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Washington, DC 20017

April 24, 2006

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

Re: Docket No. 2005D-0011 (Federal Register, Volume 71, Number 15, p. 3998-3999, January 24 2006)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and 31 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial, and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Draft Guidance for Industry on *Warnings and Precautions, Contraindications, and Boxed Warning Sections for Labeling for Human Prescription Drug and Biological Products — Content and Format*.

This draft guidance represents an important step in the right direction toward clearer, more easily understood prescription product labeling. In our comments below we offer both general and specific recommendations for enhancing the usefulness of the draft guidance to BIO member companies.

GENERAL COMMENTS

BIO recognizes the importance of the goal of this draft guidance, i.e. to assist applicants and reviewers in drafting key sections of labeling, and to "help ensure that the labeling is clear, useful, informative, and to the extent possible,

consistent in content and format” (lines 27-28). The availability of such well-drafted labeling is important to ensuring appropriate use of marketed human prescription drug and biological products.

BIO also appreciates the critical importance of the information contained in the particular sections of the product label addressed by this draft guidance. Although available data suggest that such information does not always have the desired effect (for example see Wagner et al., *FDA drug prescribing warnings: is the black box half empty or half full?*, *Pharmacoepidemiol Drug Saf.*, 2005 Nov 18), both health providers – especially those who make prescribing decisions – and patients need this information to make informed decisions regarding treatment options.

However, BIO has a number of general concerns with the guidance. First, in our view the draft guidance promotes unduly strong reliance on spontaneous reporting data and literature reports to protect drug safety. It is widely accepted that such sources often have limited utility for assessing drug safety, and are typically best used to identify areas where more systematic study is needed. While FDA has recognized the limits of such data in some contexts, in this draft guidance the Agency weighs the certainty and usefulness of these data too heavily (we provide examples below). We suggest that the final guidance explicitly explore and detail the challenges presented by the use of spontaneous reporting data and literature reports.

Second, and as we also note in more detail below, there are some sections of the draft guidance which may lead to unwarranted assumptions about similarities across a product class. Class labeling must be well-supported by good science so that it does not inappropriately influence prescriber decisions. We urge FDA to avoid the possibility that all drugs of a class are required to adopt class labeling when the data are inadequate to support this. Also, we note that FDA’s responsibility is to weigh the benefits and risks of each individual drug, rather than to compare and contrast any one drug with any other drug.

Third, BIO requests that FDA provide additional clarification of the non-quantitative terms and phrases used in the draft guidance. For example, the draft guidance refers to concepts such as “high risk” (line 118) without providing any definitions for them. The draft also uses certain ambiguous terms, such as the phrase “reasonable evidence of a causal association” (line 54). The assessment of causality has been the focus of a corpus of publications in the medical literature, and the subject of many seminars, workshops, and other venues for discussion. FDA and industry need a mutual and clear understanding of terminology in order to make proper and consistent judgments regarding what should be on a label. Most importantly, the label will be less meaningful to prescribers unless these definitional ambiguities are addressed.

SPECIFIC COMMENTS

Section II. Warnings and Precautions Section (W&P)

- II.A (lines 53-68). We request more clarification of the phrase “otherwise clinically significant,” which is used several times in the draft guidance. FDA uses this phrase to identify an adverse reaction that “does not meet the definition of a serious adverse reaction, but is still considered clinically significant” (lines 61-62). Several examples of adverse reactions that may be “otherwise clinically significant” are provided (lines 64-68), but the examples are not specific or all-inclusive, and BIO is concerned about inconsistent interpretations of this phrase across reviewing divisions and between FDA and individual sponsors.

We are not sure, for example, whether a headache treated with an OTC pain reliever would qualify as a clinically significant event as currently defined (because it would require the “addition of another drug”). We are also not clear whether a cough associated with the use of an ACE inhibitor that leads to a change in the prescription would also qualify (as a “regimen adjustment”). BIO suggests that “otherwise clinically significant” be defined in the Glossary, and that the definition clearly distinguish this phrase from the phrase “serious adverse reaction” as the two phrases should not be used interchangeably (as occurs at line 327).

BIO recommends that the bullets at lines 64-68 be made clearer and more specific through the use of illustrative examples, and that the phrase “could include” be eliminated from line 63 so that the scope of the term “otherwise clinically significant” is limited to the examples provided.

The phrase “Adverse events that significantly affect patient compliance” (line 68) is also broad. It would be helpful for FDA to give criteria for how this type of adverse event may be identified and give specific examples. For instance, nausea is a relatively common adverse event that might affect compliance with an oral medication, resulting in the inclusion of nausea in the W&P section.

II.A (lines 58-59, 387-394). BIO suggests that FDA revise the definition of “serious adverse reaction” provided in the Glossary. This definition appears to be similar to the definition in the ICH guideline E2B “Data Elements for Transmission of Individual Case Safety Reports.” However, the ICH definition is specific for the review and interpretation of individual case reports. Applying this ICH definition to the W&P section could be interpreted to mean that an adverse reaction should be included in that section based on the evaluation of an individual case, even if the particular adverse reaction is not “serious” in the vast majority of cases reported. The determination to include an adverse reaction in the W&P section should take into account other factors

such as the likelihood of occurrence, and the likelihood that the adverse reaction could result in one of the serious outcomes listed. Therefore, BIO recommends that the Glossary definition (lines 387-394) be revised to read “For purposes of this guidance, the term *serious adverse reaction* refers to any reaction at any dose if there is a reasonable likelihood that the adverse reaction will result in any of the following outcomes...,” and we request guidance on the meaning of the term “reasonable” in this context.

- II.A.2 (line 71-93, 193). An “expected adverse reaction” is one that “can be expected to occur with a drug, despite its not having been observed with that drug” (lines 73-74). Line 193 states “There would ordinarily be no reason to further subcategorize adverse reactions (e.g., separating observed and expected adverse reactions by placing them under different subheadings).” We note that it may in fact provide more clarity for expected adverse reactions to be placed in a separate subcategory within W&P so that there is a clear distinction between those adverse reactions that have been observed and those that have not.

We also note that class labeling of unobserved occurrences creates a strong potential for misinformation. We believe that “expectations” that are not based on observed events should rarely be included in the safety profile in the label of any product. For example, angiotensin converting enzyme inhibitors (ACEI) are associated with angioedema. However the risk of angioedema varies significantly by indication; in some indications, such as congestive heart failure, the risk among users of specific ACEIs varies. The class labeling approach provided for in the draft guidance would appear to preclude such distinctions.

Another example comes from the label for atorvastatin, which states: “The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals.” Yet the label for Advicor, a product approved for marketing in the United States containing niacin and lovastatin, notes that one case of myopathy was observed in a trial of 1,079 persons treated with the product for up to two years. It is not clear that class-labeling in this instance provided useful information to health provider community or patients.

To ensure that labeling is scientifically accurate, consistent, and non-arbitrary, both FDA and industry should be cautious in the use of class labeling. We ask FDA to clarify that inclusion of “expected adverse reactions” in the label is likely to be an infrequent event, typically occurring when trials for particular product were designed to exclude populations that were determined to be vulnerable to the adverse reaction with earlier members of the drug class, and that the inclusion of such “expected adverse reactions” must be well-supported by scientific evidence.

- II.A.3 (lines 114-119). Under the subheading “Incidence,” the draft guidance states “In some cases, however, the absolute risk or rate of an adverse reaction can be an important factor when deciding whether to include the reaction in this section (e.g., when the risk or rate is high).” However, no guidance is given regarding FDA’s view of what constitutes a “high risk” or “high rate,” or how to handle situations when a high rate reflects only low risk. Using clopidogrel as an example: as stated in the label for clopidogrel, the background rate for thrombotic thrombocytopenic purpura (TTP) is 4 per million per year, while that observed for users of clopidogrel is 11 per million per year. Even at a rate of 11 per million per year, the risk of TTP is quite low.

We ask that FDA set consistent numerical standards for use of phrases such as “high risk,” i.e., one in a hundred, one in a thousand, etc., and identify other factors – with numerical standards where possible – that should be taken into account to determine what is “high risk.” This type of clarity is important to ensure understanding of the label and will enable increased consistency among sponsors and among different FDA review divisions.

- II. A. 3 (lines 120-125). We ask for further clarity, perhaps through the use of examples, of how the ability to manage or prevent an adverse reaction plays into the decision to discuss an adverse reaction in the W&P section. Many serious adverse reactions can be managed; should they all be listed?
- II. A.6 (lines 146-151). This section states that the W&P section “must identify any laboratory tests helpful in following the patient’s response or in identifying possible adverse reactions.” We note that the inclusion of information about laboratory tests that is not currently included in product labels may stray into the practice of medicine. The decision to order laboratory tests helpful in monitoring response or adverse reactions must be made case-by-case by health providers for individual patients, based on underlying disease, concomitant medications, and comorbid conditions. We ask FDA to clarify that that it would often be more appropriate for the label to offer less specific recommendations, .e.g. for more frequent monitoring for select adverse reactions when concomitant medications may increase the risk of the reactions. These recommendations may be derived from clinical trials to determine the value of lab testing and appropriate monitoring frequency, but need not identify specific tests.
- II. B (lines 155-184). In the section labeled “Information to Provide,” the elements recommended for inclusion in the label are more expansive than the requirements stated in the final PLR (we discuss some of these elements individually below), and add a level of detail that could make the overall length of labeling unwieldy and result in unnecessary redundancy. BIO recommends that where possible there be a cross-reference to the Adverse

Reactions section, or other appropriate sections, rather than duplicative inclusion of information in this section. However, BIO believes FDA's recommendations to include a description of the adverse reaction and outcome (lines 158-159) and a discussion of the steps to take to reduce the risk of, decrease the likelihood, shorten the duration of, or minimize the severity of an adverse reaction (lines 163-168) are appropriate and consistent with the requirements defined in the PLR.

- II. B (line 160 and footnote 4). Among the information recommended to be incorporated into the label is “an estimate of the risk or adverse reaction rate.” The calculation of such rates is often based on assessment of postmarketing adverse event reports, and numerous problems are presented by the assessment of such reports. For example, the incompleteness of reporting based on type of event, its severity, and the geographical location of the event affects the number of reported events and, by extension, the rate. The variability in such rates was striking in the International Agranulocytosis and Aplastic Anemia Study (*Risks of agranulocytosis and aplastic anemia: A first report of their relation to drug use with special reference to analgesics*, JAMA 256(13):1749-57, 1986 Oct 3). Therefore, BIO requests clarity regarding what events should be incorporated in such rates. Are these rates to be based only on data generated from clinical trials? Should they be limited to those events occurring in the United States or events occurring globally? How do literature reports enter into such rates, if at all? We note that it is unclear how a health care provider could properly interpret such information included in the label, without a detailed understanding of how the rate was derived.

Additionally, BIO requests clarification of the term "early exposure," which is used in footnote 4.

- II. B (lines 161-162). This bullet recommends a discussion of known risk factors for the adverse reaction (e.g., age, gender, race, comorbid conditions, dose, duration of use, coadministered drugs), if known. This information is very often discussed in the medical literature, and we note that it will often be difficult or impossible to incorporate into the label a concise and accurate summary of what is often an extended and complex discussion. One question which is very likely to arise is whether the summary should be limited to studies from the United States. For example, is information on risk factors for the occurrence of aplastic anemia in the context of analgesic use from Thailand relevant for a health care provider or consumer in the United States? BIO suggests that the draft guidance be modified to note that risk factor information need only be provided when the evidence supports preparation of a concise and accurate summary, and that FDA provide a robust and clear method for assessing the relevancy of information in the context of the United States population.

- II. B. (lines 169-170). This bullet recommends “a discussion of how to treat, or otherwise manage, an adverse reaction that has occurred.” In deciding how to treat or manage an adverse reaction, a physician must make a medical judgment that takes into account the specific patient and the specific circumstances under which the patient is being treated. The manufacturer’s responsibility is to provide the physician with information necessary for safe and effective use of the drug, not to provide treatment advice. We recommend the deletion of this bullet, because physician labeling should not provide generalized patient treatment recommendations.
- II.C.1 (lines 190-194). Please clarify the Agency's preference as to the subheaders used to group related events (e.g. by body system, or other criteria?).

Section III. Contraindications Section

Overall, this section provides a welcome, detailed, and clear description of when to contraindicate a drug. However, BIO does have the following recommendations.

- III.C.1 (line 299). This bullet appears to be inconsistent with the examples provided by FDA (e.g. Imdicon), which do not contain a subheader for each contraindication and suggest that subheaders are redundant if each contraindication is listed by bullet or separated with a space.
- III.A.3 (footnote 8). This footnote calls for cross-labeling of certain drug-drug interaction (DDI) contraindications. Although BIO agrees with the patient safety rationale behind cross-labeling, we believe that footnote 8 raises significant regulatory and legal concerns which merit careful examination. Therefore, we recommend that FDA not finalize footnote 8, but instead publish a separate draft guidance on cross labeling of DDI contraindications so that sponsors and others can comment more meaningfully on FDA's proposal in this footnote.

Among the issues that a new draft guidance should address are the following. First, sponsors of different drugs do not typically have access to studies, including safety data and clinical data, not conducted by them. This may make it difficult or impossible for manufacturers to explain or defend the DDI contraindication information in its product’s label. Second, individual manufacturers' back-and-forth labeling negotiations with the Agency will not be available to different manufacturer. Again, this may make it difficult impossible for manufacturers to explain or defend their own product’s DDI contraindication information. Third, we request that FDA explain the process the Agency will use to establish the need for cross-labeling of DDI contraindications, and under what circumstances the requirement for such cross-labeling would be extended to a drug class.

This process must be capable of protecting sponsors' proprietary information. Fourth, we ask FDA to clarify that sponsors are not responsible for constant review of the labels of all other drugs to determine whether there is a cross labeling concern with their drugs. In the guidance development process, other important issues related to cross-labeling for DDI contraindications may arise.

Section IV. Boxed Warning

- IV.A (lines 323-325). This bullet states “There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction)...”. We recommend removing “e.g.” so that the scope of “serious in proportion to the potential benefit from the drug” is limited to “a fatal, life-threatening or permanently disabling adverse reaction.” This appropriately represents the types of adverse reaction to be considered and is consistent with the intent of the PLR.
- IV.A (lines 327-330). It is critical that the significance of boxed warnings not be diluted by too much detail or by listing too many events. Therefore, BIO recommends that serious adverse reactions that can be prevented or reduced in frequency not typically be included in the boxed warning. Such serious adverse reactions include DDI events, as well as serious reactions related to use in patients with a specific co-morbid disease (e.g. renal insufficiency). We suggest that the bullet at lines 327-330 be removed in its entirety.
- IV.A (lines 336-339). This short paragraph, beginning “A boxed warning can also be used in other situations to highlight warning information that is especially important to the prescriber,” is vague and requires very subjective judgments. In our view the paragraph offers no additional value beyond the examples covered in the bullets above it. Therefore, we suggest that this paragraph be deleted.
- IV.A (lines 341-346). We suggest that the term “serious” be added before the term “adverse reaction” in this paragraph. This would have the effect of limiting the types of adverse reactions suitable to be listed in a boxed warning, and adding the term “serious” would create consistency with the PLR, which states that “Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box” (PLR, 201.57(c)(1)). As we note above, it is critical that the significance of boxed warnings not be diluted by too much detail or by listing too many events. With respect to “expected serious adverse reactions,” the text in the boxed warning should state that (as FDA suggests at lines 92-93 for the W&P section) “the adverse reaction has not been observed but may be expected to occur.”

- IV.A (lines 348-351). Information identifying a drug as “the only one in its class to have a particular risk that makes it inappropriate for use as a first line therapy” (lines 350-351) should only be included in the boxed warning if the “Indications” section of the label limits the product to second-line use. The decision to use a drug as first- or second-line therapy is a medical practice decision, and is dependent on factors other than likelihood of contraindications or serious adverse reactions.

In conclusion, BIO agrees with the need to ensure that health care providers and patients have appropriate product safety information in clinical and other settings where patient safety is paramount. We understand the importance of disclosure of such safety information, and of having both the health provider community and the public understand the significance of these key sections of the product label. We are committed to working with the FDA towards optimal achievement of this goal. However, we think that this guidance needs the modifications we describe above if it is to achieve the goal of including scientifically valid, clinically meaningful information in a label that is useful and comprehensible to prescribers. We look forward to additional opportunities to discuss the issues outlined above.

Sincerely,

/s/

Sara Radcliffe
Managing Director
Science and Regulatory Affairs