



March 13, 2014

BY ELECTRONIC DELIVERY

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

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).



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

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

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

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.

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

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.
- o 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:
 - o 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:
 - o Shall assess each submission for conformance with CBE regulatory requirements; determine whether the submission should be converted into a PAS application; and
 - o May also determine that the submission be rejected, accepted, or modified (final labeling decision); or
 - o 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.
 - o 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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