

October 28, 2011
Reference No.: FDAA11020

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

VIA WEB

SUBJECT: Prescription Drug User Fee Act (PDUFA); Reopening of comment period
[Docket No. 2010-N-0128]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (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, which 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 plasma protein therapies for the duration of their lives. The therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of medically needed, life-sustaining therapies.

Introduction

PPTA thanks the Food and Drug Administration (FDA) for the opportunity to comment on the reauthorization of the PDUFA program and was pleased to participate in the April 2010 public meeting and to provide written comments on May 12, 2010. PPTA appreciates that FDA reopened the comment period for the expected duration of the public part of the reauthorization process, to ensure that all interested stakeholders have the opportunity to share their views on the matter,¹ and is pleased to provide these additional written comments.

The openness and transparency of the PDUFA IV process provided PPTA a voice to help shape PDUFA IV performance goals that directly affect our industry and ultimately

¹ See Notice; reopening of comment period, 75 Fed. Reg. 69,093, 69,093 (Nov. 10, 2010).

the patients we serve. PPTA believes the inclusion of all affected industry, as well as patients and stakeholders, is vital to the user fee program and commends FDA for continuing this during the PDUFA V reauthorization process.

General Comments

Plasma protein therapies are regulated by the Center for Biologics Evaluation and Research (CBER) and reviewed within the Office of Blood Research and Review. PPTA understands that Association members are only a small portion of the pharmaceutical industry that pay user fees, but the companies play an essential role in the patient community they serve. As noted, PPTA members are committed to assuring the safety and availability of medically needed, life-sustaining therapies.

PPTA would like to reiterate its comments during the April 2010 public meeting and in its May 2010 written comments (both attached). In particular, PPTA is pleased overall with CBER's performance under PDUFA IV and, because of the success of the user fee program, supports reauthorization of PDUFA in 2012. However, despite the strengths of the PDUFA user fee program, PPTA also would like to reiterate its concerns regarding a few areas under PDUFA IV. The concerns include the timeliness of data requests during the review process, the use of user fees to fund postmarket surveillance programs, and the continued expansion of the PDUFA program.

A New Approach to the Orphan Designation Process for Rare Disease Therapies

One of PPTA's primary concerns regarding FDA's proposals for PDUFA IV was in the area of rare diseases. On July 7, 2011, Janet Woodcock (FDA) testified before the Subcommittee on Health, Committee on Energy and Commerce, US House of Representatives, on "PDUFA V: Medical Innovation, Jobs, and Patients."² According to Dr. Woodcock, based on the April 2010 public meeting, input from the public docket, and FDA's internal analyses of program challenge areas, the Agency developed a set of potential proposed enhancements for PDUFA V, which are under internal review. The enhancements address many top priorities identified by public stakeholders and industry and the most important challenges identified within FDA. In particular, an "enhancement being considered includes FDA facilitation of rare disease drug development by issuing relevant guidance, increasing the Agency's outreach efforts to the rare disease patient community, and providing specialized training in rare disease drug development for sponsors and FDA staff."³ While PPTA appreciates FDA's consideration of the enhancement, the Association suggests that the Agency at the same time consider a new approach to the orphan designation process for rare disease therapies.

² <http://www.fda.gov/NewsEvents/Testimony/ucm261396.htm> (last visited Oct. 24, 2011).

³ *Id.*

In particular, PPTA respectfully urges FDA to change its current interpretation of the Orphan Drug Act (“ODA”) by eliminating the “clinically superior” requirement for orphan drug designation in cases where the Agency did not grant seven years of market exclusivity to the first to market drug or after the expiration of the seven years of market exclusivity.⁴ Under 21 C.F.R. § 316.20, the manufacturer or sponsor of a drug that is otherwise the “same” as an already approved orphan drug and seeking “orphan designation” for the same rare disease or condition as that drug must submit with its request plausible evidence that it may be “clinically superior” to that already approved drug. The purpose of the “clinically superior” threshold is to strike an appropriate balance between protecting the value of the seven years of market exclusivity that FDA is authorized to grant under the ODA for the first FDA approved brand for a specific rare disease or condition in a particular therapeutic class and encouraging continued innovation in treating that rare disease.⁵ A manufacturer seeking orphan designation for the subsequent product would have to demonstrate clinical superiority even if FDA has not granted seven years of market exclusivity for the first to market drug or, if granted, after the exclusivity period has expired for that drug. PPTA believes that requiring a demonstration of clinical superiority when there is no exclusivity period to protect is an interpretation of the ODA that is inconsistent with the purpose of the ODA which places a significant financial burden on drug manufacturers, patients, and the health care system as a whole.

With multiple brands in most therapeutic classes, plasma protein therapies are acutely affected by the “clinically superior” requirement that penalizes the brand diversity of well-established classes like alpha₁-proteinase inhibitor, factor VIII, factor IX, and immune globulin. These therapeutic classes are disproportionately affected by the Affordable Care Act’s (“ACA”) provisions that expanded the 340B Drug Pricing Program⁶ and established an annual pharmaceutical fee on certain branded prescription drug sales exempting only those drugs with orphan designation.⁷ The brands within these therapeutic classes of plasma protein therapies are non-interchangeable, unique biologicals despite having the same active ingredient (*i.e.*, the immunoglobulin G protein

⁴ According to the FDA’s Orphan Drug Designations and Approvals database, 370 of the 379 orphan designated drugs that FDA has approved for marketing have also been granted the seven years of market exclusivity.

⁵ See Memorandum from Marlene E. Haffner, MD, Director, Orphan Products Development, FDA, to Jay Siegel, MD, Director, Office of Therapeutics Research and Review, CBER, FDA, Re: Office of Orphan Products Development (OOPD) Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif (March 7, 2002), *available at* <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm094512.pdf> (last visited June 13, 2011).

⁶ See Patient Protection and Affordable Care Act (“PPACA”) § 7101(a), Pub. L. No. 111-148, 124 Stat. 119, 821-822 (codified at 42 U.S.C.S. § 256b(a)(4) (LexisNexis 2011)).

⁷ *Id.* at § 9008, 124 Stat. 119, 859-862, *amended by* Health Care and Education Reconciliation Act of 2010 (“HCERA”) § 1404, Pub. L. No. 111-152, 124 Stat. 1029, 1064 (codified as amended at 26 U.S.C.S. prec. § 4001 (LexisNexis 2011)).

for immune globulin therapies),⁸ yet FDA generally defines two drugs with the same active ingredient as the “same” for the purpose of the ODA regulations.⁹ In expanding the 340B program and establishing the annual pharmaceutical fee, Congress smartly excludes “orphan drugs”¹⁰ to prevent any unnecessary economic harm that could hinder research and development in the rare disease space. Most plasma protein therapies, however, will not qualify for these exclusions because most of them have not received orphan designation for their FDA approved indications, despite meeting the “rare disease or condition” threshold of affecting fewer than 200,000 patients in the U.S.¹¹ The expansion of the federal price controls and establishment of a burdensome excise tax are particularly harmful to the plasma protein therapeutics industry because of its unique cost structure.¹² Because of this new premium Congress has placed on whether

⁸ 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).

⁹ See *Baker Norton Pharms. v. FDA*, 132 F.Supp.2d 30 (D.D.C. 2001) (upholding the FDA’s definition of “same” drug under the Orphan Drug Act).

¹⁰ See HCERA § 2302, 124 Stat. 1029, 1082 – 1083, *amended by* Medicare and Medicaid Extenders Act of 2010 § 204, Pub. L. No. 111-309, 124 Stat. 3285, 3289 – 3290 (codified at 42 U.S.C.S. § 256b(e) (LexisNexis 2011)) (excluding orphan designated drugs from the definition of a “covered outpatient drug” for the purpose of the 340B program); PPACA § 9008(e)(3), 124 Stat. 119, 860 (codified at 26 U.S.C.S. prec. § 4001 (LexisNexis 2011)) (excluding the sales of drugs for which the ODA tax credit was allowed from the definition of “branded prescription drug sales” for the purpose of the annual pharmaceutical fee). The Health Resources and Services Administration, which administers the 340B program, is going beyond the plain language of the statute in its proposed rule implementing the exclusion by requiring manufacturers to continue to sell orphan drugs at the 340B price to the newly eligible 340B covered entities affected by the provision, but only allow such covered entities to use orphan drugs purchased at or below the 340B price in treating common indications, rare disease indications that lack orphan designation, and off-label conditions. See *Exclusion of Orphan Drugs for Certain Covered Entities Under 340B Program*, 76 Fed. Reg. 29183 (May 20, 2011). The Internal Revenue Service is requiring the manufacturer to have actually “claimed” the ODA tax credit in order to be eligible for the orphan drug sales exclusion from the annual pharmaceutical fee. See Internal Revenue Service, Notice 2011-9, <http://www.irs.gov/pub/irs-drop/n-11-09.pdf> (last visited June 15, 2011).

¹¹ For example, hemophilia A afflicts approximately 14,218 patients, according to the National Hemophilia Foundation. There are ten unique factor VIII therapies currently available to treat hemophilia A in the U.S., yet FDA has only granted orphan designation to one of the ten brands. An 11th brand, ReFacto, is no longer available in the U.S as of May 31, 2009, as it was phased out in favor of Xyntha. Interestingly, FDA had approved ReFacto for an orphan designated indication, but did not grant it the seven years of market exclusivity.

¹² Because of characteristics unique to human plasma-derivatives, which account for nearly two-thirds of the plasma protein therapeutics market, plasma protein therapies cost nearly four times more than traditional pharmaceutical products to produce. 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). These characteristics include the capital intensity of the facilities,

a drug is orphan designated, PPTA urges FDA to reevaluate its regulations governing the orphan designation process, particularly the application of the “clinically superior” requirement.

FDA should also closely examine the “clinical superior” requirement because of the barrier it creates to personalized medicine. Such a patient-centered, evidence-based approach to medicine was a key objective of the ACA because of its potential to improve quality of care while reducing expenditures.¹³ The plasma protein therapeutics industry prides itself on being the drug industry’s leader in the shift toward the personalized medicine paradigm. The alpha₁-proteinase inhibitor, factor VIII, factor IX, and immune globulin classes of therapies are among the most well-established therapeutic classes in medicine because the patient community has demanded brand diversity.¹⁴ Access to a full range of plasma protein therapies in each therapeutic class ensures that patients will be treated with a therapeutic intervention best suited for their individual needs, which will prevent avoidable costs in unnecessary physician visits, hospitalizations, and surgical interventions. Unfortunately, the “clinically superior” requirement creates a situation where many promising therapies may not receive FDA marketing approval because they were not first to market. This reality begs the question, are patients truly being well served under the current regulatory framework for orphan drug designation?

PPTA believes it is vital to reward past and encourage future innovation in developing therapeutic interventions for the treatment of rare diseases, disorders, and conditions. The financial incentives Congress created under the ODA are responsible for 379 orphan designated drugs receiving FDA marketing approval since its enactment. PPTA generally supports the regulatory framework that FDA created to implement the ODA, but recognizes that it should be interpreted to accelerate the research and development required to adequately serve the rare disease patient populations. With more than 25

equipment, and source material. 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); THE MARKETING RESEARCH BUREAU, INC., THE PLASMA FRACTIONS MARKET IN THE UNITED STATES 2009 41 (2010) (illustrating the capital intensity of the source material required to produce plasma protein therapies). 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 plasma collectors and fractionators.

¹³ See, e.g., THE HON. MAX BAUCUS, CALL TO ACTION: HEALTH CARE REFORM 2009 35-37 (2008) (identifying patient-centered medical homes, provider collaboration in accountable care organizations, and the interaction of interoperable health information technology with an increase in comparative effectiveness research as cornerstones of the personalized medicine paradigm).

¹⁴ See, e.g., MASAC Document #159: MASAC Recommendation Regarding Factor Concentrate Prescriptions and Formulary Development and Restrictions, MEDICAL & SCIENTIFIC ADVISORY COUNCIL, NAT’L HEMOPHILIA FOUNDATION, <http://www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu5/menu57/masac159.pdf> (illustrating the need for brand diversity for patients with bleeding disorders).

million patients in the U.S. suffering from a rare disease or condition,¹⁵ the FDA should interpret its policies to incentivize innovation. PPTA's recommendation to eliminate the "clinically superior" requirement for orphan drug designation in cases where the Agency did not grant seven years of market exclusivity to the first to market drug or, if granted, after the exclusivity period has expired will move the pharmaceuticals and biologicals industries closer to developing therapies for the nearly 7,000 identified rare diseases,¹⁶ including several bleeding disorders, that currently lack a dedicated therapeutic intervention for their treatment. PPTA further asks that its recommendation be applied retrospectively so that the more than 30 plasma protein therapies that currently lack orphan designation are appropriately classified.

Conclusion

PPTA appreciates the opportunity to comment on the reauthorization of the PDUFA program and looks forward to continued work with FDA during the process. PPTA welcomes from FDA any questions regarding these comments and/or requests for additional information.

Thank you for your consideration.

Respectfully submitted,



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

Attachments

¹⁵ See *Frequently Asked Questions*, OFFICE OF RARE DISEASES RESEARCH, NAT'L INSTITUTES OF HEALTH, <http://rarediseases.info.nih.gov/AboutUs.aspx> (last visited June 22, 2011).

¹⁶ *Id.*

May 12, 2010
Reference No.: FDAA10006

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

VIA WEB

SUBJECT: Prescription Drug User Fee Act (PDUFA); Public Meeting
[Docket No. 2010-N-0128]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) would like to thank the Food and Drug Administration (FDA) for the opportunity to participate in the Prescription Drug User Fee Act (PDUFA) V Public Meeting on April 12 and is pleased to provide these written comments. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. PPTA represent 97 percent of the Source Plasma collection centers and eight manufacturers of plasma protein therapies in the U.S. Plasma protein therapies are used in the treatment of a number of rare diseases. These diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. These therapies include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions.

PPTA participated in the PDUFA IV reauthorization process and appreciated the agency's effort to reach out to stakeholders who had not previously been included in PDUFA reauthorizations. The openness and transparency of the PDUFA IV process provided PPTA a voice to help shape PDUFA IV performance goals that directly affect our industry and ultimately the patients we serve. PPTA believes the inclusion of all affected industry, as well as patients and stakeholders, is vital to the user fee program and commends FDA for continuing this during the PDUFA V reauthorization process.

Plasma protein therapies are regulated by the Center for Biologics Evaluation and Research (CBER) and reviewed within the Office of Blood Research and Review (OBRR). PPTA understands that PPTA members are only a small portion of the pharmaceutical industry that pay user fees but these companies play an essential role

in the patient community they serve. PPTA and its members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

Overall, PPTA members are pleased with CBER's performance under PDUFA IV. CBER consistently has met PDUFA IV timeframes. PPTA members support the original intent of PDUFA, which was to provide additional resources to the FDA to establish a better managed human drug review process. PPTA recognizes that without the development of this user fee program, many life-saving therapies would not have come to fruition. Because of the success of the user fee program, PPTA supports reauthorization of PDUFA in 2012.

Despite the strengths of the PDUFA user fee program, PPTA members would like to express their concerns regarding a few areas under PDUFA IV. First, the timeliness of data requests during the review process. Data requests that occur at the end of the review process can be costly and difficult to manage. Often, these requests are poorly coordinated (i.e., several requests for the same data that have already been submitted) and occur right before a FDA action date. Also, there are often requests for significant labeling changes at the end of a review. PPTA believes better coordination and earlier communication of requests to the sponsor during the review process is needed. PPTA supported previous efforts by CBER to utilize mid-cycle reviews under Good Review Management Principles (GRMPs). However, due to other statutory PDUFA IV obligations it does not appear that mid-cycle reviews are being used consistently. Use of mid-cycle reviews would allow FDA to communicate expectations for the remainder of a review process and provide a sponsor the opportunity to clarify the scope of any requests that have been made. The consistent use of mid-cycle reviews would allow for better coordination and communication of data requests and FDA expectations providing a more predictable and transparent review process as intended by PDUFA.

Another area of concern is the use of user fees to fund post market surveillance programs. PPTA recognizes that safety needs to be an imperative part of the FDA review process. PPTA appreciates that FDA spends half of its effort and resources on drug safety activities. However, all of these activities cannot and should not be funded with PDUFA user fees. PPTA supported the use of user fees for post market surveillance programs during the peri-approval phase under PDUFA III but did not support the expansion of post market surveillance programs with PDUFA fees under PDUFA IV. PPTA believes that these programs should be funded with congressional appropriations.

PDUFA user fees should be considered a supplement to the FDA budget. As FDA moves forward with the PDUFA V reauthorization process, PPTA would like to stress the importance of containing costs of the PDUFA program. Current fees are significant. PPTA would like FDA to understand that the continued expansion of the PDUFA program will continue to drive up the fees to the detriment of companies that develop therapies for small, rare patient populations. For that reason, PPTA does not believe

there should be an expansion of any PDUFA programs. PPTA knows that there have been considerable cost increases for the agency and PPTA will continue to encourage Congress to provide FDA with adequate appropriated funding to ensure that both user fee and non-user fee programs remain viable.

Again, PPTA appreciates the opportunity to comment on the PDUFA IV program. PPTA member companies support PDUFA and look forward to working with FDA during the PDUFA V reauthorization process. Should you have any questions regarding these comments or would like additional information, please contact PPTA.

Respectfully submitted,



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

Plasma Protein Therapeutics Association (PPTA) Remarks

PDUFA V Public Meeting

Bridget Rossiter Elis, Esq.
Assistant Director, Regulatory Policy
April 12, 2010

- International trade and standards-setting organization
- Represents:
 - Plasma-derived therapies (PDUFA)
 - Recombinant analog therapies (PDUFA)
 - Source Plasma (non user fee)

Baxter
BioScience

 **GRIFOLS**

Talecris
BIOTHERAPEUTICS

CANGENE

CSL Behring

octapharma



Biotest

Ortho Clinical Diagnostics
a *Johnson & Johnson* company

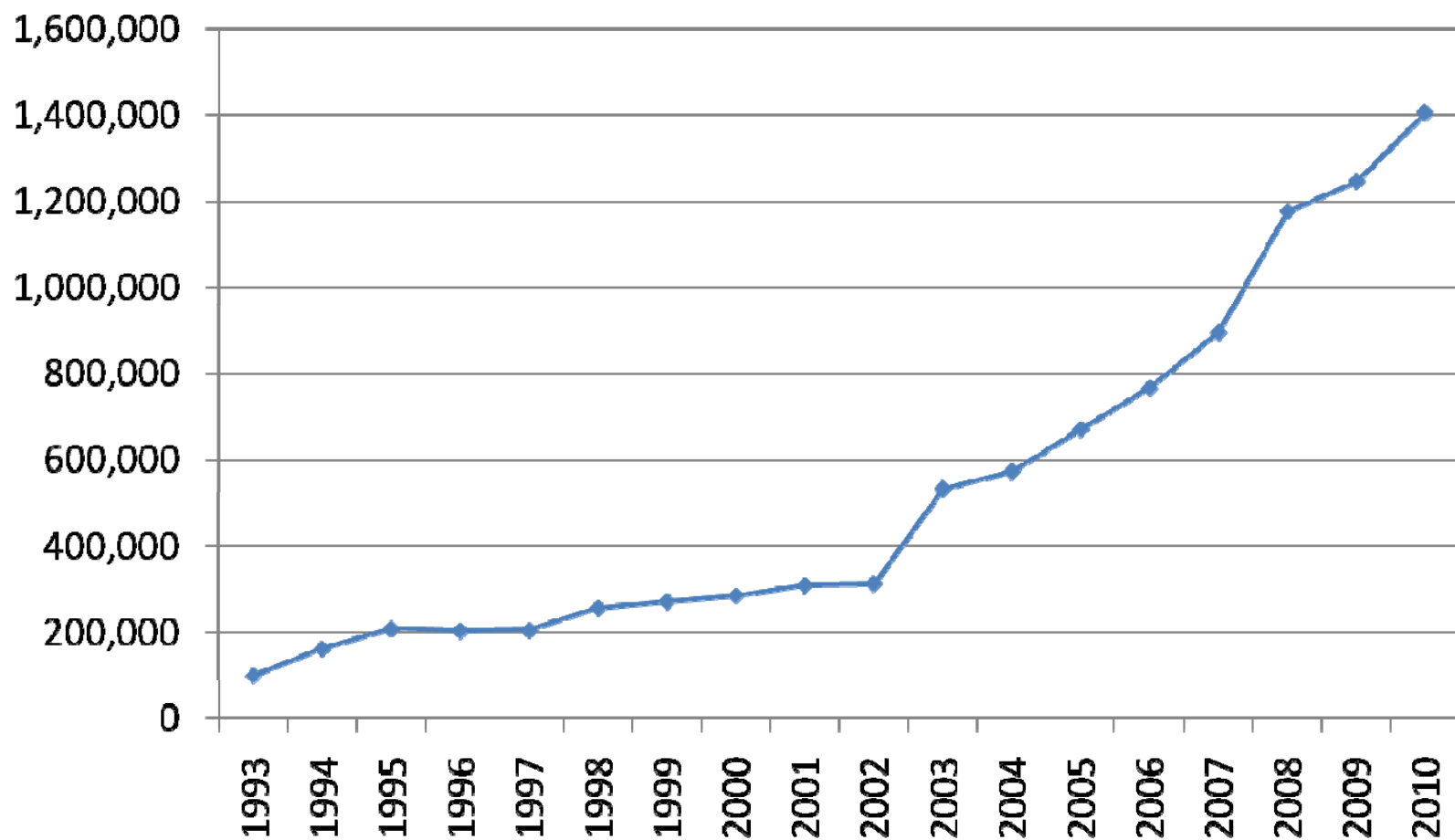
- Plasma Protein Therapies
 - Regulated by Center for Biologics Evaluation and Research (CBER)
 - Reviewed within Office of Blood Research and Review (OBRR)

- PPTA appreciated the openness and transparency of the PDUFA IV reauthorization process
- Overall PPTA members are pleased with FDA performance under PDUFA IV
- PDUFA IV goals have been met consistently
 - Current timeframes do not need to be adjusted

- Areas of concern under PDUFA IV
 - timeliness of data requests
 1. Data is requested at the end of a review
 2. Can be costly and difficult to manage within short-time frames
 - expansion of user fees towards post market surveillance
 1. Post market programs should be funded through Congressional appropriations
 2. Post market programs should not be expanded through PDUFA

- User fees should supplement FDA budget
 - Important that non user fee programs receive adequate funding
 - Congressional appropriations
- PDUFA related activities should not be expanded
 - Current fees are significant
 - Any further increases could be detrimental to smaller companies

Application User Fee Rates 1993 – 2010



- PPTA member companies support PDUFA
- PPTA appreciates the opportunity to participate in today's public meeting
- PPTA looks forward to working with FDA during the reauthorization process