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Internal Revenue Service  
CC:PA:LPD:PR (Notice 2011-9)  
Room 5203  
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**ELECTRONIC DELIVERY ([Notice.Comments@irs.counsel.treas.gov](mailto:Notice.Comments@irs.counsel.treas.gov))**

**Re: Notice 2011-9, Proposed Guidance Implementing the Annual Pharmaceutical Fee on Branded Prescription Drug Sales**

Dear Ms. Gabrysh,

The Plasma Protein Therapeutics Association (“PPTA”) would like to thank you for the opportunity to comment on Internal Revenue Service (“IRS”) Notice 2011-9. PPTA is the association that represents human plasma collection centers and the manufacturers of lifesaving medicinal therapies, including albumin, alpha<sub>1</sub>-proteinase inhibitor, antithrombin III, blood clotting factors, C1 esterase inhibitor, immune globulin, hyperimmune immune globulin, and protein C concentrate, from this human plasma.<sup>1</sup> 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.” The manufacturer membership of PPTA in the United States (“U.S.”) currently includes Baxter, Biotest, Cangene, CSL Behring, Grifols, and Talecris.

Excluding albumin, plasma protein therapies are solely approved for marketing in the U.S. by the Food and Drug Administration (“FDA”) for the treatment of rare diseases, disorders, and conditions. In the U.S., a “rare disease or condition” is generally defined as a disease or condition that affects less than 200,000 people.<sup>2</sup>

PPTA appreciates the challenges the IRS faces in promulgating the guidance implementing the annual pharmaceutical fee established in the Affordable Care Act

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<sup>1</sup> Human plasma is the clear liquid portion of blood that remains after the red cells, leukocytes, and platelets are removed. Due to its human origin, complexity, and richness in therapeutically useful proteins, human plasma is a unique biological material. See Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, in 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209.

<sup>2</sup> See 21 U.S.C. § 360bb(a)(2) (2006).

“ACA”).<sup>3</sup> Our comments today will primarily focus on our concerns with the agency’s interpretation of the orphan drug exclusion and its proposed methodology for calculating Medicare Part B sales of branded prescription drugs in Healthcare Common Procedure Coding System (“HCPCS”) codes containing a mixture of branded prescription drugs made by different manufacturers.

With regard to the orphan drug exclusion, PPTA urges IRS to use its authority to clarify that it will exclude the sales of all drugs and biologicals approved for marketing or licensed by the FDA solely for one or more rare diseases or conditions when the agency is calculating the market share of a manufacturer into the six government channels for the purpose of determining that manufacturer’s annual fee. The statute the agency is implementing is flawed in the sense that the current regulatory framework for orphan drug designations makes it impossible for most plasma protein therapies, despite being approved for marketing by FDA solely for the treatment of one or more rare diseases or conditions, to obtain the orphan designation, which is necessary to claim the Orphan Drug Act tax credit. The annual fee statute defines “orphan drug” as those drugs for which the Orphan Drug Act tax credit “was allowed.”<sup>4</sup> The proposed agency guidance in IRS Notice 2011-9 expressly requires the manufacturer to actually have “claimed” the Orphan Drug Act tax credit to be eligible for the orphan drug sales exclusion.<sup>5</sup> PPTA believes that a narrow interpretation of the “orphan drug” exclusion, as in the IRS proposed guidance, is inequitable because, as we will highlight below, many manufacturers were either unable to take the Orphan Drug Act tax credit or made the business decision to take a different tax credit that precluded a claim for the Orphan Drug Act tax credit in the same year or with respect to the same research and development expenses. Our comments today will describe the threats to access for some segments of the rare disease patient community that such an interpretation would create.

### **I. Although Well Intended, the Orphan Drug Exclusion from the Annual Pharmaceutical Fee Fails to Exclude the Sales of All Rare Disease Therapies**

The orphan drug exclusion from the annual pharmaceutical fee included in the ACA fails to fully serve the policy goal of rewarding past and encouraging future innovation in developing therapeutic interventions for the treatment of rare diseases, disorders, and conditions as it is predicated on whether the manufacturer has taken a

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<sup>3</sup> See Patient Protection and Affordable Care Act (“PPACA”) § 9008, Pub. L. No. 111-148, 124 Stat. 119, 859-862, *amended by* Health Care and Education Reconciliation Act of 2010 (“HCERA”) § 1404, Pub. L. No. 111-152, 124 Stat. 1029, 1064 (codified as amended at 26 U.S.C.S. prec. § 4001 (LexisNexis 2011)).

<sup>4</sup> See PPACA § 9008(e)(3).

<sup>5</sup> See Internal Revenue Service, Notice 2011-9, <http://www.irs.gov/pub/irs-drop/n-11-09.pdf> (last visited May 31, 2011). In order to address situations where the rights to the rare disease therapy could have been sold to another company or transferred to a successor, this proposed guidance further clarifies that the ODA tax credit for the drug could have been claimed by “any entity,” regardless of whether it was “part of the covered entity at the time the credit was claimed.” *Id.* The agency’s proposal in this instance will benefit the rare disease patient community because it would remove a potential impediment for a manufacturer in making the business decision to acquire a rare disease therapy for further development and marketing.

tax credit rather than strictly on disease prevalence. Beginning in 2011, the IRS will assess an excise tax, known as the “annual pharmaceutical fee,” on the sales volume of most branded pharmaceuticals sold into several government channels: Medicaid, Medicare Part B, Medicare Part D, the Department of Veterans’ Affairs, the Department of Defense, and the TRICARE retail pharmacy program.<sup>6</sup> In calculating the market share in these government channels for each manufacturer for the purpose of assessing the annual fee, the agency is to exclude sales of any “orphan drugs.”<sup>7</sup> As mentioned in the introduction, the statute defines “orphan drugs” as those drugs for which the Orphan Drug Act tax credit “was allowed.”<sup>8</sup> PPTA shares the opinion of the National Organization for Rare Disorders, which expressed significant concern that this statutory definition as well as the proposed IRS guidance requiring the manufacturer to actually have “claimed” the Orphan Drug Act tax credit to be eligible for the orphan drug sales exclusion could hinder innovation in the rare disease space.<sup>9</sup> With nearly 7,000 rare diseases, including some bleeding disorders, without a dedicated therapeutic intervention for their treatment, a policy that will create a barrier on future innovation in this space is counterintuitive. The downward economic pressure of the annual fee poses a threat to patient access to a number of plasma protein therapies as a result of the unique cost structure of the plasma protein therapeutics industry, which is described in great detail in Appendix A of this letter.

Nearly sixty years ago, Edwin J. Cohn developed the leading techniques for protein fractionation from human plasma, and in doing so, also presented the concept of plasma economics. In comparing plasma protein fractionation to the early development of aniline dyes from coal tar, he suggested that although the mere preparation of any single product is “cost prohibitive,” now that the individual proteins contained in the human plasma have a demonstrated therapeutic value, “one could not afford not to develop the various products that could be derived from them.”<sup>10</sup> This belief remains true today because of the complexity of the manufacturing processes and associated costs. Manufacturers of therapies derived from human plasma generally produce brands in multiple therapeutic classes from each pool of plasma in order to remain viable entities. It is also, however, important to note that immune globulin drives the plasma-derivatives market.<sup>11</sup>

A financially healthy plasma protein therapeutics industry allows manufacturers to (1) produce rare disease therapies that would otherwise be cost-prohibitive, such as antithrombin III, C1 esterase inhibitor, fibrin sealant, fibrinogen, plasma-derived (“pd”) factor IX (“FIX”), factor XIII (“FXIII”), protein C concentrate, prothrombin complex

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<sup>6</sup> See PPACA § 9008.

<sup>7</sup> *Id.* at § 9008(e)(3)

<sup>8</sup> *Id.*

<sup>9</sup> See Letter from Peter L. Saltonstall, President & CEO, Nat’l Org. for Rare Disorders, to the Hon. Max Baucus, Chairman, Senate Comm. on Finance (June 10, 2011) (attached).

<sup>10</sup> See Edwin J. Cohn, John L. Oncley, et al., *Chemical, Clinical, and Immunological Studies on The Products of Human Plasma Fractionation: I. The Characterization of the Protein Fractions of Human Plasma*, 23(4) J. CLINICAL INVESTMENT 417 (1944).

<sup>11</sup> See Albert Farrugia and Patrick Robert, *Plasma Protein Therapies: Current and Future Perspectives*, 19 BEST PRACTICE & RESEARCH CLINICAL HAEMATOLOGY 243 (2006).

concentrate, and von Willebrand factor (“vWF”);<sup>12</sup> (2) continue the research and development necessary to bring to market therapies that treat bleeding disorders that have largely been untreated or ineffectively treated;<sup>13</sup> (3) improve formulations and routes of administration for existing therapies; and (4) develop technology to increase the protein yield from each liter of plasma to address growing demand, especially for immune globulin. The annual pharmaceutical fee may, however, impede such investments by placing significant economic pressures on the industry. As we will discuss below, a significant majority of plasma protein therapies will not be eligible for the fee’s orphan drug exclusion.

### **A. FDA Regulations Preclude Most Plasma Protein Therapies from Claiming the Orphan Drug Act Tax Credit**

The Orphan Drug Act tax credit allows manufacturers to claim a tax credit equal to 50% of the qualified clinical testing expenses paid or incurred by the manufacturer or the sponsor in the taxable year on human clinical trials necessary to obtain FDA marketing approval of the drug or biological for a rare disease or condition for which it received an “orphan” designation.<sup>14</sup> This tax credit, which Congress established in the Orphan Drug Act, is among the key financial incentives available to drug manufacturers to accelerate research and development for therapies to treat rare diseases or conditions.<sup>15</sup> Other incentives include seven years of market exclusivity and the ability to apply for federally funded research grants.<sup>16</sup> Only drugs and biologicals to which FDA has granted “orphan drug” designation are eligible to receive these incentives, including the ability to claim the Orphan Drug Act tax credit.<sup>17</sup> As we will explain below, the FDA regulations implementing the Orphan Drug Act preclude most plasma protein therapies from obtaining orphan drug designation from the agency despite only possessing FDA-approved indications for the treatment of rare diseases and conditions.

Prior to submission of a new drug application (“NDA”) or a biologics license application (“BLA”), as appropriate, the manufacturer or sponsor of that product may request that FDA designate it as an “orphan drug” for the rare disease or condition for

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<sup>12</sup> See THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2009 V (2010) (providing U.S. sales by therapeutic class for 2009) [hereinafter “MRB REPORT”].

<sup>13</sup> See MASAC Document #174: MASAC Recommendations Regarding Rare Coagulation Factor Disorders, MEDICAL & SCIENTIFIC ADVISORY COUNCIL, NAT’L HEMOPHILIA FOUNDATION (“NHF”), <http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu57/174.pdf> [hereinafter MASAC #174] (requesting that manufacturers increase their efforts to give all bleeding disorder patients a viable treatment option). Deficiencies in factor II, factor V, and factor XII are among the bleeding disorders that not only currently lack a dedicated protein replacement therapy, but also lack the promise of one in the near future, as there are no therapies to treat those disorders in the clinical trial phase.

<sup>14</sup> See 26 U.S.C. § 45C (2006). The qualified clinical testing expenses must have occurred after the drug received “orphan designation” for an indication by the FDA under 21 U.S.C. § 360bb, but before the agency’s approval of that product for marketing of that rare disease or condition under the relevant new drug application (“NDA”) or biologics license application (“BLA”). See 26 U.S.C. § 45C(b)(2)(a).

<sup>15</sup> See 26 U.S.C. § 45C.

<sup>16</sup> See 21 U.S.C. § 360cc(a) (2006); 21 U.S.C. § 360ee (2006).

<sup>17</sup> See 26 U.S.C. § 45C(b)(2)(A)(ii)(I).

which it is seeking FDA marketing approval.<sup>18</sup> In the United States, a rare disease or condition is generally defined as one that treats less than 200,000 patients.<sup>19</sup>

A manufacturer or sponsor may request orphan drug designation of: (1) a previously unapproved drug; (2) a new orphan indication for an already marketed drug; or (3) a drug that is otherwise the “same” drug as an already approved orphan drug and is for the same rare disease or condition as that already approved drug.<sup>20</sup> FDA has generally defined two drugs with the same active ingredient as the “same” for the purpose of the Orphan Drug Act regulations.<sup>21</sup> The brands within each respective therapeutic class of plasma protein therapies are non-interchangeable, unique biologicals despite having the same active ingredient (i.e., the immunoglobulin G protein for immune globulin therapies);<sup>22</sup> yet two plasma protein therapies in the same therapeutic class would be considered the “same” for the purpose of the Orphan Drug Act. This mischaracterization is problematic because of the additional requirements such drugs must fulfill to receive orphan designation.

Generally, the applicable FDA regulations that govern the content and format of an “orphan drug” designation request call for a substantial application that requires, among other things, the submission of evidence demonstrating the rare disease patient population of less than 200,000 for the orphan indication being sought.<sup>23</sup> For a drug or biological that is “otherwise the same drug as an already approved orphan drug,” its manufacturer or sponsor seeking an orphan drug designation from FDA for the same indication as the previously approved orphan drug must demonstrate that it is “clinically superior” to the already approved orphan drug.<sup>24</sup> For plasma protein therapies, the different manufacturing processes described in Appendix A of this letter, such as different viral inactivation or removal techniques or different purification methods, affect the molecular structure of the active ingredient, but even those changes to the proteins would not allow two therapies “to be considered different unless the differences were shown to be clinically superior.”<sup>25</sup>

The purpose of the clinically superior threshold is to strengthen the value of the incentive of the seven years of market exclusivity under the Orphan Drug Act for the first

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<sup>18</sup> See 21 U.S.C. § 360bb.

<sup>19</sup> See 21 U.S.C. § 360bb(a)(2); see also 26 U.S.C. § 45C(d)(1). The drug may treat more than 200,000 patients if there is no “reasonable expectation” that it will be profitable. *Id.*

<sup>20</sup> See 21 C.F.R. § 316.20 (2010).

<sup>21</sup> See *Baker Norton Pharms. v. FDA*, 132 F.Supp.2d 30 (D.D.C. 2001) (upholding the FDA’s definition of “same” drug under the Orphan Drug Act).

<sup>22</sup> See, e.g., Laurence Feldmeyer et al., *Not All Intravenous Immunoglobulin Preparations Are Equally Well Tolerated*, 90 *Acta Derm Venereol* 494-497 (2010); M.H. Tsai et al., *Clinical Responses of Patients with Kawasaki Disease to Different Brands of Intravenous Immunoglobulin*, 148 *J. PEDIATRICS* 38, 38-43 (2006); see also Letter from Jordan Orange, M.D. and Kathleen Sullivan, M.D., to Anne Jacques, Dir. Clinical Pharmacy Servs., Highmark (Feb. 28, 2011) (describing the clinical differences among the brands of immune globulin) (on file with author).

<sup>23</sup> See 21 C.F.R. § 316.20

<sup>24</sup> *Id.*

<sup>25</sup> See 21 C.F.R. § 316.3(13)(ii)(A) (illustrating the impediment faced by manufacturers of subsequent market entrant plasma protein therapies in obtaining orphan designation).

FDA approved brand for that indication in a particular class.<sup>26</sup> The threshold, however, must be met even after the expiration of this exclusivity period.

FDA has consistently denied orphan drug designation requests by second to market drugs because the clinically superior threshold is difficult to satisfy.<sup>27</sup> According to the Orphan Drug Act regulations, in order to satisfy the clinically superior requirement, the manufacturer or sponsor of the subsequent NDA or BLA must demonstrate that the brand exhibits greater safety or greater effectiveness than the first to market brand.<sup>28</sup> FDA requires comparative clinical trials to make such an assessment in some cases of “safety” claims and in most cases of “effectiveness” claims.<sup>29</sup> If unable to demonstrate greater safety or effectiveness, subsequent drugs coming to market for the same indication in the same therapeutic class can also qualify as “clinically superior” to the original brand by demonstrating that the subsequent drug makes “a major contribution to patient care.”<sup>30</sup> FDA has only once granted orphan designation based on this third category of clinical superiority.<sup>31</sup>

The clinically superior threshold acutely affects the plasma protein therapeutics industry because there are multiple brands in most therapeutic classes. For example, as illustrated in in Table 1 of Appendix B of this letter, there are nine brands of immune globulin, ten brands of factor VIII (“FVIII”) (two of which are FVIII/vWF complex), and four brands of alpha<sub>1</sub>-proteinase inhibitor therapies available for consumption in the U.S. Table 2 in Appendix B reveals only one brand in each of those well-established therapeutic classes has received orphan designation from FDA. According to Dobson DaVanzo & Associates, LLC, a health economics and consulting firm, plasma protein therapies represent 32 of the approximately 41 drugs and biologicals indicated by FDA solely for the treatment of rare diseases, disorders, or conditions, but that lack an orphan designation from FDA.<sup>32</sup> While there are examples of a subsequent vWF therapy and a subsequent pdFIX therapy receiving orphan designation and marketing approval during the exclusivity period for the same indication as the previously approved “orphan drug” in the class based on clinical superiority (both were a result of different viral inactivation and removal techniques), the “clinically superior” requirement

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<sup>26</sup> See Memorandum from Marlene E. Haffner, MD, Director, Orphan Products Development, FDA, to Jay Siegel, MD, Director, Office of Therapeutics Research and Review, CBER, FDA, Re: Office of Orphan Products Development (OOPD) Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif (March 7, 2002), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm094512.pdf> (last visited June 13, 2011).

<sup>27</sup> See, e.g., *Baker Norton Pharms.*

<sup>28</sup> See 21 C.F.R. § 316.3(3).

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*

<sup>31</sup> FDA, Designating an Orphan Product: Drugs and Biologicals, Frequently Asked Questions, <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm> (last visited June 13, 2011)

<sup>32</sup> See JOAN E. DAVANZO ET AL., DOBSON DAVANZO, LLC, IDENTIFYING THERAPIES SOLELY INDICATED FOR TREATING ORPHAN DISEASES THAT DO NOT MEET THE ORPHAN DRUG EXCLUSION CRITERIA OF THE ANNUAL PHARMACEUTICAL FEE 2 (2010). These 41 drugs do not include therapies that have an approved orphan designated indication and additional rare disease indications that lack an orphan designation.

has created a scenario where, generally, only the product that is first to market in a particular therapeutic class can qualify for such designation. PPTA believes the clinically superior threshold hinders the evolution toward personalized medicine as it discourages manufacturers from developing new and improving existing therapies, thus, limiting brand diversity for the rare disease patient population. As such, we do not believe it is an appropriate threshold to determine one's annual pharmaceutical fee liability.

It should be further noted that some drugs and biologicals used to treat rare diseases, disorders, and conditions received FDA approval prior to the enactment of the Orphan Drug Act, so have been unable to receive orphan designation (and, as a result, have been ineligible for an Orphan Drug Act tax credit) with respect to these pre-Orphan Drug Act approvals. For example, the Orphan Drug Act went into effect January 1, 1983.<sup>33</sup> FDA first approved immune globulin therapies for treating primary immune deficiency diseases ("PIDDs") in 1981. While new formulations of immune globulin that came to market after enactment of the Orphan Drug Act could certainly have sought orphan designation for PIDDs, there was no incentive for the manufacturer to do so because obtaining the seven years of market exclusivity under 21 U.S.C. § 360cc(a) would have been impossible because there is not an unlimited supply of this therapy since it is a derivative of human plasma.<sup>34</sup>

### **B. Additional Reasons Manufacturers Were Unable to Claim the Orphan Drug Act Tax Credit**

PPTA further encourages the IRS to recognize the additional inequities that will occur if it narrowly interprets the annual pharmaceutical fee statute. The Orphan Drug Act tax credit was unavailable for an 18 month-period. Prior to June 1, 1997,<sup>35</sup> the Orphan Drug Act tax credit was not permanent. Between January 1, 1995 and June 30, 1996, Congress had failed to reauthorize this provision, making it impossible for manufacturers to claim the credit for qualified clinical testing expenses incurred during that time period.<sup>36</sup> PPTA strongly disagrees with any interpretation by the agency that would implement the orphan drug exclusion from the annual pharmaceutical fee based on a condition that was impossible to satisfy for a significant portion of the relevant time period for reasons beyond the control of the manufacturer. We ask the agency, as a matter of equity, to instead use its authority to clarify that the orphan drug exclusion from the annual pharmaceutical fee apply to all drugs and biologicals approved for marketing or licensed by the FDA solely for one or more rare diseases or conditions.

Such an interpretation would also prevent startup companies from being unjustly penalized. During the first 12 years following the enactment of the Orphan Drug Act, restrictive provisions associated with the Orphan Drug Act tax credit made it

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<sup>33</sup> See Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

<sup>34</sup> See 21 U.S.C. § 360cc(b)(1) (highlighting that the FDA will not grant orphan drug market exclusivity to products that are unable to meet patient access needs by themselves).

<sup>35</sup> See Taxpayers Relief Act of 1997 § 604, Pub L. No. 105-34, 111 Stat. 788, 863.

<sup>36</sup> See Small Business Job Protection Act of 1996 § 1205(b), Pub. L. No. 104-188, 110 Stat. 1755, 1775.

impossible for most new market entrants to have claimed the tax credit. For clinical testing expenses incurred from the effective date of the Orphan Drug Act on January 1, 1983 until December 31, 1994, manufacturers could not carry unused credits forward or backward;<sup>37</sup> thus, initially under the law, manufacturers had to have income and high enough tax liability to take the Orphan Drug Act tax credit, which was difficult for newer market entrants that lacked revenue.<sup>38</sup> PPTA believes this issue is another example that demonstrates that the orphan drug exclusion from the annual pharmaceutical fee being contingent on whether the manufacturer or sponsor of the drug claimed the Orphan Drug Act tax credit is flawed policy. We urge the agency to consider the broader objectives of rare disease therapy development and the value of startup companies in the rare disease space in recognizing that its proposed implementation of the orphan drug exclusion from the annual pharmaceutical fee is inconsistent with the Orphan Drug Act.<sup>39</sup>

PPTA believes it is also important to note that, generally, foreign testing expenses are not eligible for the Orphan Drug Act tax credit. Manufacturers may not claim this tax credit with respect to any clinical testing conducted outside the U.S. unless there is an insufficient U.S. testing population due to the rarity of the disease.<sup>40</sup> There are a number of business reasons why a manufacturer may choose to conduct clinical trials outside of the United States. As will discuss in Part I.C. of this letter, business decisions could have also affected whether a manufacturer even took the Orphan Drug Act tax credit when available.

### **C. In Some Instances, Manufacturers of Rare Disease Therapies May Have Made a Business Decision to Take a Different Tax Credit Instead of the Orphan Drug Act Tax Credit**

There are some tax credits that are or have been available to drug manufacturers, which could have led to a scenario where a manufacturer made a business decision to take a tax credit other than the Orphan Drug Act tax credit. For example, some manufacturers may choose to claim the R&D tax credit under 26 U.S.C.

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<sup>37</sup> See Marvin S. Lieber and Richard R. Tarantine, *Federal Tax Developments Affecting Individuals, Corporations, and Other Organizations*, 68 PA. B. ASSN. Q. 68, 70 (1997).

<sup>38</sup> See Li-Hsien Rin-Laures and Diane Janofsky, *Note: Recent Developments Concerning the Orphan Drug Act*, 4 HARV. J.L. & TECH. 269, 295 (1991). Beginning July 1, 1996, Congress reauthorized the ODA tax credit for 11 months through May 31, 1997 and reclassified it as a business credit. See Small Business Job Protection Act of 1996 § 1205. This reclassification resulted in manufacturers finally having the ability to carry back and carry forward unused portions of the credit. See 26 U.S.C. § 39 (2006). Initially under the reclassification, manufacturers could carry it back three years, or carry it forward 15 years. See Lieber, *supra*, note 37. Since 1998, manufacturers are able to carry it back just one year, but carry it forward 20 years. See Taxpayers Relief Act of 1997 § 1083(a), Pub L. No. 105-34, 111 Stat. 788, 951 (codified at 26 U.S.C. § 39(a)).

<sup>39</sup> See Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983). The preamble of the Orphan Drug Act describes the public health need for providing drug manufacturers with financial incentives to develop rare disease therapies; thus, it would be inconsistent with current law to limit these incentives, or to implement new policies based upon these incentives in a manner that would fail to treat these manufacturers equally.

<sup>40</sup> See 26 U.S.C. § 45C(d)(2)(A).

§ 41, rather than the Orphan Drug Act tax credit for its clinical testing expenses. Manufacturers may not claim both the Orphan Drug Act tax credit and the R&D tax credit for the same qualifying clinical testing expenses.<sup>41</sup> Additionally, most drug manufacturers would not likely have claimed the Orphan Drug Act tax credit during the 1980s and early 1990s because they were receiving special tax breaks for having established manufacturing operations in Puerto Rico. More than 40 of the world's largest drug manufacturers created thousands of jobs in Puerto Rico during this period in return for a tax exemption under 26 U.S.C. § 936 for all income derived from the specified facility.<sup>42</sup> Manufacturers that elected the section 936 credit in a given year could not also claim the Orphan Drug Act tax credit for any qualifying clinical testing expenses incurred during that same year.<sup>43</sup> The IRS should avoid implementing a policy that effectively penalizes drug manufacturers for not having taken the Orphan Drug Act tax credit in years prior to the credit having the significance now attached to it with its link to the annual pharmaceutical fee.

**D. The IRS Should Clarify that the Orphan Drug Exclusion from the Annual Pharmaceutical Fee Should Apply to All Drugs and Biologicals Approved for Marketing or Licensed by the FDA Solely for One or More Rare Diseases or Conditions**

For all of the reasons outlined in Part I of this letter, we respectfully request that the IRS, as a matter of equity, use its authority to clarify that the orphan drug exclusion from the annual pharmaceutical fee apply to all drugs and biologicals approved for marketing or licensed by the FDA solely for one or more rare diseases or conditions. Such an interpretation by the agency would preserve innovation in the rare disease space allowing manufacturers to make progress in bringing to market drugs or biologicals for the nearly 7,000 rare diseases currently without a dedicated therapeutic intervention for their treatment. If the agency determines implementing such a policy is inconsistent with its authority under the annual pharmaceutical fee statute, PPTA would urge IRS to at the very least base the exclusion on whether the FDA designated the product as an “orphan drug.” Again, to be eligible to claim the Orphan Drug Act tax credit, a product must have received orphan designation from FDA. PPTA has underscored significant policy problems with hinging the orphan drug exclusion on whether the manufacturer or sponsor claimed the Orphan Drug Act tax credit and strongly believes a drug's orphan designation status serves as a more appropriate condition for the manufacturer to satisfy.

## **II. Calculation of Medicare Part B Sales for Multiple-Drug HCPCS Codes**

As you know, to facilitate the determination of each manufacturer's fee liability, the Secretary of Health and Human Services (“HHS”) is to report, for each

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<sup>41</sup> *Id.* at § 45C(c).

<sup>42</sup> See U.S. GEN. ACCOUNTING OFFICE, GAO/GGD-92-72BR, PHARMACEUTICAL INDUSTRY: TAX BENEFITS OF OPERATING IN PUERTO RICO 1, 13, 16-17 (1992).

<sup>43</sup> See 26 U.S.C. § 45C(d)(2)(B). The section 936 tax credit was completely phased out by December 31, 2005.

manufacturer, for each brand name prescription drug covered by Medicare Part B, the product of the per-unit average sales price (“ASP”) or the per unit Part B payment rate for drugs without a reported ASP and the number of units paid for under Medicare Part B. The statute directs the Centers for Medicare and Medicaid Services (“CMS”) to establish a process for determining the units and the allocated price for certain products.<sup>44</sup> Unlike other “specified government programs,” Medicare Part B uses HCPCS codes for billing, not National Drug Codes. This presents difficulties for HHS in determining the number of units paid for under Medicare Part B for purposes of its Medicare Part B reporting obligation to IRS with respect to certain drugs. Specifically, for HCPCS codes that include multiple brand name drugs, HHS cannot tell how many units are attributable to each of the different manufacturers’ drugs billed under a single HCPCS code.

The therapies produced by PPTA members are often reimbursed along with other manufacturers’ products as part of a single HCPCS code and thus are particularly impacted by the inability of HHS to be able to accurately attribute units of such products to the appropriate manufacturer. For example, although as many as four different manufacturers might produce a certain blood clotting factor, each of the manufacturers’ products is billed by the physician or provider under the same HCPCS code (e.g., J7192 for FVIII recombinant). As a result, PPTA has a strong interest in ensuring that the IRS calculates each manufacturer’s share of the sales for a multiple-drug HCPCS code in a manner that is fair and consistent with the statute.

Notice 2011-9 (at p. 7) proposes to estimate Part B sales for HCPCS codes consisting of a mixture of branded prescription drugs made by different manufacturers by determining for a given HCPCS code “the utilization percentage attributed to each manufacturer as determined under the Medicare Part B Program using manufacturer reported Average Sales Price sales data” and applying that percentage to the total Medicare-allowed charges for the HCPCS code.

PPTA recognizes the difficulty of estimating Part B sales when multiple manufacturers’ drugs are reimbursed as part of a single HCPCS code and appreciates the efforts the IRS has made in Notice 2011-9 to achieve a fair estimate of each manufacturer’s share. Nevertheless, PPTA remains concerned that the IRS’s proposed use of ASP for dividing multiple-drug code sales risks inaccurately calculating Part B sales for some manufacturers. The data on which the ASP calculation is based takes account of all commercial sales in the United States, while the annual fee statute requires the IRS to consider only sales to specified government programs (in this case Medicare Part B). As a result, any manufacturer whose share of commercial sales as a whole is greater than its share of Medicare Part B sales will be required to pay a larger share of the annual fee than the statute requires. We urge the IRS to consider more carefully its proposed method of estimating sales for multiple-drug HCPCS codes to ensure that the final method is both fair and consistent with the statute’s requirements.

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<sup>44</sup> PPACA § 9008(g)(2).

### **III. Conclusion**

PPTA greatly appreciates the opportunity to provide comments on IRS Notice 2011-9. We urge the agency to give especially careful consideration to our unique segment of the biologicals industry as it implements the orphan drug exclusion from the annual pharmaceutical fee and to reevaluate its proposed method of estimating sales for multiple-drug HCPCS codes. Patients that require regular infusions or injections of plasma protein therapies as part of their treatment regimen depend on a diversity of therapies and must have access to the full range in the relevant therapeutic class. We would urge IRS to implement the annual pharmaceutical fee in a manner that PPTA believes will prevent any impediments to these lifesaving therapies. As such, PPTA respectfully requests that the IRS use its authority to clarify that the orphan drug exclusion from the annual pharmaceutical fee apply to all drugs and biologicals approved for marketing or licensed by the FDA solely for one or more rare diseases or conditions. Please do not hesitate to contact me at 202-789-3100 or by email ([jgreissing@pptaglobal.org](mailto:jgreissing@pptaglobal.org)) if you have any questions.

Sincerely,



John E. Greissing  
Sr. Director, Federal Affairs

Attachments

## Appendix A. Plasma Protein Therapies: A Unique Segment of the Drug Industry

The branded pharmaceuticals, the generics, the biologicals, the vaccines, and the plasma protein therapeutics industries not only offer different value to the patient, but also require considerably different business models because of their distinctive cost structures. The plasma protein therapeutics industry, including all U.S. recombinant blood clotting factor sales, is a \$7 billion annual market, which is approximately two percent of the total U.S. prescription drug market.<sup>45</sup>

In contrast to the broader drug industry, this niche segment of the biologicals industry is distinguished by the significant brand-to-brand competition in several therapeutic classes, as well as by the extraordinarily low prevalence of the diseases treated by each therapeutic class. Because of characteristics unique to human plasma-derivatives, which account for nearly two-thirds of the plasma protein therapeutics market,<sup>46</sup> plasma protein therapies cost nearly four times more than traditional pharmaceutical products to produce.<sup>47</sup> These characteristics include the capital intensity of the facilities, equipment, and source material.<sup>48</sup> Expenditures in these areas are due in part to the direct and indirect costs of compliance with stringent FDA regulations<sup>49</sup> and rigorous voluntary industry standards<sup>50</sup> by both the plasma collectors

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<sup>45</sup> Compare MRB REPORT, *supra* note 12, at 62 with *Channel Distribution by U.S. Sales*, IMS HEALTH INC., [http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top\\_Line\\_Data/Channel%20Distribution%20by%20U.S.Sales.pdf](http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Channel%20Distribution%20by%20U.S.Sales.pdf) (last visited October 8, 2010).

<sup>46</sup> See MRB REPORT, *supra* note 12.

<sup>47</sup> See Charles Waller, *Historical Perspective on Blood and Plasma Products*, in 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 17, fig. 2 (J.L. Valverde ed., 2005) (providing a comparison of the plasma protein therapeutics industry with the pharmaceutical industry through the analysis of Smith Barney estimates from December 2003 and the 2004 Annual Reports of major pharmaceutical companies).

<sup>48</sup> See OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, BLOOD POLICY AND TECHNOLOGY 66 (Jan. 1985) (discussing the capital intensive nature of the facilities necessary to fractionate plasma proteins); MRB REPORT, *supra* note 12, at 41 (demonstrating the capital intensity of the source material required to produce plasma protein therapies).

<sup>49</sup> See 21 C.F.R. §§ 210 – 211 (describing current good manufacturing processes); *id.* §§ 640.60 – 640.76 (detailing requirements for plasma donor suitability; plasma donor identification; medical supervision at the plasma collection facility; the plasmapheresis process; the collection and storage of plasma in a sterile setting; the pooling, storage, and transportation of collected source plasma at appropriate temperatures; labeling; laboratory screening tests; and recordkeeping); see, e.g., *id.* §§ 640.100 – 640.104 (providing federal regulations for the production of intravenous immune globulin); see also CTR. FOR BIOLOGICS EVALUATION & RESEARCH, HHS, GUIDANCE FOR INDUSTRY FOR THE SUBMISSION OF CHEMISTRY, MANUFACTURING AND CONTROLS AND ESTABLISHMENT DESCRIPTION INFORMATION FOR HUMAN PLASMA-DERIVED BIOLOGICAL PRODUCTS, ANIMAL PLASMA OR SERUM-DERIVED PRODUCTS (Feb. 1999) (describing the painstaking validation requirements for FDA licensure of a plasma fractionation center and for upgrades to an existing area of a FDA-licensed fractionation establishment).

<sup>50</sup> See PLASMA PROTEIN THERAPEUTICS ASSOC. (“PPTA”), INTERNATIONAL QUALITY PLASMA PROGRAM (“IQPP”), [http://www.pptaglobal.org/UserFiles/File/QSEAL/Program%20Description\\_v2.0\\_January%202009.pdf](http://www.pptaglobal.org/UserFiles/File/QSEAL/Program%20Description_v2.0_January%202009.pdf) (last visited Oct. 11, 2010) (providing standards for the certification of plasmapheresis centers) [hereinafter “IQPP STANDARDS”]; PPTA, QUALITY STANDARDS OF EXCELLENCE, ASSURANCE, AND LEADERSHIP (“QSEAL”), [http://www.pptaglobal.org/program/QSEAL\\_CERTIFICATION\\_PROGRAM\\_DESCRIPTION%20V1.5.pdf](http://www.pptaglobal.org/program/QSEAL_CERTIFICATION_PROGRAM_DESCRIPTION%20V1.5.pdf)

and fractionators. Threats of emerging pathogens, such as variant Creutzfeldt-Jakob disease, will continue to require manufacturers to develop new laboratory screening tests, as well as new procedures for viral inactivation and viral reduction.

The regulations and voluntary standards to which manufacturers adhere also contribute to the length of time required to produce a plasma protein therapy, which is approximately seven months from the date a plasma collection establishment collects a liter of source plasma from a “qualified donor”<sup>51</sup> to the FDA lot release of the final dosage form of a plasma protein therapy that used that plasma. Seven months is far longer than the time required to manufacture a traditional pharmaceutical product that has received FDA marketing approval.

### I. Collection and Pooling of Human Plasma

With respect to the capital intensity of the source material, manufacturers of plasma protein therapies may purchase human plasma from both plasma collection establishments and blood bank establishments as this material may be collected from donors by plasmapheresis (source plasma) or through whole blood donation (recovered plasma), respectively.<sup>52</sup> Recovered plasma and source plasma are distinguished not only by mode of collection, but also by the requirements for storage, pooling, dating, and labeling of the product.<sup>53</sup> In 2009, nearly 90 percent of human plasma collected for manufacturing use in the United States was source plasma,<sup>54</sup> which costs approximately \$148 per liter.<sup>55</sup> This price includes the costs of serological testing and the nucleic acid amplification technology (“NAT”) testing at the collection center of that liter of human plasma for HIV, HBV, and HCV,<sup>56</sup> as required by law.<sup>57</sup>

Manufacturers that possess PPTA’s “Quality Standards of Excellence, Assurance, and Leadership” (“QSEAL”) certification may only use plasma obtained from “qualified donors” for fractionation at their manufacturing establishments.<sup>58</sup> The voluntary industry standards for the “qualified donor” at both collection and fractionation

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(last visited Oct. 11, 2010) (providing standards for the certification of plasma fractionators) [hereinafter “QSEAL STANDARDS”].

<sup>51</sup> Before accepting a source plasma donation for further manufacturing into therapies, an IQPP certified plasma collection establishment must verify that the donor of such plasma has had two suitable donations within the last 6 months at that establishment. Only after satisfactory screening and negative test results for human immunodeficiency virus (“HIV”), hepatitis B virus (“HBV”), and hepatitis C virus (“HCV”) for both donations does that potential donor become a “qualified donor” and their plasma become eligible for collection. See IQPP STANDARDS, *supra* note 50, at 10.

<sup>52</sup> See 21 C.F.R. § 640.30. “Plasmapheresis is the procedure in which blood is removed from a donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.” 21 C.F.R. § 606.3(e).

<sup>53</sup> See Johan Prevot, *Glossary of Terms*, in 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 280 (J.L. Valverde ed., 2005).

<sup>54</sup> See MRB REPORT, *supra* note 12, at 16.

<sup>55</sup> *Id.* at 45.

<sup>56</sup> *Id.* at 42.

<sup>57</sup> See 21 C.F.R. § 610.40.

<sup>58</sup> See QSEAL STANDARDS, *supra* note 50, at 7.

work in concert with and in addition to existing regulatory requirements concerning donor suitability,<sup>59</sup> providing an additional margin of safety by ensuring that the donor is suitable, healthy, and committed to the process of plasma donation.

Once the collected liters of human plasma, which require special cold storage and handling, arrives at the establishment of a manufacturer of plasma protein therapies, the unique source material is pooled and then separated into individual protein fractions that are further purified for medicinal use.<sup>60</sup> Prior to pooling, however, QSEAL certified manufacturers must hold each liter of source plasma in inventory for a minimum of 60 days from the date of collection.<sup>61</sup> The purpose of this voluntary inventory hold is to allow the retrieval of the liter if negative information about the donor's health status subsequently becomes available.<sup>62</sup>

The Government Accountability Office ("GAO") has previously touted the industry's "qualified donor" standard and the inventory hold standard as vital initiatives to ensure the safety of each pool of plasma used for manufacturing therapies.<sup>63</sup> Citing the GAO study, FDA has recently proposed to add these two voluntary standards to the Code of Federal Regulations, thus, making them mandatory.<sup>64</sup> FDA's proposal has not been finalized.

Each pool from which plasma proteins are fractionated for use in U.S. licensed therapies contains no more than 60,000 donated liters, and in some cases, as few as 15,000 donated liters. For patients suffering from hemophilia or primary immune deficiency diseases, the size of the pool will not affect their risk of infection because of their overall exposure throughout the course of their lifetime. It is, however, important to note that QSEAL certified manufacturers of plasma protein therapies must test fractionation pools using NAT testing for parovirus B19, HIV, HBV, and HCV.<sup>65</sup>

## II. Protein Fractionation

Although hundreds of different proteins have been found in human plasma, many have been difficult to characterize and are present in very small quantities.<sup>66</sup>

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<sup>59</sup> See 21 C.F.R. § 640.63.

<sup>60</sup> See, e.g., WORLD HEALTH ORGANIZATION, WHO RECOMMENDATIONS FOR THE PRODUCTION, CONTROL AND REGULATION OF HUMAN PLASMA FOR FRACTIONATION (2005), [http://www.who.int/biologicals/publications/ECBS%202005%20Annex%204%20Human%20Plasma%20Fr](http://www.who.int/biologicals/publications/ECBS%202005%20Annex%204%20Human%20Plasma%20Fractionation.pdf)  
[actionation.pdf](http://www.who.int/biologicals/publications/ECBS%202005%20Annex%204%20Human%20Plasma%20Fractionation.pdf) (last visited October 8, 2010).

<sup>61</sup> See QSEAL STANDARDS, *supra* note 50, at 8.

<sup>62</sup> *Id.* at 7.

<sup>63</sup> See U.S. GEN. ACCOUNTING OFFICE ("GAO"), GAO/HEHS-98-205, BLOOD PLASMA SAFETY: PLASMA PRODUCT RISKS ARE LOW IF GOOD MANUFACTURING PRACTICES ARE FOLLOWED (1998).

<sup>64</sup> See Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use, 72 Fed. Reg. 63416, 63431 (Nov. 8, 2007).

<sup>65</sup> See QSEAL STANDARDS, *supra* note 50, at 8.

<sup>66</sup> See Cohn, *supra* note 10. See also N. Leigh Anderson and Norman G. Anderson, *The Human Plasma Proteome: History, Character, and Diagnostic Prospects*, 1 MOLECULAR & CELLULAR PROTEOMICS 845 (2002).

Approximately 120 of these proteins are “well-characterized.”<sup>67</sup> After isolating and extracting these various proteins, manufacturers of plasma protein therapies further manufacture several proteins, including albumin, blood clotting factors, and immunoglobulin G, into finished therapies.

After the plasma is pooled, it is thawed in an ice water bath at 4°C and then is loaded into a large centrifuge causing blood clotting factor proteins to separate. The blood clotting factor proteins that have separated are called “cryoprecipitate” and the remaining plasma is called “cryosupernatant.” The cryoprecipitate can be further purified to manufacturer FVIII concentrate, fibrinogen, fibrin sealant, and vWF concentrate. The cryosupernatant undergoes various chromatography techniques, which differ among manufacturers and may result in the isolation of the following proteins: factor II, factor VII (“FVII”), FIX, factor X, factor XI, FXIII, antithrombin III, protein C, and C1 esterase inhibitor. These proteins may also be further manufactured into therapies, as necessary.

For many manufacturers, the residual plasma is then put through a cold ethanol protein fractionation process, either by the Cohn-Oncley<sup>68</sup> or the Kistler-Nitschmann<sup>69</sup> methods, to cause the proteins in the plasma to precipitate into various fractions by adjusting their solubility through alcohol concentration, pH, ionic strength, protein concentrations, and temperature. For example, depending on the fractionation step, the Cohn method uses “ethanol concentration ranging from 8% to 40%, pH levels between 4.5 and 7.4, temperature ranges from -5° to -7°C, ionic strength differentials from 0.14 to 0.01, and protein concentrations from 5.1% to 0.8%. As the ethanol concentration or pH is changed, different protein fractions are obtained.”<sup>70</sup>

Under the Cohn method, fibrinogen remaining after the cryoprecipitate and cryosupernatant steps is isolated in Fraction I by bringing the pool’s ethanol level to eight percent, using buffer compounds to adjust the pH to 7.2 and adjusting the salt level to reach an ionic strength of 0.14. Additional alcohol is added to the remaining plasma bringing it to 25% ethanol, the pH is lowered to 6.9, and the ionic strength is lowered to 0.09 to extract IgG, immunoglobulin A, immunoglobulin M, plasminogen, and additional traces of blood clotting factors as part of Fractions II and III. A1PI and additional traces of blood clotting factors are isolated from Fraction IV by changing the ethanol level of the residual plasma remaining after Fractions II and III to 18 percent and reducing its pH to 5.2. The residual plasma remaining after Fraction IV is adjusted to a 40% ethanol level, a 4.8 pH, and an ionic strength of 0.11 in order to extract albumin at Fraction V.

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<sup>67</sup> Toby L. Simon, Kirsten Seidel, et al., *Preparation of Plasma Derivatives*, in ROSSI’S PRINCIPLES OF TRANSFUSION MEDICINE 276, Table 19-2 (T.L. Simon, E.L. Snyder, et al. eds., 4<sup>th</sup> ed. 2009).

<sup>68</sup> See generally Cohn, *supra* note 10.

<sup>69</sup> See generally P. Kistler and H. Nitschmann, *Large Scale Production of Human Plasma Fractions: Eight Years Experience with the Alcohol Fractionation Procedure of Nitschmann, Kistler, and Lergier*, 7 VOX SANGUINIS 414 (1962).

<sup>70</sup> Simon, *supra* note 67, at 276.

### III. Manufacturing Plasma Proteins into Medicinal Therapies

Manufacturers take these proteins that they have isolated during the fractionation process and further purify them in order to create medicinal therapies. During the purification process, manufacturers use viral inactivation and removal steps to ensure the safety of the finished therapies.

Viruses can be inactivated through heat treatment or solvent detergent treatment, or by a combination of heat and solvent detergent. Viral removal can occur through either chromatography or nanofiltration. Each manufacturer uses slightly different inactivation and removal techniques which creates differences in their respective final therapies. For example, combining heat treatment with solvent detergent as a viral inactivation step can affect the tertiary structure of the FVIII molecule and increase the risk of an immune system response in patients that are treated with the final therapy that uses those FVIII proteins.<sup>71</sup>

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<sup>71</sup> See, e.g., S.W. Pipe, The Promise and Challenges of Bioengineered Recombinant Clotting Factors, 3 J. of Thrombosis & Haemostasis 1692, 1693-1694 (2005) (citing reports that patients developed inhibitors after switching to plasma-derived FVIII virally inactivated by pasteurization in conjunction with solvent detergent treatment or other processes).

## Appendix B. Most Therapeutic Classes of Plasma Protein Therapies Contain Multiple Therapy Brands Making it Difficult for Many to Obtain Orphan Designation under the Current Regulatory Framework

**TABLE 1. Examples of Rare Diseases Treated by Plasma Protein Therapies**

Rare Disease	Estimated Prevalence in U.S.	Therapeutic Class	Plasma Protein Therapy
alpha-1 antitrypsin deficiency	10,000	alpha <sub>1</sub> -proteinase inhibitor	Aralast NP Glassia Prolastin-C Zemaira
chronic B-cell lymphocytic leukemia	110,000	immune globulin	Gammagard S/D
chronic inflammatory demyelinating polyneuropathy	40,000	immune globulin	Gamunex-C
common variable immunodeficiency	16,400	immune globulin	Carimune NF Flebogama DIF Gammagard Liquid Gammagard S/D Gammaplex Gamunex-C Hizentra Octagam Privigen
congenital fibrinogen deficiency	300	factor I	RiaSTAP
factor XIII deficiency	60	factor XIII	Corifact
hemophilia A	14,218	factor VIII	Advate Alphanate Helixate FS Hemofil M Humate –P Koate-DVI Kogenate FS Monoclate-P Recombinate Xyntha
hemophilia A w/ an inhibitor	1,163	bypassing agent	Feiba VH (anti-inhibitor complex) NovoSeven RT (rFVIIa)
hemophilia B	4,027	factor IX	AlphaNine Benefix Mononine Bebulin VH (prothrombin complex concentrate) Profilnine SD (prothrombin complex concentrate)
hemophilia B w/ an inhibitor	52	bypassing agent	Feiba VH (anti-inhibitor complex) NovoSeven RT (rFVIIa)

<b>Rare Disease</b>	<b>Estimated Prevalence in U.S.</b>	<b>Therapeutic Class</b>	<b>Plasma Protein Therapy</b>
hereditary angioedema	6,200	C1 esterase inhibitor	Berinert Cinryze
hereditary antithrombin III deficiency	155,000	antithrombin III	Thrombate III Atryn
idiopathic thrombocytopenic purpura	30,000	immune globulin	Carimune Gammagard S/D Gamunex-C Privigen Rhopylac WinRho SDF
Kawasaki's disease	5,223	immune globulin	Gammagard S/D
protein C deficiency	15,500	protein C concentrate	Ceprotrin
severe combined immunodeficiency	7,750	immune globulin	Carimune NF Flebogama DIF Gammagard Liquid Gammagard S/D Gammaplex Gamunex-C Hizentra Octagam Privigen
von Willebrand disease	13,000	von Willebrand factor	Alphanate Humate-P Wilate
Wiskott-Aldrich syndrome	3,000	immune globulin	Carimune NF Flebogama DIF Gammagard Liquid Gammagard S/D Gammaplex Gamunex-C Hizentra Octagam Privigen
X-linked agammaglobulinemia	3,000	immune globulin	Carimune NF Flebogama DIF Gammagard Liquid Gammagard S/D Gammaplex Gamunex-C Hizentra Octagam Privigen

**TABLE 2. Orphan Designated Plasma Protein Therapies**

<b>Class</b>	<b>Therapy</b>	<b>Rare Disease</b>
alpha <sub>1</sub> -proteinase inhibitor	Prolastin C (Talecris)	alpha-1 antitrypsin deficiency
immune globulin	Gamunex (Talecris)	chronic inflammatory demyelinating polyneuropathy
rho(D) immune globulin	WinRho SDF (Cangene)	idiopathic thrombocytopenic purpura
cytomegalovirus immune globulin	Cytogam (CSL Behring)	cytomegalovirus disease in organ transplant patients
hepatitis B immune globulin	Hepagam (Cangene)	hepatitis B in organ transplant patients
pdFVIII	None	hemophilia A
rFVIII	Kogenate FS (Bayer)	hemophilia A
pdFIX	AlphaNine (Grifols) MonoNine (CSL Behring)	hemophilia B
rFIX	Benefix (Pfizer)	hemophilia B
rFVIIa	NovoSeven (NovoNordisk)	hemophilia A and hemophilia B w/ inhibitors
pdFXIII	Corifact (CSL Behring)	factor XIII deficiency
Fibrinogen	RiaStap (CSL Behring)	congenital fibrinogen deficiency
C1 esterase inhibitor	Berinert (CSL Behring) Cinryze (ViroPharma)	hereditary angioedema
protein C concentrate	Ceproin (Baxter)	protein C deficiency
vWF	Alphanate (Grifols) Humate-P (CSL Behring) Wilate (Octapharma)	von Willebrand's disease



June 10, 2011

The Honorable Max Baucus, Chairman  
Senate Finance Committee  
219 Dirksen Senate Office Building  
Washington, DC 20510

Dear Senator Baucus,

Thank you for your continued leadership on the Finance Committee and your commitment to ensure that those individuals with rare diseases are able to access appropriate treatment. The National Organization for Rare Disorders (NORD) asks for your consideration with regard to a small policy correct believed to be necessary within the annual pharmaceutical fee provision of the Patient Protection and Affordable Care Act specific to the exclusion of orphan drugs.

The existing statute requires that for an orphan drug to be excluded from the annual fee, the drug must have received the section 45C orphan drug tax credit. Our concern is that while many orphan drugs have in fact received the credit, not all drugs that solely treat orphan conditions have received the credit. Moreover, if a therapy has multiple orphan indications and did not receive the orphan tax credit for each licensed indication, it would also be subject to the fee.

As written, the statute unintentionally creates an imbalance for orphan disease therapies. The statute specifically excludes those therapies that have received the orphan tax credit from the annual pharmaceutical fee while requiring those products which are solely indicated to treat the very same orphan condition(s) but did not receive the orphan drug tax credit to pay the annual pharmaceutical fee. Of greater concern, this fee as currently written may actually be a disincentive for future development of therapies to treat orphan conditions, if such products are ineligible for the orphan drug tax credit.

The Orphan Drug Tax Credit has been a successful tool to promote the development of therapies to treat a myriad of rare diseases that might otherwise been ignored. We would request that this not be infringed, however unintentionally, by having the pharmaceutical fee and its exclusion for orphan drugs expressly linked to the orphan drug tax credit. We believe the credit can be one criterion for exclusion from the fee but alternatively, if a therapy is indicated solely for the treatment of an orphan condition(s), it should also be excluded from the fee.

NORD asks the Senate Finance Committee to consider this issue as it reviews and addresses legislation in this session of Congress.

Sincerely,

A handwritten signature in black ink, appearing to read "Peter L. Saltonstall", is written over a light gray rectangular background.

Peter L. Saltonstall  
President and CEO