November 1, 2012

Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Docket No. FDA-2012-N-0967

Re: FDA Prescription Drug User Fee Act Patient-Focused Drug Development

The Immune Deficiency Foundation (IDF) would like to thank the Food and Drug Administration (FDA) for the opportunity to comment and provide feedback on its patient-focused drug development initiative. 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. We strongly commend the FDA for including primary humoral immune deficiencies in its nominated set of disease areas, as the IDF considers primary immunodeficiency diseases to be of great priority. We urge the FDA to consider PIDD a national health priority as well and conduct a patient stakeholder meeting over the next 5 years to obtain direct patient input on drug development, including patient views of risk and benefit, their hope for future treatment and views of existing therapies.

Our comments will start with background on primary immunodeficiency diseases. We will then discuss the unique nature of immunoglobulin therapies, the need to consider PIDD during the approval of products, and resources IDF would like to make the FDA aware of as it proceeds in the patient-focused drug development initiative.

BACKGROUND

Primary immunodeficiency diseases (PIDD) 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. 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.

There are more than 165 different primary immunodeficiency diseases currently recognized by the International Union of Immunological Societies (IUIS). Some affect a single cell within the immune system; others may affect one or more components of the system. The number of Americans now living with primary immunodeficiency diseases is estimated to be about 250,000, each of whom has unique needs as a PIDD patient.
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 lifelong treatment with immunoglobulin (Ig) 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. Ig replacement is not only life-saving by preventing serious acute bacterial infections (e.g., pneumonia, meningitis, etc.), but also is critical in controlling repeated or chronic “smoldering” infections that can result in progressive organ damage and long term disability.

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. As you may know, therapeutic immunoglobulins are complex biologics, available for intravenous (IVIG) and subcutaneous (SCIG) modes of administration. These medicines are derived from human blood 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.

The results of IDF’s 2006 Prevalence Survey of more than 10,000 US households indicate that twenty-two percent (22%) of PIDD patients use immunoglobulin replacement (Ig), resulting in an estimate of 55,000 patients diagnosed with a PIDD and using a biologic — Ig replacement therapy. PIDD is one of the FDA-approved indications for Ig 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. Therapy can take place in an infusion clinic, outpatient hospital setting, a physician’s office or in the patient’s home. A medical professional should be in attendance during an IV infusion to monitor the patient and respond to any adverse events. SCIG therapy usually takes place in the home and after appropriate training, a medical professional is not needed to monitor each infusion.

UNIQUE PRODUCTS
We urge the FDA to continue to be vigilant in the review of products intended for use by individuals with primary immunodeficiency diseases. Each of the branded manufacturers prepare immunoglobulin replacement therapy (Ig) 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 Ig and are excellent in replacing the proteins that individuals with PIDD cannot make themselves, they are nonetheless unique in other ways.

Since not all immunoglobulin products are the same, they are, accordingly, not interchangeable. Therefore, it is important that all patients demonstrate tolerance to a particular product, as well as a tolerance to a particular rate of infusion and their individualized infusion regimen in order to achieve the desired therapeutic response. Based on data collected from national patient surveys, we know that a sizeable number of patients tolerate some products better than others. For those patients who have tried more than one Ig therapy product, only
38% reported never having a serious side-effect or reaction to Ig therapy. Of those who reported having a serious side effect or reaction, 47% reported this reaction occurred when trying a new Ig therapy product for the first time. Seventy-two percent (72%) reported that they tolerate some Ig therapy products better than others. As a result of concerns about product tolerability, 46% of patients reported that they switched to another product, 21% refused a specific product and 22% delayed a scheduled Ig infusion. It is also necessary that a patient’s compliance with his/her therapy be monitored. A patient’s level of commitment to subcutaneous Ig (SCIG) therapy is especially fundamental when the patient will be doing self-administration in the home.

While some of the nearly 165 primary immunodeficiency diseases still resist effective treatment, these unique biologic medications are extremely important long-term therapeutic agents for many of these life-threatening disorders, now and into the future.

**CONSIDERATION OF PIDD DURING DRUG APPROVAL PROCESS**

IDF believes that a patient stakeholder meeting focused on PIDD also could touch on the following issues which may impact individuals with PIDD when reviewing products that may be intended for non-PIDD populations.

**Live Viral Vaccines** -- The American Academy of Allergy, Asthma & Immunology (AAAAI) recommends that live viral vaccines should not be administered to many patients with immunodeficiency diseases. The difference between the live and killed vaccines is an important one for those with immunodeficiency disorders since some of these patients can develop a serious infection with an attenuated virus or bacteria used in these live agent vaccines. Furthermore, family members or household contacts of many primary immune deficient patients should not receive a live viral vaccine, as they may transmit the live virus to the immune deficient family member. As the FDA seeks patient input for regulatory decision-making related to benefit-risk assessment, the PIDD patient community urges reviewers to keep these concerns in mind.

**Drug Shortages** -- Because Ig therapy has proven to be fundamental to the health of the PIDD community, the history of treatment shortages and the continued availability of therapy still cause concern for our patients. IVIG is usually considered a "maintenance" treatment, one that will be taken for life, putting added pressure on the continued need for adequate supplies. Patients have not forgotten the health problems that resulted from IVIG shortages during the 1990s. With the development of new medical uses for Ig, the possibility of Ig shortages loom and could easily create a public health emergency for patients with PIDD. We believe it may be helpful to obtain patient input regarding their experience with previous shortages and explore how FDA and the patient community can work together to communicate about access problems to help address and prevent Ig shortages in the future.

**Immunoglobulin is not Interchangeable** -- While the Affordable Care Act (ACA) provides for an abbreviated approval pathway for biological products that are demonstrated to be "highly similar" to, or "interchangeable" with, an FDA-licensed biological product, it is especially problematic for PIDD patients that a biosimilar is similar, but not identical to the original or reference biological product. Immuno-globulin therapy for those with immune deficiency is complex and the products used to treat these patients do not have specific amino acid sequences. Even slight changes in the manufacturing process can cause adverse events in PIDD patients. It may be helpful to discuss what are tolerable risks for PIDD patients who are concerned that the safety of each
product be demonstrated through clinical trials. Many patients have experienced adverse events when changing their treatment. IDF has urged the FDA to 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.

**PATIENT RESOURCES**

As the FDA moves forward with its patient-focused drug development initiative, the IDF would like you to be aware of the following resources which may be helpful to the FDA to obtain patient input:

**United States Immunodeficiency Network (USIDNET) --** The USIDNET is a NIH funded research consortium established to advance scientific research in PIDD. USIDNET assembled and maintains a registry of patients with primary immunodeficiency diseases to provide a minimum estimate of the prevalence of each disorder in the United States. The registry allows patients and families to submit their medical records to be combined with thousands of others to establish this valuable set of data.

**eHealthRecord Tool--** Recently the IDF developed an eHealthRecord which enables our patient population to easily and securely record, access and share health information. It also has the capabilities to track diagnosis, infections and symptoms; scan and save important documents; log doctors’ visits and medications; create an In Case of Emergency (I.C.E.) report; schedule and review events in the calendar; maintain infusion logs for IVIG and SCIG therapy that also track reactions and adverse events, and share, print and export the record.

**Patient and Provider Surveys --** IDF has more than 15 years of experience in data collection through national surveys of patients and providers. Previous surveys included a national patient survey of patients from the IDF database, a survey of hospital pharmacists, and a national survey of immunologists. IDF survey data is often cited in medical journals, government sponsored reports and by the media. IDF survey data has also been the focus of articles that appeared in peer-reviewed journals.

**Patient Education and Outreach --** The compassionate, professional staff at IDF also has expertise in patient education and outreach. IDF helps thousands of people in the patient and medical community gain a broader understanding of primary immunodeficiency diseases through education and outreach efforts. As a patient-driven, service-based foundation, IDF provides substantial resources to the primary immunodeficiency community. Education for patients and families living with these diseases is a key part of IDF’s mission. The Foundation not only provides educational materials and information to these individuals, it also offers crucial patient education programs to help them manage their disease. Education is spread through local patient meetings, IDF retreats, our national conference, youth programs, and teen weekends. IDF’s Operation Outreach program offers educational and networking opportunities for individuals (and their families) impacted by PIDD.

**Medical Advisory Committee --** The IDF Medical Advisory Committee (MAC) is comprised of prominent immunologists from throughout the country to support the mission of the IDF through the development of science-based standards for diagnosis and care for individuals with primary immunodeficiency diseases. These experienced medical experts in the field of treating PIDD are another valuable resource to consult as you move forward with the patient-focused drug development initiative.
CONCLUSION

On behalf of patients with primary immunodeficiency diseases, we appreciate your consideration of our comments. The IDF thanks the FDA for including primary humoral immune deficiencies on its list of nominated disease areas. We hope the FDA will continue to include PIDD as a target for patient focused drug development.

The PIDD patient community is eager to participate in the regulatory decision-making process related to benefit-risk assessment for the products that maintain their health. Our patient community has very individual experience with the Ig products they rely on, as well as the goal to maintain access to all Ig therapies in all care settings to best meet their individual care needs. The IDF patient volunteers have demonstrated their willingness to travel to Washington, D.C. to participate in education and advocacy programs. I am confident the PIDD patient community would welcome the opportunity to provide direct input regarding their opinions and experience with the agency that assures the safety and effectiveness of their therapies and discuss what matters most for future treatments and what they consider tolerable risk.

Should you have specific questions or wish to discuss our comments, please feel free to contact Lawrence A. LaMotte, Vice President, Public Policy at llamotte@primaryimmune.org or 443-632-2552.

Sincerely,

Marcia Boyle
President and Founder