UIC COLLEGE OF PHARMACY
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11 May 2018
ELECTRONICALLY FILED

Dockets Management Branch
Food and Drug Administration,
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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 modification to expedite entry of biosimilars into US markets. approval of biosimilars.

BACKGROUND:

Since its passage of H.R. 3590 in 2009, the Agency has licensed only nine products as of the date of this petition.[1] The Agency has issued several guidelines, as a draft and as final, to help the industry better understand the current thinking of the Agency on demonstrating biosimilarity, the primary element of licensing a product as a biosimilar or interchangeable biosimilar. The slow entrance of biosimilars into US market, along with a cost of $150+ Million and 7-8 years into development are untenable and need addressing and appropriate changes made to the regulatory guidance documents of the Agency to enable H.R. 3590 Sec. 7002 to benefit the American patients as widely published by the Petitioner[2],[3]. The changes suggested in this petition will help expedite the approval of biosimilars, to allow the BPC Act (BPCIA) to deliver the promise of more accessible biosimilar product for the American public.

This Citizen Petition provides a detailed discussion, both from a legal and scientific perspective, for the changes that can be made to make biosimilars more accessible.

This writing of this Citizen Petition is motivated by the comments made by the new Commissioner of FDA, Dr. Scott Gottlieb,[4] expressing the willingness of the Agency to respond to the urgent needs to reinterpret the Agency's guidelines for the approval of biosimilars.

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1 https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm

2 https://www.europeanpharmaceuticalreview.com/article/70987/obstacles-success-biosimilars-us-market/

3 http://www.bioprocessintl.com/manufacturing/biosimilars/ebook-challenges-facing-biosimilar-products-us-markets/

4 https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm

ACTION REQUESTED

To allow faster development and licensing of biosimilar products:

- The Agency should modify the current default status of requiring bridging studies between a US-licensed product and a non-US approved comparator, to establish biosimilarity.
- The Agency should present clear and open scientific views to the public, more particularly, to the prescribers that a biosimilar product has "no clinically meaningful difference" from the originator product and thus it should be acceptable for naïve patients, without getting involved with the legality of substitution.
- The Agency should encourage the development of *in vitro* immunogenicity testing methods to reduce exposure of test subjects on ethical grounds.
- The Agency should revise some of the specific statistical testing methodologies in establishing analytical similarity to remove certain contradictions in the guidance.
- The Agency should take a fresh look at the clinical relevance of the protocols and statistical methods used to establish PK/PD similarity, to make these studies more clinically relevant while reducing the cost of studies.

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 ny the Petitioner is basis of the modfications 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)].

Given below are the modifications to the Agency's guidelines in place and as practiced currently.

Allow Waiver of Bridging Studies

The cost of development of biosimilars is high and requires the developers to formulate a global strategy where one regulatory dossier is used to secure regulatory approvals in multiple jurisdictions. Since 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), the developers are required to conduct three-way studies (US-licensed product, a non-US product and the biosimilar candidte) develop their regulatory dossier. To reduce this burden of expensive studies and unnecessary exposure to humans in clinical studies, all major regulatory authorities have established clear policies on bridging studies as shown in Table 1.

Table 1 Summary of global jurisdictions for bridging data between local and foreign reference biologic product in the development of biosimilars.[5]

Jurisdiction	Key regulatory texts	Regulatory provisions
Australia	Regulation of biosimilar medicines (guidance) https://www.tga.gov.au/sites/default/files/evaluation-biosimilars-151217_0.pdf	For an FAC, a bridging study must be provided. This study may be abridged or omitted if evidence is provided that the drug is manufactured in a single site for global sales
Canada	Draft—revised guidance document: information and submission requirements for subsequent entry biologics (SEBs) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/biolog/submission-seb-exigences-pbu-eng.pdf	Bridging studies are often not required, but are required when two different references are used in clinical studies. Each reference should be shown to be analytically similar to the biosimilar, or the sponsor should demonstrate analytical similarity between the different references and perform appropriate clinical bridging studies (i.e. PK/PD studies)
European Union	CHMP/437/04 Rev 1 Guideline on similar biological medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf	Bridging studies required—most commonly only analytical data
Switzerland	AW—Administrative ordinance—Authorization of similar biological medicinal products (Biosimilars) https://www.swissmedic.ch/ZL101_00_002e_VV	Bridging data required
United States	Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Guidance for Industry http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf	Bridging studies required—usually analytical and human PK data
WHO	Guidelines on evaluation of similar biotherapeutic products (2009)[a] http://www.who.int/biologicals/areas/biological_therapeutics/biotherapeutics_for_web_22april2010.pdf?ua=1	Bridging studies between RBP/FACs of different origins not explicitly required

FAC foreign approved comparators, *PK/PD* pharmacokinetics/pharmacodynamics, *RBP* reference biologic products, *WHO* World Health Organization

[a] WHO is not a regulatory authority, but its guidances are highly influential on many regulators, especially in the emerging markets

The policies on bridging studies range from no studies to analytical similarity and PK/PD studies, the most stringent, generally considered as the default recommendation of the Agency. 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)]. Therefore, there is no legal impediment if

[5] BioDrugs (2017) 31:279–286

the Agency clarifies its position and allows the developers to request a waiver to the use of a US-licensed product as the reference product, if certain conditions, enumerated below, are met.

While the the statements made by Dr. Scott Gottlieb favor this recommendation, there is a concern at the Agency that legislative action is required to remove the condition of requiring bridging studies.[6] The petitioner finds no legal reason why this change cannot be made.

The Petitioner is requesting the Agency to allow waivers of bridging studies if the non-US comparator product:

- Has the same pharmaceutical form and route of administration as the non-US product; as currently required for the US-licensed product;
- Has the same content of active pharmaceutical ingredient as a presentation of the non-US product; as currently required for the US-licensed product;
- Has the same composition of excipients as in the US-licensed product, not allowing to prove that a different composition may not have any clinically significant difference; a position that differs from other regulatory agency guidance, to lower the bar of residual uncertainty.
- Was approved in its respective jurisdictions by essentially the same original data, including clinical safety and effectiveness data, like that of the US-licensed reference product; this requirement removes any uncertainty of allowing the use of a product that is not related to the US-licensed reference product.
- Was determined to be equivalent to the US-licensed product in any regulatory filing that presenbted a bridging study; a few examples include: established by the Agency has determined in the evaluation of a biosimilar candidate suc as remicade[7], bevacizumab[8] and insulin glargine[9] (under 505 (b)(2) until March 2020).
- Is not used in a study intended to allow interchangeable status[10] to a biosimilar product.

Encourage Substitution of a Biosimilar for Naïve Patients

The BPCIA creates two categories of biosimilar products: biosimilar and interchangeable biosimilar. The latter classification was intended to allow automatic substitution of an originator product with a biosimilar product. The complexity of the evaluation of interchangeable products, where the reference product and the biosimilar candidate products are switched and alternated in a patient population to establish that there is no reduction in efficacy or any increase in the side effects has kept the developers from securing approval of any biosimilar product as

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[6] http://www.centerforbiosimilars.com/news/gottlieb-fda-considering-an-end-to-biosimilar-bridging-studies-

[7]https://www.fda.gov/downloads/%E2%80%A6/UCM484859.pdf

[8] https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566365.pdf

[9] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000TOC.cfm

[10]Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; the Agency, February, 2012:8. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM444661.pdf. Finalized Apr 2015.; Draft Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product; the Agency, January, 2017, p. 16. https://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed 17 May 2017.

interchangeable biosimilar by the Agency, as of the date of this petition. Nevertheless, fearing that the profitability of the originator product will be substantially affected, the political actions have come fast: some states blocking substitution of interchangeable product and others specifically allowing this substitution.[11]

There is an unmet need to create a new image and status for biosimilars licensed by the Agency. In defining a biosimilar product, the Agency states:[12]

> "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."

While the status of interchangeable products is debated, the American public is unable to benefit from biosimilars as it was anticipated in the writing of the BPCIA. From a scientific and clinical view point, if a product is clinically equivalent, there is no reason it cannot be used for use in naïve patients. This view is shared by the Agency Commissioner, Dr. Scott Gottlieb,[13] who said: "payors can also lead the way in formulary design by making biosimilars the default option for newly diagnosed patients. They can share the savings with patients, maybe by waiving co-insurance."

The Petitioner is requesting the Agency:

- To declare an official position that a licensed biosimilar product has no clinically meaningful difference and that it can be substituted for the originator product when the originator product is prescribed for a naïve or new patient.
- To engage in educating prescribers that biosimilars are safe and equally effective, without any risk of additional immunogenicity, when used in naïve or new patients—the most significant barrier to the entry of biosimilars into US markets.
- To motivate and enforce adoption of biosimilars by the payors to make the pricing structure more transparent to demonstrate to patients and prescribers the real cost savings.

Allow Immunogenicity Study Waivers

Immunogenicity is defined as the propensity of the therapeutic biologics to generate immune responses to itself and related proteins or to induce immunologically related non-clinical effect or adverse clinical events. Immune responses to therapeutic biologics may also neutralize their biological activities and result in adverse events not only by inhibiting the efficacy of the therapeutic biologics, but also by cross-reacting to an endogenous protein counterpart, leading to loss of its physiological function (e.g., neutralizing antibodies to therapeutic erythropoietin cause pure red cell aplasia by also neutralizing the endogenous protein). The effect of immunogenicity in the therapeutic biologics development can be summarized as follows:

- Effects on bio-availability
- Effect on safety and efficacy
- Effect on PK including potential cross-reactivity to endogenous proteins
- Inhibition of the function of endogenous protein

[11] http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

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

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

- Injection site reactions
- Systemic reactions mild or life-threatening
- Formation of ADA (HAMA, HACA, HAHA)
- Formation of neutralizing antibodies
- Formation of immune complexes
- Formation of anti-idiotypic antibodies

Immunogenicity assessment as stated in the Agency guidelines on therapeutic biologics investigated in the target population since animal testing and *in vitro* models cannot predict immune response in humans. Also, immunogenicity has a role in demonstrating product comparability following manufacturing changes and similarity in the context of biosimilar development. Even minor changes can potentially affect the bioactivity, efficacy or safety including immunogenicity of a therapeutic biologic.

Characterization and screening for physicochemical determinants or formulation-based factors aids both in the prediction of immunogenicity and in the development of less immunogenic therapeutic agents, such as impurities, heterogeneity, aggregate formation, oxidation and deamidation in the therapeutic biologics. Moreover, predicting potential immunogenic epitopes in therapeutic biologics is an important and effective strategy to improve their safety and efficacy. A variety of preclinical immunogenicity assessment strategies are currently used during therapeutic biologics development as listed in Table 2.

Table 2 Strategies in predicting and reducing immunogenicity to therapeutic biologics

Prediction	**Reduction**
Physiochemical characterization	Deimmunization (epitope modifications)
In Silico immunogenicity assessment	Humanization
T cell epitope predictions	
B cell epitope predictions	
In Vitro immunogenicity assessment	Purity and formulations
Ex Vivo immunogenicity assessment	Purity and formulations
T cell response Modifications	
HLA binding assays	Fusion proteins
In Vivo immunogenicity assessment	Combination biologics or combination therapy

The Agency is making advances is developing this complex science of predicting immunogenicity using *in vitro* methods,[14] promoting the use of *in vitro* immunogenicity assays.

There is a clear ethical risk in testing for immunogenicity in healthy subjects, as we can make them immune positive, as we compare the US-licensed reference to a biosimilar candidate. For the Agency to move the science of *in vitro* immunogenicity testing farther, the Agency should:

- Allow developers to present *in vitro* test to request a waiver from clinical immunogenicity testing.

[14] https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm246804.htm

- Continue its internal development in finding and prescribing testing modalities that reduce the need for clinical testing of immunogenicity.

Change Criteria of Pharmacokinetic/Pharmacokinetic Testing

The recommended testing in (i)(I) of the BPCIA includes PK/PD testing that is almost invariably conducted where a biosimilar candidate is compared with a reference product. However, the statute gives the Agency discretion to vary the information required to establish biosimilarity [See 42 USC 262(k)(2)(A)(ii)], including pharmacokinetic and pharmacodynamic studies.

The protocol designs for testing of biosimilars are derived from the bioequivalence testing required in the Hatch-Waxman Act.[15] While the standard of testing of a generic chemical drug against a listed drug has worked well for decades, the same clinical study designs and statistical testing models to compare biosimilars candidates with licensed reference product may not always work because of the inherently large variability in the PK/PD responses, as well as the need to demonstrate non-inferiority as the test outcome. A key element of the Hatch-Waxman is that the developer should minimize exposure to humans and therefore, over time, the Agency has allowed waiver of bioequivalence studies where these studies are not justified. Unnecessary studies of biological drugs introduces greater risks to human subjects that include immunogenic response. The Petititoner is suggested following changes to the PK/PD studies of biosimilars:

- Waive PK studies where the product is administered by a route that does not allow sufficient concentration of the active moiety in blood, such as the intraocular administration of ranibizumab[16].
- Waive PK studies for biological drugs administered by IV route, as it is allowed for intravenously administered drugs.
- Allow developers to suggest alternate ranges of equivalence in PK studies, instead of the 80-125% range that is mostly arbitrary, based on clinical relevance.
- Allow use of alternate statistical methods to demonstrate lack of difference in C_{max}, AUC, AUC_{tot}, Clearance, all with clinical relevance in mind.
- Allow PK/PD studies is to use inclusion criteria that minimize the CV of the PK/PD parameters since of purpose of comparative evaluation can be readily met in any restricted population such using only male or female population, if there is a difference between the two populations.

Modify Tier Testing Criteria for Analytical Similarity

The Agency has recently released draft guidance on[17] "Statistical Approaches to Evaluate Analytical Similarity" of biosimilars. This is one of the most important components for stablishing biosimilarity, and a component that determines what additional studies, both clinical and CMC-related that are required. A developer identifies critical quality attributes (CQAs) and tests them on Tier 1, Tier 2, or Tier 3 level, depending on the nature of data output and the importance of the attribute to safety and efficacy of a biosimilar product.

For CQAs in Tier 1, equivalence is established by rejecting the interval (null) hypothesis: -

[15] https://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf
[16] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000715/WC500043550.pdf
[17]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM576786.pdf

$1.5\sigma R \leq 90\%$ CI of $[\mu T-\mu R] \leq 1.5\sigma$ where μT and μR are the mean responses of the test (the proposed biosimilar) product and the reference product lots, respectively. The suggests the equivalence acceptance criterion, $EAC = 1.5 * \sigma$, where σ is the variability of the reference product, the standard deviation. A statistical justification for the factor of 1.5[18] follows the idea of a scaled average bioequivalence (SABE) criterion for highly variable drug products proposed by the Agency. To achieve a desired power of the similarity test, the FDA further recommends that appropriate sample size is selected by evaluating the power under the alternative hypothesis at $\mu T - \mu R = ⅛$.

There is no clear relevance of the factor, 1.5 recommended by the Agency to test the most critical of the CQAs. For example, in presenting the briefing on the approval of Sandoz filgrastim product,[19] one of the CQA selected was protein content, and it failed initially, requiring additional batches to demonstrate analytical similarity.

The test criterion for Tier 1 testing can result in misleading results. Let us take an example of ten batches (a recommended number by the Agency) of a biosimilar candidate tested against an equal number of reference product batches for a percentage of the labeled quantity of protein. If the variation in the reference product is very small approaching to a value of zero for σ, then all comparisons will fail even if there is no clinically meaningful difference such as where the biosimilar candidate has the same average of 100, but one out of ten batches tests at 99 and the other is 101. This is not a hypothetical presentation. The Petitioner has come across these situations where an attribute is tightly controlled in the originator product based on decades of manufacturing experience. The question arises if this is a clinically meaningful difference or merely a routine observation. Take, For example, a biosimilar product that is allowed a range of 97-103 or even 95-105% in the COA, based on the history of manufacturing, yet all of these samples will fail if the σ of the reference product is extremely small. On the other hand, where an attribute has high variability (σ) for the reference product, the test will pass, while failing in a Tier 2 test where we have 90% of all values with $3*\sigma$. It is for this reason that the Agency requires a Tier 2 testing for all Tier 1 attributes. To resolve these inconsistencies, the Petitioner is suggesting the following changes to statistical modeling of CQAs in the analytical similarity testing:

- Identify CQAs and also their range of variability based on clinical meaningfulness rather than an arbitrary factor (e.g., 1.5) for Tier 1 testing.
- If a product fails Tier 1 test but passes the Tier 2 testing, allow this as acceptance of similarity.

Summary

In creating the methods for evaluation of biosimilars, the Agency has created a highly specific and scientifically significant vocabulary such “no clinically meaningful difference” and “residual uncertainty” that are highly relevant and represent a creative approach to assuring the safety of biosimilars. However, not all guidance of the Agency takes these two considerations into account fully.

The following is a summary of the recommendations made:

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[18] Chow S-C, Song F, Bai H. Analytical Similarity Assessment in Biosimilar Studies. *AAPS J.* 18(3) 2016: 670–677; doi:10.1208/s12248-016-9882-5.

[19] http://patentdocs.typepad.com/files/briefing-document.pdf

- Remove default requirements of conducting bridging studies for non-US reference product.
- Declare that biosimilars have no clinically meaningful difference from the originator product and therefore, substitutable for naïve patients.
- Remove default requirement of conducting immunogenicity testing and allow developers to offer alternate *in vitro* tests.
- Convert PK/PD protocols and statistical analysis to make the outcome clinically meaningful.
- Revise Tier 1 testing in analytical similarity.

Immediate action by the Agency will bring instant relief to US customers at a reduced cost of biosimilars.

ENVIRONMENTAL IMPACT STATEMENT

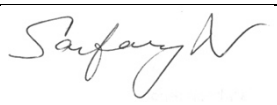
There are no Environmental Impact issues involved under 21 CFR 25.42. (Claim for categorical exclusion under 21 CFR 25.30, 25.31, 25.32, 25.33, or 25.34 or an environmental assessment under Sec. 25.40 of this chapter.)

ECONOMIC IMPACT STATEMENT

About a third of new drugs approved by the Agency are biologics. Taken together, biologics now account for about 40% of all U.S. drug spending -- and 70% of spending growth—from 2010-2015.[20] The BPCIA was intended to bring biosimilars to alleviate the cost strains on the American public, the Medicare, and the 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 these savings and make biosimilars 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	
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[20] https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm

ABOUT THE PETITIONER

Prof. Sarfaraz K. Niazi has been teaching for over four decades: pharmaceutical, biopharmaceutical, analytical, statistics and modeling sciences; he has authored over 50 major textbooks and handbooks, 100+ research papers and gave 500+ talks. He wrote the first book on biosimilars (2014) and coined "biosimilars;" he also wrote the first textbook (1979) on "bioequivalence" testing.[21] He is a major contributor to the Hatch-Waxman Act, the BPCIA and the FDA guidance that followed. Dr. Niazi's Citizen Petition to reduce human testing to establish bioequivalence was accepted by the FDA and is under comment period. He is the largest solo inventor of bioprocessing technology (100+ patents) that has helped reduce the cost of manufacturing biologics and establish analytical similarity. He serves as a consultant to major regulatory authorities in establishing a more practical pathway for the approval of biosimilars; he is also a consultant to USP. He has developed dozens of biosimilars, including several FDA filings. Dr. Niazi is also a patent law practitioner, an elected fellow of several major learned academies, and a recipient of the highest civil award; the Forbes magazine calls him "the most interesting man in the world changing the healthcare in America." As an entrepreneur, he has raised the largest funding for his biosimilars program in the history, and he was inducted into Entrepreneur Hall of Fame. He serves on the faculty of four major institutions around the world.

[21] Sarfaraz K. Niazi, Biosimilars and Interchangeable Biologicals: Strategic Elements. CRC Press, 2015; ISBN 9781482298918; Biosimilars and Interchangeable Biologics: Tactical Elements. CRC Press, 2015; ISBN 9781482298918; Biosimilarity: The the Agency Perspective, CRC Press, 2016, 978-1498750394; Biosimilars and Interchangeable Biologicals: Analytical Elements. CRC Press., 2016; Frontiers of Bioprocessing—Immune and Gene Therapy, CRC Press, 2019