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August 27, 2008

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

Re: FDA Docket 2006N-0467: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling;" Proposed Rule

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the proposed rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*.

BIO represents more than 1,200 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.

Overall, we believe the agency has done a good job of analyzing deficiencies related to the current content and format of pregnancy labeling for human prescription drug and biological products. Further, the proposed rule represents a positive step for prescription drug product labeling, particularly with respect to addressing inadvertent drug exposure early in pregnancy, clarifying the risks associated with discontinuing vital treatment for a chronic condition during pregnancy, and allowing health care professionals and patients to make better informed decisions about drug use during pregnancy.

We agree with eliminating the pregnancy categories, adding a Pregnancy and Lactation subsection to the labeling, and focusing on factual statements based on data. We also agree with the rule's emphasis on the use of human data in the Pregnancy and Lactation subsections of the labeling, particularly data generated from pregnancy registries.

We are concerned, however, that the complexity of the revised rule and categories may have the unintended consequence of creating more confusion for prescribing physicians, rather than helping them more appropriately balance risks and benefits with their pregnant patients. We offer the following additional general and specific comments, which we believe will further improve the rule and pregnancy and lactation labeling.

GENERAL COMMENTS

1. We are concerned about the potential for inconsistent implementation/ interpretation of this rule (as reflected in product labeling) among the agency's review division personnel. Therefore, we recommend that the agency establish a dedicated group of FDA specialists that review pregnancy and lactation labeling to increase labeling consistency. To further increase the chances of consistent implementation when this proposed rule is finalized, please consider including expectations about which elements of the Pregnancy and Lactation subsections, if any, are to appear in the Highlights section of the labeling.

2. We believe categorizations such as "high/moderate/low," and "sufficient" are subjective and quite likely to be misinterpreted, particularly in the absence of defining criteria. For that reason, our specific comments below recommend against the use of these terms and/or suggest definitions.

3. Proposed 21 CFR 201.57(c)((9)(i)(C)(2) states, "When both human and animal data are available, risk conclusions based on human data must be presented before risk conclusions based on animal data. A risk conclusion based on human data must be followed by a narrative description of the risks as described in paragraph (c)(9)(i)(C)(*4*) of this section." As noted in the preamble, animal data may not support, or may possibly contradict, the human data. If risk conclusions are based on appropriate human data, we recommend the rule be revised so that animal data are not required, even if available. (If, in cases where both human and animal data are available, you decide to retain the requirement that both kinds of data be presented, we recommend the Lactation subsection be revised to state that clinical data are to be presented before preclinical data.)

4. Given the intended audience for the labeling that will result from this rule (women of childbearing age and their health care professionals, according to the Summary section of the proposed rule), we do not recommend inclusion of overly technical information, such as confidence intervals, statistical power information, and assay limits, in the Pregnancy and Lactation subsections. We recommend alternatives to these proposals in the specific comments below.

5. When the rule is finalized, please consider clarifying throughout, as appropriate, that it applies to both the parent drug and any active metabolites.

SPECIFIC COMMENTS ON PROPOSED PREGNANCY SUBSECTION

Overall

1. In Section IV ("Description of the Proposed Rule") FDA sought comment on how the proposed elements in the Pregnancy section of the labeling should be ordered. We recommend the following order: Pregnancy Registry Enrollment/Contact Information; Clinical Considerations; Fetal Risk Summary; Data; and General Statement About Background Risk.

   We believe this arrangement presents these elements in order of decreasing interest, and we believe health care professionals are more interested in information contained in the Clinical Considerations section than the Fetal Risk Summary, Data, or General Statement of Background Risk sections. The proposed rule notes that failure to address inadvertent drug exposure (*i.e.*, in women who are exposed to drugs before they know they are pregnant) has been identified as one of the key weaknesses of current pregnancy labeling. The Clinical Considerations section addresses this issue and should thus be given a more prominent location in the Pregnancy section of the labeling.

Registries

2. For products with a pregnancy registry, proposed 21 CFR 201.57(c)(9)(i)(A) provides for applicable information about the registry (e.g., a telephone number) to be included in the labeling. Please consider putting this pregnancy registry information in an explicitly labeled subsection (within the Pregnancy Subsection) entitled, "Pregnancy Registry Enrollment/Contact Information." Such an explicitly labeled subsection will make it clearer and easier for health care professionals to know which part of the labeling contains information on how to enroll in a pregnancy registry.

General Statement About Background Risk

3. Proposed 201.57(c)(9)(i)(B) would require pregnancy labeling to state that "All pregnancies have a background risk of birth defect, loss or other adverse outcome, regardless of drug exposure," and that "the fetal risk summary describes [the drug's] potential to increase the risk of developmental abnormalities above the background risk." It is unclear how the agency will determine the background rate and whether it will apply to all the risks that may be included in the labeling. It is also unclear if the background rate will be specific to a particular population,

such as the population with the disease state, or the disease state being treated, or the population in general.

Background statistics change over time as new evidence is made available and accepted by the medical community. For these reasons, we recommend against the requirement to include background data in the package insert.

4. We are also concerned that the second sentence in proposed 201.57(c)(9)(i)(B) implies causality to some extent, which the data may not support. Yet, as proposed, this language would be standard introductory language regardless of risk level, even for those products with limited data that do not allow conclusions to be drawn. Accordingly, we believe this language is inappropriate and that the second sentence should be deleted when data are limited and risk conclusions cannot be made.

Fetal Risk Summary

5. In Section IV, Subsection 3 ("Fetal Risk Summary…"), Part f ("Risk conclusions based on human data"), middle column of page 30842, FDA sought comment on "whether, in situations with human data that are not sufficient, rather than classifying the risk as low, moderate, or high, the risk should instead be characterized by specific statements describing the findings, or whether the findings should be described at all if they are not readily interpretable."

    a. These categories proposed for situations where human data are "not sufficient" ("high," "moderate," and "low") are subject to a variety of interpretations, much like the A, B, C, D, and X categories the agency is proposing to delete. In addition, the rule proposes categories of "high," "moderate," and "low" risk that would be separately established on the basis of animal data (see comment 9 below). It is not clear how clinicians should advise patients with respect to these potentially conflicting classifications of risk magnitude. For example, if a risk based on "not sufficient" human data is "low," one could conclude that the drug is therefore "safe" to prescribe. But if for the same drug the risk based on animal data is "moderate," it sends a confusing message. This is the case with the KAPPAATE example in the proposal.

    We recommend against use of the "high," "moderate," and "low" descriptors for "not sufficient" human data. We believe that there should be only three different categories of risk conclusions based on either sufficient or not sufficient human data. These are 1) "Human data do not indicate an increased risk," 2) "Human data indicate an increased risk," and 3) "Insufficient data—risk conclusion not established." The first two categories are described in proposed 201.57(c)(9)(i)(C)(2)(i).

For the third category, available human data should be described but a risk conclusion should not be drawn. In adequately powered trials and registries for pregnant women, the aim is to test the hypothesis of whether the risk of events is higher in women taking the study drug compared to the background risk. Even for these adequately powered trials and registries, a conclusion for low, moderate or high risk is not drawn. In scenarios when data are insufficient, it is even more unclear how a conclusion of low, moderate and high risk can be drawn.

b. Further, the proposed rule does not provide objective criteria that could be used to assign conclusions about risk magnitudes ("high," "moderate," or "low") or what amount/kind of data are sufficient. For example, the proposed rule says "sufficient human data" are those "sufficient to reasonably determine the likelihood that the drug increases [a particular risk]." (See 201.57(c)(9)(i)(C)(2)(i).) This statement seems circular and likely to result in uneven interpretation and application. The proposal also does not discuss how the determination of sufficiency will be made or who will make it. For these reasons, we recommend that a dedicated group of FDA specialists review this determination, using sound scientific evidence, for all labeling subject to this rule, to increase the chance of consistent implementation across review divisions.

   If the decision is made to retain these risk magnitudes and the "sufficient"/"not sufficient" terms, we respectfully urge FDA to set forth within the rule objective criteria for making such category determinations rather than noting that conclusions will be made based upon data "sufficient to reasonably determine the likelihood … ." It would also be helpful if FDA would provide examples of sufficient and insufficient human data. Further, we request that FDA caution prescribers that such classifications should not be considered as scientific proof that a drug may or may not cause harm to a particular patient.

6. Proposed 21 CFR 201.57(c)(9)(i)(C)(1) says "all available data" are to be considered in the development of the Fetal Risk Summary. We recommend that this language be revised to limit Fetal Risk Summary data sources to scientifically rigorous, organized data collection schemes such as clinical or preclinical studies, and registries. These data might also be from the medical literature or show a mechanism-based potential for toxic effects. (For example, the animal data may be negative, but the affected target/pathway may suggest that there could be a risk associated with the drug.) Generally, data from spontaneous reports should not be part of the basis for this subsection.

7. Proposed 201.57(c)(9)(i)(C)(1), "Fetal Risk Summary," would require that the label "characterize the likelihood that the drug increases the risk of developmental abnormalities in humans." We believe that birth prevalence data, being the easiest to interpret and therefore most meaningful to health care professionals,

will be used to address this requirement. The proposal does not address situations where there are not appropriate comparators, however. We recommend that the agency discuss this situation in the final rule, including the significant burden and time constraints sponsors may be faced with when there are not adequate comparators. This burden must be accounted for in the economic impact section of the rule.

8. Proposed 21 CFR 201.57(c)(9)(i)(C)(2)(i) states, "Sufficient human data may come from such sources as clinical trials, pregnancy exposure registries or other large scale epidemiologic studies, or case series reporting a rare event. When human data are sufficient to reasonably determine the likelihood that the drug increases the risk of fetal developmental abnormalities or specific developmental abnormalities, the likelihood of increased risk must be characterized using one of the following risk conclusions: "Human data do not indicate that (name of drug) increases the risk of (type of developmental abnormality or specific abnormality)." or "Human data indicate that (name of drug) increases the risk of (type of developmental abnormality or specific abnormality)." Note that, typically, individual studies are not statistically powered to detect a safety signal for adverse pregnancy outcomes.

9. In proposed 21 CFR 201.57(c)(9)(i)(C)(3) FDA says that when the data on which the risk conclusions is based are animal data, the fetal risk summary must characterize the likelihood that the drug increases the risk of developmental abnormalities using one of five risk conclusions: "Not predicted to increase the risk," "Low likelihood of increased risk," "Moderate likelihood of increased risk," "High likelihood of increased risk," or "Insufficient data."

    a. Because pre-clinical data cannot always be considered predictive of human outcome, we believe the proposed use of the word "predicted" is inappropriate in the context of risk conclusions (i) to (iv) in proposed 21 CFR 201.57(c)(9)(i)(C)(3).

    b. We recommend replacing the risk conclusion proposed in (9)(i)(C)(3)(i) ("Based on animal data, [*name of drug*] is not predicted to increase the risk of developmental abnormalities [see Data]".) with "Animal data for [*name of drug*] do not indicate an increased risk of developmental abnormalities."]

    c. We recommend against use of the words "low," "moderate," and "high," as proposed in 21 CFR 201.57(c)(9)(i)(C)(3)(ii), 201.57(c)(9)(i)(C)(3)(iii), and 201.57(c)(9)(i)(C)(3)(iv), as these terms are associated with the same weaknesses as the A, B, C, D, and X categories proposed for deletion. Instead, interpretable animal data that indicate an increased risk should simply be described qualitatively (e.g., number of species with positive findings, consistency of findings, and type of findings) in the labeling.

d. In cases where there are insufficient animal data (or no animal data) on which to assess the drug's potential to increase the risk of developmental abnormalities, the labeling should state that fact, as proposed in 201.57(c)(9)(i)(C)(3)(v).

10. Proposed 201.57(c)(9)(i)(C)(4) says that, "When appropriate, the description must include…confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk." We consider it highly unlikely that health care professionals who refer to this subsection will be interested in or understand this information. For that reason, we recommend against inclusion of this information in the labeling.

11. Proposed 21 CFR 201.57(c)(9)(i)C)(4) reads, "…To the extent possible, this description must include the specific developmental abnormality (e.g., neural tube defects); the incidence, seriousness, reversibility, and correctability of the abnormality; and the effect on the risk of dose, duration of exposure, and gestational timing of exposure. When appropriate, the description must include the risk above the background risk attributed to drug exposure and confidence limits and power calculations to establish the statistical power of the study to identify or rule out a specified level of risk." Please clarify this portion of the rule to explain the meaning of the terms "reversibility" and "correctability" in this context.

Clinical Considerations

12. Proposed 21 CFR 201.57(c)(9)(i)(D)(2)(i) says, "The labeling must describe the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat." In our view it is the health care professional's responsibility to keep abreast of the latest information about the disease state and its effect on pregnant women and to apply that knowledge to treatment of each individual patient. The professional labeling is not the appropriate place for this information.

Data

13. Proposed 21 CFR 201.57(c)(9)(i)(E)(3) says, "The labeling must describe…exposure information … ." The Appendix in the proposed rule gives the impression that only mg/m^2 dose comparisons are acceptable, however, we recommend that if plasma kinetic data are available, those data should used instead of mg/m^2 or mg/kg body weight dose comparisons.

SPECIFIC COMMENTS ON PROPOSED LACTATION SUBSECTION

Risk Summary

14. Proposed 21 CFR 201.57(c)(9)(ii)(A)(1) says, "The risk summary must describe the effect of the drug on the quality and quantity of milk, including milk composition, and the implications of these changes to the milk on the breast-fed child." It is seldom feasible to evaluate the effects of the drug on the quality and quantity of milk. To be scientifically valid, such evaluation requires a study before, during, and after drug exposure. Further complicating factors are substantial inter- and intra-individual variation and small study sample size (volunteers for such studies are difficult to find). For these reasons, we recommend that this requirement be deleted from the final rule.

15. Proposed 21 CFR 207.57(c)(9)(ii)(A)(2)(i) would require that the risk summary describe the presence of the drug in human milk in one of five ways. We believe only three of these five are needed: "The drug is not detectable in human milk," "The drug has been detected in human milk," or "The data are insufficient to know or predict whether the drug is present in human milk."

16. Proposed 21 CFR 207.57(c)(9)(ii)(A)(2)(ii) would require that if studies demonstrate that the drug is not detectable in human milk, the risk summary must state the limits of the assay used. We believe information about the assay limits is both overly technical and unfamiliar to most health care professionals who may refer to the Lactation subsection of labeling. For that reason, we recommend against inclusion of this information in the labeling. We presume FDA's review of the data would consider the validity (and, therefore, the limits of the assay used) in making the recommendation to include this information in the labeling. If FDA considered the assay unreliable, or inadequately sensitive, the test results should not be included in the labeling at all. In that case, the labeling could simply state that reliable information on drug levels in human milk is not available.

CONCLUSION:

BIO appreciates this opportunity to comment on the proposed rule *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
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Biotechnology Industry Organization