September 21, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-N-2689-0001: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comment

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to participate in FDA's September 4, 2018 Public Hearing and to submit comments to the Docket on Facilitating Competition and Innovation in the Biological Products Marketplace, as this is an important topic for BIO and its members.

BIO is the world's largest biotechnology trade association, representing companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

Of particular relevance to the Hearing, BIO's membership includes all of the leading companies on the cutting-edge of biological product innovation, many of whom are also actively involved in developing and bringing to market biosimilars and interchangeable biological products. As the Federal Trade Commission predicted in its 2009 report[1] regarding the future development of the biosimilar marketplace in the United States, the complexity of developing and administering such products means that this marketplace is likely to take on the characteristics of brand-to-brand competition rather than the generic competition we see under the Hatch-Waxman Act (HWA) today. This is an important and fundamental consideration to keep in mind as we discuss how to best foster a robust competitive marketplace for biological products.

Because of our commitment to improving patient access to safe, effective, and affordable therapeutic choices, BIO was a leader in persuading Congress to create a statutory pathway for the approval of biosimilar and interchangeable biological products, known as the Biologics Price Competition and Innovation Act (BPCIA). BIO unequivocally believes that safe and effective biosimilars and interchangeable products are good for patients and good for the public health. As FDA states on its website, "When patients are prescribed a biological product, biosimilar and interchangeable products can offer additional treatment options, potentially lowering health care costs."[2]

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[1] Emerging Health Care Issues: Follow-on Biologic Drug Competition. Federal Trade Commission Report. June 2009. https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf

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

Growing the Biosimilars Marketplace:

BIO is committed to helping grow a robust biosimilar marketplace in which innovators and biosimilar manufacturers can compete on a level playing field, following a limited period of innovator exclusivity to provide the incentive necessary for companies and investors to devote the tremendous amount of resources and risk required to bring a new medicine to market. BIO believes that robust competition from other branded biological products in the same therapeutic class as well as biosimilars entering the market following the expiration of innovator exclusivities, is the best mechanism to control costs for patients and payers, while encouraging the continued investment in innovative treatments and cures for patients over time. The key to this continued investment in innovation is the ability to secure and enforce intellectual property (IP) protection in novel inventions, including important advancements to existing products, such as the development of new therapeutic indications or safer or more effective formulations or manufacturing processes.

At the same time, BIO believes that a level playing field requires that reference product sponsors, biosimilar developers, and FDA work together to ensure that reasonable access to the product samples needed to safely and efficiently conduct biosimilar development programs is achieved without impeding the ongoing product operations of the reference product sponsors. In particular, FDA efforts to facilitate sample access should not unduly burden biologics manufacturers from being able to carry out their core patient care missions. We understand the delicate balance necessary in this context and would be willing to engage further with the Agency directly as a path forward evolves.

More broadly, BIO has been a strong supporter of the Agency's efforts to advance implementation of the BPCIA. FDA has taken important steps in this regard, guided by an expert Agency working group focused on ensuring that the process of evaluation, review, and approval of products within this product category is consistent, efficient, and scientifically sound. The Agency already has finalized much-needed Guidances, including those on scientific considerations for demonstrating biosimilarity, clinical pharmacology data, and labeling of biosimilars. While we have not agreed with every aspect of the Agency's Guidances in this area, BIO applauds the Agency's overall approach thus far.

In addition, the FDA has launched important educational efforts to inform the public over the value, safety, and use of biosimilar products, including outreach materials for patients and prescribers. BIO supports the advancement of these educational efforts and encourages the Agency to further develop innovative channels for biosimilar continuing education. We would be happy to partner and help the Agency as needed on these initiatives.

It is through the Agency's hard work that, in only eight years since the passage of BPCIA, 12 biosimilars for 8 reference products have been approved. By comparison, during the same initial eight years of the companion European Union process, the European Medicines Agency (EMA) approved 5 unique biosimilars to 2 different reference products (excluding products not classified as biosimilars in the United States, such as transition products, and those with duplicate marketing authorizations by EMA). That said, there are important steps that need to be taken by FDA in order to further advance the growth of the biosimilars market. These efforts include the continuing education of not only health professionals, but also payors, patients, and caregivers, regarding the meaning, use, and value of biosimilars and interchangeable products. Furthermore, FDA promptly should finalize several outstanding Guidances, including those on the issue of interchangeability and statistical approaches to evaluate analytical similarity. BIO believes these important Guidances will

help provide regulatory certainty to biological product developers and further advance the goals of the BPCIA.

Interchangeability:

Of particular importance to BIO members is the finalization of the interchangeability Guidance. The criteria for demonstrating interchangeability are legally and scientifically different from the standards for establishing biosimilarity, and consequently demonstrating interchangeability requires additional data. In order to deem a biosimilar interchangeable with an innovator product, FDA must determine that a biologic is not only "biosimilar," but also that it "can be expected to produce the same clinical result as the [innovator] product in any given patient"; and FDA also must ensure, for products that are administered more than once, that the "risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switching." These additional criteria, which should be met through the use of clinical switching studies, are critically important to patient safety and to the Agency's faithful execution of the Act.

In fact, only an interchangeable biological product and its reference product can be subject to pharmacy-level substitution without the intervention of the health care practitioner who prescribed the reference medication. For a physician himself/herself to select and/or switch products within a class is a medical determination, not a substitution. Thus, finalization of this important Guidance in its most recent form would establish how developers can meet these additional statutory criteria to demonstrate interchangeability and further promote and grow the competitive marketplace for biological products.

Additionally, safeguards should guide substitution policies for interchangeable biologics under state law as well, since a number of state pharmacy laws are not yet drafted to incorporate these new categories of biological products.[3] Like therapeutic equivalence determinations for drugs, interchangeability determinations "serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs."[4]

Therefore, these new biological substitution laws rightly address important issues such as notification of a provider of a switch at the pharmacy and state law clarity on the permissibility of substitution of interchangeable products. These state law pharmacy standards, coupled with robust patient and pharmacist education supplied by FDA regarding the safety and efficacy of biosimilar and interchangeable biological medicines, will combine to ensure provider support and awareness of the important place these medicines play in the healthcare marketplace.

Furthermore, in addition to the "biosimilarity statement" currently required on biosimilar product labeling, FDA should require the inclusion of an "interchangeability statement" that describes what is meant by interchangeability, and clearly specifies the product's designation and with what reference product the biosimilar has been determined interchangeable. BIO is disappointed the FDA did not take up this important safety consideration as it finalized its labeling Guidance. Complete and transparent prescribing

[3] The BPCIA does not preempt state law.[3] Furthermore, state substitution laws do not "pose an obstacle to the accomplishment and execution of the full purposes and objectives of Congress."
[4] FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (37th ed. 2017), at iv.

information is essential for the accurate prescribing and dispensing of biosimilar and interchangeable biological products.

Analysis of Analytical Similarity:

BIO continues to support the FDA in its development of a Guidance on analysis of analytical similarity, which would provide clear guidance on the structural/physicochemical and functional attributes information required to show biosimilarity, the use of the analytical similarity assessment plan, and the statistical approaches recommended for evaluating analytical similarity. BIO believes that analytical similarity should be determined with a scientifically sound and evidence-based approach and that determination of the appropriate statistical approach is best determined on a product-specific basis. In addition, the discussion with FDA on the determination of analytical similarity should take place as needed during the development of a biosimilar product, as it would allow the developer to discuss key information such as lot selection and risk ranking of attributes. FDA should work with product developers to identify scientifically appropriate ways with which to deal with changes in reference product attributes over time and how statistical methods may be used appropriately in this context.

Patented and unpatented uses:

As noted by FDA in this Hearing Notice, in many cases patents or statutory exclusivities may protect one or more conditions of use for a reference product. We are aware that biosimilar applicants have sought licensure for less than all of a reference product's conditions of use. In some instances, this may be because the reference product has patented as well as unpatented uses or uses protected by regulatory exclusivity. As a general principle, if patents and/or regulatory exclusivities for the reference product, drug substance, or manufacturing have expired, a biosimilar manufacturer should be able to market its product for uses not protected by patent or regulatory exclusivity, while the reference product holder should be able to continue to benefit from uses that remain under patent or regulatory exclusivity. The biosimilar label should, of course, be clear about which conditions of use are licensed. In instances where this means less than all of the reference product's conditions of use, the label should be clear and should only contain information related to the approved uses except as otherwise required by 21 CFR 201.57(c)(6). Moreover, a designation as an interchangeable product, however, should not be possible unless the biosimilar can be classified as interchangeable for all indications available for the reference product.

Regulatory exclusivity:

Supplemental or subsequent approvals of reference products for new uses, changes in product presentation, and structural modifications of a reference product, if insufficient to provide for "first licensure" exclusivity, should receive the remainder of the reference product's original data exclusivity – a well-established construct that is known as "umbrella exclusivity." If they do not receive such exclusivity, then a reference product sponsor actually would be disincentivized to research and demonstrate any new uses or other improvements to the original product, since such changes would not only be unprotected against immediate copying but also could undermine the remaining data exclusivity of the original reference product. Accordingly, applying "umbrella exclusivity" to such improvements – as is done under the HWA with respect to small molecule drugs – strikes a

reasonable balance: the timing of biosimilar approval would remain unchanged, and innovators would not be penalized for investing in important product improvements.

It is critical that FDA apply statutory exclusivities fairly and evenly, be it in the context of reference biologics, or modified reference biologics, or in the context of biologics that were approved under New Drug Applications (NDAs) prior to the passage of the BPCIA. In this respect, BIO urges FDA to rethink its 2016 Draft Guidance on the application of data exclusivity to transition biologics approved under FDCA that will be deemed licensed under the PHS on March 23, 2020. As proposed by FDA in its 2016 Draft Guidance, biological products approved under the FDCA that have any periods of unexpired exclusivity, other than orphan drug exclusivity, when they transition to, and are deemed licensed under, the Public Health Service Act (PHSA) on March 23, 2020, would lose any such remaining period of that exclusivity upon transition. In other words, the NDA sponsor would lose any and all remaining period of data exclusivity, including 5-year new chemical entity exclusivity, 3-year new clinical investigations exclusivity, and 6-month pediatric exclusivity. In addition to forfeiting these exclusivities, the Draft Guidance also proposes that those transition products would not be considered to have been "first licensed" under section 351(a) of the PHSA, and thus would not be eligible for any remainder of data exclusivity periods that would be applicable under the BPCIA. This would result in some sponsors receiving less exclusivity for their innovative biologic than they would have received under the FDCA or the PHSA. This is clearly not what was intended by Congress when providing a choice of filing as an NDA or BLA under section 7002(e) of the BPCIA. BIO believes that a fairer solution should be explored soon and stands ready to work with FDA on this important issue.

Purple Book:

During the September 4, 2018 Public Hearing, several commenters proposed that FDA should require sponsors of reference biologics to list relevant patents in the Purple Book as a measure to provide more certainty and transparency to potential biosimilar developers and other stakeholders. BIO does not support patent listing in the Purple Book for several reasons.

First, drawing parallels to the FDA's Orange Book is misplaced because the standards of identicality between reference products and their respective generic or biosimilar products are different. A biosimilar product need not be the same as, and need not be made by the same manufacturing process as, a reference biologic. Thus, patents that claim a reference biologic, or its methods of use or manufacture, are not necessarily relevant to a biosimilar product. And requiring such patents to be listed proactively, before a biosimilar product has been developed and information about it has become available, would necessarily result in incomplete and speculative patent listings in many if not most instances. In fact, Congress considered proactive patent listing during negotiations leading to the BPCIA, and rejected this option.[5] Instead of an Orange Book–type proactive listing, Congress provided that patent information be produced through the BPCIA information exchange process.

[5] For example, H.R. 6257, one of the BPCIA's rejected predecessor bills, would have created a patent identification scheme under which a putative biosimilar developer could have required the reference BLA holder to provide a list of all owned or licensed patents that it "in good faith believe[d] relate[d]" to the reference product, including product, method, component, and process patents. This would have been required absent any access to the biosimilar application or manufacturing process information. The request could have been made at any time, including during "the initial stages of development" of the biosimilar product.

Second, it is important to keep in mind that patents are public, searchable documents, and any prospective biosimilar applicant should be able to identify the relevant patents through available sources of information. The patent provisions of both the BPCIA and of the HWA thus do not serve to merely identify patents. Their main function is to operate as a form of legal representation on the part of the reference product sponsor that affects the rights and obligations of the parties and serves as a basis for what is to be done about these patents. It is for this reason that a proactive biologics patent listing does not make sense in light of the radically different ways in which the BPCIA and the HWA treat patents. Unlike the HWA, the BPCIA expressly provides for the enforcement of process patents (which may not even be listed in the Orange Book). The biosimilar applicant is not required to make any representations about patents to the FDA (e.g., no "paragraph III" or "IV" certifications), and there is no 180-day exclusivity incentive for challenging patents. Bringing suit under the BPCIA does not trigger a stay of biosimilar approval (as it does under the HWA), and the FDA remains free to review and approve biosimilar applications regardless of patent status – even if a district court were to hold a patent valid and infringed by the biosimilar applicant.

Instead, the BPCIA created a highly structured process governing patent information exchange and litigation. Under this scheme, the burden is on the reference product sponsor to identify relevant patents in a "list it or lose it" exchange that is predicated on confidential access to the subsection (k) application and relevant manufacturing information. To superimpose a proactive Orange Book-like patent listing requirement on the BPCIA patent provisions for the mere sake of listing would be meaningless at best. Such patent information would necessarily be speculative in many if not most instances; it would do little to provide certainty for stakeholders; and it would in no way help the FDA do its job.

Finally, BIO acknowledges that, of the twelve biosimilars that have been approved by the FDA, only four are being marketed to date.[6] But more analysis and a fair appraisal of how the BPCIA is working in practice is needed before anyone can or should conclude that patent litigation is interfering with the BPCIA statutory scheme or is operating in ways not contemplated and accounted for by Congress. Patent litigation was certainly expected. The Statute goes to great lengths to provide for patent enforcement and dispute resolution, and nothing in the BPCIA creates a presumption that potentially-infringing biosimilar products would always be launched immediately upon FDA approval. In this regard, it must be emphasized that biosimilar applicants, particularly under the Supreme Court's interpretation of the BPCIA, have a high degree of control over patent litigation and when they will launch their products if approved: A biosimilar applicant normally cannot be sued for infringement before their subsection (k) application is submitted or accepted for FDA review, and need not follow the "patent dance" afterwards. Biosimilar applicants also largely can control the timing and sequencing of any litigation over patents, permitting them to make informed judgements about the timing and risks of their product launches. The FDA can approve the biosimilar application free of the patent certifications and litigation-related stays that feature so prominently under HWA.

[6] Of the eight approved biosimilar products that have not yet been launched at least two were not even subject to litigation. Four biosimilars have been launched "at risk" despite ongoing litigation; and reportedly at least four other biosimilar products are the object of license and settlement agreements that provide for market entry before the expiration of relevant patents.

Consistent with this assessment, it appears that biosimilar applicants are making considered judgments about launching some of their products at risk, delaying launch of other products pending litigation, and entering into license agreements providing for earlier, consensual market entry of yet other products.[7] Similarly, biologics innovators with valuable, investment-backed intellectual property rights at stake are seeking to enforce these rights using the statutory opportunities provided by Congress. In this sense, the limited BPCIA litigation experience so far confirms predictions that biosimilar-brand competition would be more like brand-on-brand than generic-on-brand competition.

It also is important to recall that every biosimilar application known to date involves a reference product that was first licensed before the BPCIA was enacted and for which no data exclusivity remains. For such older products, the BPCIA left many open questions as to how and when they would be litigated. The BPCIA was designed with the primary concern of creating legislation that would operate prospectively, and it contains a range of incentives under which biosimilar applicants would be encouraged to develop and apply for approval of their biosimilar products early, under detailed dispute provisions that would incentivize parties to order their affairs and resolve their disputes *before* the reference product data exclusivity expires. Thus, as biosimilars for newer biologics enter the development and approval pipeline, both litigation and market entry should become more predictable.

Conclusion:

As the biosimilar market continues to grow, BIO will continue to advocate for policies that encourage robust competition, protect patient access to the medicines their providers deem most appropriate for them, and ensure continued investment in innovative biologic medicines. BIO appreciates this opportunity to present at FDA's Public Hearing on Facilitating Competition and Innovation in the Biological Products Marketplace. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section
Senior Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

[7] And, despite speculation about so-called "pay for delay" deals involving biological product manufacturers, the negotiated licensing agreements that have been reached to date reportedly involve no more than conventional payments by the biosimilar applicant to the innovator to obtain access to its patented technology earlier than it otherwise might. Accordingly, concerns over putative payments by an innovator to keep a competitor off the market, as has been repeatedly alleged, do not appear to be justified.