American Autoimmune Related Diseases Association (AARDA)

Arthritis Foundation (AF)

Committee of Ten Thousand (COTT)

Crohn's and Colitis Foundation of America (CCFA)

Dystonia Medical Research Foundation (DMRF)

GDS/CIDP Foundation International

Hemophilia Federation of America (HFA)

Hepatitis Foundation International (HFI)

Immune Deficiency Foundation (IDF)

International Foundation for Autoimmune Arthritis

Jeffrey Modell Foundation

Lupus and Allied Diseases Association (LADA)

Lupus Foundation of America

National Alliance on Mental Illness (NAMI)

National Organization for Rare Disorders (NORD)

National Psoriasis Foundation (NPF)

Platelet Disorder Support Association (PDSA)

Pulmonary Hypertension Association (PHA)

RetireSafe

Scleroderma Foundation

Spondylitis Association of America

United Spinal Association

US Hereditary Angioedema Association (US HAEA)

US Pain

Patients for Biologics Safety & Access

May 5, 2017

Stephen Ostroff, M.D. Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. FDA-2017-D-0154 Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry

Submitted electronically via www.regulations.gov

Dear Acting Commissioner Ostroff:

Patients for Biologic Safety and Access (PBSA) applauds the Federal Drug Administration's (FDA's) release of the draft guidance on interchangeability. PBSA has long believed that guidance on the interchangeability of biologic products is necessary to ensure patient safety and to build patient confidence in the new category of therapies known as biosimilars. Congress explicitly established a high standard for interchangeability in the Biologics Price Competition and Innovation Act (BPCIA) to protect patient safety. Because interchangeable biosimilars can be switched at the pharmacy-level, without the knowledge or consent of patients and their doctors, it is vital that there be a rigorous and transparent standard for approval of these products. The draft guidance document is a critical step on the path to providing that safety and confidence.

We believe the FDA should promptly issue final guidance on interchangeability, which takes into account patient input, and should do so prior to approving any biologic as interchangeable. For patients, the issuance of final guidance takes on an urgency given the recent steps taken by major insurers and pharmacy benefit managers (PBM) in the absence of such guidance. While none of the four biosimilars approved by the FDA were approved as interchangeable products, payers are moving forward this year with formulary changes and other coverage changes that could force patients who are stable on their treatments to switch to non-interchangeable biosimilars.

Final guidance on interchangeability should appropriately reflect the clearly different and higher standard for interchangeability provided by Congress to protect patient safety. While some FDA officials have indicated the interchangeability standard is different, not higher, FDA must abide by clear Congressional intent by requiring a higher standard of approval. The BPCIA requires a biosimilar to be "highly similar to" and have "no clinically meaningful differences with" its reference biologic. However, Congress required interchangeable biosimilars be "both biosimilar to an FDA-approved reference product, and … be expected to produce the same clinical result as the reference product *in any given patient*." Congress placed an even higher standard for interchangeability for those products that are given more than once to a patient. Applicants must demonstrate for these products that "the risk in terms of safety or efficacy of alternating or switching between the biological product and the reference product will not be greater than the risk of using the reference product without alternating or switching."

The final guidance should require substantial clinical testing beyond that required for finding a product to be biosimilar. The FDA clearly recognized this at its July 12, 2016 Advisory Committee meeting. In response to a question from the Advisory

Committee chair, FDA leaders indicated that the "single-transition" data provided by the applicant is to ensure that the transition does not lead to "any major devastating immune-mediated adverse events." Additionally, the FDA stated that, "We clearly don't think that this study design would be sufficient to address interchangeability."

The final guidance should require that an application for interchangeable designation demonstrate the product is interchangeable for each condition for which the reference product is approved.

The final guidance should be designed to recognize and anticipate a future marketplace that may have multiple approved biosimilars and interchangeable products for the same indications. For example, it should take into account a future where patients may be switched to and from reference products, non-interchangeable and interchangeable biosimilars over decades for the treatment of chronic conditions. The scope of required switching studies should consider this and account for the fact that many patients take biologics for chronic conditions for many years and could be switched back and forth multiple times.

The final guidance should require interchangeable biosimilars to have distinct non-proprietary names with meaningful suffixes. If the agency decides a certain biosimilar is interchangeable with its reference product, that decision can be reflected on the label and in the Purple Book. However, it is still within the treating physician's discretion to prescribe the reference product if (s)he so chooses, based on the patient's clinical history. If two products share an identical name and suffix, the risk of a physician inadvertently substituting one product for the other becomes much greater.

Distinct names are also a necessary component of an appropriately robust pharmacovigilance system for biosimilars and interchangeable products. In the draft guidance, the FDA states, "Post-marketing safety monitoring for an interchangeable product should also have adequate pharmacovigilance mechanisms in place. Rare but potentially serious safety risks may not be detected during pre-approval clinical testing because the size of the population exposed likely will not be large enough to assess rare events." PBSA urges the FDA identify appropriate additional post-marketing surveillance requirements and resources beyond the current system for biologics to assure that any safety problem with biosimilars and interchangeable products are rapidly identified and addressed. This is crucial to build patient and prescriber confidence.

In addition, we encourage the FDA to look beyond averages for populations when looking at "exposure" to drugs. The FDA should also be looking at subsets of various populations. Many biologics treat people with rare and chronic diseases whose sensitivities to immunogenicity are high and variable between subsets of a given population. The guidance should place more emphasis on adverse events among subsets of populations.

While it is finalizing the interchangeability guidance, the FDA should take additional steps to protect patients from non-medical switching involving non-interchangeable biosimilars. We applaud the FDA's update to the Purple Book, which reads, "…In contrast, FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level." The phrase "at the pharmacy level", however, is limiting and seemingly would allow switching at levels other than at the "pharmacy level".

Some payers and PBMs seem not to be following the law or the intent of Congress by taking reference products off formularies and substituting non-interchangeable biosimilars. People covered by these payers are being forced to switch to new products. Should this practice of circumvention of the law continue to be allowed, interchangeability will have no meaning. Biosimilars' manufacturers will have no incentive to apply for an interchangeability designation.

Given the agency's previous statements on non-medical switching and the recent actions by pharmacy-benefit managers that appear to contradict the agency's intentions, we encourage the FDA to speak out and further clarify its position on this topic as soon as possible. Absent further clear and directive comments by the FDA, we expect similar policies contradicting the FDA's position will be forthcoming. PBSA asks that the FDA guidance on interchangeability address the practice of payers forcing non-medical and non-interchangeable switching and calls on the FDA to issue guidance on the substitution of non-interchangeable biosimilars, either as a part of this guidance or as a new standalone guidance to ensure patient safety.

In addition to speaking on this topic, we also respectfully request that the FDA publicly address whether the level of data it has to date, relied on to support a "single transition", is adequate to confidently support the safety of broad non-medical switching of stable patients. We also call on the FDA to require much more robust evidence in evaluating the safety of a "one-time transition.". Asking for evidence to detect only "major devastating immune-mediated adverse events" is clearly inadequate and does not promote patient confidence in a product. To ensure physician and patient confidence in biosimilars, we believe such a statement should also clarify the nature – and breadth – of data reviewed by the FDA on the safety of a single transition.

Thank you for your attention to our comments and suggestions. Once again, we commend the FDA on its efforts to help ensure patient safety is paramount in the development of biosimilars.

If you have any questions, please contact Larry LaMotte, Vice President, Public Policy, at the Immune Deficiency Foundation (IDF) at llamotte@primaryimmune.org or 443-632-2552.

Sincerely,

Lawrence A. LaMotte

On behalf of Patients for Biologics Safety and Access

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