

**Statement of
Patients for Biologics Safety and Access
Before FDA Arthritis Advisory Committee
Meetings on July 12 and 13, 2016**

As representatives of millions of American patients and their families, we write to give you input from their perspective as you consider these two significant biosimilar applications. Patients for Biologics Safety & Access (PBSA) is a coalition of 24 patient advocacy organizations dedicated to protecting patient access to safe and effective biologics.

The introduction of biologic products has been the most significant advancement in care for our communities in recent decades. Biologics have opened up a new world of combination therapies, and medicines such as immunoglobulin, clotting factor, and monoclonal antibodies that have transformed the lives of countless patients diagnosed with life-threatening and chronic diseases.

The promise of the Biologics Price Competition and Innovation Act (BPCIA) is the creation of a regulatory pathway for new, safe, and effective biosimilars, adding choice and additional treatment options for our patient communities. While our communities are eager for new and affordable treatments, patients with rare and chronic diseases are keenly aware of the possible risks associated with biologics and biosimilars, including immunogenicity and the lack of long-term safety data of new treatments. PBSA believes that the complexity and uniqueness of each biologic medicine require that FDA ensures all biologics and biosimilars are thoroughly tested and meet the highest safety standards.

First, we would like to thank Dr. Woodcock and other FDA leaders for the positive and productive meeting we had with you last month. We reference in this statement a number of the productive ideas and commitments that came out of that meeting. We are eager to continue this productive dialogue and look forward to working together in the best interests of patients.

Last March, PBSA commended FDA on its milestone approval of the first biosimilar in the United States and we have continued to actively engage with FDA on a range of issues regarding implementation of the BPCIA. Today we would like to share comments and suggestions from the patient perspective on a range of key issues applicable not only to the two pending biosimilar applications but also the broader policies regarding biosimilars.

Strong and Transparent Patient Safety Standards

First, we remain concerned that FDA has now approved the first two biosimilars and is now in the final stages of review for two others without putting in place transparent and finalized policies to safeguard patients. To date, the Agency has yet to issue final guidance on a range of issues that will impact patient safety including interchangeability, naming, labeling, switching, and indication extrapolation. While we

are pleased there has been draft guidance issued on naming and labeling, completion of final guidance on **all** of these key patient safety issues should be FDA's top priority in implementing the law.

Adequate Safety Evidence: Both the products currently under review by the Arthritis Advisory Committee over these two consecutive day meetings have no real world post-market experience. The first biosimilar approved by FDA last year (Neupogen) had quite a few years of real world experience in Europe providing additional evidence of safety. However, when compared to Neupogen the two products before the Advisory Committee now are much larger and more complex in structure, will be taken by patients for many years (versus months), and will seek to treat a number of widely varying serious chronic conditions. This lack of no real-world post-market data heightens our concerns regarding a number of important patient safety issues.

One of our coalition's founding principles is, "FDA should enforce the provisions of the Biologics Price Competition and Innovation Act (BPCIA) that a biosimilar is "highly similar" to the reference biologic and that 'there are no clinically meaningful differences' between it and the reference product "in terms of the safety, purity, and potency of the product". Without any real world longer-term experience, we have to ask on what basis it can be confidently determined that there are "no clinically meaningful differences" in the "safety" of products that will be taken by many patients for many years. It is our understanding that the evidence provided is limited to clinical studies for arthritis and psoriasis. Therefore, with the lack of other real-world safety data, the only evidence of long-term safety is based on extrapolation of data from short-term studies of patients in other conditions. We would appreciate the experts on the advisory committee to thoroughly discuss the adequacy of the data presented given the statutory requirements for approval and the confidence patients who will be taking these products for many years can have the confidence in their long-term safety.

Votes on Each Indication: An important point of discussion in both of the biosimilar advisory committee meetings to date is the need for separate committee votes on each indication sought for approval. At the February 9, 2016 Arthritis Advisory Committee meeting a committee member asked if the committee could vote on individual indications rather than one "up or down" vote on approval of all indications. The chair answered "No". FDA staff agreed and said there was no need to vote on each separately. In addition, committee members extensively discussed the differences perceived in the evidence for the studied indications versus the "extrapolated" uses. One member noted, "We are scientists, and we live by the evidence. We're being asked to live by extrapolation. It does, however, increase risk. But the alternative is that we should all go home." At the January 2015 Oncologic Drugs Advisory Committee meeting, a committee member noted, "It's a little bit bigger leap of faith to extrapolate."

By forcing a single "up or down" vote of approval for all requested indications of new biosimilars, FDA may mask potential divisions of opinion on the strength of evidence for individual indications, and discourage discussion or advice on different labeling, post market requirements, and overall level of confidence in the strength of a biosimilar application. The FDA frequently asks its advisory committees to vote separately on different proposed indications of use for the same product, we ask that FDA

obtain better, more specific, and detailed guidance on biosimilar applications by asking its biosimilar advisory committee members to vote separately on clinically studied and “extrapolated” indications of use.

In our meeting last month with Dr. Woodcock and other FDA leaders, we were pleased FDA expressed a willingness to consider our recommendation to require future biosimilar advisory committees to vote separately on indications. This would be an important step toward boosting patient and prescriber confidence in biosimilars. We urge FDA implement such a step starting with these two back to back biosimilar advisory committee meetings

Multiple Biosimilars for the Same Indications

Secondly, the back-to-back Advisory Committee meetings also represent a very significant development in the introduction of biosimilars into the United States. If the two applications being considered are ultimately approved by FDA, there will be three different biosimilars approved for a number of serious and prevalent chronic conditions, including arthritis and psoriasis. This potential scenario amplifies the importance and urgency of a number of crucial patient safety issues.

Distinct Naming and Adequate Pharmacovigilance: A key PBSA principle is biosimilars should have unique, non-proprietary names to eliminate confusion among patients and prescribers. This is essential to allow appropriate tracking of any adverse events and avoid patients getting the wrong medication. This will be especially important if there will be three or more biosimilars available for the same indications. PBSA applauds FDA for recognizing the benefits of distinct names for biosimilars in the draft guidance released last August. We concur with concerns FDA expressed in the draft when it said: “If originator biological products, related biological products and biosimilar products share the same proper name, a patient could receive a product different from what was intended to be prescribed, leading to medication errors. For example, this could occur if a biosimilar product were licensed for fewer than all the indications approved for relevant reference products and/or other approved biosimilars and/or for different routes of administration (e.g. prefilled syringe instead of a vial) for which its reference product is licensed, or is packed in a different delivery system than approved for its reference product, which may lead to confusion and dosing errors.” The potential presence of three or more biosimilars for the same indications raises additional safety concerns that should be addressed by a final guidance.

Multiple biosimilars for the same indication also points to the need for a strong adverse event reporting system that is functional and universal. Our concerns regarding biosimilar adverse event tracking were heightened in reading the recent report by GAO (Report 16-192) on FDA’s post marketing drug safety reviews of products approved by FDA using an expedited approval process. In the report GAO found that “FDA lacks reliable, readily accessible data on tracked safety issues and post market studies needed to meet certain post market safety reporting responsibilities and to conduct systematic oversight.” GAO goes on to say, “FDA has acknowledged that expediting drug application approvals can pose risks for patients,” stressing that post market monitoring for these drugs is especially important. Because BPCIA

provides for an expedited approval process for biosimilars, we have concerns about the adequacy of their system and capacity for reviewing the safety of this entirely new class of complex medications.

Comprehensive Labeling: The potential for the presence in the market of three biosimilars approved for the same indications adds urgency to the need for strong labeling requirements for biosimilars. PBSA is pleased the FDA’s draft labeling guidance requires products to be clearly labeled as biosimilars and contain standard information about immunogenicity concerns. The final guidance should be strengthened by requiring a symbol designating which indications were approved based on extrapolation of data rather than clinical testing, requiring a link in the labeling to pertinent clinical testing data and adverse event information specific to the biosimilar, and other measures we have identified in correspondence and meetings with the FDA. These requirements are necessary to help prescribers and patients have the information necessary to make fully informed choices.

Regulatory Protections Needed for Patients

Finally, there are several key areas where we feel FDA is critical in ensuring patient safety through their actions during Advisory Committee meetings. We believe these concerns must be addressed to secure patient trust in the biosimilar approval process.

Protections against Non-Medical Switching: PBSA is very concerned about the potential for patients stabilized on a biologic with a proven safety record to be switched for non-medical reasons to a biosimilar that has not been found by FDA to be interchangeable. This was a point of substantial debate and discussion at the February 9th advisory committee meeting to consider the infliximab biosimilar application. That proposed biosimilar, like the two before the FDA now, sought approval as a biosimilar, not as an interchangeable biologic. The FDA briefing materials repeatedly stated: “(Data submitted by the applicant) would support the safety of a clinical scenario where non-treatment naïve patients undergo a single transition to CT-P13.” In addition, at the Advisory Committee meeting, the FDA officials made statements regarding their expectations around switching of stable patients. Specifically Dr. Christl stated, “...there’s no expectation that the biosimilar products would be limited in labeling to treatment of naïve patients only.”

At that meeting, committee members expressed concern about the “real world” potential for patients being switched to and from biosimilars multiple times. Members also expressed concern that once switching was allowed and insurers and pharmacy benefit managers could exert pressure and provide incentives to promote the use of biosimilars.

While FDA stated at the meeting the agency doesn’t have control over what payers might do, we believe FDA must take into account likely payer actions by putting in place clear policies to protect patients, including application of robust scientific safety standards. We are concerned that failing to do so will unnecessarily put patient safety at risk by increasing potential chances of negative immune reactions. It also runs counter to Congressional intent that placed a substantially higher standard of evidence for interchangeable biologics. As outlined by the FDA, that standard is clear:

“an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be **expected to produce the same clinical result as the reference product in any given patient** and, if the biological product is administered more than once to an individual, **the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.**” (Emphasis added.)

Our concerns about unsafe switching are heightened both by the new potential presence in the market of three approved biosimilars for the same indications and by several pieces of new information.

First, the possibility of three biosimilars on the market for the same indications raises new safety questions. Is the FDA seeking evidence of the safety of switching among the three biosimilars? If so, what is the safety standard the agency is measuring against? Is the FDA seeking evidence of the safety of multiple switches to, from, and among the biosimilars and their reference products? If so, what is the safety standard the agency is measuring against?

Second, we now have direct evidence of payer intentions to promote switching. Recently, pharmacy giant CVS published, “Basics about Biosimilars: The Savings Potential and the Challenges.” In it, they spell out an aggressive intention to switch patients to biosimilars. They state: “Because biosimilars are therapeutically equivalent to reference biologics, **we expect minimal “grandfathering of patients.”**”

CVS also states: “Currently there is no pathway for biosimilars to have the legal definition of interchangeability – meaning a pharmacist cannot automatically dispense a biosimilar at the pharmacy without a change in prescription, even though biosimilars are therapeutically equivalent to biologics. **This means a formulary or step therapy approach to drive new prescriptions to the preferred agents. Our data clearly shows that exclusion formularies generate the lowest net cost by helping to maximize discounts from manufacturers, and increasing market share for the preferred product.**”

Third, there is additional real world evidence on the safety of switching regarding the previously approved monoclonal antibody biosimilar, infliximab.

- The Danish government recently required the switching of many patients from the reference biologic Remicade to the biosimilar infliximab. A recent analysis of 647 Danish patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis who had been under treatment with Remicade from 3.5 to 9 years and were switched for non-medical reasons found that **7% or 45 patients stopped treatment due to lack of effect.**¹

¹ <http://www.hcplive.com/medical-news/disease-activity-unaffected-in-patients-with-psoriatic-arthritis-who-switched-from-infliximab-to-a-biosimilar/P-1>

- Preliminary observational data from Italy where the infliximab biosimilar was introduced in 2015 was presented at European Crohn's and Colitis Organisation (ECCO) earlier this year. This abstract finds that patients with inflammatory bowel disease switched to biosimilar infliximab "showed no clear signals of difference in safety; however, after the switch, a 5-fold increase of loss of response (12.2% vs 2.3%) and a trend towards more frequent primary failure, and loss of response in UC compared with CD patients (11.3% vs 5.8%, 7.7% vs 2.6%, respectively) was found."²

Also, data regarding a one-time switch submitted with the adalimumab biosimilar ABP application before the committee on July 12 is limited and raises questions:

The trial involved 77 patients with psoriasis who were switched from Humira to the adalimumab biosimilar ABP 50. And while the sample is small, it appears that those who were switched had a lower mean response and a lower rate of response at week 50 compared to those who did not switch. And those switched also developed neutralizing anti-drug antibodies at a slightly higher rate.

This raises the question: what is the standard of evidence required by FDA? Is this really sufficient clinical data to justify non-medical switching for all conditions, including inflammatory bowel disease? We were very pleased with Dr. Woodcock's suggestion during our meeting with the agency last month that FDA could publish an official statement that switching a stable patient to a non-interchangeable biosimilar holds risks and only physicians (in consultation with patients) should make or drive such a decision. This would provide a significant pro-patient safety step and we strongly encourage FDA to promptly take this step.

Focusing on Safety Not Costs: The FDA is not authorized to consider pricing or comparative economics in its review of proposed biosimilar drugs. Rightly, in crafting the BPCIA, Congress expressly limited FDA's scrutiny to assuring no clinically meaningful differences in safety and effectiveness, and that the products are highly similar to their already-approved reference products.

However, at both previous biosimilar advisory committee meetings, there were repeated references and discussions regarding costs. At the February 9, 2016, advisory committee meeting, eight members of the committee discussed pricing or economic factors that are beyond the scope of FDA's mandate to explain their votes in support of the measure. Some notable examples include:

- "So the real purpose of this, and the reason behind this pathway, is to provide access and to reduce costs. If there isn't a rather substantial difference in cost between this agent and one which has been on the market for nearly 20 years, I would never prescribe it, and that would be my opinion."

² <https://www.ecco-ibd.eu/index.php/publications/congress-abstract-s/abstracts-2016/item/p544-prospective-observational-study-on-inflammatory-bowel-disease-patients-treated-with-infliximab-biosimilars-preliminary-results-of-the-prosit-bio-cohort-of-thex00a0ig-ibd.html>

- “[B]ecause we have the responsibility to take a risk to provide new products that are biosimilars, to reduce the cost of bringing a drug to market, and to reduce the costs to patients, we really need to go ahead and take this risk.”
- “I agree the biggest reason to do this all is in hopes that we’re going to be able to reduce cost of these medications to our patients.”
- Another committee member said he was only willing to vote for extrapolation on the hope that there would be significant impact on price. He added that he would feel a fool if the product did not result in a significantly more affordable treatment.

Advisory committee members clearly tied a willingness to accept uncertainty or serious questions about the adequacy of safety evidence to potential costs savings. At no time did FDA officials at the meeting remind committee members that their input and advice is to hinge on questions of science and evidence, and that costs should not be a factor in their discussions and advice.

We have called on FDA to use its broad discretionary authority to ensure these and future biosimilar advisory committee discussions are focused on matters of safety and efficacy, and determining biosimilarity, and that committee members are advised in advance that their advice and judgments should be based only on those matters. Failure to do so threatens to compromise patient safety and to undermine patient and prescriber confidence in the biosimilar approval process. By law there should never be a situation where advisory committee members are voting on approval of new products based on cost and not solely based on safety and efficacy.

Providing Adequate Time to Review Materials: FDA must provide affected patients and the public an adequate opportunity to weigh in with the agency prior to advisory committee meetings as it moves to implement BPCIA. Briefing materials are critical to the public understanding of issues discussed and voted upon by FDA advisory committees. FDA reviews of new drugs are confidential, so advisory committee meetings are often the first time the public has an opportunity to hear FDA’s views of a new drug. Under current FDA guidance, the agency intends to release such materials “at least two full business days” before meetings. Drug sponsor companies receive the same information much earlier. The materials for each of the first two biosimilar Advisory Committee meetings consisted of hundreds of pages of often complex clinical and scientific issues. It is unreasonable to expect patients and the public to be able to interpret and digest the critical information contained in these materials in only two days. **This is exacerbated by the fact that FDA has scheduled two back-to-back advisory committee meetings July 12 and 13, 2016.**

We have requested that for these and future biosimilar advisory committee meetings, FDA make materials available at least 5 business days in advance of the meeting. This accommodation is necessary for patients and their advocates to effectively participate in these meetings, and is critical to help patients better understand FDA’s recommendations. Additionally, more advanced materials will make it possible for patients and their advocates to develop comments and questions so that the patient voice and experience is fully heard and considered at these very important meetings.

Thank you for the opportunity to provide the views of patients on the biosimilar approval process. Given that patients are the only stakeholders who will actually use the new drugs, PBSA has a particular perspective, and we hope that FDA will provide patient groups with appropriate standing to offer these views. We are eager to work with the FDA to ensure that as the biosimilar approval process is finalized, patients will be provided with safe and effective new product options to treat their disorders at affordable costs. 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.

About Patients for Biologics Safety & Access

Patients for Biologics Safety & Access (PBSA) is a national coalition representing more than 20 patient advocacy organizations. The goal of the organization is to make sure the voices and interests of patients are heard as the FDA seeks to approve a new category of drugs known as biosimilars. PBSA's member groups include:

American Autoimmune Related Diseases Assoc.	Lupus Foundation of America
Arthritis Foundation	National Alliance on Mental Illness
Committee of Ten Thousand	National Organization for Rare Disorders
Crohn's & Colitis Foundation of America	National Psoriasis Foundation
Dystonia Medical Research Foundation	Platelet Disorder Support Association
GBS/CIDP Foundation International	Pulmonary Hypertension Association
Hemophilia Federation of America	RetireSafe
Hepatitis Foundation International	Scleroderma Foundation
Immune Deficiency Foundation	Spondylitis Association of America
International Foundation for Autoimmune Arthritis	United Spinal Association
Jeffrey Modell Foundation	US Hereditary Angioedema Association
Lupus and Allied Diseases Association	US Pain Foundation