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July 12th, 2011

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

Re: Docket No. FDA–2011–D–0164: Draft Guidance for Industry on Safety Labeling Changes; Implementation of the Federal Food, Drug, and Cosmetic Act

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "*Draft Guidance for Industry on Safety Labeling Changes; Implementation of section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act*" (Draft Guidance). This Draft Guidance addresses Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which authorizes the FDA to require or order certain safety-related changes in drug labeling. BIO views this Draft Guidance as an important step in further implementing a process for safety labeling changes that ensures patients and their physicians have access to timely, relevant, and science-based prescribing information to make informed decisions about their health. It is also important to BIO members that decisions to change safety labeling be based upon reliable information; that the process be cooperative and involve the application holder to the extent that is feasible; and that the labeling change and the process of adopting the change be in the best interest of public health.

BIO represents more than 1,100 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, sustainable agriculture, and a cleaner and safer environment. Our general comments are set forth below.

A. What Constitutes New Safety Information and How is its Validity Substantiated?

FDA's authority to require safety labeling changes pursuant to Section 505(o)(4) is premised on "new safety information." Notably, however, the Draft Guidance does not include any additional clarification on FDA's interpretation of what constitutes "new safety information." The Draft Guidance includes only a very brief section entitled "What Does New Safety Information Mean" in which only the broad statutory language itself is excerpted.

Specifically, the Draft Guidance states, in relevant part, that "new safety information" is defined as "information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by [FDA]" about:

- "A serious risk or an unexpected serious risk associated with the use of the drug that [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved [REMS] for the drug", **or**

- "The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]." (lines 100-110)

Rather than merely reiterating the broad contours of the statutory definition itself, we recommend that FDA further expand this discussion in the Draft Guidance to provide additional clarification as to FDA's interpretation of "new safety information," including examples of the types of information that would be deemed to trigger the 505(o)(4) process and examples of what would not.

Additionally, FDA should address the level of credibility, reliability, or support for new safety information that would warrant a safety labeling change requirement or order. New safety information can be presented by a variety of sources and contain varying levels of detail and investigation into such information. While Appendix A of FDA's Draft Guidance provides examples of sources of new safety information, the Draft Guidance is not clear on how information will be treated when coming from different sources that may have differing levels of reliability, or the extent to which FDA will evaluate or further confirm the information.

The Draft Guidance should distinguish between the types of information that may be considered preliminary, compared to information that would be vigorous enough to support a labeling change. This additional guidance would be helpful for industry and other stakeholders to understand and, where applicable, respond appropriately to the Agency's notification that a safety labeling change is warranted.

We recommend that FDA consider further clarifying that the level of safety information required to trigger a safety labeling change under Section 505(o)(4) is not merely cumulative information already reflected in the drug labeling or previously considered by FDA. The Agency should also ensure that "new safety information" deemed sufficient to trigger the 505(o)(4) process is only that substantiated by specific evidence rather than based on mere supposition or extrapolation. Clarification is also needed concerning the distinction between what FDA will consider a "serious" risk, as compared to other risks that would not be considered to fall within the 505(o)(4) paradigm.

Finally, the Guidance states that when evaluating new safety information, the multidisciplinary team will determine "If the safety information is relevant to more than one member of a drug class" (Lines 131-132). We ask that FDA provide additional guidance as to how FDA intends to interpret when safety information is "relevant" to more than one member of a drug class.

B. Notification of Application Holder(s)

FDA's Draft Guidance proposes to provide information to the application holder(s) regarding the source from which the new safety information is derived and a brief description of "what the new safety information is about". (line 188) BIO believes that more complete information is necessary to enable the application holder to adequately respond to a notification from FDA. We encourage FDA to provide more than a summary of the new safety information in the notification letter. An FDA notification should include the actual data that the Agency reviewed, or at least a detailed description of the new safety information, the source of the new information, and any evaluation or analysis of such information that was conducted by FDA. Further, after review of the Agency's assessment, application holders should have the opportunity to request further information, including the data supporting the revised safety labeling text if deemed necessary in forming a response to the Agency's notification.

The Draft Guidance does not specify to what extent informal communications can or should be initiated by the FDA in the process. Given that new safety information can have a variety of sources and contain varying levels of assessment, FDA should recognize that the application holder may also have pertinent information to contribute to the evaluation. Accordingly, we encourage FDA to include in the guidance an informal discussion process between the FDA and the application holder in which:

- The team created to evaluate the safety should be encouraged to engage the application holder in informal discussions prior to the decision being finalized, and

- The individual within the FDA who is to send the labeling change notification should contact the designated representative of the Sponsor at least 24 hours prior to sending the letter, to provide opportunity for an informal discussion regarding the new safety information.

C. Proper Categorization of Safety Labeling Changes

FDA's Draft Guidance indicates in sections IV(A) and IV(B) that mandatory label changes under 505(0)(4) may in some cases be made as a changes-being-effected supplement (CBE), pursuant to 21 CFR 314.70(c). We believe this is fundamentally incorrect, and that any labeling changes ordered by FDA pursuant to 505(o)(4) -- that receive prior FDA review and implicit, if not explicit, approval before implementation -- should be characterized as a prior approval supplement (PAS).

The use of a CBE to implement FDA-mandated labeling changes under 505(o)(4) would be inconsistent with the current definitions, regulation, nature and history of CBEs. For example, FDA's preamble to its 2008 proposed labeling rule makes clear that CBEs are Sponsor-initiated changes "made in advance of the agency's review and approval" of such a change.[1] Under 505(o)(4), FDA will have reviewed the labeling language before the Sponsor is ordered to submit the labeling change supplement. Further, a CBE submission would require that "if a Sponsor intends to utilize the limited CBE procedure set forth in 314.70(c)(6)(iii) or 601.12(f), it must possess information regarding causation sufficient to satisfy the criteria set forth in 201.57(c)..." [2] In contrast, under an FDA-ordered 505(o)(4) labeling change, it is not clear that a Sponsor would have evidence of causation. Finally, a CBE is characterized by a Sponsor determining what safety labeling language to employ and, again, this is inconsistent with the 505(o)(4) process, which represents a safety labeling change that is ordered by FDA.

D. Timelines

The timelines in the statute are quite short in some instances, and the Draft Guidance interprets the statute to mean calendar days in all instances when days are referenced. Given the short time frame and the importance of addressing safety issues adequately, we encourage FDA to allow for a grace period for certain exchanges (particularly where the time periods are 5 days) when the last day falls on a weekend or federal holiday, making the responses due the following business day. Additionally, the 30-day time period for sponsor submission of a labeling supplement or rebuttal statement following FDA notification should begin upon the day that the sponsor receives the notification (rather than on the date that FDA issues the notification letter as stated in the current draft).

The Agency should retain the ability to grant an extension beyond 30 days for the initial response to a notification letter and during the discussion period, if requested by application holders for valid reasons. The Draft Guidance should also explicitly state that such an extension may be sought by applicants for reasons similar to those stated within the Draft Guidance (*i.e.*, the need to consider, discuss and propose alternative language, consider additional information or obtain agreement with higher management levels).

[1] 73 Fed. Reg. 2848, 2849 (2008).
[2] 73 Fed. Reg. 2851 (2008), (citing FDA's regulations addressing content and format of prescription drug labeling).

The timeliness may be further complicated in instances where the product involved is the subject of a REMS. We encourage FDA to provide further detail regarding the specific applicability of the issues addressed in the Draft Guidance to REMS products. For example, if the required safety labeling changes are also included in an approved REMS (including any Elements to Assure Safe Use (ETASU) components), it would be useful to know what the specific timelines would be incorporating the required changes. BIO requests that FDA clarify the approval process when revising a REMS is warranted, and address the incorporation of such safety labeling changes into any corresponding REMS documents.

The timelines for FDA responses are well structured and are, in many instances faster than those required of the FDA when the Sponsor initiates a proposed label change related to new safety information and the Sponsor would like to obtain the FDA's input on the proposed labeling change prior to implementation. In certain circumstances it may be useful to allow the Sponsor to request that the FDA initiate this process in order to expedite the process and allow the Sponsor to obtain FDA's feedback on an expedited basis.

E. Multidisciplinary Team

The Draft Guidance states that "FDA will form a multidisciplinary team to evaluate information that may be new safety information that should be incorporated into a drug's labeling under section 505(o)(4)." (lines 130-131) We request more information in regard to who will be involved in the multidisciplinary team that will be evaluating information that may be new safety information that should be incorporated into a drug's labeling. BIO recognizes that different scenarios may call for different compositions of expertise in the team. However, given the challenges associated with communication across offices, such as between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), it is critical to have clear lines of communication and defined roles and responsibilities within the multi-disciplinary team in order to successfully meet the statutorily-specified timelines.

F. Public Disclosure of Safety Labeling Letters

The Draft Guidance states that safety labeling notification letters that apply to multiple application holders may be posted on FDA's website rapidly, but that single-sponsor-specific notification letters will be considered confidential commercial information and not be made publicly available until the applicable labeling supplement has been approved. (lines 396-401)

We request that the Agency also provide clarification on the intended timeframe for posting of product labeling with new safety labeling changes on its website following the issuance of an order for a safety labeling change. Specifically, if an application holder intends to pursue an appeal of the order through the dispute resolution procedure, the application holder's case and position may be weakened if the new safety labeling text is already available in the public domain prior to the conclusion of the appeals process.

Additionally, upon submission of a CBE or a Prior Approval Supplement, where consensus has been reached by the Agency and the application holder on the safety labeling text, the Draft Guidance states that FDA will approve the supplement generally within 15 calendar days. Since the new approved labeling is expected to be available on the application holder's website within 10 calendar days of approval, the Agency should provide a written or verbal communication to the application holder(s) if FDA cannot issue an approval letter within the 15 calendar day timeframe.

G. Non-Delegation

We note that statute requires that "Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research)." (505(o)(5)) We request additional information in the Draft Guidance regarding how FDA is interpreting and implementing this provision to ensure that the safety labeling process is being initiated by staff with sufficient authority and expertise.

H. Exemption from User Fees

As application holders are notified of safety labeling change requests from FDA and are expected to submit prior approval supplements or changes being effected supplements in response, these supplements modify the labeling to add a restriction that would improve the safe use of the drug. We request that the Agency clarify that these submissions do not contain clinical data and are exempt from user fees (Guidance for Industry – Submitting Separate Market Applications and Clinical Data for Purposes of Assessing User Fees).

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Safety Labeling Changes; Implementation of the Federal Food, Drug, and Cosmetic Act." We provide specific line-by-line comments in the following table. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director
Science and Regulatory Affairs
Biotechnology Industry Organization

/S/

Sandra J.P. Dennis
Deputy General Counsel for Healthcare
Biotechnology Industry Organization

SPECIFIC COMMENTS:

LINE	ISSUE	PROPOSED CHANGE
A. What is New Safety Information?		
Line 132	As discussed in our general comments, additional clarity should be provided throughout the guidance on how FDA intends to assess class labeling changes.	Please clarify
B. What Types of Safety Labeling Changes Might Be Required Under Section 505(o)(4)?		
Line 151	Please clarify if the intent is to update "any" safety section of labeling.	We suggest updating the sentence to include the term "... in any of the following sections ...".
Line 161	We would appreciate clarity as to the term "normally." What would "normally trigger" a safety labeling change? That is, the sentence implies that on some occasions updates to the Adverse Drug Reaction (ADR) section would be appropriate.	Thus, we suggest deletion of the term "normally."
Line 168	We recommend using the term "prescribing information" to be consistent with current labeling practices, as opposed to the term "professional labeling."	Recommend using the term "prescribing information."
C. How Will FDA Review the Required Labeling Supplement or Rebuttal Statement?		
Line 266-268	Clarification is needed to better understand the process, including issuance of the notification, should one or more application holder(s) for a class of drugs disagree with the class change order.	Please clarify
Line 267	For additional clarification.	Please consider inserting the phase "or safety labeling change order" within this

		sentence.
Line 276	Please advise if this is within the 30 days.	Please provide a specific time frame.
Line 284	For additional clarification.	Please add phrase: "(and any extension periods, as applicable)"
E. When Should New Labeling Be Available?		
Line 390	There is a lack of clarity on website posting of CBE submitted labeling.	Please provide greater clarity on website posting of CBE submitted labeling, per CBE Guidance (Sept., 2006).
Lines 392-394	Please provide a timeframe when FDA will issue Guidance regarding the timeframe for availability of the package inserts (PI), patient package inserts (PPI), and Medication Guides (MG).	Please clarify
V. DISPUTE RESOLUTION		
Line 412	We would appreciate consideration for 'business' days as opposed to 'calendar' days, as 5 calendar days may include a weekend from a Thursday or Friday dated change order.	Recommend 'business days'
Line 416	Please clarify if FDA will align all labeling within a drug class before approval. If not, will there be opportunity after approval for application holders to dispute differences in labeling within a class of drugs?	Please clarify
VI. ENFORCEMENT OF REQUIREMENTS FOR SAFETY LABELING CHANGES		
Line 451	Please clarify business or calendar days.	Recommend 'business days'