Comments of  
American Plasma Users Coalition (A-PLUS)  
To the Food and Drug Administration  
December 31, 2010

The American Plasma Users Coalition (A-PLUS) is a coalition of national patient advocacy organizations created to address the unique needs of over 125,000 patients with rare diseases that use life-saving plasma protein therapies. The disorders that the coalition represents include Guillain-Barré syndrome and Chronic Inflammatory Demyelinating Polyneuropathy, Hemophilia, Primary Immunodeficiency Diseases (PIDD) and Immune Thrombocytopenia.

Years ago, a diagnosis of the disorders represented by our coalition meant extremely compromised lives, not just for the patients, but for their families as well. Today, with early diagnosis, continued access to needed treatments, plasma protein therapies, and specialized medical professionals, individuals impacted by these disorders can live healthy, productive lives.

Plasma protein therapies are very complex biologics prepared from plasma pooled from thousands of donors. These therapies differ in terms of donor pools, manufacturing, and final formulation. A number of these differences can, and do, affect individuals’ tolerability, risk of adverse events, infusion rate, and potential efficacy. The U.S. Food and Drug Administration (FDA) recognizes each plasma protein brand as unique, requiring manufacturers of each drug to develop and complete an individual clinical trial protocol to receive licensure. This is due to the differences in basic fractionation and the addition of various modifications for further purification, stabilization and virus inactivation or removal that yields products clearly different from one to the other.

Recommendations

*A-PLUS urges the FDA to exclude plasma protein products from its abbreviated biosimilar approval pathway until the science advances significantly.* A-PLUS member patients with immunodeficiencies, bleeding disorders, various neuromuscular and peripheral nerve disorders and immune thrombocytopenia, face risks from adverse reactions to biosimilars that have not been adequately tested. Decisions regarding biosimilarity, interchangeability, and patient safety, have a significant impact on our patient populations. We are not currently confident that the proposed pathway adequately assures safety and efficacy. Allowing a biosimilar product to forgo human clinical trials makes it impossible to accurately claim that the follow-on product will have the same effectiveness and immunogenic response as the reference product. This short-cutting will result in therapies that promise to be effective, but are actually harmful to the patient. Moreover, the risks of interchangeably substituting the biosimilar for the reference product are too great to be allowed. We welcome the arrival of new drugs, but we are not willing to sacrifice our health and safety to expedite the process. Given the broad implications of this law for individuals with these rare and chronic diseases, an exemption for plasma protein therapies is the only viable way to ensure the well-being of patients.
Recently, the European Medicines Agency (EMA) opted to exclude plasma protein products from its regulatory pathway for biosimilars. We urge the FDA to do the same. Specifically, the EMA noted that “[i]n view of the complex and variable physico-chemical, biological and functional characteristics of the products. . . it will not be acceptable to submit a reduced clinical dossier when claiming similarity to a reference medicinal product.” At a point when the FDA is appropriately focusing on international harmonization, this new pathway should not result in disparate treatment. Patients deserve to have similar safety standards, no matter where they receive their product.

While our primary recommendation is to exclude plasma protein products from the biosimilar pathway, we feel it is important to comment on the key issues that must be addressed in approving biosimilars. These issues are: 1. clinical trials; 2. Interchangeability; and 3. post-market surveillance.

Biosimilarity

Given the potential differences in therapeutic responses, **any approval pathway for biosimilars needs to include clinical trials to establish the safety and efficacy of products.** Data from these trials can then be used by physicians when making prescribing decisions on behalf of their patients. Especially given the highly immunogenic nature of biological products, the FDA should not waive the requirement for clinical studies. Patients must have clinical data that ensures that the new biological product is safe and effective. In fact, the FDA should rely most heavily on clinical studies, not animal studies.

For example, in 2008, the Immune Deficiency Foundation (IDF) performed a national survey of its patients, examining treatment experiences and preferences among patients with primary immunodeficiency diseases. That survey highlighted some of the critical issues with maintaining the safety and efficacy of immunoglobulin (IgG). Among patients that are no longer being treated with IgG therapy, 8% stopped due to safety issues or side effects. In addition, just 33% of those receiving IgG reported that they tolerate all immunoglobulin products similarly, with 33% receiving the product intravenously and 28% receiving it subcutaneously. Therefore, even among the FDA-approved products for individuals with PIDD, the therapeutic response may differ.

Interchangeability

Even without the introduction of biosimilars, each branded manufacturer prepares immunoglobulin replacement therapy (IgG) products, non-recombinant clotting factors, and other therapies in different ways, using different purification procedures, viral inactivation steps, and different ways of packaging the final product. Although they all are excellent in replacing the high titered antibodies and proteins that individuals with primary immunodeficiency diseases, hemophilia, various neuromuscular and peripheral nerve disorders and immune thrombocytopenia cannot make themselves, they are nonetheless unique in other ways.

Patient experiences validate these differences. There is no question that all the FDA approved IgG therapy and non-recombinant clotting factor products available on the U.S. market today are clinically effective. However, we know that a sizeable number of patients tolerate some products better than
others. This remains the case today, even though the manufacturers of these products have made tremendous strides in the tolerability of these life-saving therapies.

According to the 2008 IDF National Treatment Survey of PIDD patients with antibody deficiencies requiring immunoglobulin replacement, 41% of the patients tolerated some IgG therapy products better than others. Of the patients who reported having a side effect or reaction they would describe as serious from their IgG therapy:

- 28% reported having a “serious” side-effect or reaction when they tried a new IgG product for the first time, and
- 13% had a “serious” side effect or reaction when they switched products.

Based on unpublished data from the IDF 2008 survey, *Treatment Experiences and Preferences among Patients with Primary Immunodeficiency Diseases*, patients are at greater risk of adverse events when switched to a new product. Due to the seriousness of these reactions some patients have taken drastic steps to avoid having these problems, including 24% who refused a particular product and 15% who delayed their infusion due to concerns about product tolerability.

Hemophilia and other bleeding disorders have a similar concern with adverse reactions. In hemophilia, individuals can develop a resistance to medication, an inhibitor. This prohibits the individual’s body from effectively utilizing the replacement clotting factors and patients with inhibitors suffer severe consequences, prolonged bleeding, pain and disability. Treatment of a person with hemophilia and an inhibitor requires alternative medical treatments that are great hardships, time intensive and extremely costly (often a million dollars per year or more). Inhibitors occur in all demographics of people with hemophilia, but are more prevalent in some minority populations. Substituting or switching products is believed to contribute to the triggering of inhibitors and products should never be interchanged without careful consideration of the attending physician and patient.

To truly determine that a proposed interchangeable biological product can be “expected to produce the same clinical result as the reference product in any given patient,” the FDA must require clinical trials that demonstrate that the two products provide the exact same clinical result in a large cohort of patients.

*Because of the many unanswered questions surrounding the safety of biosimilars, as well as the special sensitivities of patients with* primary immunodeficiency diseases, hemophilia, various neuromuscular and peripheral nerve disorders and immune thrombocytopenia, *the FDA should take all necessary steps to prohibit automatic substitution with an original biologic.* “Biosimilars” are aptly named because they are similar -- but not identical -- to the original reference product. Due to these small but potentially significant differences, interchanging biosimilars with original versions creates a complex risk-benefit assessment that can only be made safely by the patient’s physician.

The prescriber and patient should always be involved in decisions regarding selection of the biological product a patient receives. *Automatic retail substitution of biotech medicines is not appropriate and*
could be dangerous. Unique identification is critical to ensure accurate traceability in the event of an adverse experience as well as prevent inadvertent substitution and medical errors.

Post-Market Surveillance

Unlike small-molecule pharmaceuticals, plasma protein therapies such as IgG and non-recombinant clotting factors can differ in terms of processing and end composition, and hence why they are not recognized by major regulatory authorities around the world as biosimilars. An example that highlights how different manufacturing processes can affect final product composition and patient tolerability is the worldwide voluntary withdrawal of an immunoglobulin product initiated in 2010 by a major manufacturer due to increased reports of thromboembolic events. The root cause of these events is thought to be due to a change in manufacturing process approved by the FDA that led to increased levels of a procoagulant factor (Factor Xla). This recall highlights the fragility of the supply and demand surrounding immunoglobulins, as well as the impact that small differences in manufacturing can make. If small differences can spark a worldwide recall in the production of a product in which the manufacturer had years of experience, what small differences can occur when a separate entity is trying to reproduce the manufacturing process in a different plant, using potentially different methods and processes?

Therefore, there are real benefits to consistency and keeping track of which brand a patient receives, how much the patient receives, how often a patient receives it, and how it may be infused, even without the introduction of potential additional products. Given the potential for adverse reactions, especially as a patient tries a new product for the first time or switches to another product, the FDA must not only require specific clinical studies examining those switches within human subjects, but also needs to require additional post-marketing surveillance to monitor this potential risk. Such post-marketing surveillance should include the brand and lot information. A-PLUS recognizes the need for patients to maintain careful monitoring of their medications, but the patient cannot be the only entity providing such monitoring.

As patient advocates, we recognize the desire to have additional biological products available with the goal of lower patient cost. However, if post-marketing surveillance activities are not implemented properly so that the FDA can clearly examine which biologic – whether innovator, biosimilar or both – a patient received, when a safety issue is discovered, the FDA would be faced with the difficult decision to potentially withdraw or severely limit patient access to all of the products until more information is gathered about the particular safety issue. This would severely hamper patient access.

Summary

We thank the Food and Drug Administration for asking for comments from stakeholders in order to discuss key issues of relevance to patients. The members of A-PLUS look forward to continuing to work with the FDA’s key scientists to ensure that the approval pathway for biosimilar products addresses key issues of importance to A-PLUS. Like the EMA, the FDA should exclude plasma protein therapies from its biosimilar pathway until the science advances significantly. Specifically, given the potential differences in therapeutic responses, any approval pathway needs to include clinical and non-clinical...
trials to establish the safety and efficacy of biosimilars. Especially given the highly immunogenic nature of biological products, the FDA should not waive the requirement for clinical studies. In fact, The FDA should rely most heavily on clinical studies, not animal studies. To truly determine that a proposed interchangeable biological product can be “expected to produce the same clinical result as the reference product in any given patient,” the FDA must require clinical trials that demonstrate that the two products provide the exact same clinical result in a large cohort of patients.

Given the potential for adverse reactions, especially as a patient tries a new product for the first time or switches to another product, the FDA must not only require specific clinical studies examining those switches within human subjects, but also needs to require additional post-marketing surveillance to monitor this potential risk. A-PLUS recognizes the need for patients to maintain careful monitoring of their medications, but the patient cannot be the only entity providing such monitoring. Because of the many unanswered questions surrounding the safety of biosimilars, as well as the special sensitivities of our patients with primary immunodeficiency diseases, hemophilia, various neuromuscular and, peripheral nerve disorders and immune thrombocytopenia, the FDA should take all necessary steps to prohibit automatic substitution with an original biologic.

We look forward to working with you to establish an approval pathway that protects patients. If you have any questions, please feel free to contact Lawrence A. La Motte of the Immune Deficiency Foundation, llamotte@primaryimmune.org or 443-632-2552.

Sincerely,

GBS/CIDP Foundation International
Committee of Ten Thousand
Hemophilia Federation of America
Immune Deficiency Foundation
Jeffrey Modell Foundation
National Hemophilia Foundation
Platelet Disorder Support Association
Patient Services Incorporated