UIC COLLEGE OF PHARMACY
Chicago • Rockford

9 March 2019

ELECTRONICALLY FILED

Dockets Management Branch
Food and Drug Administration,
Room 1-23 12420 Parklawn Drive
Rockville, MD 20857
(301) 827-6860

CITIZEN PETITION

RE: The Biologics Price Competition and Innovation (Subtitle A) of Title VII—Improving Access to Innovate Medical Therapies (H.R. 3590), where Sec. 7002 details "Approval Pathway for Biosimilar Biological Products." Suggestions on a modification to expedite the acceptance of biosimilars by stakeholders by withdrawing the FDA guidance on "Nonproprietary Naming of Biological Products"[1] and modifying the official characterization of biosimilars.

BACKGROUND

Since its passage of H.R. 3590 in 2009, the Agency has licensed 18 biosimilar products as of the date of this petition[2] and five of them are in the market. The Agency has issued several guidelines[3], as a draft and as final, to help the stakeholders better understand the current thinking of the Agency on demonstrating biosimilarity, the primary element for licensing a product as a biosimilar or as an interchangeable biosimilar.

In 2018, the Agency withdrew a pivotal guidance, "Statistical Approaches to Evaluate Analytical Similarity,"[4] and issued a new Biosimilars Action Plan (BAP),[5] in response to the concerns of the industry about the delays in the approval of biosimilars that included a citizen petition and other documents filed by the petitioner[6].

A key initiative in the BAP includes providing more clarity on the evaluation and licensing of biosimilars and to assure stakeholders of the safety and efficacy of biosimilars. However, two immediate actions are required by the FDA to achieve these goals.

- The Agency states that "there is no clinically meaningful difference between a biosimilar

[1] https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf
[2] https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm
[3] https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm290967.htm
[4] https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm611409.htm
[5] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf
[6] https://www.regulations.gov/searchResults?rpp=25&po=0&s=Sarfaraz%2Bniazi&fp=true&ns=true

and a reference product,[7]" which, according to some vested interests, is interpreted as that there *is* a difference and since the biosimilars are allowed extrapolation of indications, without testing in patients, there is no way for the FDA to ascertain that there is no clinically meaningful difference. I have collected this information directly from several ad board meetings with hundreds of primary and specialty care physicians in 2018.

- The Agency differentiates biosimilar products with a four-letter suffix in the guidance, "Nonproprietary Naming of Biological Products."[8] The mindset of stakeholders comes from the use of suffixes like Jr., the II, that are intended to identify different people; biosimilars are widely promoted as separate products, even the two biosimilars are not considered similar to each other, by many vested interests, mainly because of the naming system adopted by the FDA. The naming guidance as cited above had initially suggested attaching a suffix to all biological products, the original BLA (351(a)) and the aBLA (351(k)) to the reference product. However, in a surprise move, on 7 March 2019 the Agency changed the policy and removed the application of a suffixes to the originator products, contrary to the earlier guidance of the Agency[9,10]. This sudden change has further harmed the biosimilar industry significantly. Now it is more encouraging for the originators to claim that there is indeed a difference and further deteriorating the trust by prescribers and patients in the FDA.

On 14 February 2019, Health Canada, faced with the same decision-making for naming the biosimilars chose the option of using both the brand name and the common name; coupled with a DIN, they concluded that there is no pharmacovigilance risk, as the petitioner had suggested in the past.[11]

This Citizen Petition provides a compelling argument, both from a legal and a scientific perspective, to make immediate amendments to the FDA policies to prevent damage to the reputation of biosimilars. This submission of this Citizen Petition is motivated by the comments made by Commissioner of FDA, Dr. Scott Gottlieb,[12] expressing the willingness of the Agency to respond to the urgent needs to reinterpret the Agency's guidelines for the approval of biosimilars.

ACTION REQUESTED

To remove impediments to adoption of biosimilar products:

- The Agency should modify the naming guidance by eliminating the requirement of a suffix to nonproprietary name, add a condition to use a brand name for biosimilars and continue to use an NDC on the label.
- The Agency should modify the use of "no clinically meaningful difference," to "clinically similar," to avoid this double-negative statement to be misconstrued and misinterpreted.

---

[7] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicapplications/Biosimilars/ucm580419.htm#nodiff

[8] https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf

[9] dehttps://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632870.htm

[10] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf

[11] https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/biosimilar-biologic-notice-to-stakeholders-drugs-naming-of-biologics.html

[12] https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm

- The Agency should warn the biosimilar products companies not to suggest that their biosimilar is superior to another biosimilar.
- The Agency should warn the originator companies from promoting wrongful advice to prescribers and patients about the ability of the FDA to judge the safety and efficacy of biosimilars.

STATEMENT OF GROUNDS

BACKGROUND

The BPCIA defines and mandates the information required for licensure of biological products as biosimilar or interchangeable.

> ''(i) REQUIRED INFORMATION. —An application submitted under this subsection shall include information demonstrating that
>
> - ''(I) the biological product is biosimilar to a reference product based upon data derived from—
>   - ''(aa) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
>   - ''(bb) animal studies (including the assessment of toxicity); and
>   - ''(cc) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product;
> - ''(II) the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product;
> - ''(III) the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;
> - ''(IV) the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and
> - ''(V) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

The BPCIA further stipulates:

> ''(ii) DETERMINATION BY SECRETARY. —The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.

The following finding by the Petitioner is the basis of the modifications requested in this petition:

> While the BPCIA requires that a biosimilar be shown to be similar to its locally licensed originator (that is, a product approved under Sect. 351(a) of the Public Health Service Act of 1942, as amended), it also expressly gives the Agency discretion to vary the information required to establish biosimilarity [See 42 USC 262(k)(2)(A)(ii)].

The Agency has developed several guidance documents to assist in the development and final regulatory approval of biosimilars as listed below[13]:

- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2), **Draft** Guidance for Industry (PDF - 679KB) CDER/CBER, December 2018

[13] https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm444891.htm

- Questions and Answers on Biosimilar Development and the BPCI Act; Guidance for Industry (PDF - 343KB) CDER/CBER, December 2018
- Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry (PDF - 229KB) CDER/CBER, January 2017
- Labeling for Biosimilar Products Guidance for Industry (PDF - 285KB) CDER/CBER, March 2016
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry (PDF - 169KB) CDER/CBER, April 2015
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; Guidance for Industry (PDF - 144KB) CDER/CBER, April 2015
- Reference Product Exclusivity for Biological Products Filed Under; **Draft** Guidance (PDF - 99KB) CDER/CBER, August 2014
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Draft Guidance (PDF - 150KB) CDER/CBER, May 2014

COUNT 1

The subject of this petition is the Agency guidance and its update: Nonproprietary Naming of Biological Products Guidance for Industry[14,15] that applies specifically to biosimilars. Initially, the Agency had published a proposed rule in the *Federal Register* of August 28, 2015 (80 FR 52224) ("Designation of Official Names and Proper Names for Certain Biological Products"). In 2017, the Agency finalized the guidance: "This guidance describes FDA's current thinking on the need for biological products licensed under the Public Health Service Act (PHS Act) to bear a *nonproprietary name* that includes an FDA-designated suffix. Under this naming convention, the nonproprietary name designated for each *originator biological product*, *related biological product*, and *biosimilar product* will be a proper name that is a combination of the *core name* and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters. The suffix format described in this guidance applies to originator biological products, related biological products, and biosimilar products previously licensed and newly licensed under section 351(a) or 351(k) of the PHS Act. FDA is continuing to consider the appropriate suffix format for *interchangeable products."*

On 7 March 2019, the Agency issued an update[16] to the above guidance: "FDA no longer intends to modify the proper names of biological products that were licensed under the PHS Act without an FDA-designated suffix in their proper names. FDA also does not intend to apply the naming convention to the proper names of transition biological products."

The BPCIA does not require that biosimilars bear a label that identifies the non-proprietary name with a suffix to differentiate them from the reference product. The naming guidance is not part of the biosimilar products guidance, but it applies directly to biosimilars. The scientific and regulatory reason provided by the FDA to justify this guidance relates to the pharmacovigilance of the biosimilars; however, there is no rationale for this concern, as each product carries an NDC that has long been used to trace product identity without any history of issues in the effectiveness of this system. The NDC system is elaborate, for example, the first biosimilar approved by the FDA, Zarxio[17], carries several NDCs 61314-318-01, 61314-318-05, 61314-318-10, 61314-326-01, 61314-326-05, 61314-326-10 to trace every possible presentation.

[14] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM632806.pdf
[15] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf
[16] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632870.htm
[17] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c0d1c22b-566b-4776-bdbf-00f96dad0cae

If the FDA still considers that the NDC is not sufficient, then the stance was taken by Health Canada, of requiring a brand name, will be more than sufficient.

This petition requests the FDA to modify or withdraw its naming guidance immediately, more particularly now that it has been revised to exclude originator products, creating a definite doubt in the minds of prescribers and patients about the similarity of biosimilars to the reference products.

COUNT 2

In defining a biosimilar product, the Agency states:[18]

> "A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing the Agency-approved reference product."

The use of a double-negative creates an exploitable uncertainty that has caused much damage to the safety and efficacy image of biosimilars, including the ability of the FDA to educate prescribers and patients. This statement is explained to prescribers as follows: "the FDA considers that a biosimilar may have many differences, but they may not be clinically meaningful, yet there can be clinical differences. However, if no testing is done in patients, it means there is no clinical response available to compare; the FDA cannot guarantee that a biosimilar product will provide a similar clinical response in all indications."

The BPCIA allows extrapolation of indications, meaning that a biosimilar product need not be tested in patients for each indication that is being allowed to the biosimilar product. In some instances, there need not be any study in patients to establish biosimilarity, such as products that have validated pharmacodynamic markers; the FDA is also promoting the use of *in silico* pharmacokinetic studies in place of testing in patients. It is now widely recognized that testing of biosimilars in patient populations does not add to safety and efficacy evaluation for a variety of reasons, as described by the petitioner in several publications[19, 20, 21, 22]. The key issues ranging from justifying the M1 and M2 values, finding a uniform population, justifying a single study to allow extrapolation are debated in favor of not testing in patients. The FDA needs to update its characterization of biosimilars using a more clear and transparent language.

This petition suggests that the FDA use a statement "A biosimilar is a biological product that is analytically and clinically similar to an existing the Agency-approved reference product."

ENVIRONMENTAL IMPACT STATEMENT

There are no Environmental Impact issues involved under 21 CFR 25.42. (Claim for categorical exclusion under 21 CFR 25.30, 25.31, 25.32, 25.33, or 25.34 or an environmental assessment under Sec. 25.40 of this chapter.)

ECONOMIC IMPACT STATEMENT

---

[18] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm

[19] http://www.bioprocessintl.com/wp-content/uploads/2018/01/16-1-BiosimilarseBook.pdf?submissionGuid=ba89dcc5-a456-4ef0-849d-bceda94f16a3

[20] https://www.europeanpharmaceuticalreview.com/article/70987/obstacles-success-biosimilars-usmarket/

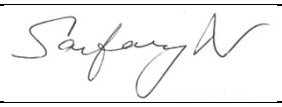
[21] http://www.gabionline.net/Biosimilars/Research/Impact-of-proposed-changes-to-FDA-approach-to-biosimilars; http://gabi-journal.net/rationalizing-fda-guidance-on-biosimilars-expediting-approvals-and-acceptance.html

[22] https://www.centerforbiosimilars.com/contributor/sarfaraz-niazi/2018/12/the-fda-biosimilar-action-plan-making-biologics-more-accessible

About a third of new drugs approved by the Agency are biologics. Takeniologics now account for about 40% of all U.S. drug spending -- and 70% of spending growth—from 2010-2015.[23] The BPCIA was intended to bring biosimilars to alleviate the cost strains on the American public, the Medicare, and Medicaid. It is anticipated that by 2020, biosimilar products could save over $50 B per year if their entry is expedited. The petition presented here identifies scientifically justified and legally available options that the Agency can exercise immediately to realize to enhance adoption of adoption making them more accessible.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the petition" (21 CFR 10.30).

Signature	
Petitioner, in his capacity	Sarfaraz K. Niazi, Ph.D., SI, FRSB, FPAMS, FACB, Adjunct Professor of Biopharmaceutical Sciences
The University of Illinois, College of Pharmacy, and The University of Houston 20 Riverside Drive, Deerfield, IL 60015	Phone 1-312-297-0000; Fax: 1-312-297-1100; Email: sniazi3@uic.edu, niazi@niazi.com

ABOUT THE PETITIONER

Prof. Sarfaraz K. Niazi has been teaching for over four decades: pharmaceutical, biopharmaceutical, analytical, statistics and modeling sciences; he is the sole author of over 70 major textbooks and handbooks, 100+ research papers and has given 500+ talks. He has written the largest number of books on biosimilars; he is sole inventor of 100+ US patents in bioprocess technology, formulations, NCEs and analytical testing. Dr. Niazi is also a patent law practitioner, an elected fellow of several major learned academies, an inductee into Entrepreneur Hall of Fame, and a recipient of civil awards. He serves on the faculty of several major institutions around the world and advises regulatory agencies on creating rational biosimilar guidance to make biosimilars accessible. Dr. Niazi has been developing biosimilars for over 25 years with regulatory filing across the globe including the FDA.

[23] https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm