

**Testimony of
Marcia Boyle
President and Founder
Immune Deficiency Foundation**

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The Immune Deficiency Foundation (IDF) is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases (PIDD) through advocacy, education and research. I am the President and Founder of the IDF, as well as the mother of a now-grown son living with PIDD. Therefore, I am able to share my first hand experience witnessing the impact that adverse reactions to biological products have on the patients IDF represents.

Primary immunodeficiency diseases occur in persons born with an immune system that is either absent or hampered in its ability to function. While not contagious, these diseases are caused by hereditary or genetic defects and can affect anyone, regardless of age or sex. The World Health Organization recognizes more than 150 primary immunodeficiency diseases, which are a group of rare disorders. Some affect a single cell within the immune system; others may affect one or more components of the system. While some of the nearly 150 primary immunodeficiency diseases still resist effective treatment, biologic medications are extremely important long-term therapeutic agents for many of these life-threatening disorders, now and into the future.

Years ago, a diagnosis of PIDD meant extremely compromised lives, not just for the patients but for their families as well. Today, with early diagnosis and appropriate lifelong therapies, many patients with that same diagnosis can live healthy, productive lives. The majority of individuals diagnosed with a PIDD have antibody disorders, many of which require life-long treatment with immunoglobulin to replace missing or improperly functioning antibodies needed to fight infection. Without lifelong treatment with immunoglobulin, individuals with PIDD would be unable to fight off even minor infections, including the common cold.

In 2005, IDF conducted a landmark national telephone survey of 10,000 random households in the United States, which resulted in an estimate of approximately 250,000 persons diagnosed with a PIDD. Twenty-two percent (22%) of these patients use immunoglobulin replacement (IgG), resulting in an estimate of 55,000 patients diagnosed with a PIDD and using a biologic -- IgG replacement therapy. PIDD is one of the FDA-approved indications for IgG and represents a major use of the immunoglobulin therapy in the United States. For individuals with PIDD, these therapies provide temporary replacement to a wide spectrum of antibodies, which help fight off serious infections. For this and many other reasons, IDF and the patients we represent have such an enormous stake in the regulatory framework the FDA establishes to provide an approval pathway for biosimilars.

Immunoglobulin therapy is a very complex biologic prepared from plasma pooled from thousands of donors. Immunoglobulin 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 immunoglobulin brand as *unique*, requiring each drug to develop and complete an individual clinical trial protocol to receive licensure, even if it is from the same manufacturer. This is a result of 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.

The first responsibility of the FDA is to ensure that biosimilars are manufactured and prescribed safely. This is an area of special concern to IDF because patients, like my son, with immunodeficiencies face risks from adverse reactions to biosimilars that have not been adequately tested for safety and efficacy. As you craft your regulatory framework, we urge you to implement safety provisions that will maximize the therapeutic benefits of these drugs, while minimizing their special risk factors. Given the broad implications of this law for individuals with PIDD, my testimony today will focus on issues related to biosimilarity, interchangeability, and patient safety. Specifically, I would like to highlight the need for *clinical trials* to establish the safety and efficacy of biosimilars, respectfully request that the pathway not include immunoglobulins, advocate for strong post-market surveillance for biosimilars, and to request that the FDA prohibits automatic substitution.

Biosimilarity

In 2008, IDF performed a national survey of patients, examining treatment experiences and preferences among patients with PIDD. That survey highlighted some of the critical issues with maintaining the safety and efficacy of IgG. Among patients that are no longer being treated with IgG therapy, eight percent stopped due to safety issues or side effects. In addition, just one-third 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 FDA-approved products for individuals with PIDD, the therapeutic response may differ.

Given the potential differences in therapeutic responses, any approval pathway for biosimilars needs to include clinical and non-clinical trials to establish the safety and efficacy of those products. Data from these trials then can be used by physicians when making prescribing decisions on behalf of our 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, FDA should rely most heavily on clinical studies, not animal studies.***

As a Board member for the International Patient Organisation for Primary Immunodeficiencies (IPOPI), ***I further urge the FDA to exclude immunoglobulins from its biosimilar pathway until the science advances significantly.*** Recently, when performing a similar review, the European Medicines Agency (EMA) opted to exclude immunoglobulins from its regulatory pathway for biosimilars, and I 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 the product.

Interchangeability

Even without the introduction of biosimilars, each of the branded manufacturers prepare immunoglobulin replacement therapy (IgG) in a different way, using different purification procedures, viral inactivation steps, and different ways of packaging the final product, some being dry powders and others in liquid form. Thus, although they all contain IgG and are excellent in replacing the proteins that individuals with PIDD cannot make themselves, they are nonetheless unique in other ways.

Patient experiences validate these differences. There is no question that all FDA approved IgG therapy products available on the U.S. market today are clinically effective at reducing the rate of serious infections for individuals

with PIDD for which IgG therapy is indicated. However, based on data collected from over 15 years of IDF national patient surveys, 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, a 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.

Therefore, there are real benefits to keeping track of which brand and lot of IgG a patient receives, how much the patient receives, and how often a patient receives it, 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. IDF recognizes the need for patients to maintain careful monitoring of their medications, but the patient cannot be the only entity providing such monitoring.***

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,” FDA must require clinical trials that demonstrate that the two products provide the exact same clinical result in a large cohort of patients.

Unlike small-molecule pharmaceuticals, plasma therapies such as IgG 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. To highlight how different manufacturing processes can affect final product composition and patient tolerability, a worldwide voluntary withdrawal was 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 XIa). 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?

As a patient advocate and a mother, I 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, 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.

Patient safety

Because of the many unanswered questions surrounding the safety of biosimilars, as well as the special sensitivities of our patients with primary immunodeficiency diseases, the FDA should take all steps necessary 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.** Unique identification is critical to ensure accurate traceability in the event of an adverse experience as well as prevent inadvertent substitution and medical errors.

I would like to thank the Food and Drug Administration for having this public hearing to discuss key issues of relevance to patients, and I 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 IDF. 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, FDA should not waive the requirement for clinical studies. In fact, FDA should rely most heavily on clinical studies, not animal studies. Further, like the EMEA, the FDA should exclude immunoglobulins from its biosimilar pathway until the science advances significantly. 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,” 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. IDF 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, the FDA should take all steps necessary to prohibit automatic substitution with an original biologic.