Dear Madam/Sir:

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. I am therefore able to share my first-hand experience witnessing the impact that adverse reactions to biological products can have on the patients whom IDF represents.

IDF has previously presented testimony on biosimilars to the FDA in 2010 and 2012. We continue to be deeply interested in FDA’s efforts to implement the Biologics Price Competition and Innovation Act (BPCIA) because of the substantial impact on our members. Our members typically experience a healthcare system that takes years to identify the appropriate providers, receive an accurate diagnosis, and identify the best treatment course that will bring greater stability to their daily lives.

As patient advocates, we want to ensure that patient safety is a priority as FDA implements the BPCIA. This message is especially timely given the recent news that FDA has accepted the first application for approval of a biosimilar. Many organizations that represent patient populations similar to ours have indicated the critical importance of the patient perspective on the BPCIA implementation issues FDA is considering.
Biologics are complex molecules that are grown in living cells. Because they are patterned after proteins the body itself produces, biologics can treat many serious diseases in ways conventional medicines cannot. Biologic medicines have dramatically transformed the lives of many of our members and their families. As biosimilars become available in the United States, we want to ensure they are safe, accessible, and affordable.

This draft guidance is the first scientific biosimilar guidance issued by FDA in over two years. A careful review and analysis of the draft indicates that without appropriate modifications, the guidance has the potential to provide inadequate safeguards for patients. The draft guidance fails to give appropriate recognition of the tremendous variations in the complexity of biologics – from insulin to immunoglobulin – and the substantial differences in therapeutic responses to biologics from patient to patient. It is crucial that FDA standards for the review and approval of biosimilars not provide for a “one-size-fits-all” approach that could threaten patient safety.

Section IV(I) (Statistical Comparison of PK and PD Results) In order to be deemed “bioequivalent” and therefore approvable, a generic small molecule drug must show that its PK profile (absorption, distribution, and excretion of the drug within the body) is within 80-125 percent of the PK profile of the innovator drug. However, on page 13, the draft guidance says that the 80-125 percent range “may be” acceptable for deeming a biosimilar to have similar PK profile, but that this is not a required or default range. Should a sponsor wish to deviate from the 80-125 percent, they should provide scientific justification to do so. IDF believes that, in the case of biologics, such variances can only be tolerated based on solid scientific data that complies with specific requirements outlined by FDA. To that end, the guidance should include explicit language requiring the submission of appropriate scientific data to justify such a deviation. This is essential to protect patient safety.

Section IV(G) (Pharmacodynamic Measures) On page 12, the draft guidance states that PK and PD studies “may be sufficient to completely assess clinically meaningful differences between” the biosimilar and the innovator biologic. However, it goes on to state that: In such instances, “a full evaluation of safety and immunogenicity would still be necessary either before or after approval.” (Emphasis added.) IDF is concerned that patients could be at risk if such an evaluation is done only after a biosimilar product has been approved. From a patient point of view, that is too late; the damage can be done. Immunogenicity is extremely frightening to patients - especially rare disease patient populations. For patients with primary immunodeficiency diseases who
already have genetic immune problems, it is critical that a full evaluation of safety and immunogenicity is conducted prior to approval.

**One-Size-Fits-All.** The draft guidance applies to all biosimilars, from more simple biologics such as insulin or human growth hormone to the extremely complex and large biologics like immunoglobulin. This means that FDA may be applying a “one-size-fits-all” approach to biosimilars. For example, the draft guidance states that, in “some instances,” PK and PD testing may “complete the clinical evaluation” of a biosimilar. FDA does not limit this statement to less complex biosimilars. In other words, in some cases (possibly even involving more complex biologics), FDA might approve a biosimilar without any comparative clinical safety and effectiveness studies assuring that the biosimilar and its reference product do not have clinically meaningful differences in safety and effectiveness. This is not scientifically justified as the considerations involved in biosimilar development vary greatly by product type (and individual product). The European Medicines Agency (EMA) has recognized this and has issued nine different product-class specific guidelines, rather than attempting to cover these complex issues in a clinical pharmacology guidance applicable to all biosimilars.

It is IDF’s position that the FDA should simply eliminate, like the EMA, the larger, more complex biologics (like immunoglobulin) from the pathway until there is significant experience with the regulation of the more simple biologics in the biosimilars pathway. Biologics vary dramatically and there is no reason to expect that biosimilars would act any differently. For example, there are a dozen or so immunoglobulin products in the marketplace for use in immunoglobulin replacement therapy. Each is unique and patients who appear to have the same health background “on paper” may react very differently to each product.

**Statutory “Highly Similar” Standard Must be Upheld.** Under the BPCIA, a biosimilar must be both “highly similar” and have “no clinically meaningful differences,” when compared to the innovator biologic product. But FDA’s new draft guidance could be read to suggest that a biosimilar could be merely “similar” and still receive approval. On page 5, the draft speaks to an assessment of “similar” within a development phase continuum. Such an approach would be inconsistent with the language of the statute and Congressional intent and pose serious risks to patients. The statute requires both a high degree of similarity at the structural level and no clinically meaningful differences because clinical studies, although a critical piece of the premarket development process, will often not be large enough to fully reveal the potential clinical profile of a
biosimilar that is only “similar” at the structural level. A high degree of similarity at the structural level is the *only* justification for an abbreviated clinical development program. Patients should be confident that any biosimilar on the market is as safe and efficacious as the reference product. This requires that both parts of the statutory requirement be met. Therefore, the guidance should explicitly clarify that in no instance can a biosimilar be merely “similar,” but must be “highly similar” to the reference product and meet all other statutory requirements.

Thank you for your attention to this important issue. For questions regarding these comments, please contact Larry LaMotte, Vice President, Public Policy, Immune Deficiency Foundation, at llamotte@primaryimmune.org or 443-632-2552.

Respectfully,

Marcia Boyle
President & Founder