VIA ELECTRONIC SUBMISSION

November 17, 2017

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

Re: Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access (Docket No. FDA-2017-N-3615)

The Biotechnology Innovation Organization ("BIO") would like to supplement the comments we filed on September 19, 2017 to better inform the Docket on Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access.[1] Following submission of our comments pursuant to the initial closing date, other stakeholder comments were filed that raise issues of significant concern to BIO and our members. To ensure stakeholder interests in this issue are fully and accurately reflected, BIO submits these supplemental comments for FDA's consideration.

BIO represents almost 1,000 biotechnology 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, and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO appreciates FDA's willingness to hear diverse viewpoints on this important topic. Though it is Congress that is ultimately responsible for defining the proper balance between the public policy goals underlying the Hatch-Waxman system, we support the Agency's efforts to examine whether its implementation of the system can be improved – both to spur greater innovation and to ensure robust generic entry upon the expiration of patents and any other federally-granted exclusivities.

BIO's primary comment letter outlines numerous issues for FDA's consideration on this important topic; this supplement, however, focuses on a single issue: substitution of interchangeable biologic products.

Specifically, while FDA has yet to even finalize the process for determinations of interchangeability for biosimilar products, it has approved several biosimilar medicines, and has

[1] *See:* Comment from Biotechnology Innovation Organization BIO, September 19, 2017, *available at:* https://www.regulations.gov/document?D=FDA-2017-N-3615-0062.

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proposed interchangeability Guidance for industry consideration and comment.[2] The topic of interchangeability generally, and state laws regulating substitution specifically, are thus important and timely public policy discussions. In that vein, it was suggested at the public hearing on this Docket that FDA's interchangeability determination for biological products *require* substitution under state law, and that states may not impose any conditions on pharmacies related to substitution of an interchangeable biologic product for a prescribed reference product.[3] As we discuss more fully below, this position misunderstands both the statute and the law of preemption, and it would intrude into a domain of law traditionally left to the states.

To be clear, BIO and its members support the creation of a robust marketplace for biosimilar and interchangeable biologic medicines. In fact, many of our members have begun research programs in the biosimilar space as an adjunct to their traditional innovator platforms. In our view, it is critically important for the marketplace to have policies in place that ensure robust patient access to any and all medicines determined medically appropriate – whether brand, generic, biosimilar, or interchangeable. As such, our industry, along with a diverse stakeholder group that includes both generic and biosimilar manufacturers, have worked within states to ensure current state pharmacy practice laws have a clear and open pathway for pharmacist substitution of interchangeable biologic products.

Following the statements made during the public hearing, follow-up comments have been submitted to FDA outlining more specifically the, in our view, flawed legal reasoning underlying the claim that FDA determinations of interchangeability preempt state substitution laws, and that certain state pharmacy practice updates that have been passed in the wake of the Biologics and Price Competition and Innovation Act of 2009 (BPCIA) conflict with the statute.[4] To be clear, nothing could be further from the truth.

Because the practice of medicine and the practice of pharmacy are, and have always been, regulated and licensed at the state level, almost every state has a pharmacy practice act regulating things like product selection and substitution. In each of these laws the state regulatory body generally sets forth a process for when and how a pharmacist may freely substitute a generic drug for a prescribed branded version (or a different prescribed generic) without intervention of the prescribing physician.[5] This is consistent with FDA Orange Book practice, where FDA makes clear in its own guidance on the use of the Orange Book that

[2] FDA Docket No. FDA-2017-D-0154: Draft Guidance for Industry on Considerations in Demonstrating Interchangeability with a Reference Product (January 18, 2017).
[3] *See* Final Meeting Transcript, The Hatch-Waxman Amendments: Ensuring A Balance Between Innovation and Access at 166-167 (July 18, 2017).
[4] 42 U.S.C. § 262(i)(3).
[5] *See e.g.* New Hampshire Statutes, Chapter 381: Pharmacists and Pharmacies, Section 381:47-d Pharmacies; Substituting Generic Drugs ("Pharmacies, including mail-order pharmacies may substitute generically equivalent drug products for all legend and non-legend prescriptions unless the prescribing practitioner handwrites "medically necessary…"")

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"professional care and judgement should be exercised in using the Orange Book" and that certain cases will exist where the "physician's specification of [a particular] product is appropriate."[6]

In other words, the designation of a generic product as therapeutically equivalent is a scientific determination that does not obviate the need for professional decision-making at both the physician and the pharmacist level. There is, therefore, an appropriate and necessary role for state laws in outlining the circumstances, authorities, and communication protocols for product substitution. This is exactly what state pharmacy practice laws do and it is exactly what will become necessary for interchangeable products as well.

The federal legislative language on interchangeability, in fact, confirms this reading. In addition to laying out a scientific standard for interchangeability determinations, the PHSA defines interchangeability to mean that the product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[7] Put another way, it explains that interchangeable biologics are "substitutable." 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."[8] The PHSA does not expressly preempt state law.[9] And nothing in the legislative history suggests Congress intended interchangeability determinations to preempt state law. Indeed, the available evidence suggests the opposite.[10] Nor is there any basis to claim that state substitution laws "pose an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" giving rise to preemption.[11] This misunderstands what FDA is doing when it determines that two drugs, or biologics, are substitutable. The states enacted drug substitution provisions well before enactment of the Hatch-Waxman Amendments.[12] For nearly 40 years, the federal government has shared its "scientific judgment" about substitutability, while the states themselves addressed the act of substitution, which involves questions of "social and economic policy."[13] Here too, rather than preempting state law, FDA's interchangeability determinations provide necessary advice to the states, for each to translate into policy considering factors

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[6] *See* Orange Book Preface Section 1.6 *available at:* https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm.
[7] 42 U.S.C. § 262(k)(4) (standard), § 262(i) (definition).
[8] FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (37th ed. 2017), at iv.
[9] Compare 21 U.S.C. § 360k(a).
[10] During the key markup of the Kennedy-Enzi-Hatch-Clinton bill that would be enacted, Senator Coburn proposed an amendment to clarify that the definition of interchangeability would not affect State law, and Senator Clinton responded that the amendment was not necessary because the language did not require substitution in the first instance. *Senate Committee Passes Follow-On Biologics Bill*, WASHINGTON DRUG LETTER, July 2, 2007.
[11] Hines v. Davidowitz, 312 U.S. 52, 67 (1941).
[12] Henry G. Grabowski & John M. Vernon, *Substitution Laws and Innovation in the Pharmaceutical Industry*, 43 LAW & CONTEMP. PROBS. 43 (1979).
[13] FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (37th ed. 2017), at vii ("FDA believes that products classified as therapeutically equivalent can be substituted") and x ("Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers.")

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specific to the state's demographics, culture, and economy, as well as any policy and legal considerations unique to the state.[14]

BIO appreciates FDA's interest in promoting a balanced approach to patient safety and biopharmaceutical competition, and we encourage FDA to seriously consider all sides of the complex issues raised in this area. With respect to interchangeable biologic products, however, we think continuing to consider comments submitted, and ultimately finalizing the Draft Guidance already issued is the most prudent course of action to ensure the marketplace can evolve and patients can ultimately benefit from a broader array of treatment options. Beyond that, we urge FDA to consider the issues we raise in our primary comments on this instant Docket for purposes of evaluating potential future action in the context of Hatch-Waxman. We look forward to a productive continuing discussion with the Agency on this important topic.

Regards,

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[14] To be sure, many state pharmacy laws have very precise definitions of "drug" for purposes of permitting substitution. Often times the term is defined in a way that could exclude certain biologic products, thus eliminating the state law authority of a pharmacist to actually substitute an interchangeable biologic product absent a change in state law. For instance, under South Dakota existing statute pharmacists may only substitute drugs deemed "therapeutically equivalent" where the manufacturer of the substituted drug holds an approved abbreviated new drug application by FDA. In this example, products approved via Biologics Licensing Application would need to be somehow included within existing statute to permit certain substitutions. *See* Laws and Rules Related to the Practice of Pharmacy § 36-11-46.1: Dispensing Equivalent Drug Products.

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