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March 17, 2008

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2008N-0021: Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) wishes to thank the Food and Drug Administration (FDA) for the opportunity to submit comments on *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*. BIO welcomes this reaffirmation of the agency's longstanding processes for incorporating new safety information into a product label so that patients and physicians receive timely, accurate, and relevant information about the benefits and risks of a drug or biologic necessary to make well-informed choices about therapy.

BIO represents more than 1,150 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 technologies, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

FDA'S PROPOSED REGULATORY AMENDMENT IS VALUABLE FOR COMMUNICATING NEW SAFETY INFORMATION:

Medical product labels contain vital information on a particular product's uses, warnings, contraindications, precautions, and adverse events. When new information relevant to a

product's benefit/risk profile becomes available, a manufacturer will seek FDA approval to update the product label so that patients and physicians have access to relevant, credible, useful information regarding a particular therapy. Since 1982, FDA's Changes Being Effectuated (CBE) supplement procedure has allowed sponsors, in limited circumstances, to amend a product label to reflect new safety information while FDA is reviewing the supplemental application. FDA can then accept, reject, or request that the manufacturer modify the revised labeling. FDA's proposed codification of the CBE process is useful because it clarifies the exact circumstances in which the CBE process should be initiated to enact a label change, rather than the prior approval labeling supplement pathway.

CBES SHOULD CONTINUE TO BE USED ONLY IN LIMITED CIRCUMSTANCES

BIO appreciates this formal explanation of agency expectations that CBE supplements should be filed only "to reflect newly acquired information" for which there is "evidence of a causal association."

Newly Acquired Safety Information: It is inherently reasonable when a sponsor updates a product label while FDA is reviewing the CBE supplement, that the label change should be driven by new, emerging scientific data. Medical products undergo extensive clinical testing prior to FDA evaluation to characterize the benefits and risks of that product. At the time of approval, FDA ensures that appropriate, scientifically-supported warnings, precautions and contraindications are included on the product label. Therefore, any additional changes to the product label in the post-market context should be derived from newly acquired safety information, such as "data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events of a different type or greater severity or frequency than previously included in submissions to FDA, or new analyses of previously submitted data (e.g., meta-analyses)." (P. 2853)

This emphasis on newly acquired information as the basis of CBE supplements helps to ensure that the public receives notification of relevant, emerging safety information; that the label is not revised to add information previously reviewed by the agency; and that the risk of confusion by information that may be added and later removed is minimized.

BIO would appreciate additional clarification regarding the time period in which previously submitted safety information is still considered to be new. Specifically, the notice states that "FDA intends to consider information "newly acquired" if it consists of data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product." (p. 2850, emphasis added) BIO would appreciate additional information regarding what the agency considers "a reasonable time period" in which previously submitted safety information can be considered to be newly

acquired when a sponsor submits a CBE supplement. A process for formally notifying the sponsor after FDA completes its review of previously submitted safety information may help to draw the distinction between newly acquired safety information and previously reviewed data. Additionally, BIO notes that the proposed revision to 21 CFR 314.3, “Definitions”, does not include a provision regarding when information submitted within a reasonable time period prior to the CBE supplement will still be considered new. We recommend that the Definition be revised to reflect fully FDA’s stated intention.

Evidence of a Causal Association: Additionally, BIO supports FDA’s effort to assure that any new changes to product labeling implemented prior to FDA review are based on reasonable evidence of a causal association. Changes must be based on credible information so that patients and providers make rational, justified choices about medical treatment. If non-relevant or unsubstantiated safety claims were to be included on a product label, then the public would have less confidence in the validity of these claims, leading to confusion and uncertainty. Indeed, the addition of unnecessary information on a product label would have the additional consequence of diluting and detracting from other relevant warnings and contraindications on the label that patients should heed. Further, unnecessary label additions—i.e. over-warning—can result in under-treatment.

The proposed rule provides consistency with FDA’s existing prescription drug labeling regulations in 21 C.F.R. part 201, which state that: “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 definitively established.” 21 C.F.R. section 201.57(c)(6). Accordingly, the proposed CBE clarification regarding evidence of a causal association further illustrates that a labeling change warrants reasonable evidence of causation, but does not represent a conclusion or definitive establishment of causation.¹

PROPOSED AMENDMENT REFLECTS EXISTING REGULATORY POLICY:

The proposal is consistent with existing FDA authority, FDA’s current policies in implementing the full prescribing information, and FDA’s mission to protect and promote the public health. FDA authority to amend these regulations is derived from the original authority to establish the CBE procedure and the proposal is consistent with Congressional and societal expectations that the FDA have ultimate authority over a product label. In enacting the *Food and Drug Administration Amendments Act of 2007* (FDAAA), 21 U.S.C. 355(o)(4)(I), Congress provided FDA with additional authority to require labeling changes under expedited timelines, when the Agency becomes aware of new safety information that it believes should be included in the labeling. 21 U.S.C.

¹ In a regulatory proceeding involving the addition of a warning to the labeling for over-the-counter products containing diphenhydramine, FDA stated that its “decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action [t]o mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, causation.” Final Rule, Labeling of Diphenhydramine-Containing Drug products for Over-the-Counter Human Use, 67 Fed. Reg. 72555 (Dec. 6, 2002.)

section 355(4). The proposed clarifications of the CBE process further helps to ensure that reliable new safety information reaches patients and medical professionals in a timely manner.

FDA CONTINUES TO BE THE ULTIMATE AUTHORITY OVER THE PRODUCT LABEL:

U.S. drug and biologic regulation is based on the premise that “the ultimate authority over drug, biologic, and medical device labeling, therefore, continues to rest with FDA.” (p. 2849) Like all types of labeling supplements, FDA carefully reviews the labeling changes proposed under a CBE supplement, and will choose to accept, modify or reject the proposed changes as the agency sees fit. FDA should consider reaffirming and clarifying in the regulations that it will provide a written response to the sponsor describing FDA’s grounds for approval, disapproval, or request for modifications to the CBE supplement. It also may be helpful for the agency to establish a process for receipt notification of the CBE supplement as well as a reasonable timeframe for it to respond to the sponsor.

The CBE regulation strikes a balance by establishing an appropriate pathway for quick dissemination of certain important new safety information, while maintaining Agency control to assure that labeling is in the best interests of patients and their physicians.

CONCLUSION:

BIO appreciates this opportunity to comment on FDA’s proposed rule on *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*. These changes to clarify the process for submitting CBE supplements to the agency will help to ensure that patients and physicians receive relevant, emerging safety information in a timely way. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

John M. Taylor, III
Executive Vice President for Health
Biotechnology Industry Organization