August 25, 2014

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


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Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices (Draft Guidance).

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.

I. General Comments

As with the FDA’s recently published revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (Revised Draft Reprint Guidance), BIO continues to support FDA efforts to clarify its views on biopharmaceutical manufacturer communication to health care professionals of truthful and non-misleading medical or scientific information, including, in this instance, certain “new risk information” that may be inconsistent with the risk information contained in the product label. BIO agrees with FDA’s acknowledgement of the significant public health value of the provision of truthful and non-misleading scientific and medical publications on new risk information to health care professionals. Information about new risk information can be of critical importance for physicians and their patients. As FDA explains in the Draft Guidance, “FDA recognizes that the safety profile of a drug evolves throughout its lifecycle as the extent of exposure to the product increases, and it can be helpful for health care practitioners to receive significant new risk information about an approved product in a timely manner.”¹ BIO concurs that health care professionals should be able to receive truthful and non-misleading published information from the manufacturer regarding new risk information about a product, in a timely manner.

¹ Draft Guidance, lines 55-58.
We further note that, as BIO has commented previously, the provision by a manufacturer of such truthful and not misleading information has constitutional protection under the First Amendment as speech. Accordingly, so long as the information distributed by the firm is truthful and not misleading, even if the content or distribution method may be inconsistent with this Draft Guidance, the speech itself should not be the basis of an enforcement action.

In this regard, BIO appreciates FDA’s confirmation that this Draft Guidance, like other FDA guidance documents, does not impose a legally enforceable responsibility on manufacturers, and also that FDA’s use of “should not” in the Draft Guidance does not create an independent legal prohibition. In other words, FDA acknowledges that manufacturer distribution of information in a manner other than as recommended in the Draft Guidance is not in and of itself prohibited, and further that there may be other appropriate means of communicating truthful and non-misleading information concerning new risk information.

To the extent that FDA utilizes this Draft Guidance, or later issued final guidance, however, to restrict truthful and non-misleading communication, FDA should ensure that the recommendations are narrowly tailored to meet compelling public health goals. Certainly BIO supports the importance of the information contained in FDA-approved product labeling, and does not argue that the distribution of new risk information should substitute for FDA-approved product labeling. At the same time, however, BIO believes prescribers and other professionals in the health care process are sophisticated and discerning consumers of scientific and medical content. FDA should be cautious about placing undue or broad restrictions on manufacturers sharing truthful and non-misleading scientific and medical information with health care professionals and individuals at health care entities that may be relevant to patient care and the exercise of sophisticated professional judgment.

On the whole, the Draft Guidance provides helpful information for manufacturers about how FDA would view or interpret manufacturer sharing of such truthful and non-misleading new risk information that appears in medical or scientific publications. BIO’s detailed comments are below.

a. Scope of the Draft Guidance

In the “Background” section of the Draft Guidance, FDA notes that it “anticipates that the earliest distribution of new risk information will generally involve distribution of recently published studies, as opposed to textbooks or clinical practice guidelines” and that in this Draft Guidance FDA is providing guidance for companies that distribute new risk information in reprints or digital copies of a published study. Further, FDA later indicates that it “does not intend to object to the distribution of new risk information that...is distributed by a firm in the form of a reprint or digital copy of a published study,” assuming the publication meets certain content and distribution

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1 Sorrell v. IMS Health, Inc. 113 S.Ct. 2653, 2659 (2011) ("[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment").
3 Draft Guidance, lines 32-36.
4 Id, lines 58-61.
principles.\textsuperscript{6} This is a narrower scope than FDA asserted recently in the draft Guidance on Distributing Scientific and Medical Publications on Unapproved New Uses (Draft Revised Reprints Guidance). Specifically, the recently issued Draft Revised Reprints Guidance includes, in addition to reprints, FDA recommendations on the distribution of scientific and medical publications such as clinical practice guidelines and medical textbooks. FDA does not offer rationale for its narrower scope in this risk information Draft Guidance.

BIO notes that limiting the scope of this Draft Guidance to reprints limits scientific exchange and dialogue. BIO suggests, therefore, FDA should include scientific and medical publications as appropriate for the distribution by a firm of “new risk information” for purposes of this Draft Guidance. Physicians and other health care professionals are sophisticated consumers of medical and scientific information. The important consideration should be whether the content includes new risk information, and is truthful and not misleading, rather than a pre-ordained type of publication in which the information may be contained.

\textit{b. Criteria for Determining Whether New Risk Information is Appropriate for Distribution to Health Care Professionals and Health Care Entities}

In the Draft Guidance, FDA urges firms to carefully consider the reliability and persuasiveness of the new risk information that “suggests that an adverse reaction or other risk currently in approved labeling is not causally related to a drug or less consequential than is reflected in the labeling, or that otherwise refines the characterization of an adverse reaction identified in approved labeling.”\textsuperscript{7} BIO concurs, and believes this is an important consideration for manufacturers.

As mentioned previously, we note that in the Introduction to this Draft Guidance, FDA confirmed that the Draft Guidance does not impose a legally enforceable responsibility on manufacturers,\textsuperscript{8} and also that FDA’s use of “should not” in the Draft Guidance does not create an independent legal prohibition.\textsuperscript{9} It is reasonable to conclude this guidance document does not therefore render risk information with other data sources or distribution methods as necessarily prohibited. BIO requests FDA clarify this position in light of FDA’s later statement in the Draft Guidance that “[d]istribution of information that is not consistent with this guidance may render the labeling of a drug false or misleading.”\textsuperscript{10} In other words, we request FDA clarify in any final Guidance that new risk information distributed by the manufacturer in a manner that does not conform with this guidance is not necessarily prohibited as false or misleading labeling.

BIO notes further that the provision by a manufacturer of truthful and not misleading scientific or medical information (including new risk information, however defined) has constitutional protection under the First Amendment as speech.\textsuperscript{11} Accordingly, so long as the new risk information distributed is truthful and not misleading, even if distributed in a manner that may be

\textsuperscript{6} Id, lines 205-208.
\textsuperscript{7} Id, lines 193-197.
\textsuperscript{8} Id, lines 32-36.
\textsuperscript{9} Id.
\textsuperscript{10} Id, lines 205-210.
\textsuperscript{11} Sorrell v. IMS Health, Inc. 113 S.Ct. 2653, 2664 (2011) (noting that the reality of the importance of protected commercial speech “has great relevance in the fields of medicine and public health, where information can save lives.”)
inconsistent with this Draft Guidance, the speech alone should not be the basis of an enforcement action.

c. Data Source

i. Practicality

BIO appreciates FDA’s recommendations on appropriate data sources for new risk information that may be distributed in accordance with this Draft Guidance. BIO is concerned, however, that some of the suggestions may be too ambiguous to be of clear practical use. For example, FDA indicates that the data source for the new risk information “must be at least as persuasive as the data sources that underlie the existing risk assessment” that is being rebutted, mitigated, or refined. This is surely a judgment based, subjective standard. Further, it may not be the case that peer reviewed publications necessarily meet the FDA recommendation that the article contain a “fair characterization of all relevant information in the safety database, including contrary or otherwise inconsistent findings.”12 In short, the manufacturer cannot control the actions of the authors of these studies, and so therefore cannot ensure that the authors include information from the safety database including inconsistent findings or otherwise provide a “fair characterization.” Nonetheless, FDA implies that only studies that themselves address such contrary evidence can be distributed. Accordingly, BIO asks FDA to modify this recommendation.

In order to assist firms in navigating this inherent subjectivity, at minimum FDA should modify its recommendation to state that FDA recognizes the challenges and therefore that reasonable differences in judgment would not render such distribution inconsistent with this Guidance. BIO further asks FDA to modify this recommendation because it will create problems in determining what can or cannot be distributed, and may inhibit or stifle the distribution of important new risk information by the firm for reasons outside the control of the firm.

ii. Eligibility of pharmacoepidemiologic studies

BIO greatly appreciates that FDA has recognized the importance of pharmacoepidemiologic studies in both this Draft Guidance and the 2005 Guidance for Industry titled Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. In launching the Sentinel Initiative in 2008, FDA also acknowledged the usefulness of automated health care data sources, including electronic health record systems, insurance claims databases, and registries. In some instances, FDA has required the completion of pharmacoepidemiologic studies, or the analysis of data generated from automated health care data sources, as part of a drug’s post marketing commitments. In other cases, analyses of pharmacoepidemiologic data have been used to help further characterize the risk-benefit profile of drugs seeking label extensions in difficult-to-study patient populations. BIO agrees with the Agency’s assessment of the value and use of pharmacoepidemiologic analyses and automated health care data, and asks that FDA expand on its thinking about these studies in the Guidance. Specifically, BIO requests additional clarity on what the FDA considers a pharmacoepidemiologic study, including real world evidence collected retrospectively through large independent payer databases or academic collaborations, as well as

12 Draft Guidance, lines 231-232.
other examples. BIO looks forward to continuing to collaborate with FDA to further optimize the use of these resources as the field of data analytics continues to grow and evolve.

iii. Study Standards

In the Draft Guidance, FDA addresses what it believes to be appropriate standards for a study or analysis distributed by a manufacturer as new risk information inconsistent with the product label. Specifically, FDA recommends “the study or analysis should meet accepted design and other methodologic standards for the type of study or analysis (e.g., provides a clear description of the hypothesis tested, acknowledges and accounts for potential bias and multiplicity) and should be sufficiently well-designed and informative to merit consideration in assessing the implications of a risk.” BIO notes that pivotal trials assessing drug treatments for chronic diseases often have open-label extension phases designed to gather additional data to assess the drugs’ long-term safety. In some cases, data from the open-label extensions of multiple phase 3 trials in a development program are pooled to increase the amount of drug exposure data. Subsequently, the increased amount of drug exposure data improves the scientific rigor of the safety analyses. Therefore, BIO requests that FDA consider results from open-label extensions of clinical trials published in independent, peer-reviewed journals as acceptable sources of data to refine risk information in the approved labeling.

In addition, FDA recommends that “[t]he conclusions of the study or analysis should give appropriate weight and consideration to, and should be a fair characterization of, all relevant information in the safety database, including contrary or otherwise inconsistent findings.” In reality, third-party researchers and unsponsored investigators conducting the studies of interest may not have full access to all relevant information in proprietary safety databases. Similarly, Sponsors may not have immediate or direct access to all relevant safety information from third-party researchers when drafting publications. Thus, we request that FDA qualify the characterization of “all relevant information in the safety database” by removing “all” and adding “when available” to the language to read “... should be a fair characterization of, relevant information in the safety database, when available, including...” BIO reiterates that these requirements or conditions on a particular study or publication may not in fact always be feasible, and urges FDA to reconsider, as such a recommendation may inhibit distribution of important new risk information.

d. Distribution

i. Cover Sheet/Disclosure of Financial Interest

As with the FDA’s recent Revised Draft Reprint Guidance, FDA recommends the new risk information be distributed with a cover sheet, contain a prominent statement including information on any author known to the manufacturer as having a financial relationship with the manufacturer, or with a product of the manufacturer that is included in the publication, including the nature or amount of such relationship.

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13 Draft Guidance, lines 214-218
14 Draft Guidance, lines 230-232
As BIO has commented previously,\(^{15}\) this financial disclosure recommendation presents compliance challenges for manufacturers because the amount of a financial interest can be difficult to ascertain and, even when fully ascertained, is generally a fluid amount – i.e., it may change over time – requiring recurring revisions to the financial interest statement accompanying the distributed publication.

BIO here reiterates our recommendation from prior comments that the Agency consider instead a financial-disclosure approach in which a firm discloses generally known author financial interests existing at the time of publication. This recommended approach is similar to that used for peer-reviewed journals, whereby the author discloses her or his financial relationships with specific manufacturers broadly, as opposed to disclosing a specific dollar amount or listing the types of engagements contributing to the financial interest. In addition, BIO notes that the Center for Medicare & Medicaid Services shall soon publish comprehensive reported data covering physician financial relationships with manufacturers on the CMS Open Payments reporting system website, as required by law. BIO suggests, therefore, that the most efficacious and least burdensome approach to financial interest disclosure would be an Agency recommendation that firms simply refer the reader to the CMS disclosure site.

\[ \text{ii. Statements by Representative of Firm} \]

With respect to distribution of new risk information, FDA recommends in this Draft Guidance “any statements made by a representative of the firm to a recipient concerning the reprint should be consistent with its content and the information in the disclosure cover sheet.”\(^{16}\) If one combines this recommendation with the FDA’s prior recommendation in this Draft Guidance that distribution of information outside this Guidance may render the product label false or misleading, this would lead to the conclusion that a verbal statement made by a representative other than as recommended here in and of itself could render the product labeling false or misleading. As noted previously, the First Amendment protects truthful and not misleading speech, and therefore such speech alone should not in and of itself be restricted. Specifically, in \textit{US v. Caronia}, the Second Circuit held that the First Amendment precludes a conviction based on a pharmaceutical manufacturer representative’s truthful and non-misleading speech alone.\(^{17}\)

\[ \text{II. Conclusion} \]

BIO and its members are appreciative of FDA’s efforts and for FDA’s Draft Guidance for manufacturers concerning how FDA would view or interpret manufacturer distribution of “new risk information” to health care professionals and health care entities. As explained in detail in these comments, we urge FDA to ensure that any proposed constraints in the Draft Guidance, when finalized, are narrowly tailored to meet the Agency’s public health goals and do not impede scientific and medical dialogue and debate, and the exchange of important information concerning public health and patient care.

\(^{15}\) BIO Comments on Revised Draft Guidance for Industry on Distributing Scientific Medical Publications on Unapproved New Uses- Recommended Practices

\(^{16}\) Draft Guidance, lines 264-265

\(^{17}\) \textit{U.S. v. Caronia}, 703 F.3d 149, 169 (2d Cir. 2012).
Thank you again for the opportunity to comment. We would be please to provide further input or clarification of our comments, as needed.

Sincerely,

/s/
Jeffrey S. Peters
Deputy General Counsel, Health
Biotechnology Industry Organization