United States Senate

COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS

WASHINGTON, DC 20510–6300

April 30, 2015

Stephen Ostroff, MD
Acting Commissioner
U.S. Food and Drug Administration
10901 New Hampshire Avenue
Silver Spring, MD 20993

Dear Acting Commissioner Ostroff:

We write to express concern and raise questions over how the Food and Drug Administration (FDA) is implementing critical elements of the biosimilar product pathway established by the Biologics Price Competition and Innovation Act.[1] Earlier this week, FDA released the first final guidance on the biosimilar pathway, and we are encouraged by this positive development. Yet FDA still has not provided guidance on many fundamental issues, and much of the guidance it has provided is in draft form. Resolving unsettled questions about the biosimilar approval pathway is critical to ensuring that patients have access to safe and effective biosimilars, and we urge FDA to act expeditiously to publish and finalize additional guidance on which the public can rely. It is important to us that this pathway become a successfully functioning one, as Americans will benefit from greater competition and more treatment options.

FDA has not provided sufficient guidance on important issues relating to the review and approval of license applications for biosimilar products, such as naming, interchangeability, and production of patent information. Members of Congress wrote to FDA in 2013 and 2014 to urge the agency to provide guidance on many of these issues,[2] and have raised questions in hearings about these and other important scientific and public policy questions integral to the success of biosimilars in the United States. Despite this repeated urging, FDA did not make public its policy on the review and approval process before moving forward with the first approval of a biosimilar product.

FDA's failure to resolve fundamental science and policy questions prior to approving a biosimilar for the first time last month raises a number of serious concerns. For example, because FDA still has not announced a policy on nonproprietary names for biosimilar products, FDA approved the product with a "placeholder" nonproprietary name that may not be "reflective of the agency's decision on a comprehensive naming policy for biosimilar and other biological

[1] 42 U.S.C. § 262(k).
[2] *See, e.g.*, Letter from L. Alexander et al. to S. Burwell (Aug. 1, 2014); Letter from O. Hatch et al. to M. Hamburg (Nov. 13, 2013).

products."[3] It is unclear to us what it means for a nonproprietary name to be a "placeholder," what authority FDA has to make such a designation, or what treatment a "placeholder" name will receive once FDA formalizes a naming policy. In addition, we are concerned that hospitals, consumers, patients, doctors, and others may be confused by a name that appears temporary or not fully approved.

We also are concerned that much of the guidance FDA has provided on the biosimilar pathway remains in draft form. Although we are encouraged that FDA recently finalized three draft guidance documents, FDA did not finalize these documents until *after* reviewing and approving the first biosimilar application, and much of FDA's guidance still is not final—to the extent it has been issued at all. This is problematic because draft guidance documents do not provide adequate notice to the public about FDA's approval process because they do not necessarily represent FDA's current thinking on the topics addressed and do not bind FDA staff in any way.[4]

FDA's failure to issue complete and final guidance before beginning to review and approve biosimilar applications raises significant questions. In particular, it is not clear to what extent FDA staff has been following draft guidance when reviewing biosimilar applications. And, if FDA staff has not been following draft guidance when reviewing applications, it is not clear what agency policies, if any, have been governing the process.

For example, in February 2012, FDA issued draft guidance in which it advised that the "[l]abeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that … [t]his product (has or has not) been determined to be interchangeable with the reference product."[5] But the first approved labeling for a biosimilar product—which was approved as biosimilar to, but not interchangeable with, its reference product—contains no statement regarding the product's interchangeability status. Indeed, the label does not even include the word "biosimilar," which could further increase consumer confusion about how this product relates to the reference biologic.[6] And, earlier this week, FDA issued a final version of the 2012 guidance document in which it deleted, without explanation, all discussion of what the labeling should say about a product's interchangeability status.[7] Given FDA's earlier statement in draft guidance that information regarding interchangeability status is "necessary" for health professionals to make prescribing decisions, we are concerned that FDA has made its policy on this issue *more* uncertain, even while approving the first biosimilar product.

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[3] Zarxio News Release.

[4] FDA, Information for Industry (Biosimilars), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm.

[5] FDA, *Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* at 21 (Feb. 2012).

[6] Zarxio Prescribing Information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125553lbl.pdf.

[7] FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* at 21 (Apr. 28, 2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

The Biologics Price Competition and Innovation Act, passed over five years ago, was meant to foster competition and improve choices for American patients, and all of us want the biosimilars pathway it established to succeed. However, FDA's opaque implementation process is creating a troubling degree of uncertainty for patients, doctors, manufacturers, and other stakeholders who are invested in the success of this pathway.

We respectfully request that FDA answer the following questions by May 22, 2015:

1. What is a "placeholder" nonproprietary name, and what is FDA's legal authority to issue and/or to change such a name? How do "placeholder" nonproprietary names differ from other forms of nonproprietary names, including (a) established names under Section 505(e) of the federal Food, Drug, and Cosmetic Act (FDCA); (b) interim established names as recognized under *Novartis Pharmaceuticals Corp. v. Leavitt*[8]; and (c) proper names under Section 352(a)(1)(B)(i) of the Public Health Service Act (PHSA)?

2. What is the process for changing a "placeholder" nonproprietary name, and what is the estimated economic impact of such a change? In the event a "placeholder" nonproprietary name changes, what steps would FDA and the manufacturer take to avoid potential confusion among patients and public health professionals and to ensure that no misbranded product is sold on the market?

3. What guidelines have FDA staff members been following in reviewing biosimilar applications? Please provide copies of all written guidelines provided to staff regarding such review since February 2012. Has any staff member been instructed either to follow, or not to follow, recommendations in any of the draft guidance documents that FDA has published regarding biosimilarity or interchangeability (including documents that were in draft form at the time of review but have since been finalized)?

4. Under what circumstances does FDA consider it necessary for a biosimilar product to disclose in its labeling that it has or has not been found interchangeable with its reference product (or other products found biosimilar to the same reference product)? Why did FDA (a) withdraw the draft guidance it published on this issue and (b) approve labeling for a biosimilar product that contains no such disclosure?

5. What guidance documents regarding biosimilar or interchangeable products does FDA currently intend to publish, and on what schedule? Please provide: (a) the schedule on which FDA currently intends to finalize or withdraw each draft guidance document that FDA has published on these topics, if FDA has not provided it already; and (b) a list of additional guidance documents that FDA currently intends to publish on these topics, including the anticipated timeframe for publication and whether FDA intends to publish the document in draft or final form.

[8] 435 F.3d 344, 351–52 (D.C. Cir. 2006).

6. Why has FDA declined to provide guidance regarding whether the information exchange provisions of Section 351(*l*) of the PHSA are mandatory? If FDA is not providing such guidance because of pending litigation between private parties, please provide FDA's position on the circumstances under which private litigation precludes FDA from issuing guidance regarding statutes within its jurisdiction.

7. How is FDA communicating with and educating patients regarding biosimilars, including on issues such as biosimilarity, extrapolation, and interchangeability?

We also urge FDA to prioritize the publication of final guidance on the issues identified above, and to improve the transparency of its biosimilar review and approval process going forward.

If you have any questions, please have your staff reach out to Chairman Alexander's staff Grace Stuntz and Lowell Schiller at (202) 224-6770.

Sincerely,

Lamar Alexander
Chairman

Michael B. Enzi
U.S. Senator

Richard Burr
U.S. Senator

Johnny Isakson
U.S. Senator

Mark Kirk
U.S. Senator

Orrin G. Hatch
U.S. Senator

Pat Roberts
U.S. Senator

Bill Cassidy, M.D.
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