathic thrombocytopenic purpura, Kawasaki syndrome, primary immune deficiency disease, 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 Jan. 28, 2009).

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lacks a sufficient level of the alpha1-proteinase inhibitor protein; a patient suffering from hemophilia A lacks a non-mutated factor VIII protein; and a patient suffering from primary immune deficiency disease ("PIDD") lacks a sufficient level of immunoglobulin G protein. Regular infusions of the appropriate plasma protein therapy best suited for the individual needs of the patient are generally required for the duration of the life of the patient in order to reduce hospitalizations, increase life expectancy, and improve quality of life.

PPTA supports comparative clinical effectiveness research that both advances the treatment of individual patients and recognizes the unique nature and value of targeted therapies that benefit patients with rare, chronic, and debilitating diseases disorders, and medical conditions. With respect to certain diseases, including many rare diseases, and the therapies used to treat these diseases, comparative clinical effectiveness research has limited utility. For example, because each individual patient reacts differently to each plasma protein therapy, patients must have access to the complete range of plasma protein therapies in each therapeutic class. Moreover, in this current economic environment, resources expended in the furtherance of comparative clinical effectiveness research should be limited to cases where the information produced from such research has value to the physician in the treatment of their individual patients.

Without question, comparative clinical effectiveness research is a critical component of health care reform because, in most cases, it will improve patient care by affording patients and physicians with the opportunity to truly make evidence-based treatment decisions. The inclusion of $1.1 billion in Federal funding allocated for the conduct and support of such research and the establishment of the Federal Coordinating Council for Comparative Effectiveness Research in the American Recovery and Reinvestment Act of 2009 (Pub. L. 111-5) clearly demonstrates the value Congress believes the results of comparative clinical effectiveness research will bring to the health care system in the United States. We applaud the willingness of you and your staffs to consider our comments on where rare diseases fit into this essential health care reform policy.

Thank you for your consideration. If you would like to further discuss these recommendations, please contact Jay Greissing (jgreissing@pptaglobal.org) or Jon McKnight (jmcknight@pptaglobal.org) in our office at 202-789-3100.

Sincerely,

Julie Birkofer

Julie Birkofer
Vice President
PPTA North America

Attachment

APPENDIX

1. Comparative clinical effectiveness research should only be utilized when it will advance the treatment of individual patients.

Consistent with the congressional intent of the comparative effectiveness research provision in the American Recovery and Reinvestment Act of 2009, the Comparative Effectiveness Research Act must also "recognize that a 'one-size-fits-all approach to patient treatment is not the most medically appropriate solution to treating various conditions…"[2] This principle is particularly applicable to many rare diseases. For example, patient tolerability and clinical response to plasma protein therapies used to treat rare diseases varies not only because each patient is unique, but also because each formulation within each therapy class available in the U.S. market uses a different manufacturing process. In short, plasma protein therapies are not interchangeable.

Depending on the protein fractionation and manufacturing processes, some proteins found in human plasma may end up in low concentrations in the final dosage form of a therapy which may have "far-reaching effects" on its safety and efficacy.[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 these [therapies]."[4]

The complexity of the molecules, such as immunoglobulin G, factor VIII ("FVIII"), von Willebrand factor, and alpha$_1$-proteinase inhibitor, and their post-translational modifications also impact the unique nature of the final dosage form.[5] For example, FDA has stated that all four alpha$_1$-proteinase inhibitor therapies in the market are "somewhat heterogeneous in terms of protein composition and chemical structures."[6] Specifically, the agency notes that although 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 and…chemical modifications which arise during manufacturing and occur at minor to substantial levels varying from [therapy] to [therapy]."[7]

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[2] *See* H.R. Rep. No. 111-16 at 453.
[3] *See* Basil Golding, MD, Dir. of Plasma Derivatives, U.S., Dep't of Health & Human Servs., Clinical Trial Endpoints for Immune Globulin Intravenous (IGIV) (Mar. 26, 1999) (transcript available at http://www.fda.gov/ohrms/dockets/ac/99/transcpt/3504t2.pdf.).
[4] *Id.*
[5] *See, e.g.*, Andrew Chang, Assoc. Dir, Div. of Hematology, U.S., Dep't of Health & Human Servs., Licensed Therapeutic Protein Products with Known Structural Modifications, Address Before the Blood Products Advisory Committee (Nov. 4, 2005) (transcript available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4190t2.rtf.) (describing the complexity of the von Willebrand factor protein).
[6] *See* 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 Jan. 28, 2009).
[7] *Id.*

Physicians must continue to have autonomy to consider an individual patient's symptoms, medical history, and physical characteristics in making patient-specific determinations as to the best course of treatment. With regard to the excipient content in different brands of IVIG, a patient with certain genetic characteristics or comorbidities may be more prone to serious adverse reactions. For example, the sucrose content may create a higher risk of renal failure in some patients.[8] The sugar content will also affect whether a particular brand of IVIG should be given to a diabetic.[9] The sodium content could be problematic for patients with hypertension.[10] Both sodium and sugar content may affect the osmolality of the final IVIG therapy – physicians often prefer to use a low volume of IVIG with low osmolality in treating those patients who are also suffering from congestive heart failure or compromised renal function.[11] Additionally, physicians may also choose to administer a brand of IVIG with lower pH for those patients with small peripheral vascular access or a tendency toward phlebitis.[12]

When considering hemophilia, it should be noted that 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 FVIII. The risk of such development may be due to commencing or changing treatment, or changes in the manufacturing process of a 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.[13] The European Medicines Agency recently concluded a study of rFVIII that revealed cases of recurring inhibitors are especially prevalent after switching from one rFVIII therapy to another in previously treated patients.[14] Because of this immunogenicity risk in hemophilia patients, limitation of patient access must not be an unintended consequence of the Comparative Effectiveness Research Act.

Moreover, any limitation of access for hemophilia patients could significantly expand the inhibitor market; thus, if unnecessary comparative effectiveness research is conducted, it could potentially drive up health care costs, rather than contain them. For example, there are approximately 1,270 hemophilia patients with an inhibitor in what is a $909 million annual market in the U.S.[15] The treatment of inhibitor patients is difficult because each patient reacts differently to the various treatments and therapies. Several therapeutic approaches may be required to control bleeds in such patients. For inhibitor patients with FVIII deficiency,

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[8] *See* Georg Lemm, MD, Ph D, *Composition and Properties of IVIg Preparations that Affect Tolerability and Therapeutic Efficacy*, 59 NEUROLOGY S28 (2002)
[9] *Id.*
[10] *Id.*
[11] *Id.*
[12] *Id.*
[13] *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)
[14] *See* Press Release, The European Medicines Agency, EMEA Completes Review of Recombinant Factor VIII Products and Inhibitor Development (July 31, 2007) *available at* http://www.emea.europa.eu/pdfs/human/press/pus/31022507en.pdf.
[15] *See* THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2007 152 (2008)

physicians will either infuse them at a high dose of FVIII so that their immune system stops producing antibodies, or they are treated with recombinant factor VIIa or activated prothrombin complex concentrate.[16] While many inhibitor patients achieve immune tolerance within six to nine months, 25 percent of the patients treated require immune tolerance treatment regiments for the duration of their lives.[17]

As evidenced by the unique nature and value of the above described plasma protein therapies, there are some treatments that are used for the same medical conditions that have different attributes and may interact differently with individual patients. Conducting comparative clinical effectiveness research in these rare disease areas will not likely produce information that will be useful to physicians in treating their individual patients, because it is likely that the individual patient reaction to the different treatments will be determinative as to the choice of treatment.

PPTA Recommendation #1:

On page 3, after line 2, insert the following:

> "(C) TREATMENT OF RARE DISEASES.—When evaluating medical treatments, services, and items for the treatment of a rare disease, as described in paragraph (7), such research shall not be conducted in instances where it is unlikely to yield information that will improve the treatment of patients suffering from such a disease.".

On page 3, after line 17, insert the following:

> "(6) PLASMA PROTEIN THERAPIES.—The term 'plasma protein therapies' means a therapy, including alpha$_1$-proteinase inhibitor, blood clotting factors, and immune globulin, derived from human plasma, as well as blood clotting factors produced by using recombinant DNA technology.
>
> "(7) RARE DISEASE.—The term 'rare disease' means a disease, disorder, or medical condition with a prevalence of fewer than 200,000 affected individuals in the United States.".

On page 4, strike lines13 through 23, and replace with the following:

> "(c) PURPOSE.—The purpose of the Institute is to improve health care delivered to individuals in the United States by advancing the quality and thoroughness of clinical evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, and managed clinically, while recognizing that a 'one-size-fits-all' approach is not the most medically appropriate solution to treating various conditions, especially rare diseases. The Institute

[16] *Id*. at 150.
[17] *Id*. at 151.

shall use research and evidence synthesis, as appropriate, and disseminate its findings with respect to the relative outcomes, clinical effectiveness, and appropriateness of the medical treatments, services, and items described in subsection (a)(2)(B) in a manner that will empower patients and physicians to make the appropriate treatment decisions together."

On page 5, line 20, strike "and".

On page 5, line 24, strike "." and insert "; and".

On page 5, after line 24, insert the following:

"(vi) the variance in clinical response and tolerability to certain medical treatments, services, and items, including the multiple brands in each class of plasma protein therapies, by patients suffering from rare diseases due to genetic variations among patient populations or subpopulations, as well as comorbidities."

On page 6, after line 23, insert the following:

"(iii) THE RELATIVE VALUE OF RESEARCH PROJECTS FOR RARE DISEASES.—When pharmaceuticals or biologicals that are used for the treatment of the same rare disease lack therapeutic equivalence because of their heterogeneity in terms of chemical structure and protein content despite using the same active agent in the manufacturing process, the Institute shall determine that it should not conduct new research, as described in subparagraph (2)(A) of this paragraph, evaluating the use of such pharmaceuticals or biologicals in the treatment of such rare diseases."

2. Clinical data lack robust evidence for evaluating the clinical effectiveness of treatments for rare diseases.

Because of the limited patient populations for rare diseases, clinical trials for therapies used to treat these diseases are often not feasible, and when they are, they are often so small that a knowledge gap about long-term benefits and effectiveness of the therapy are often not known until well after the therapy is in the market. This inability to obtain statistically significant results suggests comparative clinical effectiveness will not provide relevant information for physicians in treating their individual patients.

While diseases with greater patient populations and multiple treatments may readily lend themselves to a comparison of clinical effectiveness, trial data on most rare diseases is insufficient because so much of the drug use in treating them is off-label. Moreover, since patients with rare conditions may receive a range of treatment interventions in the absence of a consensus "standard of care" or any recent clinical guideline, it can be difficult to establish a consistent comparator for comparative effectiveness research. Additionally, because patient reactions to plasma protein therapies vary widely from one therapy to another, as discussed in

section 1 of this Appendix, conducting comparative clinical trials may present ethical questions if patients are required to switch from one therapy to another.

PPTA Recommendation #2:

On page 7, line 13, after "studies", insert the following before the period:

"except when evaluating the treatment of rare diseases".

3. The use of cost-effectiveness analysis measured through quality adjusted life years ("QUALYs") should not be considered when evaluating prescription drugs used to treat rare diseases.

The National Institute of Clinical Evidence ("NICE") in the United Kingdom is a strong example of the dangers of considering cost effectiveness. The December 3, 2008 edition of *The New York Times* describes how British citizen Bruce Hardy was unable to get an expensive new drug to help treat his kidney cancer strictly because of its cost, which was $54,000 for six months of treatment. QUALYs, which NICE uses in their economic analysis, cannot adequately measure cost effectiveness of treating rare diseases because of the multiple variables involved. For example, patients requiring plasma protein therapies to treat their rare diseases must receive regular infusions for the duration of their lives. While these lifesaving therapies are expensive, they are often the only treatment option available and the value they bring to consumers and the health care system as a whole in terms of reduced hospitalizations, increased life expectancy, and improved quality of life is difficult to measure. This is true whether or not the Food and Drug Administration ("FDA") has approved the therapy for use in treating the particular rare disease.

As you know, under Medicare Part A and Part B, the Centers for Medicare and Medicaid Services ("CMS") generally only covers items and services that are "reasonable and necessary for the diagnosis or treatment of illness or injury…"[18] Should the agency use its authority to issue national coverage determinations to make such a determination[19] based on the results of comparative clinical effectiveness research, formulary-like situations that would impede patient access to the complete range of products in a specific class could occur for certain classes of drugs through cost-effectiveness analysis. For the above reasons as well as those outlined in section 1 of this Appendix, the Comparative Effectiveness Research Act must limit CMS' authority to use government supported comparative clinical effectiveness research data in making any determinations that would limit coverage for therapies used to treat rare diseases.

PPTA Recommendation #3:

On page 41, after line 18, insert the following:

[18] *See* 42 U.S.C. § 1395y(a) (2007).
[19] *See* 42 U.S.C. § 1395y(l).

"LIMITATION ON APPLICATION OF GOVERNMENT SUPPORTED COMPARATIVE EFFECTIVENESS RESEARCH
"SEC. 1183. The Administrator of the Centers for Medicare and Medicaid Services shall not use findings from comparative clinical effectiveness research, or any cost-effectiveness analysis, such as that measured through measured through quality adjusted life years, supported with Federal funds, including funds provided by the Agency for Healthcare Research and Quality, as the basis for determining that an item or service is reasonable and necessary for the treatment of a rare disease, as defined in paragraph (a)(7) of section 1181 of this title, under section 1862(a)(1)(A) of this Act (42 U.S.C. § 1395y(a)(1)(A)) in cases where –

(a) such a determination would result in denial of coverage of the item or service for patient populations or subpopulations who would likely benefit from improved clinical or other patient-related outcomes, such as through increased life expectancy, improved quality of life, reduced hospitalizations, adherence, patient reported outcomes, or independence and productivity; or

(b) evidence exists that demonstrates that genetic variations among patient populations or subpopulations, as well as comorbidities are associated with differences in patient tolerability and clinical response to an item or service that is subject of the research."

4. The Health Care Comparative Effectiveness Research Institute created by the Comparative Effectiveness Research Act must include adequate representation of patients, physicians, and manufacturers, including a permanent advisory panel on rare diseases, to ensure an open and transparent process.

Section 804 of the American Recovery and Advisory Act of 2009 creates a "Federal Coordinating Council for Comparative Effectiveness Research, the duties of which are to "coordinate the conduct or support of comparative effectiveness and related health services research" and "advise the President and Congress on…infrastructure needs…and organizational expenditures" for such research conducted by the Federal Government. While this council will have no role in mandating coverage or reimbursement policies for public or private payers, the lack of patient and physician representation is troublesome, even in its advisory and coordination role.

In order to ensure information produced from the comparative clinical effectiveness research is relevant to decisions made by physicians and patients in the clinical setting, each study must have a dedicated advisory panel consisting of a patient suffering from the disease, disorder, or medical condition being evaluated and a physician with the relevant clinical experience. For example, if comparing the clinical effectiveness of certain drugs, the physician on the advisory panel should be required to have specialty experience prescribing or administering the drugs under consideration. Moreover, the Comparative Effectiveness Research Act should be amended to include a permanent advisory panel on rare diseases. A separate patient advisory council of

this nature is imperative to ensure the rare disease community is adequately represented and the nuances of their treatment plans are properly articulated to the study advisory panels and, in turn, those conducting the studies. Such recommendation is especially necessary if you choose not to adopt PPTA Recommendation #1 in this Appendix.

PPTA Recommendation #4:

On page 11, line 14, strike "may" and replace with "shall".

On page 11, line 15, strike "permanent or".

On page 11, beginning on line 15, strike "as determined appropriate by the Institute", and replace with "for each research topic under consideration".

On page 12, after line 10, insert the following:

> "(C) Permanent Advisory Panel for Rare Disease.—For the purpose of establishing a comparative effectiveness research agenda for rare diseases, determining the relative value and feasibility of conducting such research on a particular rare disease, and advising the Institute on designing studies, where appropriate, for rare diseases, the Institute shall appoint a permanent advisory panel that shall include representatives of patients that suffer from rare diseases and physicians with clinical experience in treating rare diseases."

On page 19, line 20, after "(1)(B)", insert the following:

> "recommendations by the permanent advisory panel for rare diseases under paragraph (5)(C),".

On page 20, line 2, after "agenda,", insert the following:

> "recommendations regarding rare diseases,".

On page 20, line 5, after "agenda,", insert the following:

> "recommendations regarding rare diseases,".

On page 24, line 20, after "consumers", insert the following:

> ", including at least 1 representing the rare disease community".

On page 24, line 22, after "surgeons", insert the following:

> "and at least 1 physician with clinical experience in treating rare diseases".

On page 26, beginning on line 8, strike “pharmaceutical” and replace with “drug”.

On page 26, line 10, after “developers”, insert the following:

“, including at least 1 member representing either the pharmaceuticals industry, the biologicals industry, or the plasma protein therapeutics industry.”