VIA ELECTRONIC SUBMISSION

September 18, 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") welcomes the opportunity to submit written comments to supplement our previous live testimony to the FDA's open docket on the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access. BIO appreciated the opportunity to participate in FDA's July 18th public meeting on this important topic and we are happy to supplement the record with these written comments.

BIO represents more than 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.

I. Overview

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. Yet, in doing so, there are basic and indisputable facts about the overall success of the existing system that must not be overlooked or ignored.

The Hatch-Waxman system is a unique and balanced approach that successfully has accomplished two critical objectives – incentivizing the unpredictable and expensive venture of developing new medicines for patients in need, while also bringing lower-cost generic pharmaceuticals to market in a timely fashion to enhance competition, choice, and access for the patients of today and tomorrow. This system allows patients to benefit from a robust innovation cycle that introduces new and better drugs followed later by the roll-out of lower-priced generic medicines.

Under this system, the government is, in essence, allowing competitors to "free ride" off the massive investment made by the innovator in order to facilitate greater market competition and lower drug costs over time. To give innovators a reasonable opportunity to secure a favorable return on their investments – including for the 90% of clinical research programs that fail to lead to the approval of a new drug – federal law restricts generic competition for a limited period of time and provides innovators with certain procedural protections to guard against premature or unsafe generic entry.

And while few would claim that this system is perfect, it has largely worked as intended. Innovation has thrived, to the benefit of patients, and today nearly 90 percent of all prescriptions filled in the United States are for less expensive generic versions of once-novel drugs – according to some estimates, saving more than $1.67 trillion in drug costs over the last decade alone.

But the Hatch-Waxman system is not the only route to pharmaceutical product competition. Innovative medicines often face vigorous brand-to-brand competition that also drives down prices in the nearer term.

As the Federal Trade Commission (FTC) has noted, "[a]pproval of a breakthrough or pioneer drug product is increasingly followed by entry of a subsequent branded product(s). The head start that the breakthrough product has had over subsequent branded products has decreased over the past three decades from 8.2 years during the 1970s to 2.25 years in the 1990s.[1]" In fact, all of the breakthrough products studied during the 1990s had branded competitors in clinical development at or before their approval. More recent data shows that this time frame continues to shrink, and is just around two years now. Thus, the often-claimed notion that brand drugs have "monopolies" simply is not accurate. Moreover, the success noted above for chemical drugs under Hatch-Waxman has led to a similar model being applied to the expanding biologics and biosimilars market. To date, under the framework established by the Biologics Price Competition and Innovation Act, FDA has approved six biosimilar medicines for sale in the United States. And, according to published estimates, there are between 20 and 50 ongoing biosimilar development programs moving towards FDA approval. All of this is coming at a time when FDA guidance on these products is in its infancy; we have every expectation that, as regulatory guidance and experience in this emerging market matures, even more biological products will begin to enter the market to increase competition.

We recognize that, despite the tremendous success of the Hatch-Waxman Amendments in facilitating the current generic marketplace, certain areas of minimal competition endure. That said, FDA recently issued a suite of proposals that could very well change that dynamic. By publishing a list of products in a non-competitive market and then facilitating expedited review of corresponding abbreviated new drug applications ("ANDAs"), companies now have additional incentives to focus on historically ignored molecules and disease areas. What is more, Commissioner Gottlieb, at the public hearing for this Docket, announced two additional

[1] *See:* https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf

measures FDA is taking to facilitate better and more streamlined reviews of ANDAs.[2] Insofar as one goal of this Docket exercise is to examine ways to bolster the already robust generic drug market, it seems likely that this entire suite of recent proposals, with time, should make significant progress towards that goal. At a minimum, we would anticipate the proposals could help improve the currently very low rate of first-cycle ANDA approvals, which appears to be the biggest bottleneck to more ANDA products being brought to market.[3] That said, if the goal is truly to examine the "balance" currently playing out under the Hatch-Waxman paradigm, we would propose looking beyond just generic access, as there are several issues underlying the "balance" of Hatch-Waxman that are, in our view, out of line and hindering. For this reason, we offer several suggestions beyond the singular question of generic access for the Agency's consideration.

Consistent with the foregoing, as an initial matter BIO strongly urges FDA to allow the numerous generic program reforms it recently has announced to matriculate through the marketplace and evaluate their impact prior to making any further changes to the Hatch-Waxman system. Nevertheless, we offer the following comments, consistent with the questions posed in the Federal Register Notice, as a supplement to our public testimony.

II. Specific Responses

a. How has the balance struck in the Hatch-Waxman Amendments been affected by practices and trends related to the following:

i. Innovator drug product labeling

During the public hearing at FDA, many speakers raised issues for FDA's consideration related to labeling. Most of these comments, however, focused on minor tweaks FDA could make in approvals and supplement reviews – none of which, in our view, would have a meaningful impact on the "balance" question FDA is seeking to explore. We offer, instead, comments on a unique issue that, if further reconciled, we believe could benefit the overall biopharmaceutical marketplace – both innovator and generic – by injecting certainty into labeling questions and therefore spurring more proactive development and real-world reporting and collaboration. Specifically, we propose that FDA take a further look at the rules related to "changes being effected" (CBE) labeling supplements.[4]

This topic is not new. In fact, BIO and many other stakeholders submitted substantial comments to FDA the last time this topic was considered in 2014 and 2015.[5] Unfortunately, the process continues to operate in a suboptimal manner by excluding ANDA holders and therefore

[2] See, *Remarks as Prepared for July 18 FDA Part 15 Public Meeting, Generic Drug Competition*, By Scott Gottlieb, MD, Commissioner of Food and Drug Administration (Announcing forthcoming publication of a Good ANDA Assessment Practices MAPP and Good ANDA Submission Practices Guidance).
[3] *See Main Challenge for Generic Drugmakers? First Cycle Approvals, FDA says*, Zachary Brennan, Regulatory Focus (April 4, 2017) *available at:* http://www.raps.org/Regulatory-Focus/News/2017/04/04/27264/Main-Challenge-for-Generic-Drugmakers-First-Cycle-Approvals-FDA-Says/
[4] 21 C.F.R. §§ 314.70 and 601.12.
[5] *See* Docket No. FDA-2013-N-0500 Proposed Rule: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products.

inhibiting robust labeling supplements on both sides of the Hatch-Waxman paradigm – placing the sole onus on NDA holders. In fact, the FDA rulemaking process has never been closed out; the docket remains open at the proposed rule phase.

BIO proposes that FDA revisit this CBE process, inject some finality into the rules, and permit both NDA and ANDA holders in a multi-source environment to participate directly with FDA in the CBE process. And, consistent with the comments we have previously submitted on this topic[6], we urge FDA to finalize the CBE authority so that either the NDA or ANDA holder may propose a CBE labeling supplement for FDA review. Following a proposed CBE supplement application submitted to FDA, under our proposal, neither party would be obligated to update its label until FDA makes a formal determination on the application. This sort of dual-sided CBE process will significantly assist FDA in achieving labeling change parity for all applicant holders and ensure that practitioners and patients alike have access to timely and essential safety information necessary to balance the risks and benefits of a drug when making decisions about medical therapy. Further, and consistent with the aims of the instant Docket request, it will promote participation in the labeling process by both innovator and generic applicants, thus furthering the "balance" shared by these parties under the Hatch-Waxman paradigm.

ii. Other regulatory processes, including the citizen petition process

FDA's citizen petition process is a critical tool for manufacturers to notify FDA of potential safety and other risk concerns associated with applications or potential applications under section 505(b)(2) or (j) of the FD&C Act or under section 351(k) of the Public Health Service Act for biosimilar products. In fact, ever since the general implementation of the citizen petition process at FDA in the late 1970s,[7] this protocol has facilitated critical, safety and evidence-based petitions to the Agency, many of which have been the catalyst for important FDA actions.[8] Beyond dealing just with drug approvals, citizen petitions are important tools for many entities to make requests of FDA in the realm of health policy, guidance, and other components of FDA's regulatory sphere. In the drug space in particular, these communications straddle both sides of the regulatory domain – both innovators and generic applicants use them in communicating to FDA.[9] In fact, Section 505(q) was passed specifically to place parameters around the process of submitting a petition related to a pending abbreviated new drug application, freeing Agency time to consider petitions on a multitude of non-product-approval matters.[10] In short, these communications are an essential component for Agency engagement in many aspects of regulated products. Moreover, citizen petitions aid in creating an administrative

[6] Attachment A.
[7] 44 Fed. Reg. 22,323 (April 13, 1979).
[8] *See e.g.* FDA Docket Nos. 2001P-0323 and 2003-P-0274 (pertaining to the legality of FDA's interpretation of §505(b)(2)); and FDA Docket No. 94P-0513 (pertaining to issues surrounding approved drugs used in death penalty cases).
[9] Note recently filed petitions in April 2017 by a Section 351(k) applicant pertaining to further regulatory review of similar applications.
[10] 21 U.S.C. § 355(q).

record and therefore facilitate meaningful judicial review of Agency decisions – critical components of Administrative Procedure Act agency action checks.[11]

We recognize that FDA has long focused on what it has deemed to be abuses of the citizen petition process intended to delay ANDA and other applications, and thus market entry of the attendant products. This concern has resulted in multiple policy changes. But at what point will even more policy changes impinge on the important, and Constitutionally-protected, communications aspects facilitated by citizen petitions on a variety of important matters? The countless modifications over the past decade of the overall petition process, and FD&C Act §505(q) specifically, have streamlined and refined this important engagement tool. FDA now has considerable discretion to summarily deny a petition at any point if it finds that it was submitted for purposes of delaying approval, which now – in turn – provides incentive for manufacturers to submit petitions as early in the process as possible.[12]

What is more, manufacturers must now provide certifications of the timeliness of these petitions, disclose information known to the petitioner that is "unfavorable to the petition," and even certify that the petitioner has "taken reasonable steps to ensure that any representative data and/or information which [is] unfavorable to the petition" was disclosed to the Agency.[13] On balance, there is significant statutory hindrance for a party that obtains important information that might warrant notification to the Agency, but who waits for some mythological "right time" in the future, rather than filing a petition once the appropriate facts and supporting information has been gathered to substantiate the filing.

Accordingly, it has become increasingly difficult to contemplate any further policy changes in this area that would not undermine the important scientific, regulatory, and legal functions facilitated by these petitions.[14]

It also is important to emphasize, given the many statements made during the public hearing on this issue, that in order to make the required certifications under § 505(q) – which carry with them penalties for perjury if made improperly – a manufacturer may not know all of the salient facts that give rise to a needed citizen petition until *after* an ANDA is filed. Focusing solely on the timing of the petition, therefore, is misleading. Similarly, just because a petition is denied does not mean the evidence it contains is insignificant. Instead, a denial could represent differing scientific viewpoints between the Agency and the submitter. FDA has recognized this point before, indicating that sometimes a petition may not raise "persuasive scientific or

[11] §505(q)(1)(F), in fact, recognizes this critical task in specifying the time frame required for final agency action on a filing. And FDA's own regulations require that an interested party file a petition – and obtain final Agency action on that petition – before seeking judicial review of an Agency decision. 21 C.F.R. § 10.45.

[12] §505(q)(1)(E). It is also worth noting that FDA reported in its Seventh Annual Report to Congress that it has never summarily denied a petition under this provision. *See* Seventh Annual Report to Congress on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2014. *Available at:* *https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM464282.pdf*

[13] *See* §505(q)(1)(H).

[14] Many Agency actions have been shaped by issued raised with FDA first in citizen petitions. *See e.g.* FDA-2003-P-0002 (related to ANDAs omission of certain important labeling information), and FDA-2003-P-0227 (related to the appropriate bioequivalence methodology for certain ANDA reviews).

regulatory issues," but that it can nonetheless raise "valid scientific or regulatory issues" that warrant consideration.[15]

In sum, the citizen petition process is an important mechanism necessary for manufacturers to provide information to the Agency outside of the general drug application filing process. Consistent with the same discussions in the context of manufacturer communications with healthcare professionals, a product's manufacturer is often in the best position to identify important safety issues surrounding its own products. As such, that manufacturer's ability to timely and freely inform FDA when the Agency is evaluating generic medications seeking to reference the manufacturer's product data is critical. Both the Agency and the public at large stand to benefit greatly from this sharing of information. Citizen petitions often raise important scientific issues that must be addressed before a generic can be approved. Further, as FDA acknowledged at the public hearing, the Agency learns a great deal about innovator products post-approval, and often that learning continues after a generic application has been filed. FDA raised genuine concerns about how to update the ANDA filing to reflect that new information learned about the innovator product post-ANDA filing, and the use of citizen petitions can allow a chance to bring that information to light. We urge FDA not to impose additional constricting regulations on the use of citizen petitions as a tool in communicating important information to the Agency. Not only could this threaten the public health, but it could, at this point, begin to seriously threaten manufacturers' Constitutionally-protected ability to petition the Agency outside of the active drug review process.

b. Access to Study Samples for Generic Producers and Single Shared REMS

i. Study Samples

We continue to hear public discussion surrounding innovator drug manufacturers blocking access to or otherwise refusing to sell product samples to aspiring generic manufacturers for purposes of testing. What we do not see, however, is any concrete evidence of this practice. In fact, the overall marketplace dynamic counsels in the opposite direction: The Association for Accessible Medicines released a report indicating that almost 90% of prescription medications dispensed in the United States are generic.[16] Earlier this year FDA approved the sixth biosimilar medicine for sale in the United States, and reports show that between 20 and 50 additional biosimilar programs are under development.[17] In short, the marketplace is robust and expanding.

And while FDA reports that it has received something in the realm of 150 inquiries from generic drug companies related to sample access problems, we do not have any insight into the diversity or breadth of these inquiries. In other words, it is not clear how many individual generic applicants are represented in this number, or how many innovator companies or drug products are at issue. Furthermore, we have no insight into the reasons for access problems in

[15] *See* FDA Report to Congress: Encouraging Early Submissions of Citizen Petitions for Stay of Agency Action (February 2009) *available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm348670.pdf*

[16] Association for Accessible Medicines, *2017 Generic Drug Access & Savings in the U.S. available at: http://accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf*

[17] *Bracing for the Biosimilar Wave,* Asher Mullard, Nature Reviews Drug Discovery 16, 152-154 (March 1, 2017) *Available at: http://www.nature.com/nrd/journal/v16/n3/full/nrd.2017.36.html?foxtrotcallback=true.* We would also note that Commissioner Woodcock, at the public hearing in July noted that over 50 biosimilar programs were underway.

such cases or their resolution. What we do know, however, is that in the emerging world of biosimilar development – for which samples may be required in larger volume and for a longer period of time than for traditional small molecule generic studies – there are many research programs underway, many of which, presumably, have reconciled a sample procurement protocol.

We recognize that facilitating access to samples has nonetheless become a key objective in both the regulatory and legislative arenas. As such, we would like to provide some concrete thoughts related to this issue for FDA consideration as it contemplates any path forward.

Initially, it is important to remember that, in cases where an innovator product has a REMS, FDA has determined that this product was not approvable – its benefits did not outweigh its risks – without the implementation of a REMS system and possible safe use and access restrictions. An innovator company with a REMS restricted product makes a commitment to FDA and, importantly, to the public that it will ensure the safe handling, distribution, and dosing of the product. This obligation applies not just in normal prescription-driven sales of the product, but also in sales like those at issue in this discussion – to potential generic competitors. Thus, it is not that simple for a company to sell a product to a potential generic study program without evaluating a number of contingencies.

While FDA has long indicated its willingness to provide a support letter assuring an innovator that a generic applicant has protections and protocols in place to facilitate appropriate handling of samples consistent with the REMS, most times this is only the beginning of an innovator's inquiry. Once the product has been transferred to a potential generic applicant, there is little protection for the innovator against a claim arising out of the action or inaction of the generic entity if misuse – intentional or unintentional – leads to the adverse event sought to be mitigated by the access restrictions associated with the product's REMS. Harm to patients-which is the last thing an innovator expects or wants- is the worst-case result of this misuse. In addition, downstream liabilities – particularly state product liability laws – can be used to pursue an innovator manufacturer for actions completely beyond its control. This sort of liability, as well as possible indemnification by the generic applicant, is a necessary consideration prior to sales of testing samples. While these concerns are most acute in the REMS product area, they nonetheless also exist with respect to non-REMS products, given that almost all drug products can create adverse effects in certain patients, especially if not handled or administered properly.

Additionally, and particularly with respect to smaller biologics manufacturers, the ability to supply the requested samples on a specific timetable is a real and considerable factor when evaluating requests. Not every marketed product is produced on a mass-market scale. In negotiating with a generic manufacturer on a sample access request, the innovator may need to address how long a proposed study may require samples and balance that with anticipated patient demands over the same time horizon. In particular, many biologics are manufactured in small quantities from discrete cell lines, generally based upon anticipated patient needs, and are not quickly reproduced if unforeseen demand arises. Biologic batches can take time to grow and refine. Accordingly, quantity and timing limitations require serious consideration when evaluating policies aimed at broadening access to generic study samples.

Notably, these supply and liability issues persist whether or not FDA has certified the safety and handling protocols of the generic manufacturer seeking such samples. Thus, the issue of sample access may continue to merit public discussion, but the discussion must encompass all of the interconnected factors necessarily considered by an innovator prior to a product's sale.

Moving forward, we urge FDA to consider finalizing its draft guidance on sample access – issued but never finalized more than three years ago – in a way that takes account of the issues raised above, through formal notice and comment rulemaking. Further, regulations should outline specific procedures for the Agency to revise or even revoke a letter issued to a generic applicant if information becomes available to the Agency indicating that the manufacturer can no longer appropriately control product subject to a REMS. Finally, since we see no specific statutory authority for a sale of REMS-controlled samples in the context of generic studies, we would urge FDA to outline the legal basis it is operating under when issuing these support letters and for its conclusion that it will not consider these sales a violation of the innovator's REMS.[18]

ii. Single Shared REMS

Section 505-1(i)(1)(B) of the Food Drug & Cosmetic Act (FD&C Act) generally requires a generic drug and the referenced innovator product to share a single REMS once both are approved.[19] In these situations, companies work off the same documents and policies and procedures in administering the access protocols called for in the REMS. This system has allowed FDA to approve 8 single shared system REMS with access restrictions, which is particularly notable given that most of the other 30 NDA products that currently have a REMS with ETASU remain subject to statutory or patent exclusivities (meaning that the statutory shared system requirement is not the proximate impediment to ANDA approval).[20] It thus appears that manufacturers have been able in many cases to work effectively within the current statutory structure.

To be sure, FDA also retains considerable discretion to waive the single shared system requirement in cases where the Secretary determines that either the burden of creating a single shared system outweighs the benefit of such single system *or* some aspect of the innovator's system is protected by a patent.[21] In fact, FDA has exercised this discretion on at least three occasions of which we are aware. Thus, it is difficult to consider how this system could be "improved" as discussed by the Agency in recent accounts without completely changing the statutory paradigm, including in ways that may potentially risk patient safety. More likely, FDA could be better served by taking a harder look at circumstances appropriate for use of its waiver authority.

Specifically, it seems at least conceivable that the Agency could adopt a more flexible approach to the issue of waiving the shared system requirement when evaluating "impasses" that arise in manufacturer negotiations, so long as it does so in a manner that is consistent with the

[18] *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD,* Draft Guidance for Industry, December 2014.
[19] *See* 21 U.C.C. § 355-1.
[20] *See Statement of Erika Leitzan,* Testimony before the Committee on the Judiciary's Subcommittee on Regulatory Reform, Commercial, and Antitrust Law, U.S. House of Representatives, "Antitrust Abuses of the FDA Approval Process." July 27, 2017.
[21] 21 U.S.C. § 355-1(i)(1)(B)(i)-(ii).

overall purpose of the REMS scheme itself. For example, FDA might deem it necessary not to wait until both statutory triggers are met before making a waiver determination. Nevertheless, the issues necessary to be considered and reconciled when agreeing to a single shared system are critically important for both the innovator and the generic applicant, as well as stakeholders, such as prescribers and pharmacists. But ultimately, they are most important to the patient, as there are clearly identified patient safety risks associated with these products. It is thus essential that any effort by the Agency to introduce more "flexibility" into the waiver determination process not reflect a weakening of the Agency's REMS safety standards, or otherwise come at the expense of patient safety or public health. Moreover, where a waiver is granted, it is critical that the Agency ensure that patients and providers understand precisely which safety measures are shared among the approved systems and, equally important, where they diverge.

One policy, for example, that FDA should consider adopting in this regard is to work first to finalize a shared system – or a waiver – with the innovator and a first filing ANDA applicant before moving forward with approvals for follow-on generic products. This process should lead to more timely and ultimately more consistent shared system decisions, which will benefit patients and providers with more clarity and quicker access to lower cost generic products.

III. Conclusion

BIO appreciates FDA's interest in promoting a balanced approach to biopharmaceutical competition, and encourages the Agency to seriously consider all sides of the complex issues raised in this area. We understand that many of the issues discussed in the Federal Register notice have complicated histories and that easy answers may be scarce. Nevertheless, we hope any additional regulatory changes in furtherance of FDA's stated goal to increase generic competition take account of both the already robust generic marketplace and the tremendous new authorities FDA recently has announced in this area. We look forward to a productive continuing discussion with the Agency on this important topic.

Regards,

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Appendix A

Biotechnology Industry Organization

March 13, 2014

BY ELECTRONIC DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
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Re: Docket No. FDA–2013-N-0500 Proposed Rule: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the "Proposed Rule: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products."

BIO represents more than 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, industrial 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.

Introduction

Ensuring patient safety throughout a product's lifecycle is of the utmost priority of BIO member companies. Accordingly, BIO member companies take their post-market pharmacovigilance obligations and responsibilities seriously. These responsibilities and obligations include the development of written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA; the prompt review of all adverse experience information obtained or otherwise received from any source; and reporting and record keeping. This also includes the separate and distinct ongoing obligation to work with FDA to ensure that labeling is kept up to date as information accumulates.[1] We want to emphasize the shared nature of this responsibility, as FDA is the only entity that has full information about the safety profile of a particular product or related products, and is the entity with ultimate authority and decision-making power over a product's labeling.

[1] FDA regulations require that "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i) (implementing 21 U.S.C. § 502(f)(2), which provides that a drug lacking "adequate warnings" is misbranded).

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As the above post-market pharmacovigilance and labeling requirements apply to all manufacturers — innovator (New Drug Application (NDA)/Biologics License Application (BLA) holders) and generic (Abbreviated New Drug Application (ANDA) holders) — BIO supports the Agency's efforts to create parity among application holders with respect to the "changes being effected" (CBE) labeling supplement process.

Currently, NDA and BLA holders may request changes to FDA-approved labeling by submitting a supplemental application, which must satisfy all the regulatory requirements that apply to original applications.[2] Most label changes appropriately require prior FDA approval obtained through the prior approval supplement (PAS) process,[3] although certain safety-related labeling changes may be made and brought to FDA's attention simultaneously through a CBE supplement.[4] The CBE process is limited to certain specific safety-related changes: to add or strengthen a contraindication, warning precautions, or adverse reaction for which evidence of a causal association satisfies original application requirements; to add or strengthen a statement about drug abuse dependence, psychological effect, or overdose; to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product; to delete false, misleading, or unsupported indications for use or claims of effectiveness; or to implement a PAS request that FDA specially requests be submitted as a CBE.[5]

BIO believes that opening the CBE process to ANDA holders furthers the patient safety and public health objectives that underlie this process. However, we also believe that the CBE process overall would benefit from greater clarity and Agency accountability.

Indeed, in the Proposed Rule, the Agency does not provide adequate details on the process, timelines, and obligations, if any, of the relevant parties concerning the receipt of an ANDA holder's label changes, particularly with respect to the Agency's own responsibilities in this regard. In addition, given that all FDA labeling changes ultimately require FDA approval, the current and proposed systems leave too much uncertainty as to the possibility of or timeline for Agency approval or rejection of label changes made pursuant to the CBE process.

In Section I of our comments, we address the elements of the Proposed Rule that we believe do not serve the interests of patient safety, parity, and public health. In Section II.a, we offer policy solutions and ideas to better achieve labeling change parity and clarity for multi-source NDA and ANDA application holders; and in Section II.b, we offer, for future Agency consideration, policy solutions and ideas for single-source NDA and

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[2] *See* 21 C.F.R. § 314.70 and 21 C.F.R. § 314.3(b), respectively.
[3] *See* 21 C.F.R. § 314.70(b).
[4] *See* 21 C.F.R. § 314.70(c).
[5] *See* 21 C.F.R. § 314.70(c)

ANDA products and all BLA products. These proposed solutions are intended to ensure that practitioners and patients alike have access to consistent, essential, timely and accurate scientific information needed to balance the risks and benefits of a drug when making decisions about medical therapy. It is important to note that inconsistent information that is made available, even on a temporary basis while FDA reviews any proposed changes, increases the potential for confusion amongst health care providers and patients.

I. Concerns with the Proposed Rule

A. NDA Holder Responsibilities in Relation to an ANDA CBE-0 Submission

Under the Proposed Rule, ANDA holders notify the corresponding NDA holder of the proposed labeling changes and supporting data concurrently with their CBE-0 submission to FDA. The Proposed Rule also provides a mechanism for the NDA holder or other ANDA holder(s) to either submit a separate and distinct CBE-0 supplement or correspondence to their NDA/ANDA file regarding the proposed changes.

In discussing the reasoning for NDA holder notification by the ANDA holder, the Agency states that "[i]t is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by an NDA holder for the RLD [reference listed drug] as well as other ANDA holders."[6] And that the Agency's "analysis of whether the labeling change proposed by an ANDA holder in a CBE-0 supplement should be approved (and required for inclusion in the labeling of all versions of the drug) would benefit from the views of the NDA holder for the listed drug that was the basis for ANDA submission."[7] The Agency also argues that NDA notification and FDA's consideration of information from other applicants is "intended to mitigate concerns that a single ANDA holder may not possess sufficient data to perform an adequate assessment of the potential new safety concern raised by the newly acquired information."[8]

While NDA holders are obligated to evaluate all safety information from any source,[9] BIO is concerned that the proposed process and FDA's proffered reasoning provides little guidance to an NDA holder on when and how the NDA holder should act on the information, what the NDA holder should do if it is in possession of inconsistent or conflicting information, or how the FDA expects several or multiple parties (NDA and ANDA holders) to achieve or attain a consistent label, absent clear requirements for Agency review and approval notification to all parties. The FDA also appears to be

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[6] 78 FR 67985, 67989, col. 3.
[7] 78 FR 67985, 67991, col. 2.
[8] 78 FR 67985, 67991, col. 3.
[9] 21 C.F.R. § 314.150.

creating an expectation of an innovator response/submission, which may constitute a de-facto regulatory request from FDA to an NDA holder.

We are equally concerned that the Proposed Rule fails to account for the fact that some generic drugs may be associated with adverse events that warrant safety labeling changes that do not occur with the innovator drug or even other generic versions of the same drug, and that a CBE-0 will be the only formal mechanism by which an ANDA holder can request a label change even under such circumstances. But NDA holders should not be obligated to serve as a resource for FDA's investigation of an ANDA holder's proposed labeling change or be *required* to take measures above and beyond their current regulatory obligations. BIO requests that FDA clarify and confirm that the Agency is not imposing any new requirement on the NDA holder to work with the Agency to confirm or refute the safety labeling change being proposed in the ANDA holder's CBE-0 submission. We also request that FDA confirm that the only obligation of a NDA holder, outside of any aggregate safety analysis performed with respect to any periodic safety reporting requirements (*e.g.*, annual periodic adverse drug experience reports (PADERs) or periodic adverse experience reports (PAER)), is to determine whether any action, labeling or otherwise, is required for its own product.

In addition, we note that the Proposed Rule provides that "[i]n situations in which the safety information prompting the submission of the CBE-0 supplement would require a label change for other drugs containing the same active ingredient, even if approved under a different NDA, FDA may also send a supplement request letter to the persons responsible for those other drugs."[10] We ask FDA to further elaborate on the above proposed process. For example, the Agency should consider how the proposed process would address the situation of a multi-source product that is also the active ingredient in one or more single-source fixed-dose combination products, and how the Agency would involve those combination product Sponsors in the process. We recognize that there are complexities of labeling beyond just that of the single agent active ingredient labeling.

Last, the Proposed Rule requires an ANDA holder to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the reference listed drug (RLD) at the same time that the supplement to the ANDA is submitted to the FDA. BIO believes this responsibility should rest with the Agency. However, if this feature is retained in the final rule, we believe ANDA holders also should be required to notify all other ANDA holders when a CBE-0 is submitted, not just the RLD NDA holder. This requirement would be consistent with the stated intent of the Proposed Rule to "to ensure that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements."[11]

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[10] 78 FR 67985, 67992, col. 2.
[11] 78 FR 67985, 67989, col. 1.

B. Immediate Public Web Posting of CBE-0 Submissions

The Proposed Rule provides for the real-time public release of all CBE-0 submissions on an active FDA webpage, simultaneous with FDA receipt of the proposed labeling change. The Agency intends to make a free tool available that will notify any subscriber of updates to the CBE-0 webpage. BIO believes that, contrary to FDA's intent to enhance transparency and facilitate access by health care providers and the public to labeling containing newly acquired safety information,[12] the immediate web posting of safety labeling changes submitted as CBE-0 supplements, even on a temporary basis, will most likely increase patient, provider, and marketplace confusion, and may unfairly and unnecessarily saddle certain drugs and classes of drugs with safety information and warnings that are later not approved or deemed inappropriate.

The immediate web posting of CBE-0 submission without proper context or understanding will not enhance patient safety or the public health, and, in fact, may have the opposite effect. The proposed web site appears to act more as an information repository and less as resource by which patients, providers, and the marketplace can understand and evaluate with caution and care the reasoning for any one proposed change. Confusion and misunderstanding would be increased in the case of multi-source products that may have several different submissions pending with no underlying context or analysis of what is likely to be divergent labeling. Moreover, the immediate public posting of CBE-0 submissions, especially even prior to a FDA finding that the submission meets CBE-0 requirements, will make it very difficult to retract a CBE-0 submission later deemed inappropriate. Accordingly, BIO urges the Agency to not permit any public posting of CBE submissions until the Agency has reviewed and made a final labelling determination.

If the Agency's final rule does provide for the immediate web posting of various labeling proposals from different manufacturers of the same drug, then the web site should also display a prominent statement to all users explaining that proposals for changes to labeling based are based on information that each individual manufacturer has been able to evaluate concerning the risks and benefits of its products and that other manufacturers of the same products may have evaluated different information concerning the same product or analyzed the information differently. The statement also should suggest that health care providers be alert to other proposals concerning the safety and efficacy of the product and that FDA, as the final decision maker on approved labeling, will consider all proposals and will post such final labeling upon approval.

C. *Immediate Distribution of Dear Healthcare Provider Letters by ANDA Holders*

Under the Proposed Rule, an ANDA holder may distribute a "Dear Health Care Provider" (DHCP) letter, immediately following submission of a CBE-0 application, regarding the proposed labeling change. Similar to our concerns discussed above in relation to immediate web posting, BIO is concerned that this provision in the context of multi-source products may only serve to increase prescriber confusion and uncertainty and, therefore, may not serve the interests of patient safety and public health.

In addition, while the Proposed Rule specifically requires that the CBE-0 application meet the regulatory requirements for such submissions, there is no corresponding FDA requirement to review and find the CBE-0 submission is actually compliant prior to the release of the DHCP letter. Thus, the DHCP letter may be released not only prior to final FDA approval of the labeling change, but even prior to a threshold finding of CBE-0 compliance. This is particularly problematic for multi-source products given FDA's acknowledgement that there is concern that a "single ANDA holder may not possess sufficient data to perform an adequate assessment of the potential new safety concern raised by [] newly acquired information."[13] Also, the premature dissemination of a DHCP letter absent proper context and analysis may unnecessarily cause increased and unfounded prescriber concerns for patient safety for an entire class of products, especially as the Proposed Rule notes "most health care practitioners are unlikely to review product labeling for each generic drug [] that may be substituted for the prescribed product when making treatment decisions."[14]

D. *CBE-0 Submissions for "Highlights of Prescribing Information"*

BIO requests FDA reconsider its proposal to revise current CBE-0 regulatory requirements to now allow the submission of CBE-0 supplements for changes to the "Highlights of Prescribing Information." BIO believes that such changes are best requested and reviewed under current requirements for the submission of a PAS. As "Highlights" are intended to summarize the information that is most important for prescribing a drug safely and effectively, and to organize the information into logical groups to enhance accessibility, retention, and access to the more detailed information, these sections have an increased impact on patient safety and public health. Accordingly, any requested changes should receive heightened assessment and scrutiny prior to dissemination. This is especially true in the context of multi-source products where divergent "Highlights" may serve only to amplify provider, patient, and marketplace confusion.

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[13] 78 FR 67985, 67991, col. 3.
[14] 78 FR 67985, 67989, col. 2-3.

E. Changes to Medication Guides

While the Proposed Rule does not address changes to Medication Guides, for policy reasons similar to those discussed above in relation to "Highlights," BIO requests FDA clarify that any proposed changes to Medication Guides continue to require, as per current regulations, prior Agency approval. However, if the Agency permits the CBE process to be used for changes to the "Highlights" section, then it should also allow such changes to the Medication Guides as well, as they are required to be consistent with prescriber labeling.[15]

II. Proposed Changes to the CBE Process that Support Patient Safety, Public Health, and Application Holder Parity

As all manufacturers—innovator and generic—must comply with the extensive set of regulations designed to ensure the post-approval safety of their drugs, BIO believes that, by incorporating a few policy ideas and process changes into the Proposed Rule and the current CBE application system, FDA can achieve labeling change parity for all application holders, ameliorate the concerns discussed above, and ensure that practitioners and patients alike have access to timely and essential safety information needed to balance the risks and benefits of a drug when making decisions about medical therapy. BIO supports a CBE supplement model that increases clarity and FDA accountability, is open to all application holders, and recognizes the differing needs of single and multi-source products.

BIO proposes, for FDA consideration, two process and accountability models for the CBE supplements—one for multi-source NDA and ANDA products and one for single-source NDA and ANDA, and all BLA products. Implementation of the models below, combined with robust oversight of application holder adherence to post-market pharmacovigilance regulatory obligations, would advance the shared industry and Agency obligation to ensure scientifically accurate information appears on drug product labeling.

A. Proposed CBE Supplement Models for Multi-Source NDA and ANDA Products

As explained in more detail below, BIO proposes that FDA revise its CBE supplement process for multi-source NDA and ANDA products to better achieve labeling parity and clarity of action for all application holders. BIO proposes that the Agency provide prompt (within five days) communication of receipt and instructions to the submitter, as

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[15] Please note that this comment is intended to address the change process for Medication Guides that are not part of a REMS. If the Medication Guide is part of a REMS, then any changes should continue to be submitted through a PAS, as there are other components of the REMS that could be affected.

well as notice and instruction to the other interested application holders. This would be followed by a 30-day Agency evaluation period, during which the Agency must evaluate the submission, including an evaluation of the appropriateness of the submission as a CBE supplement, as well as for possible final Agency labeling decision.

BIO proposes two alternative models for Agency action at or by the conclusion of that initial 30 day period. The first approach, as described in more detail below, would enable the Agency to ensure consistency of multi-source product labels, provides clarity of roles, actions, and timelines for both NDA and ANDA holders, and minimizes the potential for patient and health care professional confusion. However, should the Agency not adopt this first proposal, BIO proposes in the alternative a revised CBE supplement model that allows for a slightly longer period of temporary discordance between multi-source NDA and ANDA product labels, yet still provides the important elements of clarity of timelines for Agency action and Agency direction to both NDA and ANDA holders.

Specifically, BIO proposes, in both of our proposed models, for all multi-source products, whether the CBE supplement is filed by an NDA holder or an ANDA holder, that:

- Within five days of Agency receipt of a CBE supplement:
    - The Agency would confirm receipt and instruct the submitter, in writing, to refrain from making any labeling changes, including distributing DHCP letters, prior to FDA review and further instruction.
    - The Agency would notify, in writing, other interested application holders of the request, and instruct them to refrain from making any labeling changes, including distributing DHCP letters, prior to FDA review and further instruction. FDA also would direct that other application holders refrain from submitting new or similar supplements, unless the application holder has received independently information such that it would ordinarily initiate a CBE supplement submission. FDA also would at this time provide instructions on how the other application holders may provide the Agency with any relevant information, including information contrary to the CBE submission, if they so choose.
- Next Step – Option 1

Following the initial notification described above, BIO proposes a 30-day Agency review period, upon the conclusion of which the Agency must either make a final labeling decision or determine that it needs more time to make a final labeling decision, and then

instruct all interested application holders to take no action until such final decision. Specifically:

- Within 30 days of receipt, the Agency:
    - Shall assess each submission for conformance with CBE regulatory requirements; determine whether the submission should be converted into a PAS application; and
    - May also determine that the submission be rejected, accepted, or modified (final labeling decision); or
    - May also determine that the Agency needs more time to decide whether the submission should be rejected, accepted, or modified (delayed final labeling decision).

- At the end of the 30-day review period, the Agency's determination would be communicated, in writing, to all interested application holders.
    - If, at the end of the 30-day review period, FDA makes a final labeling decision (*i.e.*, accepts, rejects, or modifies the CBE submission), the Agency's communication shall include instructions, including timelines, for application holder compliance, if required, and such decision may be made publicly available by the Agency and/or application holders.

    - If, at the end of the 30-day review period, the Agency determines that the submission meets CBE requirements, but also determines that the Agency needs more time to make a final labeling decision (*i.e.*, to accept, reject, or modify the CBE submission), that decision would be communicated, in writing, to the submitter and all interested application holders, along with instructions to all parties to refrain from making any labeling changes, including distributing DHCP letters, until the Agency reaches a final labeling decision.
        - The Agency then would have an additional 60 days to make a final labeling decision.

    - At the end of the additional 60-day review period, the Agency's final labeling determination would be communicated, in writing, to all interested application holders. Such communication would include instructions, including timelines, for application holder compliance, if required.

- Upon written communication to all application holders of the Agency's final labeling decision, such decision may be made publicly available by the Agency and/or application holders.

- Next Step – Option 2

To the extent that FDA does not adopt BIO's Option 1 as discussed above, BIO maintains its proposal for an initial 30 -day Agency review period, and suggests the Agency adopt the following alternative process for Agency action at the end of the 30-day review period. This second proposal differs from the above preferred approach largely in that this second proposal would permit submitters to make an immediate label change following the Agency evaluation of CBE conformance, and thus allow discordant labels between the submitter and other interested application holders during the 60-day period for a final Agency labeling decision. Specifically:

- Within 30 days of receipt, the Agency:
  - Shall assess each submission for conformance with CBE regulatory requirements; determine whether the submission should be converted into a PAS application; and
  - May also determine that the submission be rejected, accepted, or modified (final labeling decision); or
  - May also determine that the Agency needs more time to decide whether the submission should be rejected, accepted, or modified (delayed final labeling decision).

- If at the end of the 30-day review period, the Agency determines that the submission meets the requirements for a CBE supplement, but determines that it needs more time to make a final labeling decision (*i.e.*, accept, reject, or modify), then FDA will:
  - Communicate that decision, in writing, to the submitter, and also allow the submitter to implement labeling changes as per the submission, including distributing DCHP letters.
  - Communicate that decision, in writing, to all other interested application holders, along with instructions to refrain from making any labeling changes, including distributing DHCP letters, until the Agency reaches a final labeling decision.
  - The Agency would then have an additional 60 days to make a final labeling decision (*i.e.*, accept, reject, or modify).

- At the end of the additional 60-day review period, the Agency's final labeling determination would be communicated, in writing, to all interested

application holders. Such communication would include instructions, including timelines, for application holder compliance, if required.

- Upon written communication to all application holders of the Agency's final labeling decision, such decision may be made publicly available by the Agency and/or application holders.

B. Proposed CBE Supplement Model for Single-Source NDA and ANDA Products, and all BLA Products

To similarly improve the process and accountability within the overall CBE process, and ensure parity among application holders, BIO proposes for future Agency consideration the following CBE model for all single-source NDA and ANDA products, and all BLA Products, whether the CBE supplement is filed by an NDA, BLA, or an ANDA holder.

- Within five days of Agency receipt of a CBE supplement:
  - The Agency would confirm receipt and instruct the submitter, in writing, to refrain from making any labeling changes, including distributing DHCP letters, prior to FDA review and further instruction.
- Within 30 days of receipt, the Agency:
  - Shall assess each submission for conformance with CBE regulatory requirements; determine whether the submission should be converted into a PAS application; and
  - May also determine that the submission be rejected, accepted, or modified (final labeling decision); or
  - May also determine that the Agency needs more time to decide whether the submission should be rejected, accepted, or modified (delayed final labeling decision).
- If, at the end of the 30-day review period, FDA makes a final labeling decision (*i.e.*, accepts, rejects, or modifies), the Agency's communication shall include instructions, including timelines, for application holder compliance, if required, and such decision may be made publicly available by the Agency and/or application holder.
  - If at the end of the 30-day review period, the Agency determines that the submission meets CBE requirements, but determines that it needs more time to make a final labeling decision (*i.e.*, accept, reject, or modify), that decision would be communicated, in writing, to the submitter, along with instructions to refrain from making any

labeling changes, including distributing DHCP letters, until the Agency reaches a final labeling decision (*i.e.*, accepts, rejects, or modifies).

- The Agency then would have an additional 60 days to make a delayed final labeling decision (*i.e.*, accept, reject, or modify).

However, should the Agency not adopt the above proposal, BIO recommends in the alternative that the Agency adopt a process for single-source NDA and ANDA products, and all BLA Products, that is the same as our proposed Option 2, above, for multi-source products, modified for the single application holder context.

Conclusion

BIO appreciates this opportunity to comment on the "Proposed Rule: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products." We believe that the CBE process can be strengthened in ways that will improve public health, and we would be pleased to provide further input or clarification of our comments, as needed. Please feel free to contact me at 202 962 9220 if you have any questions or if we can be of further assistance. Thank you for your attention to this important matter.

Respectfully submitted,

/s/
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Legal & Intellectual Property