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: Approval Pathway for Biosimilar and Interchangeable Biological Products Public Hearing; Request for Comments [Docket No. 2010-N-0477]

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 Approval Pathway for Biosimilar and Interchangeable Biological Products Public Hearing [hereinafter, "Public Hearing"] on November 2-3, 2010, 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 products and recombinant analogues, collectively referred to as plasma protein therapies. Plasma protein 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 plasma protein therapies for the duration of their lives. Plasma protein 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 member companies are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Introduction

PPTA welcomes the opportunity to discuss plasma protein therapies at public hearings and via written submissions. The Association appreciates FDA's efforts to create a forum to obtain input on specific issues and challenges associated with the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCIA),[1] part of the Patient Protection and Affordable Care Act of 2010 (PPACA).

[1] Federal Register / Vol. 75, No. 192 / Tuesday, October 5, 2010 / Notices, p. 61497

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BPCIA adds, at the end of section 351 of the Public Health Service (PHS) Act, subsection 351(k), "Licensure of Biological Products as Biosimilar or Interchangeable."[2] FDA, particularly the Center for Biologics Evaluation and Research (CBER), clearly recognizes the uniqueness of plasma protein therapies and their vital role for patients with a number of rare diseases; PPTA's comments are limited to the effects of BPCIA on plasma protein therapies.

General comments

At the Public Hearing, PPTA emphasized the importance of a global approach to the consideration of biosimilars. As plasma protein therapies are marketed globally, harmonization between United States (US) and European Union (EU) requirements, practically speaking, will prevent the necessity of different clinical plans in the US and the EU. FDA's consideration of biosimilars follows chronologically that of both the EU's European Medicines Agency (EMA) and the World Health Organization (WHO). Adopted by its Committee for Medicinal Products for Human Use (CHMP) in September 2005, and effective October 30, 2005, EMA's Guideline on Similar Biological Medicinal Products provides, regarding "Blood or plasma-derived products and their recombinant alternatives":

> In view of the complex and variable physico-chemical, biological and functional characteristics of the products listed in the BPWG [Blood Products Working Party] guidelines mentioned below, it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product. As a result, applications for such similar products will still need to satisfy the safety and efficacy requirements described in these BPWG guidelines for "new products".[3]

WHO followed suit on October 19-23, 2009, when its Expert Committee on Biological Standardization (ECBS) adopted Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), the scope of which ECBS limited:

> This guideline applies to well-established and well-characterized Biotherapeutic products such as recombinant DNA-derived therapeutic proteins.
>
> Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope of this document. WHO recommendations and regulatory guidance for these products are available elsewhere … .[4]

[2] PPACA § 7002(a)(2)
[3] CHMP/437/04 Guideline on Similar Biological Medicinal Products (Adopted September 2005), p. 7
[4] WHO Expert Committee on Biological Standardization, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) (Adopted 19-23 October 2009), p. 4

At the Public Hearing, PPTA supported an FDA approach, similar to the above EMA and WHO approaches, for all plasma protein therapies. However, BPCIA does not allow FDA to be as far-reaching as either the EMA or the WHO with respect to recombinant analogues. New subsection 351(k)(8) provides:

> (A) In general.—The Secretary may, after opportunity for public comment, issue guidance … with respect to the licensure of a biological product under this subsection. Any such guidance may be general or specific. …
> (E) Certain product classes.—
> (i) Guidance.—The Secretary may indicate in a guidance document that the science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license as provided under this subsection for such product or product class.[5]

At the Public Hearing, PPTA supported specific guidance documents for plasma protein therapies; while much is known about such therapies, potentially relevant scientific and technical factors in the therapies are numerous, highly variable, and often unknown. It is impossible to test for all biochemical differences in final products through biochemical assays; even if such testing became possible, it would be impractical. It also is impractical to identify, strictly through biochemical assays, all other differences between a new plasma protein therapy and an already-licensed one or to determine how such differences might react with particular patient characteristics.

When a manufacturer makes a change to its already-licensed product, the manufacturer and FDA have a baseline of clinical experience on which to make judgments about the likely effect that change will have, if any, on the product, keeping all other variables constant. When a new manufacturer produces a plasma protein therapy through its own, unique manufacturing process, all variables are not being held constant. The new manufacturer, who does not have access to the already-licensed manufacturer's trade secrets and proprietary manufacturing data, cannot know the ways in which its process differs from that of the licensed manufacturer.

Further, as a practical matter, FDA cannot discern all the subtle differences that could be material, simply by comparing the manufacturing processes as described in the two manufacturers' biological license applications. Only through real experience in patients is it possible to know with confidence whether biochemical differences between different manufacturers' plasma protein therapies have material impacts on clinical safety and effectiveness.

[5] PPACA § 7002(a)(2)

FDA has adopted, as its own guidance, an International Conference on Harmonisation (ICH) document, Q5E Comparability of Biotechnological/Biological Products Subject to Change in their Manufacturing Process (Q5E). Q5E lays out recommendations about all factors a manufacturer should consider when attempting to demonstrate that its own product, following a manufacturing change, is comparable to its product before the change. However, Q5E applies only to "[p]roducts where manufacturing process changes are made by a single manufacturer … "[6] and not to a manufacturer trying to compare its product to another manufacturer's product. The limitation reflects, in part, the critical importance of manufacturing process considerations, including a "well-defined manufacturing process with its associated process controls [that assure] that acceptable product is produced on a consistent basis."[7]

Even if processes appear to be identical based on records, some undetected differences about, *e.g.,* new plant locations or personnel carrying out the processes, may make material differences. The abilities to recognize all variables that must be kept constant and to keep them constant invariably depend to a great degree on "the extent of the manufacturer's knowledge of and experience with the process … ."[8] Subtle changes to plasma protein therapies are difficult to detect; predicting how those changes might affect patients is extremely challenging.

Because they are so complex, plasma protein therapies vary in manufacturing process and product characteristics from manufacturer to manufacturer. A new plasma protein therapy manufacturer, with its own plant and its own manufacturing process, who does not have access to details about the reference product's manufacturing process, has little hope of duplicating the process without introducing some material differences. Showing comparability requires an established, reliable baseline and the ability to hold all variables constant except for the change or changes in question. However, holding all variables constant and identifying all differences between two manufacturing processes is extremely difficult, even when one has full access to all records on both processes, when the product is a plasma protein therapy.

For plasma derived products, the process truly defines the product; small differences in manufacturing methodologies can result in unexpected differences in the therapies. As such, PPTA supports a specific guidance document that indicates that, as of the date of the guidance, the science and experience do not allow approval of an application for a license under new subsection 351(k) for plasma derived products. PPTA also supports a specific guidance document with strict criteria for approval of an application for a license under new subsection 351(k) for recombinant analogues.

Federal Register questions[9]

[6] Q5E, p. 4
[7] Q5E, p. 9
[8] Q5E, p. 9
[9] Federal Register / Vol. 75, No. 192 / Tuesday, October 5, 2010 / Notices, pp. 61498-61501

At the Public Hearing, in addition to providing general comments regarding plasma protein therapies, PPTA responded to Federal Register questions on Biosimilarity and Interchangeability. Below are comments on those topics and the remaining questions.

A. Biosimilarity

1. *What scientific and technical factors should the agency consider in determining whether the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components?*

As discussed above, while much is known about plasma protein therapies, potentially relevant scientific and technical factors in the therapies are numerous, highly variable, and often unknown. Testing alone cannot guarantee a biological product is "highly similar" to a reference product, as potentially relevant product characteristics are too numerous to test for all of them, or even to discover them.

2. *What scientific and technical factors should the agency consider in determining the appropriate analytical, animal, and clinical study or studies to assess the nature and impact of actual or potential structural differences between the proposed biosimilar product and the reference product?*

Plasma protein therapies are used to treat small patient populations on a continuing, life-long basis. At present, it is impractical, if not impossible, to identify all differences between a biological product and a reference product, as such products are process-dependent. Further, it is impossible to anticipate how much product differences may affect outcomes and adverse-event profiles in patients with different characteristics.

Patients' risks from plasma protein therapies approved without actual human clinical experience cannot be predicted or measured; the interactions between the products' many potentially relevant characteristics and the patients' own potentially relevant characteristics are too varied and complex to nail down without testing the products in humans. The rarity and unpredictability of relevant patient characteristics are such that manufacturers cannot even set a baseline for each characteristic by performing clinical trials on a characteristic-by-characteristic basis. Thus, manufacturers cannot show they have identified and analyzed all potentially relevant product characteristics.

3. *What range of structural differences between a proposed biosimilar product and the reference product is consistent with the standard "highly similar" and may be acceptable in a 351(k) application if the applicant can demonstrate the absence of any clinically meaningful differences between the proposed biosimilar product and the reference product?*

For plasma protein therapies, no range of structural differences is consistent with the standard "highly similar" or may be acceptable in a 351(k) application. In particular, the nature of plasma derived products, the patients using them, and rare but serious adverse events they can cause make it impossible to rule out all clinically meaningful differences in a second manufacturer's follow-on product without testing the follow-on thoroughly in humans. Many variables relating to characteristics both of the patient and the product influence the risk that a patient will have such adverse events. Genetic and non-genetic factors play a role in determining the risk; small differences in manufacturing methods, including fractionation, purification, stabilization, and viral inactivation, can produce structural differences. Such structural differences (*e.g.,* heterogeneity in the chemical structure of molecules, class and structure of antibodies, impurities) can interact with particular patient characteristics in ways that are clinically meaningful but impossible to detect, measure, or recognize without efficacy and safety data from human clinical studies. In other words, how exactly manufacturing-induced changes interact with particular patient characteristics to determine the risk of adverse events is unknown; too many variables are at play with too few patients to isolate them.

4. *Under what circumstances should the agency consider finding that animal studies or a clinical study or studies are "unnecessary" for submission of a 351(k) application?*

PPTA recognizes the need for clinical studies of plasma protein therapies; however, patient populations that receive the therapies are small. PPTA supports novel approaches, as currently employed by reviewers in CBER.

Plasma derived products

As stated, PPTA supports a specific guidance document that indicates that, as of the date of the guidance, the science and experience do not allow approval of an application for a license under new subsection 351(k) for plasma derived products. However, should FDA not issue such guidance, PPTA supports, as for recombinant analogues, a specific guidance document with strict criteria for approval of an application for a license under new subsection 351(k) for plasma derived products. In such a case, while animal studies are "unnecessary" for submission of a 351(k) application,[10] clinical studies are not "unnecessary" unless strict criteria are met. In particular, the biological and reference products should be manufactured by similar processes and have similar analytical profiles; the reference product should have a long history of safety and efficacy.

[10] The "case-by-case" approach to preclinical safety evaluation recommended by ICH Guideline S6, Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (S6), is based largely upon product attributes highlighting appropriate species selection with special attention to immunologically mediated effects and their relevance for patients. Although the scope of S6 addresses the possible inclusion of plasma derivatives, the relevancy of specific species as well as the antigenicity of human plasma derivatives in animals makes the application of some methods of evaluation infeasible. Biologicals. 2010 Jul; 38(4): 494-500

Recombinant analogues

As stated, PPTA supports a specific guidance document with strict criteria for approval of an application for a license under new subsection 351(k) for recombinant analogues. In such a case, neither animal nor clinical studies are "unnecessary" for submission of a 351(k) application, unless strict criteria are met. In particular, the biological and reference products should be manufactured by similar processes and have similar analytical profiles; the reference product should have a long history of safety and efficacy.

B. Interchangeability

1. *What factors should the agency consider in determining whether a proposed interchangeable biological product can be "expected to produce the same clinical result as the reference product in any given patient"?*

As small differences in manufacturing can result in significant changes in plasma protein therapies, it is well-understood that such therapies are not interchangeable within their respective product classes. The interactions of such changes with patient characteristics are numerous and highly variable. Further, within their respective product classes, plasma protein therapies are brand-specific and address unique patient needs.

2. *What factors should the agency consider in evaluating the potential risk related to alternating or switching between use of the proposed interchangeable biological product and the reference product or among interchangeable biological products?*

While plasma protein therapies generally have favorable adverse-event profiles, rare but serious adverse events can occur (*e.g.,* formation of inhibitors caused by immunogenicity, particularly in patients receiving clotting-factor therapies; thromboses). Such adverse events often result from interactions between product and patient characteristics; small differences in manufacturing also can result in different adverse-event profiles in patients due to excipients or contaminants in such therapies.

C. Patient Safety and Pharmacovigilance

Except for Part 2 below, PPTA has no comments on Question C.

2. *What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?*

PPTA supports an FDA requirement of Phase IV, post-marketing surveillance of biosimilar and interchangeable products. Given BPCIA's abbreviated approval pathway, such surveillance is vital to ensure appropriate pharmacovigilance for such products.

D. The Use of Supportive Data and Information

PPTA has no comments on Question D.

E. Definition of a Biological Product

PPTA has no comments on Question E.

F. Guidances

1. What types of guidance documents for industry should be a priority for the agency during the early period of implementation?

FDA should not approve a product or product class under new section 351(k) before both determining that the existing science and experience are sufficient to allow the Agency to do so and issuing specific guidance documents. Such an approach is consistent with both that of the EU[11] and FDA's Good Guidance Practices.[12] As stated, specific guidance documents for plasma protein therapies are important; while much is known about such therapies, potentially relevant scientific and technical factors in the therapies are numerous, highly variable, and often unknown.

For plasma derived therapies, the process truly defines the product; small differences in manufacturing methodologies can result in unexpected differences in therapies. As such, PPTA supports a specific guidance document that indicates that, as of the date of the guidance, science and experience do not allow approval of an application for a license under new subsection 351(k) for plasma derived products. PPTA also supports a specific guidance document with strict criteria for approval for a license under new subsection 351(k) for recombinant analogues. These specific guidance documents should be priorities for FDA during the early period of implementation.

2. Section 351(k)(8)(E) of the PHS Act permits the agency to indicate in a guidance document that the science and experience, as of the date of the guidance document, with respect to a product or product class (not including any recombinant protein) does not allow approval of a 351(k) application for such a product or product class. What scientific and technical factors should the agency consider in determining if the existing science and experience are sufficient to

[11] CHMP/437/04 Guideline on Similar Biological Medicinal Products (Adopted October, 2005)
[12] 21 CFR § 10.115

allow approval for a product or product class under section 351(k) of the PHS Act?

As stated, PPTA supports a specific guidance document that indicates that, as of the date of the guidance, science and experience do not allow approval of an application for a license under new subsection 351(k) for plasma derived products.

G. Exclusivity

PPTA has no comments on Question G.

H. Transition Provisions

PPTA has no comments on Question H.

I. User Fees

PPTA has no comments on Question I.

Conclusion

PPTA appreciates the opportunity to comment on the Approval Pathway for Biosimilar and Interchangeable Biological Products and looks forward to continued work with FDA on specific issues and challenges association with implementation of BPCIA. PPTA welcomes from FDA any questions regarding these comments or requests for additional information.

Respectfully submitted,

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