

January 17, 2012
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

VIA WEB

SUBJECT: Proposed Rule Amending FDA December 29, 1992 (57 Fed. Reg. 62076)
Orphan Drug Regulations [Docket No. FDA-2011-N-0583].

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (“PPTA”) would like to thank you for the opportunity to comment on the Food and Drug Administration’s (“FDA” or “The Agency”) proposed amendments to the Agency’s 1992 Orphan Drug Regulations, (57 Fed. Reg. 62076).¹ Given the breadth of FDA’s review of the orphan drug program in developing its proposed rule, we appreciate the significance of the proposals, and wish to provide insight into their potential affect on the plasma protein therapeutics industry. Further, we offer a revision to Title 21, Code of Federal Regulations (21 CFR), Subpart C— Designation of an Orphan Drug that is consistent with the statute, but removes impediments to innovation in development of and patient access to therapies for orphan indications.

Because the plasma protein therapeutics industry almost exclusively comprises therapies indicated for the treatment of rare diseases, disorders, and conditions, PPTA is particularly sensitive to policies that may hinder or help patient access to the therapeutic intervention best suited for their individual needs; thus, PPTA respectfully recommends that FDA consider the following:

- The revision of the regulations we propose furthers the Orphan Drug Act’s intent to help patients coping with life-threatening rare diseases and conditions by protecting incentives that stimulate research and development into safe and effective treatments for patients with unmet medical needs;
- In recent years, Congress has begun using orphan drug designation as a means to identify drugs that treat patients with rare disorders for the purposes of determining eligibility for legislated obligations including, taxes, fees, and discounts;

¹ Orphan Drug Regulations, 76 Fed. Reg. 64868 (proposed Oct. 19, 2011).

- Congressional use of orphan drug designation as a determination for these protections instills significant and unprecedented value in the actual designation of a drug as an orphan drug;
- Because second-to-market² plasma protein therapies are often unable to demonstrate clinical superiority, many are unable to gain orphan drug designation under current regulatory interpretation and thus, despite being solely indicated to treat rare diseases, are excluded from the protections afforded orphan designated products;
- Exclusion from these newly enacted protections associated with orphan drug designation may hinder innovation for rare disease therapies and threatens to reduce patient access to safe and effective treatment;
- Acting within its legislated authority and the plain language of the ODA, the Agency should eliminate the clinical superiority requirement for orphan designation, while maintaining the requirement for obtaining orphan drug exclusivity;
- Eliminating the clinical superiority requirement for orphan designation, while maintaining the requirement for orphan exclusivity protects the value of orphan exclusivity and advances the overall intent of the ODA to stimulate development of rare disease therapies.

PPTA Background

PPTA represents human plasma collection centers and the manufacturers of lifesaving medicinal therapies, including albumin, alpha1-proteinase inhibitor, antithrombin III, blood clotting factors, C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, and protein C concentrate, 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.” The manufacturer membership of PPTA in the United States (“U.S.”) currently includes Baxter, Biotest, Cangene, CSL Behring, Grifols and Kedrion.

Excluding albumin and fibrin sealant, 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

² For ease of reference, in this comment, the term “second-to-market” will refer to any drug that is the same drug as an already approved orphan drug, being investigated for the same rare disease indication as that already approved orphan drug. For instance, if drug A is an orphan drug approved for the treatment of Wiscott-Aldrich Syndrome (“WAS”), and drugs B, C, and D are all the same as drug A, and are also under investigation for the treatment of WAS, drugs B, C, and D will be referred to as “second-to-market” drugs.

generally defined as a disease or condition that affects less than 200,000 people.³ The majority of the rare conditions that require treatment with plasma protein therapies are genetic, chronic, and life threatening, including alpha-1 antitrypsin deficiency, chronic B-cell lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, hereditary angioedema, hereditary antithrombin III deficiency, protein C deficiency, primary immune deficiency diseases, such as common variable immunodeficiency, X-linked agammaglobulinemia (Bruton's disease), DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, and graft-versus-host diseases, and bleeding disorders, such as hemophilia A, hemophilia B, congenital fibrinogen deficiency, Von Willebrand's disease, and factor XIII deficiency, cytomegalovirus disease associated with transplant patients, hepatitis B reinfection in liver transplant patients, idiopathic thrombocytopenic purpura, infant botulism, Kawasaki's disease, rabies, rhesus incompatible pregnancies, and tetanus.

As representatives of a segment of the drug industry with considerable experience in treating rare diseases, disorders, and conditions, PPTA recognizes the important policy rationale for establishing the clinical superiority requirement for orphan drug approval as it relates to marketing exclusivity. However, we believe the elimination of clinical superiority for the purposes of orphan drug designation will benefit patients with rare disorders.

Orphan Drug Act

In 1983, confronting a shortage of drugs available for the treatment of rare diseases, Congress passed the Orphan Drug Act.⁴ The framers of the ODA recognized that this shortage was due to the specific challenges faced by innovators in the rare disease space. Specifically, Congress acknowledged that innovators of rare disease therapies were often unable to bear the high cost-high risk calculus of exploration given the restricted nature of the targeted patient populations.⁵ Addressing the two underlying elements of the problem in separate provisions of the statute, Congress:

³ See 21 U.S.C. § 360bb(a)(2) (2006).

⁴ Prior to the passage of the ODA, only 34 drugs were available on the U.S. market for the treatment of rare diseases. 1982 U.S.C.C.A.N. 3581.

⁵ Leading into Congressional negotiations concerning the ODA, the Subcommittee on Health and the Environment of the Committee on Energy and Commerce published a study regarding the availability of treatment options for patients living with rare diseases, concluding that:

"[o]rphan drugs are predominantly used in the treatment of rare diseases. They are not profitable. It is difficult to conduct human clinical trials to prove their effectiveness because there are so few people with any given disease. Most are not patentable. They cause more adverse side effects, on average, than drugs for common diseases. There are many drugs for rare diseases which are not approved and [not] on the market."

See 1982 U.S.C.C.A.N. 3579, 3580.

(1) reduced the cost of orphan drug exploration by providing research and development (“R&D”) grants and by providing the Orphan Drug Tax Credit that covers up to 50 percent of qualifying clinical trial costs;⁶

(2) provided a secure marketing exclusivity to rare disease therapies to increase the potential for viable recoupment.⁷

Together, these provisions create a conducive environment for the development of therapies use to treat rare diseases. Notably, however, while these two provisions work concomitantly towards their shared goal of encouraging the research, development, and marketing of therapies used to treat rare diseases, Congress instilled each with its own unique role in achieving that goal.

The first provision, providing grants for R&D and the Orphan Drug Tax Credit for up to 50 percent of qualifying clinical testing expenses, is intended to encourage broad participation in the exploration of rare disease therapies.⁸ Lowering the cost of rare disease research and development to a point commensurate with their restricted potential for recoupment, Congress sought to enable these costs to be justified with regularity.⁹ Reflecting the intent for broad participation in the exploration of rare disease therapies, the plain language of the ODA affords liberal access to these incentives. Specifically, to qualify for orphan designation, the Act merely requires that sponsors: (1) make a request for orphan designation prior to filing a marketing application, and (2) demonstrate that the drug for which the request has been made is under investigation for a rare disease indication and that if approved, the approval would be for that rare disease indication.¹⁰

It is evident by the statutory language that Congress intended the role of this provision to encourage as many innovators as possible to enter the rare disease space. Notably, there is no indication in the statute that access to these lowered costs should be restricted in any way, rather any such restriction would seem to contradict the purpose of opening the possibility of rare disease exploration to the maximum number of innovators. It is important to note that access to the Orphan Drug Tax Credit can only be achieved with orphan drug designation.

In contrast to the open and accessible language of the first provision, under the second provision the ODA very clearly works to protect an approved orphan product’s marketing exclusivity by significantly restricting other sponsors from breaking that

⁶ See Federal R&D grants: 21 U.S.C. § 360ee(a), Clinical trial tax credit: 42 U.S.C. § 236.

⁷ See 21 U.S.C. § 360cc(a).

⁸ United States Congress House Committee on Energy and Commerce. Subcommittee on Health and the Environment. Preliminary Report of the Survey on Drugs for Rare Diseases. Prepared for the Subcommittee on Health and the Environment, Committee on Energy and Commerce. Washington: U.S. Government Printing Office; 1982.

⁹ *Id.*

¹⁰ 21 U.S.C. §360bb(a)(1).

exclusivity. The Act narrowly limits the possibility of breaking the seven years of exclusivity to cases where an orphan drug with exclusivity experiences a shortage and is unable to meet the demands of its rare disease patient population. The intended role of this provision is to protect the value of the marketing exclusivity and inject a predictable value into the prospect of marketing a rare disease therapy.¹¹

These provisions lower the cost of research and development, and improve the predictability of recoupment, enabling innovators to more regularly justify exploration of rare disease therapies.

Orphan Drug Regulations

It is without question that FDA's implementation and management of the orphan drug program has been a success, as it is because of the Agency's leadership that today more rare disease patients than ever before have access to life-sustaining therapies. This leadership began on January 29, 1991, when, recognizing the need for a more defined orphan drug pathway, FDA published its proposed rules implementing the ODA.¹² Over the course of two years, FDA held multiple public hearings and invited comment from many orphan drug stakeholders. From these meetings and comments FDA found that while the tax credits and R&D grants provided innovators easier access to the rare disease space, marketing exclusivity was considered a primary incentive for orphan drug development.¹³ Accordingly, the finalized orphan drug regulations were structured to adhere to the intent of the ODA, narrowly limiting the possibility of breaking first-to-market exclusivity to cases of supply shortages and cases in which the second-to-market product is shown to be clinically superior to the first-to-market.¹⁴ Principally, the clinical superiority requirement is meant to ensure: (1) "that improved therapies will always be marketable and that orphan drug exclusivity does not preclude significant improvement in treatment of rare diseases," and (2) that the orphan exclusivity period is heavily protected.¹⁵ These objectives are achieved by requiring that sponsors seeking to prove clinical superiority demonstrate their drug, "provide[s] a significant therapeutic advantage over and above that provided by an approved orphan drug [...]."¹⁶ The

¹¹ Congress recognized that the costs associated with developing therapies for the treatment of rare diseases needed to be met with a more predictable recoupment. In 1988 Congress recognized that establishing seven years of marketing exclusivity provided that predictability, stating, "The Committee's expectation about the importance of this provision [marketing exclusivity] was accurate. It has been quite valuable as an incentive, even though it does not necessarily make a drug profitable or give it significant commercial value. It does provide greater certainty as to the potential return from the sale of the drug." 1988 U.S.C.A.N. 48.

¹² 56 Fed. Reg. 3338 (1991).

¹³ 21 C.F.R. § 316.3(b)(13).

¹⁴ *Id.*

¹⁵ In the final rule, answering comments regarding clinical superiority, FDA stated, "[i]t is within FDA's authority to define what is the "same" and what is a "different" drug. "Clinical superiority" is a rational and permissible means of making this distinction. FDA understands the difficulties inherent in proving clinical superiority but believes the requirement is necessary in order to protect the value of the primary incentive that Congress created in the Orphan Drug Act. If FDA allows exclusive marketing rights to be eliminated without evidence of clinical superiority or based on shoddy evidence, the incentive will be worthless." *Id.*

¹⁶ Definition of clinical superiority, See 21 CFR §316.3

regulations specify that clinical superiority may be demonstrated through improved effectiveness, safety, or a major contribution to patient care.¹⁷ In promulgating the rule, FDA was explicit that the clinical superiority requirements were adopted for the purposes of protecting the value of orphan exclusivity. It is clear from the history of the program that clinical superiority is an effective tool for protecting the value of that exclusivity. However, as will be discussed in greater detail below, FDA also uses this clinical superiority as a barrier to orphan designation to the detriment of plasma protein therapies.

In addition to using clinical superiority to protect orphan exclusivity, FDA also requires any second-to-market sponsor seeking designation to, “present a plausible hypothesis that its drug may be clinically superior to the first drug.”¹⁸ A plausible hypothesis, as defined by FDA, is, “an explanation of why the proposed variation [in the second-to-market drug] may be clinically superior to the first drug.”¹⁹ Establishing this barrier to orphan designation, FDA intended to create, “a liberal designation policy [...] because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval.”²⁰ Through implementation, FDA further stated that, “a liberal designation policy is appropriate despite the possibility that it might lead to wider use of the tax credit provisions under section 4 of the Orphan Drug Act because the agency doubts that sponsors will deliberately conduct fruitless research just to obtain the tax credits.”²¹ Regrettably, because of their unique biologic-human derived character, the stated liberal nature of FDA’s designation policy does not apply to second-to-market plasma protein therapies. Rather, many plasma protein therapies are barred from designation despite their being solely indicated to treat one or more rare diseases or conditions, contradicting: (1) the stated intent of the Agency to provide liberal access to designation, (2) the intent of the ODA to lower the barriers to orphan drug exploration, and (3) the plain language of the ODA.

PPTA recognizes the importance of the clinical superiority requirement for the protection of orphan drug exclusivity. However, the Association contends that requiring a plausible hypothesis of clinical superiority to achieve orphan drug designation eliminates an important opportunity to encourage investment in needed treatments and investment that benefit individuals with rare disorders. A more accurate implementation of the ODA would provide liberal access to orphan drug designation to all drugs seeking approval

¹⁷ “[M]ajor contribution to patient care” should be interpreted narrowly, while the other pathways are typically only available through comparative clinical trials. Haffner, *Orphan Products, Ten Years Later and Then Some* 49 Food & Drug L.J. 593, 599 (1994). Notably, the only example given by the FDA as a “major contribution to patient care” was the development of an oral dosage where only a parenteral option had been available previously. Joseph A. Levitt & John V. Kelsey, *The Orphan Drug Regulations and Related Issues*, 48 Food & Drug L.J. 525, 529 (1993).

¹⁸ 21 C.F.R. § 316.20, et seq.

¹⁹ *Id.*

²⁰ 56 Fed. Reg. 3338 (1991).

²¹ *Id.*

for an orphan indication, while at the same time maintaining clinical superiority as a strong protection for marketing exclusivity.

Congressional Treatment of Orphan Designation

Since the rules implementing the Orphan Drug Act became final in 1992, many plasma protein therapies have been unable to achieve orphan drug designation because of the requirement to demonstrate a plausible hypothesis of clinical superiority. Consequently, this means that many plasma protein therapies are unable to benefit from the Orphan Drug Tax Credit, and federal grants, which by FDA's own account are relatively minor incentives, intended to be broadly accessible.²² Today, in addition to being unable to claim the Orphan Drug Tax Credit and federal grant incentives, drugs unable to achieve orphan designation are also excluded from other more recent beneficial Congressional orphan policies. By hinging these benefits on orphan drug designation, unprecedented value has been instilled in the actual designation of a product as an orphan drug, amplifying the significance of FDA's clinical superiority requirement for orphan designation.

Beginning in 1997, with the second Congressional reauthorization of the prescription drug user fee act ("PDUFA II"), Congress exempted orphan designated products from application fees, and in certain cases from product and establishment user fees.²³ Because most plasma protein therapies are unable to satisfy the clinical superiority requirement for orphan designation, many second-to-market plasma products face over \$1.5 million in user fees,²⁴ a figure projected to rise even higher through PDUFA V reauthorization.²⁵ Assessing these high fees for regulatory review on products solely indicated to treat one or more rare diseases contradicts the purpose of the ODA and discourages plasma protein innovation.

The Affordable Care Act ("ACA") of 2010 yet again saw Congress turn to orphan designation as the most convenient proxy for protection of drugs used to treat rare diseases. Specifically, the ACA establishes the annual pharmaceutical fee as an excise tax assessed on the pharmaceutical industry based on the volume of a manufacturer's branded prescription sales.²⁶ Under the ACA, makers of orphan products that took the orphan tax credit may exempt those products from their calculated volume and reduce their annual fee tax liability.²⁷ Because the orphan tax credit is only available to orphan

²² *Id.*

²³ 21 U.S.C. § 379h.

²⁴ 21 C.F.R. § 314.60.

²⁵ On July 28, 2011, FDA announced its intention to consider increasing user fees for PDUFA V. See FDA Commissioner Margaret Hamburg's testimony before the Senate Committee on Health, Education, Labor, and Pensions regarding PDUFA V negotiations. Available at: <http://www.fda.gov/NewsEvents/Testimony/ucm265170.htm>

²⁶ 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 (WestLaw 2011)).

²⁷ *Id.* at §9008(e)(3).

designated products, those second-to-market plasma protein orphan population therapies incapable of designation are fully exposed to the cost of the annual pharmaceutical fee. Exposure to the annual fee is no small matter, given that the pharmaceutical industry was assessed a \$2.5 billion tax beginning in 2011, a figure that will reach \$4.1 billion in 2018 before retreating slightly to an annual charge of \$2.8 billion extending into perpetuity.²⁸

In addition to the annual pharmaceutical fee, the ACA expanded the definition of covered entities that are eligible to participate in the 340B Drug Discount Program and purchase covered outpatient drugs at statutorily discounted prices.²⁹ A full third of all U.S. hospitals are 340B entities. Recognizing that exposing orphan drugs to such widespread discounts could have a chilling effect on rare disease innovation, Congress carved orphan designated products from the 340B discounts for the newly covered entities.³⁰ Barring access to orphan designation for second-to-market plasma protein therapies subjects these rare disease therapies to the steep 340B discount.

Using orphan drug designation, Congress is reaching for the closest possible bright line to differentiate drugs that treat rare disorders from commonly used drugs.

Clinical Superiority Acutely Impacts the Plasma Protein Therapeutics Industry

The Agency's clinical superiority requirement for orphan designation impacts the entire plasma protein industry because the industry's brand diversity and rare disease product portfolio. FDA's barrier to orphan designation places downward economic pressure on the plasma protein industry's capacity to innovate and explore rare disease therapies, in turn hindering patients' access to the therapeutic intervention best suited for their individual needs.

FDA's requirement that sponsors of second-to-market products present a plausible hypothesis of clinical superiority prevents many plasma protein products from achieving orphan drug designation. This affects plasma protein therapeutics industry significantly because the various drugs within each therapeutic class of products are considered to have the same principal molecular structures and would not be considered different under the regulations without a showing of clinical superiority, despite the fact that each therapy is a unique, non-interchangeable biological product. This has important ramifications for the plasma industry because it has developed an exceptionally diverse selection of branded products within each therapeutic class, thus the industry's portfolio is predominantly composed of second-to-market products indicated to treat rare diseases, but not orphan designated.³¹ Because each brand of plasma protein therapeutics gives rise to unique pharmacokinetics and pharmacodynamics on a per

²⁸ *Id.*

²⁹ 42 U.S.C. §256b(a)(4)(M)-(O).

³⁰ *Id.* at §256b(e).

³¹ See Appendix A, Table 1, Examples of Rare Diseases Treated by Plasma Protein Therapies.

patient basis, plasma protein patients rely on a diversity of selection for access to the product that provides the most safe and effective treatment.³²

In addition to its brand diversity, the industry is uniquely characterized by its focus on rare disease populations. Accordingly, by barring second-to-market plasma protein products from orphan designation, FDA is exposing the industry's rare disease portfolio to user fees, the annual pharmaceutical fee, and steep 340B discounts. This exposure discourages innovation for rare diseases, contradicting the overall purpose of the ODA, and threatening access for patients living with rare diseases.

The recent Congressional expansion of federal mandatory discount programs and creation of the annual pharmaceutical fee have amplified this effect to a point of detriment, threatening the industry's capacity to continue to explore rare disease therapies.

Solution

FDA's October 19, 2011 proposed rule provides an opportune time for the Agency to protect the integrity of the orphan drug program and safeguard rare disease therapies.³³ FDA can provide this protection to rare disease therapies by eliminating the requirement to show a plausible hypothesis of clinical superiority for orphan drug designation, consistent with the ODA's intent while maintaining the requirement for orphan exclusivity.³⁴ Amending the orphan drug regulations in this way will protect the value of orphan exclusivity and advance the overall intent of the ODA to stimulate development of rare disease therapies.

Orphan designation and marketing exclusivity are subject to separate statutory provisions, and were intended to serve distinct purposes within the orphan drug program.³⁵ FDA should grant orphan drug designation to a drug without providing it with orphan exclusivity. This is best demonstrated by the "horseraces" that periodically occur in the orphan approval process.³⁶ Specifically, when FDA grants orphan

³² 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).

³³ The October 19, 2011 proposed rule amending the Agency's 1992 orphan drug regulations clarifies the Agency's stance on clinical superiority, providing FDA the opportunity to comprehensively address the clinical superiority requirement as it pertains to orphan designation. Orphan Drug Regulations, 76 *Fed. Reg.* 64868 (proposed Oct. 19, 2011).

³⁴ See Hyman Phelps, & McNamara, White Paper Analysis, providing a legislative and regulatory analysis of FDA's treatment of clinical superiority, and proposal to solve the problems that arise by eliminating the clinical superiority requirement for orphan designation, while maintaining the requirement for marketing approval.

³⁵ *Id.*

³⁶ See e.g., In the 1997 horse race between Baker Norton's Paxene and Bristol-Myers Squibb's Taxol, both were considered the same drug, and orphan designated for the same orphan indication, AIDS related Kaposi's Sarcoma. BMS' Taxol was approved first and Baker Norton was required to wait out the 7 year exclusivity period. While Baker

designation to multiple drugs, considered to be the same drug and intended to be approved for the same orphan indication, the Agency prompts a race to marketing approval. The winner of these races is provided seven years of marketing exclusivity, while remaining therapies are barred from the market until the exclusivity expires or they prove their product is in some way clinically superior to the already approved product. Notably, once the seven years of marketing exclusivity has expired the remaining products may come on the market and while not afforded exclusivity they remain orphan designated. This latter point is significant as it demonstrates FDA's legislated discretion to separate designation from exclusivity. The orphan drug "horserace" exemplifies FDA's willingness to encourage rare disease exploration by providing designation to multiple drugs, while at the same time maintaining the clinical superiority requirement for orphan exclusivity so as to preserve its value. PPTA urges FDA to similarly exercise its discretion by amending the orphan drug regulations to eliminate the clinical superiority requirement for orphan designation while maintaining it for marketing approval.

In light of the recent Congressional use of orphan designation, and the added burden that it places on the plasma protein industry, PPTA contends that FDA must ensure appropriate access to designation if it is to maintain the integrity of the incentive structure that has benefited patients with rare disorders over the last two decades. This can be accomplished through the following amendments to the orphan drug regulations:

1. Remove 21 C.F.R. § 316.20(b)(5)
2. Revise 21 C.F.R. § 316.23 by adding © as follows:
 - “(c) (1) Upon request by the sponsor, any orphan-drug designation request that was denied, placed in abeyance, or otherwise not granted solely on the basis of failing to show a plausible hypothesis of clinical superiority to an already-approved drug may be reinstated.
 - (2) FDA will grant such request for orphan-drug designation in accordance with 21 C.F.R. § 316.24.
 - (3) Any such request must be made within 180 days after the effective date of this regulation.”
3. Remove 21 C.F.R. § 316.25(a)(3)
4. Revise proposed 21 C.F.R. § 316.34(c) as follows:

“(c) If a drug is otherwise the same drug as a previously approved drug, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to substantiate demonstrate, at the time of marketing approval, ~~the hypothesis of clinical superiority over the previously approved drug that formed the basis for designation.~~”³⁷

These changes would permit second and subsequent drugs to be designated as orphan drugs even if they are the same drugs as already-approved drugs, regardless of whether the first drug has existing orphan drug exclusivity, had orphan drug exclusivity that has expired, or was never designated nor granted orphan drug exclusivity.³⁸ It is important to make clear that these regulatory amendments do not affect the existing requirement for a demonstration of clinical superiority for the purposes of approving a second drug when the first drug has orphan drug exclusivity.³⁹ PPTA fully supports maintaining the value of the orphan exclusivity incentive. Because the ACA provisions affecting orphan designation require that sponsors have been designated at some point in the past, PPTA requests that these amendments be partially retroactive. Applying these new regulations to any designation requests that were denied, placed in abeyance, or otherwise not granted for failing to present a plausible hypothesis of clinical superiority to an approved drug allows sponsors affected by the retroactive language of the ACA to be protected in kind. Importantly, the proposed amendments comprehend that any orphan drug designation will be effective as of the date granted by FDA and do not allow the designation itself to be retroactive, nor do the amendments allow for retroactive relief under other programs (e.g., the proposal does not intend that a sponsor be able to submit a waiver request for past user fees on the basis of new drug designation).⁴⁰

Conclusion

The orphan drug program by all measures is a success, stimulating the exploration and marketing of over 380 drugs used to treat rare diseases and conditions. While FDA’s management of the orphan drug program can be credited for much of its success, the incentive structure established by FDA’s 1992 implementation underlies every aspect of the program. Congressional use of orphan drug designation in policies creates additional barriers to bringing drugs and therapies to treat rare disease patients to market in a landscape where the orphan drug designation conveys benefits and protections unintended by the ODA. By amending the orphan drug regulations to allow for designation without a showing of clinical superiority while maintaining the requirement for marketing exclusivity, FDA will protect the integrity of the orphan drug program, encourage broad exploration for rare diseases, and allow for the development of brand diversity such that patients will have access to the therapy best suited to their

³⁷ See Hyman, Phelps, & McNamara, White Paper Analysis.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ *Id.*

individual needs. Accordingly, PPTA urges FDA to adopt in its final rule the regulatory amendments outlined in this comment.

Thank you for your consideration.

Respectfully Submitted,



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

Hyman, Phelps & McNamara, P.C.

WHITE PAPER

The Need for Changes to the Food and Drug Administration's Orphan Drug Regulations:

A Case for Delinking Orphan Designation
and Clinical Superiority

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Executive Summary

Congress enacted the Orphan Drug Act (“ODA”) in 1983 to provide incentives to encourage private companies to develop and bring to market drugs intended for rare diseases or conditions (also known as orphan diseases). The incentives were intended to create an atmosphere to encourage competition among sponsors of orphan drugs, while protecting the investment made by private companies by providing marketing exclusivity for the first drug approved for an orphan indication.

The ODA, as amended, and the Food and Drug Administration’s (“FDA’s”) implementation of the statute have been, by many measures, very successful in encouraging companies to bring drugs for such rare diseases or conditions to market. However, FDA’s current interpretation of the ODA does not permit orphan drug designation for many therapies that treat rare diseases or conditions and has a particularly detrimental effect on certain classes of drugs, including plasma protein therapies, by preventing access to the benefits and protections afforded products designated as orphan drugs. This limitation in the current ODA framework with respect to orphan drug designation diminishes its intent, which is to encourage the development of therapies for rare conditions and to take into account the high cost and risk of pursuing development of the therapies. In light of the purpose of the statute, it should be interpreted broadly to encourage sponsors to endeavor to provide patients with orphan diseases choices in their treatments as are generally available for non-orphan diseases. The limitation with respect to orphan drug designation is compounded by its recent use by Congress to provide additional protections for orphan drugs, placing significance on orphan drug designation that was not predicted or foreseen by the ODA or its implementing regulations.

Under FDA’s current regulations, many second-to-market products, including several plasma protein therapies, seeking orphan designation for the same indication as an already approved orphan drug, are considered to be the “same drug” as the approved drug for purposes of orphan drug designation. This has a significant effect on the plasma protein therapeutics industry because the various drugs within each therapeutic class of products are considered to have the same principal molecular structures and would therefore not be considered different under the regulations without demonstrating clinical superiority. This is of particular concern for plasma protein therapies, which are non-interchangeable, unique biological products, despite the similarities in molecular structure among products in each therapeutic class. In such cases, FDA will not designate a second-to-market drug as an orphan drug unless the designation request includes a medically plausible hypothesis of clinical superiority (based on safety, effectiveness, or major contribution to patient care).

This White Paper will explore the current legislative and regulatory regime pertaining to orphan drug designation and exclusivity, focusing on FDA’s current requirement for a showing of a plausible hypothesis of clinical superiority for orphan

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drug designation for second-to-market products and the potential negative effects on the development of therapies for patients with rare diseases. Specifically, this White Paper will discuss in detail the following issues:

- In recent years, Congress has begun using orphan designation as a means to provide orphan drugs special consideration from legislated obligations, including certain taxes, fees, and discounts.
- Congressional use of orphan designation as the underpinning for protection instills significant and unprecedented benefit in the designation of a drug as an orphan drug.
- Because second-to-market plasma protein therapies that treat rare disorders are often unable to present a plausible hypothesis of clinical superiority, many are unable to obtain orphan drug designation and thus are excluded from the protections afforded orphan-designated drugs.
- Exclusion from these newly enacted protections may stifle innovation for rare disease therapies and threatens to reduce patient access to treatment.
- The complex manufacturing process for plasma protein therapies and the unique, non-interchangeable biological products it yields rely on increased investment and innovation in research and development as well as technology in order to meet growing needs of patients with rare diseases.
- Acting within its legislated authority, FDA should eliminate the requirement to include a plausible hypothesis of clinical superiority from the orphan drug designation process, while maintaining a clinical superiority requirement for orphan drug exclusivity determinations.
- Eliminating the requirement for a plausible hypothesis of clinical superiority from orphan drug designation, while maintaining a clinical superiority requirement for orphan drug exclusivity, protects the value of orphan drug exclusivity and advances the overall intent of the ODA to stimulate innovation in the development of rare disease therapies.
- FDA's recent proposal to amend the orphan drug regulations provides an opportunity for consideration of a proposed regulatory solution to this problem.

Hyman, Phelps & McNamara, P.C.

I. Issue

Congress enacted the Orphan Drug Act (“ODA”) in 1983 to provide incentives to encourage private companies to develop and bring to market drugs intended for rare diseases or conditions.¹ As will be discussed in more detail below, the statute provides for both a designation process in which sponsors can request that the Food and Drug Administration (“FDA”) designate their drugs as drugs intended for orphan diseases and a period of marketing exclusivity to provide a more predictable potential for recouping the investment to bring the product to market. Approximately 200 orphan diseases now have drugs approved for their treatment,² which indicates the ODA has been successful in encouraging the development of orphan drugs.³

However, FDA, which was charged with promulgating regulations to implement the ODA, has interpreted one aspect of the statute in such a way that has a detrimental effect on sponsors of drugs intended for the treatment of certain rare diseases. Specifically, FDA has incorporated into the orphan drug designation process a requirement that a sponsor seeking orphan drug designation for a drug that is otherwise the “same” as a drug that is already approved for the same orphan use present a medically plausible hypothesis of clinical superiority in order to be granted orphan drug designation. Under FDA’s current regulations, if a second-to-market drug intended for an orphan disease is “too similar” in structure to the already-approved first-to-market drug or cannot make a showing of a plausible hypothesis of clinical superiority (based on safety, effectiveness, or major contribution to patient care), FDA will not designate it as an orphan drug. While each plasma protein therapy is a unique biological product for which no generics or substitutions currently exist, many plasma protein therapies have the same principal molecular structures such that they are deemed too similar to be considered different under the regulations without showing a plausible hypothesis of clinical superiority. Moreover, they are generally unable to meet FDA’s standard for showing clinical superiority. If such drugs are not designated as orphan drugs pursuant to the statute, they are ineligible for a number of protections Congress has provided for drugs intended to treat rare disorders subsequent to the enactment of the ODA, even though the drugs are or would be indicated for the treatment of orphan diseases.

¹ In this White Paper, the term “drug” will refer both to drugs subject to new drug applications under section 505(b) of the Federal Food, Drug, and Cosmetic Act (“FDC Act”) and biological products subject to biologics license applications under section 351 of the Public Health Service Act.

² See OOPD Recent Publications, OOPD News Archive, *available at* <http://www.fda.gov/forindustry/developingproductsforrareconditions/ucm217869.htm> (last visited Dec. 30, 2011).

³ Prior to the enactment of the ODA, there were 34 orphan drugs marketed by pharmaceutical companies. See H.R. Rep. No. 97-840, at 7 (1982), *as reprinted in* 1982 U.S.C.C.A.N. 3577, 3579.

Hyman, Phelps & McNamara, P.C.

II. Legislative/Regulatory Background

- A. Congress enacted the ODA to stimulate the development of drugs for rare diseases and conditions.

With the enactment of the ODA in 1983, Congress sought to stimulate research into and development of drugs for rare diseases and conditions. The statute currently defines a “rare disease or condition” as

any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.⁴

The ODA was intended “to reduce the costs of developing . . . and to provide financial incentives to develop” drugs for rare diseases and conditions.⁵ Accordingly, the ODA did two important things: (1) it created a process for designation of drugs for rare diseases or conditions⁶ and (2) it provided for a number of incentives for drugs that have been designated for rare diseases or conditions, including tax credits for certain “qualified testing expenses” for such drugs,⁷ grants for the development of such drugs,⁸ and seven years of marketing exclusivity for such drugs.⁹

First, section 526 of the FDC Act provides for the designation by FDA of drugs for rare diseases or conditions. Specifically, this statutory provision provides that a sponsor of a drug “may request [FDA] to designate the drug as a drug for a rare disease or condition.”¹⁰ It further states that “[i]f the Secretary finds that a drug for which a request is submitted under the subsection is being or will be investigated for a rare disease or condition and” any marketing application for the drug “would be for use for such disease or condition, the Secretary shall designate the drug as a drug for such disease or condition.”¹¹ The only two conditions precedent to the Secretary granting designation are: (1) the designation request be submitted prior to submission of the

⁴ 21 U.S.C. § 360bb(a)(2).

⁵ 21 U.S.C. § 360aa note. *See Orphan Drug Act: Hearings before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce, 97th Cong., 2d Sess. 13 (1982)* (“In order to provide some incentive for the development of . . . orphan drugs, the Committee’s bill includes an exclusive marketing right for the sponsor of such a drug.”).

⁶ 21 U.S.C. § 360bb.

⁷ 26 U.S.C. § 45C(b)(2)(A).

⁸ 21 U.S.C. § 360ee.

⁹ 21 U.S.C. § 360cc. The original statute provided marketing exclusivity only for drugs that were not subject to any patent protection. *See ODA, Pub. L. No. 97-414*. This was changed by the Orphan Drug Amendments of 1985, Pub. L. No. 99-91.

¹⁰ 21 U.S.C. § 360bb(a)(1).

¹¹ 21 U.S.C. § 360bb(a)(1) (emphasis added).

Hyman, Phelps & McNamara, P.C.

marketing application for the drug¹² and (2) the drug be investigated for a rare disease or condition, as defined by the statute.

The legislative history of the original statute makes it clear that the purpose of the designation process is to provide a gatekeeping mechanism to allow only drugs intended for rare diseases or conditions access to the benefits provided in the ODA.¹³ In describing the designation process, the legislative history states:

Upon the request of a sponsor, the FDA would make a determination of whether the drug (or biological) is in fact for a rare disease or condition. The FDA would evaluate (1) what specific indication or use the drug will be, is, or has been tested for, and (2) whether the drug would be used for a rare disease or condition, if it were approved (or in the case of a biological, a license were issued) by the FDA as safe and effective for the indication or use for which it will be, is being, or was tested. If the FDA determines that drug or biological is for a rare disease or condition, the FDA would be required to designate it.¹⁴

The legislative history does not reveal any Congressional intent for the statute to be interpreted to provide other restrictions on the designation process.

Second, section 527 of the FDC Act provides protection in the form of marketing exclusivity for drugs intended for rare diseases or conditions.¹⁵ Specifically, if a drug is designated under section 526 of the FDC Act, upon approval of the marketing application for the drug, “the Secretary may not approve” another marketing application “for such drug for such disease or condition for a person who is not the holder of such approved [marketing application] until the expiration of seven years from the date of approval of the approved [marketing application].”¹⁶ The term “such drug” was not defined in the statute. The legislative history of the statute indicates that the purpose of section 527 was to provide market protection to incentivize sponsors to develop orphan drugs.¹⁷

¹² 21 U.S.C. § 360bb(a)(1). This timing requirement was added to the statute through the Orphan Drug Amendments of 1988, Pub. L. No. 100-290.

¹³ H.R. Rep. No. 97-840, at 8-9.

¹⁴ H.R. Rep. No. 97-840, at 9 (emphasis added).

¹⁵ 21 U.S.C. § 360cc(a).

¹⁶ 21 U.S.C. § 360cc(a) (emphasis added).

¹⁷ See H.R. Rep. No. 97-840, at 11. As noted above, the original statute provided marketing exclusivity only for drugs that were not subject to any patent protection. See *supra* note 9. This was changed in 1985 due to a recognition that even drugs with patent protection may need market exclusivity in order for sponsors to be encouraged to bring them to market. See H.R. Rep. No. 99-153, at 2-7 (1985), as reprinted in 1985 U.S.C.C.A.N. 301. The legislative history stated that “orphan drugs have to be treated specially if they are to be developed. . . . The Act and this bill do attempt to reduce the disincentives for their development and give drug company sponsors some certainty as to the drug approval process at FDA and the market conditions they will face upon approval.” *Id.* at 6.

Hyman, Phelps & McNamara, P.C.

The text of the two provisions of the ODA and the accompanying legislative history make it clear that the orphan drug designation process (section 526 of the FDC Act) was designed to be open and accessible, preventing only those drugs that were not intended for rare diseases from accessing the benefits and protections provided by the rest of the statute, while orphan drug exclusivity (section 527 of the FDC Act) was meant to provide the market protection for those new drugs that were ultimately approved for rare diseases.

B. FDA subsequently issued regulations to implement the provisions of the ODA.

In 1992, FDA promulgated regulations implementing the ODA. Up until this time, FDA was operating under interim guidance. FDA's early guidance regarding orphan drug designation did not include a clinical superiority element. For example, FDA's Interim Guidelines for Obtaining Designation of a Drug as an Orphan Drug did not include any reference to presenting a plausible hypothesis of clinical superiority in order to obtain designation.¹⁸ Similarly, in a Federal Register notice revising the policy regarding the timing for submission of an orphan drug designation request, FDA stated that "section 526 of the [FDC Act] required that FDA so designate the drug provided that the agency finds that: (1) the drug 'is being or will be investigated for a rare disease or condition;' and (2) approval of a marketing application for the drug 'would be for use for such disease or condition.'"¹⁹ The Federal Register notice makes no mention of a plausible hypothesis of clinical superiority in the designation process.

When FDA promulgated regulations in 1992, they provided for, among other things, the content and format of a request for orphan drug designation,²⁰ the timing of such requests,²¹ the conditions under which FDA must grant or deny such requests,²² the conditions under which FDA may revoke orphan drug designation,²³ and the scope and recognition of orphan drug exclusive approval.²⁴ FDA stated in the preamble to the regulations that it "came to its conclusions by seeking as much as possible to protect the incentives of the [ODA] without allowing their abuse. FDA believes the final rule achieves the best balance possible between protecting exclusive marketing rights and fostering competition."²⁵

¹⁸ See Office of Orphan Products Development, FDA, Interim Guidelines for Obtaining Designation of a Drug as an Orphan Drug (Nov. 1984) (on file with author).

¹⁹ 53 Fed. Reg. 47,577 (Nov. 23, 1988).

²⁰ 21 C.F.R. § 316.20.

²¹ 21 C.F.R. § 316.23.

²² 21 C.F.R. §§ 316.24, 316.25.

²³ 21 C.F.R. § 316.29.

²⁴ 21 C.F.R. §§ 316.31, 316.34.

²⁵ 57 Fed. Reg. 62,076, 62,077 (Dec. 29, 1992).

Hyman, Phelps & McNamara, P.C.

In an attempt to interpret “such drug” in section 527 of the FDC Act pertaining to orphan drug marketing exclusivity, FDA defined the term “same drug” to be used in determining whether a subsequent drug is the same as one that has already been approved.²⁶ There are different standards for determining whether a drug is the same as a previously approved drug based on the chemical and structural similarity of the two drugs, though in all cases, a subsequent drug will not be considered to be the same as a previously approved drug if the second drug “can be shown to be clinically superior to the first drug.”²⁷ Approval of a subsequent drug during the first drug’s period of exclusive approval for treatment of the same rare disease or condition or for the subsequent sponsor to obtain its own period of orphan drug exclusivity once the exclusivity for the first drug is gone would require evidence of the clinical superiority of the subsequent drug.²⁸ The stated purpose for adopting a clinical superiority requirement in the exclusivity determination was protection of the orphan drug marketing exclusivity incentive created by the ODA while not deterring companies from developing superior therapies.²⁹ According to the regulations, a drug is clinically superior if it “is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug),” which can be accomplished by demonstrating greater effectiveness or greater safety or by making a major contribution to

²⁶ 21 C.F.R. § 316.3(b)(13). *See also Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30 (D.D.C. 2001) (finding FDA’s definition of the “same drug” in the context of orphan drug marketing exclusivity – not orphan drug designation – to be a permissible construction of the statute).

²⁷ *Compare* 21 C.F.R. § 316.3(b)(13)(i) *with* 21 C.F.R. § 316.3(b)(13)(ii). For drugs “composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug” is the same drug, unless it can be shown to be clinically superior to the approved drug. 21 C.F.R. § 316.3(b)(13)(ii).

²⁸ 21 C.F.R. § 316.3(b)(3); 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991). For ease of reference, in this White Paper, a determination pertaining to marketing exclusivity refers both to a decision to approve a second drug for an orphan indication when the first drug has orphan drug marketing exclusivity and a determination to grant a second drug its own period of orphan drug marketing exclusivity. Both determinations are dependent on a showing of clinical superiority if the drugs are otherwise the same drugs for the same orphan use.

²⁹ *See* 57 Fed. Reg. at 62,078 (“Clinical superiority” “constitutes the best tool for giving effect to the intent of Congress to provide incentives for potential sponsors to develop safer and more effective orphan drugs.”). *See also id.* (“FDA understands the difficulties inherent in proving clinical superiority but believes the requirement is necessary in order to protect the value of the primary incentive that Congress created in the Orphan Drug Act. If FDA allows exclusive marketing rights to be eliminated without evidence of clinical superiority or based on shoddy evidence, the incentive will be worthless.”).

Hyman, Phelps & McNamara, P.C.

patient care.³⁰ The bar for demonstrating clinical superiority in order to achieve orphan exclusivity is high.³¹

In addition to using the “same drug” definition, including the concept of clinical superiority, for purposes of marketing exclusivity, FDA imported the requirement into the orphan drug designation request process. When the regulations were proposed and finalized, FDA did not explicitly state why it imported the idea of clinical superiority into the designation process. In the preamble to the proposed rule, FDA indicated that it considered and rejected an even stricter proposal because it wanted “to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval.”³² More recently, FDA stated that “permitting orphan-drug designation of a drug that is already approved for the orphan indication could result in inappropriate ‘evergreening’ of exclusive approval periods.”³³ FDA further stated that it believed “that a liberal designation policy is appropriate despite the possibility that it might lead to wider use of the tax credit provisions under . . . the [ODA] because the agency doubts that sponsors will deliberately conduct fruitless research just to obtain the tax credits.”³⁴ FDA thus interpreted the ODA to permit it to require a sponsor seeking orphan drug designation for a second drug that is “otherwise the same drug as an already-approved orphan drug” to provide “an explanation of why the proposed variation may be clinically superior to the first drug.”³⁵ The regulations state that FDA will refuse to grant an orphan drug designation request if, among other things, “[a] drug that is otherwise the same drug as one that already has orphan drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug.”³⁶

³⁰ 21 C.F.R. § 316.3(b)(3).

³¹ With respect to greater efficacy, the regulation states that “[g]enerally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trial would be necessary,” 21 C.F.R. § 316.3(b)(3)(i). The regulation indicates that the bar may be lower for demonstrating greater safety. *See* 21 C.F.R. § 316.3(b)(3)(i). With respect to the major contribution to patient care ground for demonstrating clinical superiority, the regulation states that it will only be shown in “unusual cases,” 21 C.F.R. § 316.3(b)(3)(iii), and it has been rarely used as a basis for approving a second drug for an orphan use when the first drug has orphan drug exclusivity. *See* Kurt R. Karst, The Unusual Case of the “MC-to-PC” Orphan Drug Designation/Approval, *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/01/the-unusual-case-of-the-mctopc-orphan-drug-designationapproval-.html (Jan. 6, 2009).

³² 56 Fed. Reg. at 3340.

³³ 76 Fed. Reg. 64,868, 64,870 (Oct. 19, 2011). Evergreening is the term used to describe the process of attempting to obtain multiple sequential periods of exclusivity for the same drug to extend the length of marketing exclusivity afforded to the drug.

³⁴ 56 Fed. Reg. at 3340.

³⁵ 21 C.F.R. § 316.20(b)(5).

³⁶ 21 C.F.R. § 316.25(a)(3).

Hyman, Phelps & McNamara, P.C.

FDA recently issued a proposed rule to amend its orphan drug regulations based on its experience with orphan drugs in the nearly 20 years since the regulations were initially promulgated.³⁷ Among other things, the proposed amendments to the regulations would, if finalized as drafted, broaden the regulation to require a plausible hypothesis of clinical superiority in order to obtain orphan drug designation so that it would apply in any situation in which the same drug had already been approved for the orphan disease or condition, without regard to whether the drug has existing orphan drug exclusivity, was granted orphan drug exclusivity that has since expired, or was never designated nor granted orphan drug exclusivity.³⁸

In contrast to the position taken above, FDA does not interpret the ODA to require a plausible hypothesis of clinical superiority in order to designate multiple drugs that are structurally the same and intended for the same orphan disease prior to approval of one of the drugs for that orphan disease (the so-called “horse race” scenario).³⁹ Rather, when there is no approved drug product for an orphan disease, FDA will designate multiple drugs in the race for approval that are structurally the same and intended for the same orphan disease without consideration of whether the second drug seeking orphan drug designation may be clinically superior to a drug that is already designated. Moreover, once a drug is approved for an orphan use and granted marketing exclusivity, any other drugs that were designated as orphan drugs prior to the first drug’s approval do not lose their orphan designation. These situations illustrate that there is nothing that either permits or requires FDA to link designation of a drug as an orphan drug to whether it will ultimately obtain marketing exclusivity. It is true that orphan drug designation is a condition precedent to obtaining marketing exclusivity; however, in certain circumstances (*e.g.*, when the second drug in the horse race is approved after the first drug’s exclusivity has expired), FDA has interpreted the statute to give it the authority to not provide marketing exclusivity to the second drug without a demonstration of clinical superiority, consistent with the intent of the statute.

III. Impact on Plasma Protein Therapeutics and Patients

- A. Congress has used orphan drug designation to provide benefits in the form of exclusion from certain obligations under various programs.

Over time, Congress has used orphan drug designation under section 526 of the FDC Act as a basis for carving drugs out of categories of obligations under various programs. First, Congress has exempted drugs that are designated as orphan drugs from

³⁷ See generally 76 Fed. Reg. 64,868.

³⁸ 76 Fed. Reg. at 64,870, 64,877-79. This has been FDA’s practice for years, but FDA is proposing to bring the regulations in line with its current practices, in this and other areas.

³⁹ See 76 Fed. Reg. at 64,872; *Baker Norton Pharms.*, 132 F. Supp. 2d at 32 (“Because the drug is designated as an orphan drug before it is approved, more than one applicant may receive orphan designation for what later may be deemed the same ‘drug’ for treatment of the same disease or condition.”).

Hyman, Phelps & McNamara, P.C.

certain user fees. Specifically, in 1997, Congress amended the user fee provisions of the FDC Act to provide an exception from the human drug application and supplement user fees when the application or supplement is for a drug that has been designated as a drug for a rare disease or condition pursuant to section 526 of the FDC Act.⁴⁰ In addition, a drug that is designated as an orphan drug under section 526 of the FDC Act is exempt from product and establishment user fees provided certain additional conditions are met.⁴¹

Second, as part of the Affordable Care Act of 2010, Congress established an annual pharmaceutical fee under which drug manufacturers are required to pay a fee based on the volume of the sales of their branded prescription drugs to certain government programs, excluding drugs “with respect to which [an orphan drug tax] credit was allowed for any taxable year.”⁴² This exception does not apply to any orphan drugs after the date on which such drug is approved by FDA for marketing for any indication other than the orphan indication for which the tax credit was allowed. An orphan drug tax credit cannot be obtained without orphan designation. Accordingly, while the availability of the orphan drug exclusion from the annual pharmaceutical fee depends on factors in addition to designation of a drug as an orphan drug, the underpinning of the exclusion is designation of a drug as an orphan drug. Therefore, certain products intended for orphan diseases cannot avail themselves of the orphan drug exception from the pharmaceutical fee.

Third, also as part of the Affordable Care Act, Congress expanded the definition of covered entities that are eligible to participate in the 340B Drug Discount Program and purchase covered outpatient drugs at no more than statutorily mandated ceiling prices.⁴³ At the same time, Congress also excluded from the definition of a covered outpatient drug those drugs sold to the newly-eligible covered entities that are designated under section 526 of the FDC Act for rare diseases or conditions.⁴⁴

⁴⁰ 21 U.S.C. § 379h(a)(1)(F).

⁴¹ 21 U.S.C. § 379h(k). This exemption was added by the Food and Drug Amendments Act of 2007, Pub. L. No. 110-85. Prior to this, requests for waivers of product and establishment fees for orphan drugs were considered under waivers necessary to protect the public health or waivers to prevent a barrier to innovation. *See* 21 U.S.C. § 379h(d)(1)(A), (B); H.R. Rep. No. 102-895, at 17 (1992) (“The Committee believes that this provision will give the FDA sufficient authority to waive fees for orphan drugs designated under section 526 of the FFDC Act, unless such waiver is not necessary to the protect the public health or it is apparent that the fee will not be a disincentive to innovation because the drug will be profitable and would have been developed in any event. . . . The Committee expects that FDA will grant an exemption from user fees where the fees would be a barrier to innovation.”).

⁴² Section 9008(e)(3) of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, as amended by section 1404 of the Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152.

⁴³ 42 U.S.C. § 256b(a)(4)(M)-(O). Under the provision, children’s hospitals, free-standing cancer centers, critical access hospitals, sole community hospitals and rural referral centers became eligible to participate in the 340B Drug Discount Program.

⁴⁴ 42 U.S.C. § 256b(e).

Hyman, Phelps & McNamara, P.C.

Accordingly, there are a number of significant protections unrelated to orphan drug exclusivity that Congress intended to provide for orphan drugs, which are contingent on orphan drug designation under section 526 of the FDC Act. These protections reflect Congress's acknowledgment of the difficulty in bringing treatment for rare disorders to market and the need for incentives to make sure that companies have the resources to develop therapies for these patients. Each new orphan drug that comes to market, whether it is a new chemical entity, a new indication for an existing orphan drug, or a second drug that provides an alternative to an existing orphan drug for a particular orphan indication, provides a benefit to patients suffering from orphan diseases by advancing patient access to the therapeutic intervention best suited for each patient's individual needs.

- B. FDA's current and proposed implementation of the ODA has a detrimental effect on plasma protein products.

Plasma protein therapies, which are plasma-derived products and recombinant analogues, are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of the therapies for the duration of their lives.⁴⁵ Because of characteristics unique to human plasma-derivatives, which account for nearly two-thirds of the plasma protein therapeutics market, plasma protein therapies can cost nearly four times more than traditional pharmaceutical products to produce.⁴⁶ These characteristics include the capital intensity of the facilities, equipment, and source material. Expenditures in these areas are due in part to the direct and indirect costs of compliance with stringent FDA regulations and rigorous voluntary industry standards by both the plasma collectors and fractionators. Manufacturers of therapies derived from human plasma generally produce products in multiple therapeutic classes from each pool of plasma and work to: (1) produce rare disease therapies that would otherwise be economically difficult to produce given the extremely small patient populations and the high manufacturing costs; (2) continue the research and development necessary to bring to market therapies that treat bleeding disorders that have largely been untreated or ineffectively treated; (3) improve formulations and routes of administration for existing therapies; and (4) increase investment in manufacturing capacity to meet growing patient needs.⁴⁷

The requirement for a plausible hypothesis of clinical superiority in order for a drug to be designated as an orphan drug acutely affects the plasma protein therapeutics industry because there are multiple drugs in most therapeutic classes. For example, as illustrated in Table 1 of Appendix C, there are nine brands of immune globulin, ten

⁴⁵ See Appendix A, Plasma Protein Therapeutics Industry Overview.

⁴⁶ See Appendix B, Plasma Protein Therapies: A Unique Segment of the Drug Industry.

⁴⁷ See Appendix A.

Hyman, Phelps & McNamara, P.C.

brands of factor VIII (“FVIII”) (two of which are FVIII/vWF complex), and four brands of alpha1-proteinase inhibitor therapies available in the United States.⁴⁸ As illustrated in Table 2 of Appendix C, only one drug in each of those well-established therapeutic classes has received orphan designation from FDA.⁴⁹ According to a health economics and consulting firm, plasma protein therapies represent 33 of the approximately 41 drugs indicated by FDA solely for the treatment of rare diseases, disorders, or conditions, but that lack an orphan drug designation from FDA.⁵⁰ This is because the different manufacturing processes for plasma protein therapies described in Appendix B, such as different viral inactivation or removal techniques or different purification methods, produce differences in the final product that may not, in most cases, be significant enough to allow two therapies with the same active ingredient to be considered different under FDA’s regulations.⁵¹

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 requirement to show a plausible hypothesis of clinical superiority to obtain 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.⁵² While there are a small number of examples of FDA granting designation to plasma protein therapies on the basis of a plausible hypothesis of clinical superiority, in many

⁴⁸ See Appendix C, 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.

⁴⁹ See Appendix C.

⁵⁰ See J.E. Davanzo et al., Dobson Davanzo, LLC, Identifying Therapies Solely Indicated for Treating Orphan Diseases that do not Meet the Orphan Drug Exclusions Criteria of the Annual Pharmaceutical Fee 2 (2010) (on file with author). These 41 drugs do not include therapies that have an approved orphan designated indication and additional rare disease indications that lack an orphan designation.

⁵¹ See 21 C.F.R. § 316.3(b)(13)(ii)(A) (illustrating the impediment faced by manufacturers of subsequent market entrant plasma protein therapies in obtaining orphan designation).

⁵² See Letter from Timothy R. Coté, M.D., M.P.H., Director, Office of Orphan Products Development, to Stanley Ammons, Octapharma USA, Inc., Re: Designation request # 06-2341 (June 24, 2010), available at <http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0213-0009> (stating that Wilate, the second drug intended for the orphan indication, was granted designation “on the basis of the hypothesis that Wilate was superior to Humate-P” and that exclusivity was granted due to a determination that Wilate offered “greater viral safety in comparison to Humate-P”); Letter from Marlene E. Haffner, M.D., M.P.H., Director, Office of Orphan Products Development, to Mr. Stewart H. Mueller, Armour Pharmaceutical Company (Aug. 31, 1992) (on file with author) (stating that “[i]n view of the evidence of improved viral safety of Mononine™, CBER has concluded that Mononine™ is probably a safer drug than AlphaNine® and, therefore, is a different drug within the meaning of the [ODA]. Hence, it is licensable.”). In addition, a recombinant factor IX product (Benefix) was later found to be clinically superior to both Mononine and Alphanine and approved in spite of their marketing exclusivity due to a finding that the recombinant product was safer than the human plasma-derived products with respect to transmitting human viruses. See Benefix™, Summary Basis for Approval, at 10-13 (Feb. 1997), available at <http://www.fda.gov/downloads/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasmaproducts/ucm058970.pdf> discussion.

Hyman, Phelps & McNamara, P.C.

cases, the requirement would prevent plasma protein products from being granted orphan drug designation, a valuable benefit that is provided for in the ODA without the qualification implemented by FDA. The requirement to show a plausible hypothesis of clinical superiority to obtain designation may also have an effect of limiting brand diversity for the rare disease patient populations as sponsors may be discouraged from developing new therapies and improving existing therapies if they are not able to avail themselves of the additional protections Congress has linked to orphan drug designation. Given lifelong use of plasma protein therapies by the rare disease patients they serve and the life-threatening conditions they face, combined with the unique manufacturing process for each therapy that results in differences in the final products that may affect patient tolerability, it is important to ensure that patients have access to the therapy best suited for their individual medical needs.⁵³

IV. Proposed Solution

- A. FDA's current orphan drug rulemaking presents an opportunity to provide a solution to this problem.

As noted above, FDA has initiated rulemaking to amend the regulations implementing the ODA.⁵⁴ This is an opportune time to revisit FDA's decision to incorporate a requirement to show a plausible hypothesis of clinical superiority, one that is nowhere in section 526 of the FDC Act, into the orphan drug designation process.

As discussed in detail previously, orphan drug designation and marketing exclusivity are subject to separate statutory provisions and serve distinct purposes such that they ought to be treated differently from one another. Orphan drug designation was created to serve a gate-keeping function so that only drugs for orphan diseases could access the benefits provided by the ODA, the most important of which was marketing exclusivity. The fact that a clinical superiority requirement might be appropriate in determining whether a drug is the "same drug" for purposes of orphan drug marketing exclusivity does not mean that it is appropriate or a permissible construction of the ODA for FDA to incorporate such a requirement into the designation process. There is no disagreement that, with regard to determinations pertaining to orphan drug marketing exclusivity,

⁵³ See, e.g., L. 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) (on file with author) (describing the clinical differences among the brands of immune globulin).

⁵⁴ See 76 Fed. Reg. 64,868. Comments on the proposed rule must be received by FDA no later than January 17, 2012.

Hyman, Phelps & McNamara, P.C.

Congress left it to FDA to define “such drug” as used in 21 U.S.C. § 360cc and provided no guidance on the meaning of this term. Thus, it is within FDA’s authority to define what is the “same” and what is a “different” drug. “Clinical superiority” is a rational and permissible means of making this distinction. FDA understands the difficulties inherent in proving clinical superiority but believes the requirement is necessary in order to protect the value of the primary incentive that Congress created in the Orphan Drug Act. If FDA allows exclusive marketing rights to be eliminated without evidence of clinical superiority or based on shoddy evidence, the incentive will be worthless.⁵⁵

Nor is there any dispute that it is important to protect orphan drug marketing exclusivity and the vital role that the clinical superiority requirement plays in this process. However, these facts speak only to requirements pertaining to marketing exclusivity; they provide no support for the proposition that clinical superiority has any relevance to the designation process.

Moreover, there is no policy reason that multiple drugs for the same orphan indication that are considered to be the same drug under the regulations cannot all be designated as orphan drugs, even when there is already an approved drug for that same orphan indication.⁵⁶ Rather, a statute that is intended to provide incentives for the development of products for orphan diseases should be interpreted broadly to encourage sponsors to endeavor to provide patients suffering from orphan diseases choices in their treatments as are generally available for non-orphan diseases. Moreover, incentives to encourage additional companies to bring therapies to market, even if those therapies are the “same drug” as an approved product under FDA’s regulations, may lead to beneficial changes in the treatment of patients.⁵⁷ Furthermore, orphan drug designation now has broader import than orphan drug exclusivity – it is used by FDA and other federal programs to provide certain protections (apart from marketing exclusivity), all of which are intended to recognize the difficulty in developing and producing therapies that treat rare patient populations.

⁵⁵ 57 Fed. Reg. at 62,078.

⁵⁶ In fact, there is no logical distinction between this situation and the situation where there is no approved drug for an orphan condition and FDA does not require a second sponsor seeking orphan drug designation to present a plausible hypothesis of clinical superiority. This is because FDA can still require evidence of clinical superiority when making the decision to approve the second drug or grant marketing exclusivity without regard to whether a plausible hypothesis of possible clinical superiority was provided during the designation process.

⁵⁷ For example, greater patient access to recombinant Factor VIII provided the opportunity for prophylactic treatment regimens, which has led to better results for hemophilia patients. See J.S. Stonebraker et al., A Study of Reported Factor VIII Use Around the World, World Federation of Hemophilia, Facts and Figures No. 9 (Dec. 2010), available at http://www.wfh.org/2/docs/Publications/Treatment_Products/Monographs/FF9_Factor-VIII-use.pdf.

Hyman, Phelps & McNamara, P.C.

Accordingly, FDA should remove the requirement for submission of a plausible hypothesis of clinical superiority from the orphan drug designation process. As discussed above, the designation process, on the one hand, and the determinations regarding approval and exclusivity, on the other hand, are separate and do not need to have symmetrical requirements regarding clinical superiority. Indeed, the opposite is true – in light of the statutory language and the purpose of the statute, incorporation of a requirement to show a plausible hypothesis of clinical superiority into the designation process is an impermissible construction of section 526 of the FDC Act. Appendix D provides proposed regulatory language to implement the necessary changes. These changes would permit second and subsequent drugs to be designated as orphan drugs even if they are the same drugs as already-approved drugs, regardless of whether the first drug has existing orphan drug exclusivity, had orphan drug exclusivity that has expired, or was never designated nor granted orphan drug exclusivity.

It is important to note that these regulatory amendments would have no effect on the existing requirement for a demonstration of clinical superiority for purposes of approving a second drug when the first drug has orphan drug exclusivity. This would be consistent with Congressional intent in enacting the ODA and creating orphan drug marketing exclusivity. Nor would the proposed changes lead to “evergreening” of exclusive approval periods, a concern expressed by FDA, since the clinical superiority requirement would remain intact for purposes of orphan drug marketing exclusivity. If a second-to-market drug is not found to be clinically superior to the first-to-market drug, it will not be entitled to its own period of marketing exclusivity, regardless of whether it is designated as an orphan drug.

Finally, this change to the regulations pertaining to the orphan drug designation process must be partially retroactive so that sponsors of any designation requests that were denied, placed in abeyance, or otherwise not granted for failing to present a plausible hypothesis of clinical superiority to an approved drug may have those designation requests evaluated without regard to a plausible hypothesis of clinical superiority and without regard to whether the drugs have already been approved. Therefore, the regulatory proposal includes a provision that outlines a process for dealing with any designation requests that may have been denied, placed in abeyance, or otherwise not granted for failing to present a plausible hypothesis of clinical superiority to an approved drug. Appendix D contains the proposed language, including a proposed window of time in which affected sponsors could apply for reconsideration of the

Hyman, Phelps & McNamara, P.C.

decision.⁵⁸ This proposal for retroactive relief to allow for reconsideration under the new regulations would be a one-time window and would not permit reconsideration in perpetuity. The proposal anticipates that any orphan drug designation would be effective as of the date granted by FDA and neither expects the designation itself to be retroactive nor expects retroactive relief under other programs (*e.g.*, the proposal does not intend that a sponsor be able to submit a waiver request for past user fees on the basis of new orphan drug designation).

Moreover, the retroactive application of the proposed changes to the regulations would not have a detrimental effect on any other parties' rights. As discussed above, the proposal would not change FDA's regulations or interpretation pertaining to determinations of marketing exclusivity. The grant of orphan drug designation to additional drugs, including those already approved for the rare diseases or conditions that are the subject of the designation request, would have no impact on any other sponsor's marketing exclusivity, "one of the strongest incentives in the [ODA] for encouraging research and development of treatments for rare diseases and conditions."⁵⁹

- B. FDA's current interpretation of section 526 of the FDC Act is arbitrary and capricious and would fail under a *Chevron Step One* analysis.

Judicial review of an agency's statutory interpretation follows principles articulated by the Supreme Court in *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*⁶⁰ *Chevron* analysis requires that a court first determine whether Congress has "directly spoken to the precise question at issue," in which case the court's duty is to give effect to the "unambiguously expressed intent of Congress."⁶¹ In determining whether Congress has addressed the precise question at issue, a court must "look to the

⁵⁸ We note that some sponsors may not have sought orphan drug designation for their products prior to submission of their marketing applications because they relied on FDA's interpretation of the statute and determined they could not show a plausible hypothesis of clinical superiority to an approved product. The statute currently states that a request for orphan drug designation shall be submitted prior to submission of a marketing application for that orphan indication. 21 U.S.C. § 360bb(a)(1). However, upon a change in FDA's interpretation, it may be within FDA's authority to interpret the statute to permit a grace period for the submission of orphan drug designation requests subsequent to the submission of marketing applications in order to prevent injustice for those sponsors that relied in good faith on FDA's erroneous construction of section 526 of the FDC Act. FDA followed a similar approach in 1988 after the ODA was amended to require submission of an orphan drug designation request prior to submission of the marketing application for that use. In that situation, FDA provided a grace period to permit submission of orphan drug designation requests in certain cases in which marketing applications had already been submitted. See 53 Fed. Reg. at 47,577.

⁵⁹ Memorandum from Marlene E. Haffner, MD, Director, Orphan Products Development, FDA, to Jay Siegel, MD, Director, Office of Therapeutics Research and Review, CBER, FDA (Mar. 7, 2002), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm094512.pdf>.

⁶⁰ 467 U.S. 837 (1984).

⁶¹ *Chevron*, 467 U.S. at 842-43.

Hyman, Phelps & McNamara, P.C.

provisions of the whole law, and to its object and policy.”⁶² If the statute is silent or ambiguous on the question at issue, the second step of the *Chevron* analysis requires that the court determine whether the agency’s interpretation is based on a permissible construction of the statute.⁶³

In this case, FDA’s current interpretation of section 526 of the ODA to require a plausible hypothesis of clinical superiority during the orphan drug designation process cannot survive the first step of the *Chevron* analysis. First, FDA’s interpretation is inconsistent with the plain meaning of the statute. The statute does not provide for a plausible hypothesis of clinical superiority in order for FDA to grant designation. As discussed above, the only two conditions precedent to FDA granting designation are: (1) the designation request be submitted prior to submission of the marketing application for the drug and (2) the drug be investigated for a rare disease or condition, as defined by the statute.

Second, adding a requirement to show a plausible hypothesis of clinical superiority to obtain designation is not necessary “to avoid ‘a result demonstrably at odds with the intentions of [the] drafters.’”⁶⁴ With the ODA, Congress intended to provide incentives for the development of orphan drugs, including competition among sponsors to bring orphan drugs to market, and protect the marketing exclusivity of the first drug approved for an orphan indication. Arguably, a clinical superiority requirement is consistent with the latter concern, but it is contrary to the first concern. If a sponsor knows that it will not have access to the benefits or protections associated with orphan drug designation because its drug would be the “same” as a drug already on the market, it may decide not to pursue development of an orphan drug, which would not be in the interests of patients suffering from the orphan disease and would be contrary to Congress’s intent.

Third, FDA’s current clinical superiority requirement is too blunt an instrument to protect the rights of the sponsor of the first-to-market drug.⁶⁵ While FDA’s current interpretation can be said to protect the rights of the first-to-market drug, it does so in a way that unnecessarily causes significant harm to second-to-market drugs. Such harm far outstrips any benefit to the first-to-market drug because it extends long past the expiration of the first drug’s marketing exclusivity. Accordingly, as in the *Mova* case, “FDA could have adopted a more narrow solution” to the mechanism for protecting

⁶² *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1067-68 (D.C. Cir. 1998).

⁶³ *Chevron*, 467 U.S. at 843. “[U]nder *Chevron* step two, we ask whether an agency interpretation is ‘arbitrary or capricious in substance.’ But we think the more apt analytic framework in this case is standard ‘arbitrary [or] capricious’ review under the [Administrative Procedure Act].” *Judulang v. Holder*, 565 U.S. ____ (2011) (slip op. at 9, n.7) (internal citation omitted).

⁶⁴ *Mova*, 140 F.3d at 1069 (citation omitted).

⁶⁵ *See Mova*, 140 F.3d at 1069 (finding FDA’s “successful defense” requirement in the interpretation of the FDC Act to fail under *Chevron* step one).

Hyman, Phelps & McNamara, P.C.

orphan drug marketing exclusivity.⁶⁶ Instead, it adopted a broad rule, which it cannot show is necessary to implement Congressional intent.

- C. If FDA fails to take into account the changed circumstances in its current rulemaking after being made aware of those circumstances through comments, FDA's interpretation of the ODA may be arbitrary and capricious.

Even assuming FDA's interpretation of section 526 of the FDC Act was not initially arbitrary and capricious, FDA's construction may now be found to be "arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with law" under the Administrative Procedure Act ("APA"), based at least in part on Congress's expanded use of orphan drug designation. In reviewing agency action, a court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment."⁶⁷ Agency action is arbitrary and capricious if, among other reasons, "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise."⁶⁸ In this case, FDA's orphan drug regulations, including the proposed regulation if finalized as currently drafted, fail to consider an important aspect of the problem, *i.e.*, the harmful effect of the requirement to show a plausible hypothesis of clinical superiority to obtain designation on second drugs that are otherwise the same as first drugs. This harmful effect has been increased by Congress's decision to extend the concept of orphan drug designation to other situations than those originally contemplated by Congress, *e.g.*, user fees, the pharmaceutical fee, and the 340B Drug Discount Program. If FDA were to maintain its current interpretation without considering these and other relevant factors, FDA's regulations would be arbitrary and capricious under the APA.

V. Conclusion

The ODA and FDA's implementation of the statute have done much to spur innovation of orphan drugs. However, FDA's interpretation of the ODA to incorporate a clinical superiority requirement into the orphan drug designation process is contrary to the statute and Congressional intent and has had a detrimental effect on at least one

⁶⁶ *Mova*, 140 F.3d at 1069.

⁶⁷ *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416-17 (1971).

⁶⁸ *Motor Vehicle Mfrs. Ass'n v. State Farm Mutual Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

Hyman, Phelps & McNamara, P.C.

segment of the drug industry – the plasma protein therapeutics industry. This has been and will continue to be compounded as Congress has used (and may continue to use) orphan drug designation as a requirement for access to additional benefits or exclusions from obligations. Accordingly, a minor change to FDA's orphan drug regulations is in order and can be accomplished through the rulemaking that FDA has already initiated.

APPENDIX A



Plasma Protein Therapeutics Industry Overview

PPTA is the international trade association and standards-setting organization for the world's major collectors of source plasma and manufacturers of plasma-derived products and recombinant analogues, collectively referred to as plasma protein therapies. Many 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. The majority of the rare conditions that require treatment with plasma protein therapies are genetic, chronic, and life threatening, including alpha-1 antitrypsin deficiency, chronic B-cell lymphocytic leukemia, chronic inflammatory demyelinating polyneuropathy, hereditary angioedema, hereditary antithrombin III deficiency, protein C deficiency, primary immune deficiency diseases, such as common variable immunodeficiency, X-linked agammaglobulinemia (Bruton's disease), DiGeorge syndrome, Wiskott-Aldrich syndrome, severe combined immunodeficiency, and graft-versus-host diseases, and bleeding disorders, such as hemophilia A, hemophilia B, congenital fibrinogen deficiency, Von Willebrand's disease, and factor XIII deficiency, Cytomegalovirus disease associated with transplant patients, hepatitis B reinfection in liver transplant patients, idiopathic thrombocytopenic purpura, infant botulism, Kawasaki's disease, rabies, rhesus incompatible pregnancies, and tetanus.

Members are committed to assuring the safety and availability of these medically necessary, life-sustaining therapies. Manufacturers of therapies derived from human plasma generally produce products in multiple therapeutic classes from each pool of plasma to (1) produce rare disease therapies that would otherwise be economically difficult to produce given the extremely small patient populations and the high manufacturing costs;¹ (2) continue the research and development necessary to bring to market therapies that treat bleeding disorders that have largely been untreated or ineffectively treated; (3) improve formulations and routes of administration for existing therapies; and (4) increase investment in manufacturing capacity to meet growing patient needs.

¹ 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) ("MRB REPORT").

APPENDIX B

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.¹

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,² plasma protein therapies cost nearly four times more than traditional pharmaceutical products to produce.³ These characteristics include the capital intensity of the facilities, equipment, and source material.⁴ Expenditures in these areas are due in part to the direct and indirect costs of compliance with stringent FDA regulations⁵ and rigorous voluntary industry standards⁶ by both the plasma collectors and fractionators.

¹ Compare THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2009 V, at 62 (2010) (providing U.S. sales by therapeutic class for 2009) [hereinafter "MRB REPORT"] 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 (last visited October 8, 2010).

² See MRB REPORT, *supra* note 1.

³ 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).

⁴ 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).

⁵ 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).

⁶ 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 (last visited Oct. 11, 2010) (providing standards for the certification of plasmapheresis centers) [hereinafter "IQPP STANDARDS"]; PPTA, QUALITY STANDARDS OF EXCELLENCE, ASSURANCE, AND LEADERSHIP

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”⁷ 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.⁸ 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.⁹ In 2009, nearly 90 percent of human plasma collected for manufacturing use in the United States was source plasma,¹⁰ which costs approximately \$148 per liter.¹¹ 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,¹² as required by law.¹³

Manufacturers that possess PPTA’s “Quality Standards of Excellence, Assurance, and Leadership” (“QSEAL”) certification may only use plasma obtained from

(“QSEAL”),

http://www.pptaglobal.org/program/QSEAL_CERTIFICATION_PROGRAM_DESCRIPTION%20V1.5.pdf (last visited Oct. 11, 2010) (providing standards for the certification of plasma fractionators) [hereinafter “QSEAL STANDARDS”].

⁷ 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.

⁸ 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).

⁹ 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).

¹⁰ See MRB REPORT, *supra* note 1, at 16.

¹¹ *Id.* at 45.

¹² *Id.* at 42.

¹³ See 21 C.F.R. § 610.40.

“qualified donors” for fractionation at their manufacturing establishments.¹⁴ The voluntary industry standards for the “qualified donor” at both collection and fractionation work in concert with and in addition to existing regulatory requirements concerning donor suitability,¹⁵ 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.¹⁶ 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.¹⁷ 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.¹⁸

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.¹⁹ Citing the GAO study, FDA has recently proposed to add these two voluntary standards to the Code of Federal Regulations, thus, making them mandatory.²⁰ 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.²¹

¹⁴ See QSEAL STANDARDS, *supra* note 6, at 7.

¹⁵ See 21 C.F.R. § 640.63.

¹⁶ 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 (last visited October 8, 2010).

¹⁷ See QSEAL STANDARDS, *supra* note 6, at 8.

¹⁸ *Id.* at 7.

¹⁹ 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).

²⁰ See Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use, 72 Fed. Reg. 63416, 63431 (Nov. 8, 2007).

²¹ See QSEAL STANDARDS, *supra* note 6, at 8.

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.²² Approximately 120 of these proteins are “well-characterized.”²³ 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-Oncley²⁴ or the Kistler-Nitschmann²⁵ 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.”²⁶

Under the Cohn method, fibrinogen remaining after the cryoprecipitate and cyrosupernatant 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

²² 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). See also N. Leigh Anderson and Norman G. Anderson, *The Human Plasma Proteome: History, Character, and Diagnostic Prospects*, 1 MOLECULAR & CELLULAR PROTEOMICS 845 (2002).

²³ 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., 4th ed. 2009).

²⁴ See generally Cohn, *supra* note 22.

²⁵ 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).

²⁶ Simon, *supra* note 23, at 276.

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.

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.²⁷

²⁷ 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 C

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 ₁ -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)

Rare Disease	Estimated Prevalence in U.S.	Therapeutic Class	Plasma Protein Therapy
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

Class	Therapy	Rare Disease
alpha ₁ -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	Ceprotrin (Baxter)	protein C deficiency
vWF	Alphanate (Grifols) Humate-P (CSL Behring) Wilate (Octapharma)	von Willebrand's disease

APPENDIX D

Proposed Revisions to Orphan Drug Regulations

1. Remove 21 C.F.R. § 316.20(b)(5)
2. Revise 21 C.F.R. § 316.23 by adding (c) as follows:

“(c) (1) Upon request by the sponsor, any orphan-drug designation request that was denied, placed in abeyance, or otherwise not granted solely on the basis of failing to show a plausible hypothesis of clinical superiority to an already-approved drug may be reinstated.

(2) FDA will grant such request for orphan-drug designation in accordance with 21 C.F.R. § 316.24.

(3) Any such request must be made within 180 days after the effective date of this regulation.”

3. Remove 21 C.F.R. § 316.25(a)(3)
4. Revise proposed 21 C.F.R. § 316.34(c) as follows:

“(c) If a drug is otherwise the same drug as a previously approved drug, FDA will not recognize orphan-drug exclusive approval if the sponsor fails to substantiatedemonstrate, at the time of marketing approval, ~~the hypothesis of~~ clinical superiority over the previously approved drug ~~that formed the basis for designation.~~”