Plasma Protein Therapeutics Association

June 27, 2011
Reference No.: FDAA11012

Division of Dockets Management (HFA-305) **VIA WEB**
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

SUBJECT: Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563 [Docket No. FDA-2011-N-0259]

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. The therapies 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. 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. Members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

General Comments

PPTA is pleased to provide these comments on the Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563.[1] PPTA strongly supports the Food and Drug Administration (FDA) in its efforts, "[i]n accordance with Executive Order 13563, 'Improving Regulation and Regulatory Review,' [to] conduct[] a review of its existing regulations to determine, in part, whether they can be made more effective in light of current public health needs and to take advantage of and support advances in innovation."[2] PPTA is eager to "help ensure that FDA's regulatory program is more effective and less burdensome in achieving its regulatory objectives"[3] by providing

[1] Federal Register / Vol. 76, No. 81 / Wednesday, April 27, 2011 / Proposed Rules, pp. 23520-2
[2] *Id.* at 23520
[3] *Id.*

147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
tel: 202.789.3100 · 410.263.8296 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.pptaglobal.org
PPTA Offices in Washington · Annapolis · Brussels · Tokyo

comments on transparency, the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and rare diseases.

FDA Could Revise its Existing Review Framework through Transparency

Transparency is key to "meet[ing] the objectives of E.O. 13563 regarding the development of a plan with a defined method and schedule for identifying certain significant rules that may be obsolete, unnecessary, unjustified, excessively burdensome, or counterproductive."[4] Overall, FDA communicates effectively and has made efforts to become more open and transparent. PPTA appreciates the efforts of FDA to attend meetings and share information with industry. It is vital that this type of dialogue continue, allowing industry and regulators to communicate fully concerns and to understand better decisions. It is important that consumers as well as industry have confidence in FDA, which plays a vital role in consumer protection and safety. Continuation of these efforts by FDA would help the Agency "best obtain and consider accurate, objective information and data about the costs, burdens, and benefits of existing regulations and whether there are existing sources of data that FDA can use to evaluate the post-promulgation effects of regulations over time" and thus "best … evaluate and analyze regulations to expand on those that work and to modify, improve, or rescind those that do not."[5]

In particular, PPTA appreciates FDA's ongoing efforts through its Transparency Initiative, including the Agency's establishment of a Transparency Task Force. PPTA has participated in FDA Public Meetings on Transparency and in the Transparency Task Force Listening Session, has submitted comments to the Agency regarding transparency, and has discussed transparency at the FDA-PPTA Liaison Meeting. There is an abundance of information available on the FDA website, including information on regulations. To this point, PPTA believes that FDA's web-based resources, FDA Basics and FDA Basics for Industry, will assist the public and industry, respectively, in better understanding the Agency's functions and the information already available. PPTA appreciates FDA's April 2011 release of a final version of the Strategic Priorities FY 2011-2015 and the Agency's implementation of the first of the proposals in its report proposing 21 actions to increase disclosures about Agency activities. PPTA also is encouraged that FDA is reviewing comments, including those submitted by the Association, received on the "FDA Transparency Initiative: Improving Transparency to Regulated Industry"; the Association looks forward to the Agency's recommendation of specific proposals to the FDA Commissioner for consideration.

PPTA also has specific comments on the functioning of FDA's "current processes for reviewing regulations[,] how those processes might be expanded or otherwise adapted to meet the objectives of E.O. 13563[, and] factors that [the Agency] should consider in

[4] *Id.* at 23521
[5] *Id.*

selecting rules for review and prioritizing review."[6] For example, in May 2011, FDA announced that the Agency is disclosing more information about inspections and court actions and now has a web portal on its enforcement activities. The actions implemented among the first of the proposals in FDA's report proposing 21 actions to increase disclosures about Agency activities. While PPTA appreciates the actions and recognizes that FDA also will begin to disclose additional information about Agency evaluations of filers and to expand disclosure of Untitled Letters at the end of 2011, the Association suggests that the Agency also post 483s from each inspection on the web portal. Such an action would provide regulated companies with additional transparency about the standards to which their products are held under current regulations, would allow for greater openness and predictability, and would improve the necessary, cooperative working relationship of industry and regulators. In turn, industry would be better equipped to provide effective feedback to FDA on reviewing regulations, considering factors in selecting rules for review, and prioritizing review.

Further, PPTA reiterates its comments on the "FDA Transparency Initiative: Improving Transparency to Regulated Industry" regarding communicating information about Agency procedures and product application review process. PPTA respectfully requests that FDA set a goal to post on the Agency Web site all slide presentations that are delivered by Agency employees to external offices; one suggestion for helping to achieve such a goal is beginning earlier the process of making presentations 508 compliant. PPTA also requests that FDA focus not only on reorganization of already-available resources but also on practical actions that would increase transparency (*e.g.,* holding further discussions with industry about application tracking systems). Again, these actions would provide regulated companies with additional transparency about the standards to which their products are held under current regulations and thus with the ability to advise effectively FDA on improving regulation and regulatory review.

Regulations That Should Be Reviewed at This Time

Name of regulation: CLIA regulations
FDA Center Regulating Product: Center for Devices & Radiological Health
Code of Federal Regulations cite: 42 CFR Part 493

Brief Description of Problem

As part of donor-screening and quality-assurance procedures, PPTA members perform not only FDA-required tests but also tests required for the Association's International Quality Plasma Program and Quality Standards of Excellence, Assurance and Leadership certifications. Most donor-screening tests, which ensure that plasma donated by individuals will meet the standards established by FDA for safety, purity, and

[6] *Id.*

potency,[7] are done in central testing laboratories that perform "tests of moderate complexity" and "tests of high complexity";[8] however, some donor-screening tests are performed on-site at the approximately 400 member Source Plasma centers in the U.S. On-site donor-screening tests are "waived tests,"[9] with the exception of the total protein test.[10] While some member Source Plasma centers use older, analog refractometers to perform the total protein test, other centers use newer, digital refractometers (*e.g.,* digital Reichert TS Meter-DSP[11]). Government regulators have assigned total protein tests by refractometers, regardless of type, to the "tests of moderate complexity" category under CLIA.[12]

Available Data on Cost or Economic Impact

Because PPTA member Source Plasma centers screen donors for total protein and total protein tests by refractometers have been assigned to the "tests of moderate complexity" category under CLIA, centers must meet applicable requirements described at 42 CFR § 493.20, Laboratories performing tests of moderate complexity: "subpart C or subpart D, and subparts F, H, J, K, M, and Q of this part."[13] Members incur very significant costs to maintain compliance with CLIA and to ensure that center medical directors meet qualifications to direct laboratories that perform "tests of moderate complexity"; member estimates of costs associated with CLIA registration and fees range from $2,000 to $3,400 per center per year, exclusive of even more significant, indirect costs related to training, certification, and compliance activities (*e.g.,* use of COLA).

Proposed Solution

Because FDA's assignment of total protein tests by refractometers, regardless of type, to the "tests of moderate complexity" category under CLIA is burdensome to industry

---

[7] *See* 21 CFR § 600.3(n)

[8] Under the CLIA law, laboratory requirements must be based on the complexity of tests performed. Under the regulations, FDA assigns commercially marketed in vitro diagnostic tests to one of three categories based on potential risk to public health: waived tests, tests of moderate complexity, and tests of high complexity. Under the law, "waived tests" must meet certain criteria that were excerpted without elaboration in the regulations at 42 CFR § 493.15(b); 42 CFR § 493.15(c) lists waived tests. In other words, "waived tests" are: (1) tests listed in the regulation; (2) tests for which the manufacturer or producer applies for waiver, if the test meets the statutory criteria and scientifically valid data are provided; and (3) tests cleared by FDA for home use.

[9] *E.g.,* 42 CFR § 493.15(c)(8) (spun microhematocrit). *See* 21 CFR 640.3(b)(3) (hemoglobin level of no less than 12.5 g/dL or hematocrit level of no less than 38%)

[10] *See* 21 CFR § 640.65(b)(2)(i) (total protein level of no less than 6.0 g/100 mL)

[11] The Reichert TS Meter is registered with FDA as a Refractometer for clinical use under 21 CFR § 862.2800 and thus Class I and exempt from premarket notification procedures (*i.e.,* PMN or 510(k)).

[12] *E.g.,* ATAGO SP-D Digital Serum Protein Refractometer, ATAGO T-2 Clinical Refractometer, ATAGO A300CL Clinical Refractometer, ATAGO N Serum Protein Refractometer, ATAGO SUR-NE REFRACTOMETER, ATAGO T2-NE REFRACTOMETER, Reichert TS Meter

[13] *See* 42 CFR § 493.20

and digital refractometers are simple to use, FDA should consider plasma used in a digital refractometer to measure total protein as a "simple sample" such that the test's categorization as "waived" is not precluded. Categorization of the total protein test by digital refractometer as "waived" would provide an incentive for industry to standardize use of digital refractometers to measure total protein in centers. Such standardization would encompass more robust technology, simplify training, and result in more consistent operation across industry.

Sample collection for the total protein test by digital refractometer is precisely the same as that for the spun-microhematocrit test because digital refractometers use plasma from the spun-microhematocrit test, a "waived test" per 42 CFR § 493.15(c)(8). Once the spun-microhematocrit test is performed, the capillary tube containing the red blood cells and plasma is removed from the centrifuge and inserted in a plasma-harvesting dispenser. Although the total protein test uses plasma from centrifugation, sample manipulation is not required to perform the assay. The purpose of the centrifugation is to manipulate the sample for the "waived" spun-microhematocrit test, not for the total protein test; when the total protein test begins, no sample manipulation is required, and the sample is "simple." By contrast, if the spun-microhematocrit test were not performed, then the purpose of the centrifugation would be to manipulate the sample for the total protein test; in that case, sample preparation would be required to perform the assay, and the sample would not be "simple."

Experiences of the member Source Plasma centers that use digital refractometers to perform total protein tests demonstrate that the test is a simple procedure with little health impact. The intended users of digital refractometers are donation-center employees who have prior training in blood borne pathogens, also known as universal precautions; in the hands of these test operators, the total protein test by digital refractometer is a simple procedure. Using the digital refractometer is as simple as reading the total protein level directly from the instrument display visible within the optical path according to manufacturer specifications. Preventative maintenance consists of wiping plasma from the refractometer between usages according to manufacturer specifications. Machine calibration is accomplished by running standards at two levels prior to use. While older, analog refractometers require water calibration via a manual adjustment of analog scale with a jeweler's screwdriver, digital refractometers offer accurate, simple, electronic, water calibration at the push of a button. Digital refractometers are battery-operated, portable, and automatic and measure accurately, consistently from technician to technician, and electronically the same scale as analog refractometers. While older, analog refractometers require trained operators with experience and knowledge of proper use, simple operational software and interface-onscreen instructions guide technicians through digital-refractometer results.

Rare Diseases

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

PPTA respectfully urges FDA 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 after the expiration of the seven years of market exclusivity if granted.[14] 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 Orphan Drug Act ("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.[15] 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 inconsistent with the purpose of the ODA and also 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 because of the agency's definition of "same" drug; thus, well-established classes like alpha$_1$-proteinase inhibitor, factor VIII, factor IX, and immune globulin are disproportionately affected by the Affordable Care Act's ("ACA") provisions that expanded the 340B Drug Pricing Program[16] and established an annual pharmaceutical fee on certain branded prescription drug sales.[17] The brands within each respective therapeutic class of plasma protein therapies are non-interchangeable, unique biologicals despite having the same active ingredient (i.e.,

---

[14] 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.

[15] *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).

[16] *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)).

[17] *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)).

the immunoglobulin G protein for immune globulin therapies),[18] yet FDA generally defines two drugs with the same active ingredient as the "same" for the purpose of the ODA regulations.[19] In expanding the 340B program and establishing the annual pharmaceutical fee, Congress smartly excludes "orphan drugs"[20] 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 less than 200,000 patients in the U.S.[21] 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.[22] Because of

---

[18] *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).

[19] *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).

[20] *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).

[21] 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.

[22] 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,

this new premium Congress has placed on whether 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.[23] The plasma protein therapeutics industry prides itself on being the drug industry's leader in the shift toward the personalized medicine paradigm. The alpha$_1$-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.[24] 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 many 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 improved 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.

[23] *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).

[24] *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,[25] the FDA should remove any policies that create barriers to 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,[26] 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.

FDA Review Process for Orphan Drug Marketing Applications

At a June 2010 FDA public hearing, PPTA presented its Perspective on FDA Review Process for Orphan Drug Marketing Applications to the Agency's rare disease committee, formed in March 2010, regarding the means by which the Agency reviews data from non-clinical studies and clinical trials and makes decisions about marketing authorizations and postmarketing surveillance for patients with rare diseases; the Association thereafter submitted comments to the docket on Considerations Regarding FDA Review and Regulation of Articles for the Treatment of Rare Diseases. PPTA reiterates its focus on: (1) need for global regulatory strategy (harmonization); (2) need to consider past foreign studies not conducted under U.S. Investigational New Drug Applications (INDs); (3) need for better and international registries and their use for efficacy, as well as safety and patient identifications; and (4) recognition, in terms of process validation and current Good Manufacturing Practices (cGMPs), that orphan drugs may be manufactured less frequently and with legacy equipment and processes.

Clinical-Trial Harmonization

As noted, plasma protein therapies are marketed for the treatment of small patient populations; even on a global basis, the patient populations are small. PPTA's most important goal is harmonization, more appropriately termed global regulatory strategy, across different regional regulatory bodies. To accomplish this goal, international regulatory bodies must communicate and work together to develop compatible requirements and to recognize the unique issues that occur when developing policies that affect finite patient populations with lifelong treatment needs; PPTA recognizes that these actions are occurring more often.

Past Foreign Studies Not Conducted Under INDs

---

[25] *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).
[26] *Id.*

One challenge is harmonizing the number of patients required for a study; some members of these populations may be subjects in several studies. Another challenge is the fact that some therapies considered for marketing in the U.S. have been available for years in other regions. To bring these therapies to the U.S., FDA needs to consider studies that were performed outside of the U.S., sometimes years before, not under IND requirements.

Patient Registries

The use of patient registries, ideally on an international basis, is of vital importance to the development of therapies for patients with rare plasma protein disorders. While FDA has agreed with PPTA that patient registries are important resources, the Agency currently appears to use patient registries to identify patients for possible recruitment and for safety monitoring but not for efficacy; the Association is disappointed that the Agency does not seem enthusiastic about accepting patient-registry data in an expanded role (or in-lieu of double-blind, placebo-controlled, clinical-trial data) to meet design requirements. PPTA encourages FDA to expand its acceptance of patient-registry data.

Facilities/Equipment

The realities of manufacturing therapies for patients with rare plasma protein disorders should be considered. While no one would advocate for different standards for cGMPs, these therapies may not be produced as often as other drugs, and some of these therapies were developed years ago and may have been validated on legacy facilities and/or equipment that are not as cutting-edge as those on which newer products have been validated. As new requirements are put in place for process validation and cGMPs, these therapies' special manufacturing characteristics must be considered for the therapies to remain viable marketing options for manufacturers.

Orphan Drug Review

The above illuminates the differences of rare disease therapies and the need for practical approaches to clinical-trial designs and review parameters based on the populations targeted by such therapies. PPTA encourages FDA, during review processes, to recognize such differences and to adopt such approaches. Currently, even with orphan drug designations, once rare disease therapies are in the therapeutic office/division, such therapies are treated no differently than non-rare disease therapies. Yet, at the FDA public hearing, one speaker testified that there are more similarities between orphan drugs in different classes that between orphan drugs and non-orphan drugs in the same class; another speaker testified that the Agency has authority to be flexible regarding orphan drugs and suggested that the Agency have one division reviewing only orphan drugs.

Conclusion

PPTA appreciates the opportunity to comment on the Periodic Review of Existing Regulations; Retrospective Review Under E.O. 13563 and looks forward to continued work with FDA on its efforts to conduct a review of its existing regulations to determine whether they can be made more effective in light of current public health needs and to take advantage of and support advances in innovation. 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