Plasma Protein Therapeutics Association

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

SUBJECT: Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases; Public Hearing [Docket No. 2010-N-0218]

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 Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases Public Hearing [hereinafter, "Public Hearing"] on June 29-30, 2010. PPTA 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 represents 97 percent of the Source Plasma collection centers and eight manufacturers of plasma protein therapies in the U.S.; these companies provide 60 percent of the world's needs for these therapies.

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. Plasma protein 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 limits substantially life expectancy, and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA member companies are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Introduction

PPTA applauds FDA for holding this Public Hearing. PPTA believes that this is an important issue and that all stakeholders need to be engaged to identify solutions.

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Opportunities, such as this Public Hearing, are important to discuss the medical issues related to patients with rare plasma protein disorders and the scientific and regulatory challenges that manufacturers face in product development and approval. PPTA appreciates FDA efforts to review available laws, regulations, and policies with a focus on facilitating development of biological products used to treat patients with rare plasma protein disorders. This review is part of an FDA paradigm shift, over the last several years, from reviewing a drug merely for its orphan indication, to also reviewing the drug as part of the overarching goal of providing therapies to patients with rare disorders. 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). In June, 2005, CBER sponsored a public workshop entitled Biological Products for Treatment of Rare Plasma Protein Disorders. An important first step, the workshop provided an opportunity to examine the role of the regulator, as both a reviewer of orphan indications, as well as a partner in advancing development of therapies for people with rare plasma protein disorders; manufacturers, patients, and academia were heard. PPTA is pleased with FDA's progress since the workshop; recent approvals indicate FDA is taking tremendous strides in providing a new paradigm for review and approval of therapies to treat rare plasma protein disorders.

Recent Law

PPTA also is encouraged by the passage of the recent public law (Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, 2010, Public Law 111-80, section 740), which calls for the establishment of a committee of FDA employees to consider the means by which FDA reviews the data from non-clinical studies and clinical trials and make decisions about marketing surveillance and post-marketing surveillance for these patient populations, as well as by the March 11, 2010, establishment of the committee. PPTA recognizes that this Public Hearing was another step in a long process but believes that it opened further avenues of communication between FDA, patient communities, and industry.

Public Hearing

At the Public Hearing, in response to the applicable question, Question 1, delineated in the Federal Register notice of April 30, 2010 (Vol. 75, No. 83), PPTA presented its Perspective on FDA Review Process for Orphan Drug Marketing Applications, which focused 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.

To assist further FDA in facilitating development of biological products used to treat patients with rare plasma protein disorders, PPTA provides these written comments in response to Federal Register Question 1:

Orphan drug marketing applications are reviewed under the same review process and statutory standards regarding demonstration of safety, effectiveness, and product quality as drugs for patients with non-orphan diseases or conditions. FDA is sensitive to the unique needs of patients with rare diseases as it makes approval decisions regarding the overall risk-benefit profile of therapies for the particular patient population for which they are being considered. Please comment on whether this practice has adequately addressed the needs of patients with rare diseases. If improvements are suggested, please provide specific examples/suggestions for any recommended changes.

a. Clinical trial harmonization

Although some progress in harmonizing clinical trials has been made, PPTA would like to see such results formalized in consistent guidance, similar to the recommendations of the National Organization for Rare Diseases, and harmonized, in the U.S. and abroad. Plasma protein therapies are marketed globally 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 have been occurring more often.

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.

FDA should view the Inspector General (IG)'s June, 2010, report, Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials, as an opportunity to provide assurance of oversight, by partnering with international regulators and by leveraging its resources in setting standards for inspections, training, and education. In particular, PPTA suggests that FDA focus on the IG's recommendation that FDA continue to develop inspectional agreements with foreign regulatory bodies, as a way for FDA to expand its oversight of foreign clinical trials. The development of these inspectional agreements is a vital step toward international clinical trial harmonization.

b. Clinical trial design

Double-blind, placebo-controlled clinical trials are burdensome, expensive, and not feasible for small patient populations; issues include study size, participant recruitment and compliance, endpoints, and surrogate/biomarker use. The special needs of the industry's small patient populations must be recognized; consequently, novel designs, such as patient registries, one-arm studies, historical controls, adaptive clinical trials, phase IV studies, and pharmacovigilance, in the U.S. and abroad, must be considered.

1. Design issues

When patient populations are small, study size is an issue; as noted, some members of populations may be subjects in several studies. This issue leads to participant-recruitment problems; few subjects exist, and even fewer are willing to participate. Another issue is compliance; patients with rare plasma protein disorders require treatment for, not a short time, but the duration of their lives. Patients should be active participants in determining their enrollment, participation, and compliance; regulators can impart to patients regulatory needs, but also should consider patient needs, in determining why and how patients participate. Study endpoints also should be evaluated carefully, based on pre-approval requirements and information gathered post-approval in phase IV and/or surveillance. In addition, surrogate endpoints and biomarkers, if properly identified, developed, and standardized, always should be considered.

2. 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, FDA currently appears to use patient registries to identify patients for possible recruitment and for safety monitoring but not for efficacy; PPTA is disappointed that FDA 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.

3. 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 GMPs, 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.

c. 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 Public Hearing, one speaker testified that there are more similarities between orphan drugs in different classes than between orphan drugs and non-orphan drugs in the same class; another speaker testified that FDA has authority to be flexible regarding orphan drugs and suggested that FDA have one division reviewing only orphan drugs.

While supporting review of orphan drugs within a single organizational structure, PPTA also supports, as an interim or alternative solution, the inclusion of an Office of Orphan Product Development (OOPD) representative, with expertise in rare diseases and authority to represent the needs of patients, on each review committee for a therapy indicated for treatment of a rare disease.

In addition to the above, PPTA encourages FDA to develop dispute resolution policies and procedures that include the OOPD in resolutions of disagreements in the review of therapies with indications for treatment of rare diseases. It is important that OOPD be involved in review dispute resolution in order to include flexibility that is available in current legislation and regulations but may not be institutionalized in reviewer practices.

Again, PPTA appreciates the opportunity to comment on the Considerations Regarding Food and Drug Administration Review and Regulation of Articles for the Treatment of Rare Diseases. PPTA member companies look forward to working with FDA on this issue. Should you have any questions regarding these comments or would like additional information, please contact PPTA.

Respectfully submitted,

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Plasma Protein Therapeutics Association