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

April 19, 2016

The Honorable Dr. Robert Califf
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf,

As the representative of millions of Americans who rely on high-quality health care, including biologic drugs, we are writing to share with you patient interests, concerns and specific recommendations regarding Food and Drug Administration (FDA)'s implementation of the Biologics Price Competition and Innovation Act (BPCIA).

First, we want to congratulate you on your confirmation as FDA Commissioner. We thank you for your willingness to take on this extremely important and challenging position. As advocates for patients, we wish you well and look forward to working with you throughout your tenure as Commissioner.

Patients for Biologics Safety & Access (PBSA) is a coalition of 24 patient advocacy organizations dedicated to protecting patient access to safe and effective biologics. Together, our organizations represent millions of Americans who suffer from serious, life-threatening diseases that are difficult to diagnose and treat. Our members typically experience a health care system that takes years to identify appropriate providers, produce an accurate diagnosis, and discover the best course of treatment to bring greater stability for more optimal health outcomes. As you well know, biologics are medicines made from living organisms that are far more complex and difficult to develop and manufacture than traditional chemical drugs. The introduction of biologic products to treat complex, chronic, and rare diseases has been the most significant transformative advancement in care for our communities in recent decades. Biologics have provided many patients with an effective therapy – many for the first time in their lives.

As patient advocates, our goal is to ensure that patient safety is paramount as the FDA implements the Biologics Price, Competition, and Innovation Act (BCPIA). The promise of BPCIA is the creation of a regulatory pathway for new, safe, and effective biosimilars that could add choices 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 for new treatments.

We are now at a critical phase of implementation of the BPCIA. FDA has approved the first two biosimilars, has held two Advisory Committee meetings on biosimilar applications, and has a number of other applications pending action this year.

In addition, FDA issued its draft guidance on product labeling, has committed itself to finalizing its naming guidance and issuing draft guidance on interchangeability this year.

We are grateful that Dr. Janet Woodcock has recently agreed to meet with PBSA representatives to discuss our repeated requests to engage with FDA in the development and dissemination of patient education materials, and look forward to getting that meeting scheduled. However, based on our observations of FDA's actions and the agency's responses to our requests to date, we have serious additional concerns that we believe must be addressed to ensure the safeguarding of patient safety, and to secure patient trust in the biosimilars' approval process. We respectfully provide the following patient-focused comments, concerns, and specific recommendations for action.

Biosimilar Labeling to Promote Transparency and Patient Safety

PBSA commends FDA for publishing draft guidance on the labeling of biosimilars, which, along with the FDA's draft guidance calling for biosimilars to have distinct non-proprietary names, is a positive step forward. We are pleased the guidance requires products to be clearly labeled as biosimilars and contain standard information about immunogenicity concerns.

We call on FDA to assure that the final guidance take other important steps, including a requirement that biosimilar labels specify which indications were approved based on extrapolation of data, rather than clinical testing. The final labeling guidance should also require the inclusion of pertinent clinical data and adverse events specific to the biosimilar, as well as a statement declaring whether or not the product has been approved as interchangeable. This will help prescribers and patients have the information necessary to make a fully informed choice about whether to use the original biologic medicine or biosimilar.

Taking Precautions to Prevent Multiple Switches without Adequate Safety Testing

PBSA is very concerned that FDA's statements and the materials it made public in advance of the February 9, 2016 Arthritis Advisory Committee meeting to consider the infliximab biosimilar application may hasten switching of stable patients to biosimilars that have **not** been found by FDA to be interchangeable.

While the application before the FDA 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. Leah Christl stated, "…there's no expectation that the biosimilar products would be limited in labeling to treatment of naïve patients only."

At the Advisory Committee meeting, panel members expressed concern about the "real world" potential for patients being switched to and from biosimilars multiple times once switching was allowed. Although FDA made statements on their expectations for use in non-naïve patients, they did not specifically address the numerous committee member concerns raised about the potential for multiple switches that could become a reality for patients as insurers and pharmacy benefit managers 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 you must take into account likely payer actions by putting in place appropriate safeguards. We are concerned that failing to do so will effectively give a green light to payers to impose practices promoting multiple switches of stable patients. While we know this would not be FDA's intent, it would 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.

Given what we know about payer practices that will likely continue and expand in the future, we ask FDA – in addition to our recommendations noted above for the final guidance on labeling – to put in place clear policies to protect patients who are doing well on their current biologic from being switched multiple times. We also ask that FDA apply a robust scientific standard to its determinations of when switching to or from a biosimilar might be safe, taking into account likely payer practices to promote biosimilar use.

Assuring FDA Transparency and Patient Input

It is critical that the FDA have clear review standards and processes in place to protect patient safety and ensure efficacy of biosimilar medicines prior to making decisions about these applications. It is also vital the process used to develop these standards is transparent so patients and the public have a full and fair opportunity to review, interact, and comment upon these standards before they are finally adopted. To date, and contrary to its own policy of transparency, FDA has not published final guidances on a range of issues that will impact patient safety, including interchangeability, naming, labeling, and indication extrapolation.

We call on FDA to promptly publish draft guidance on interchangeability and final guidance on naming, and to incorporate patient advocate suggestions in final guidance on these topics. We also look forward to publication of a final guidance on labeling once FDA has reviewed and appropriately incorporated comments.

Getting Advisory Committee Guidance on Extrapolated Indications

FDA relies substantially upon the advice of its advisory committees in determining whether proposed biosimilar products should be approved. Advisory committees are charged with determining whether biosimilars are highly similar to, and have no clinically meaningful differences from, their reference products. Advisory committees are asked to evaluate whether adequate scientific and clinical evidence exists to support licensure of biosimilar products not only for indications of use that are clinically studied, but also indications of use that are not clinically studied – instead, the evidence for safety, purity, and potency is "extrapolated" from the clinical studies of other uses of the drug.

This was a point of discussion in both the biosimilar advisory committee meetings to date. 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. 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. While we understand that under the Federal Advisory Committee Act, advisory committees cannot modify the questions put before them by FDA, given that in other contexts 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.

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 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."
>
> "[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 costs should not be a factor in their discussions and advice.

Therefore, we call on FDA to use its broad discretionary authority to ensure 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. We should never have a situation where advisory committee members are voting on approval of new products based on cost, not solely based on safety and efficacy.

Providing Adequate Time to Review Materials

The 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 this landmark piece of legislation.

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. In 2000, the FDA agreed to settle litigation brought by patient and consumer advocates to publicize advisory committee briefing materials. 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. While most of the information in drug sponsors' advisory committee materials do not qualify for an exemption under the FOIA, and therefore must be disclosed, the key question remains *when* it is disclosed. 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.

Therefore, we request that for 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 in advance for taking the time to consider our views on these very important patient protection issues. As we have said, we welcome the introduction of additional treatment options provided by biosimilars, but we want to assure that patient safety is in no way diminished in the process. We are eager to work with you on these issues and look forward to your response. If you have any questions regarding any of the issues raised here, please contact me.

Sincerely,

Lawrence A. LaMotte
On behalf of Patients for Biologics Safety and Access

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