The Immune Deficiency Foundation (IDF) is the national patient organization, founded in 1980, 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 a mother of a son living with PIDD.

The patients we represent have an enormous stake in the Food and Drug Administration's (FDA) regulatory framework for biosimilars. In IDF’s November 2010 testimony to the FDA on the biosimilars pathway, we outlined our thinking on biosimilarity, interchangeability, and clinical trials as they relate to patient safety, especially for individuals with primary immunodeficiency diseases. IDF is keenly interested in the FDA’s development of a regulatory framework and guidance documents for biosimilar manufacturers. We believe the agency’s foremost responsibility is to ensure that biosimilars are manufactured and prescribed safely.

Primary immunodeficiency diseases are a constellation of disorders disrupting the immune system resulting in a spectrum of illnesses. In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. There are more than 150 different primary immunodeficiency diseases currently recognized by the World Health Organization. The number of Americans now living with primary immunodeficiency diseases is estimated to be about 250,000 with between 35,000 and 55,000 on immunoglobulin replacement therapy.

Many patients diagnosed with primary immunodeficiency diseases require biologic medicines for long-term management. Specifically, antibody (immunoglobulin) replacement therapy is used to replace missing or improperly functioning antibodies needed to fight infection. Without lifelong immunoglobulin treatments, individuals with PIDD would be unable to fight off even minor infections, including the common cold. PIDD is one of the FDA-approved indications for immunoglobulin replacement (IgG) and represents a major use of the immunoglobulin therapy in the United States.

Therapeutic immunoglobulins are complex biologics, available in intravenous (IVIG) and subcutaneous (SCIG) modes of administration. These medicines are derived from human blood product, or plasma, sourced from over a thousand donors. Manufacturing changes, the composition of donor pools, and final formulations can impact our patients' tolerability, the infusion rate, and potential efficacy and safety of the product.

Currently, the FDA recognizes each immunoglobulin brand as unique and requires each drug to develop and complete an individual clinical trial protocol to receive licensure, even if it is from the same manufacturer. This reflects the many processing steps involved in plasma fractionation, purification, stabilization and virus inactivation or removal that yields products that are distinct from one to another.
As biosimilars are developed and approved in the United States, we urge the FDA to take steps that uphold patient safety above all else. IDF patients face additional risks from adverse reactions to biosimilars that have not been adequately tested for safety and efficacy so the following measures should be incorporated in the FDA’s final biosimilar guidance documents:

- **Restrict Immunoglobulin therapies from the biosimilars pathway;**
- **Require clinical and nonclinical trials for biosimilars; and**
- **Track and Trace and Automatic Substitution policies must reflect the safety of biosimilars and the sensitivities of patients with primary immunodeficiency diseases.**

**Restrict Immunoglobulin Therapies from the Biosimilars Pathway.** Unlike small-molecule drugs, plasma therapies such as IgG are natural proteins of the human body and can differ in terms of processing and end composition.

The fragility of this class of medicines is demonstrated by the worldwide voluntary withdrawal of an IgG product in 2010 by a major manufacturer due to increased reports of thromboembolic events thought to be caused by a change in the manufacturing process approved by the FDA.

The FDA should exempt immunoglobulin therapies from the biosimilars pathway until the science advances significantly. This policy will be in keeping with the European Medicines Agency (EMEA), which opted to exclude immunoglobulin from its regulatory pathway for biosimilars. It will also ensure that the FDA is appropriately focusing on international harmonization.

**Require Clinical and Nonclinical Trials for Biosimilars.** In 2008, IDF performed a national survey to examine treatment experiences and preferences among patients with PIDD. That patient survey highlighted ongoing challenges to safety and efficacy of IgG therapy:

- Just one-third of IVIG users (33%) and 28% of SCIG users report that they tolerate all immunoglobulin products similarly;
- Nearly half of SCIG users (48%) and 37% of IVIG users reported that they tolerate some immunoglobulin products better than others;
- And, among patients that are no longer being treated with IgG therapy, eight percent cited safety issues or side effects as a reason for stopping.

Given the divergent therapeutic responses to FDA approved products, clinical and analytical studies should be required to establish the safety and efficacy of all biologic and biosimilar products. Clinical data, not animal studies, are the best indicator of patient responses from a new biological product. Physicians rely on clinical trial results when making informed decisions about treatment options. To demonstrate the safety of these products for vulnerable patient populations, this requirement should not be waived.

**Interchangeability Designations, Track and Trace and Automatic Substitution policies must reflect the many unanswered questions surrounding the safety of biosimilars and sensitivities of patients with primary immunodeficiency disease.** IDF’s 2008 survey, *Treatment Experiences and Preferences among Patients with Primary Immunodeficiency Diseases* found patients are at greater risk of adverse events when switched to a new product. Specifically, 41% of the patients tolerated some IgG therapy products better than others. Of the patients who reported having side effects from their IgG therapy:

- 28% reported having a ‘serious’ side-effect or reaction when they tried a new IgG product for the first time;
• 13% had a “serious” side effect or reaction when they switched products; and
• 24% of patients refused a particular product and 15% delayed their infusion due to concerns about product tolerability.* (*unpublished data from the 2008 IDF survey)

Current science cannot demonstrate that two different products will provide the exact same clinical result in a large cohort of patients or that switching patients from one product to another will pose no additional risks. It is therefore necessary that the FDA require products to undergo clinical trials to determine that a proposed interchangeable biological product can be “expected to produce the same clinical result as the reference product in any given patient.”

Additional post-marketing surveillance also is needed to protect patients, especially as new products are made available. All products, including biosimilars, should carry unique nonproprietary names, as well as brand and lot information to quickly trace a product to an adverse event.

Finally, the FDA must take concrete steps to prohibit automatic substitution of a biosimilar with an original biologic. Unlike generic drugs, biosimilars can never be identical copies of a reference product. The choice of product should not be determined by a pharmacist, regulator, or insurer, but by a physician in consultation with his/her patient.

In summary, all medicines must be thoroughly tested and meet the highest safety standards set by the FDA. Immunoglobulin therapies should be exempt from the biosimilars pathway until the science advances significantly. However, at minimum, given the unique properties of biosimilars, and immunoglobulin therapies in particular, the focus should be on making sure that the biosimilars approval process meets the same strict criteria required for current manufacturers.

On behalf of patients with primary immunodeficiency diseases, I want to thank you for your consideration and look forward to the final guidance documents that give thoughtful deliberation to our patients’ concerns.