May 2, 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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices (Revised Draft Guidance).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 previous Guidance on this topic (2009 Guidance),¹ BIO continues to support FDA’s clarification of its views on the dissemination of medical journal articles and medical or scientific reference publications that contain truthful and non-misleading information, including new information about the uses of approved drugs, biologics and medical devices. In addition, BIO supports FDA’s inclusion in this Revised Draft Guidance of recommendations regarding manufacturer provision of medical journals and texts, as well as Clinical Practice Guidelines (CPGs), that similarly contain truthful and non-misleading information, including new information, about the uses of approved drugs, biologics, and medical devices.

BIO agrees with FDA that the provision of truthful and non-misleading scientific and medical information to health care professionals has public health value. Information about new or potential new uses can be critical for physicians and their patients. As FDA explains in the Revised Draft Guidance, many medicines are prescribed for unapproved uses, some of which may be a part of an emerging standard of care, or may in fact already be the standard of care. Health care professionals and other relevant individuals involved in the provision of health care and health insurance should be able to receive truthful and non-misleading published information

regarding potential medical options for patients, regardless of the source of distribution of such information. On the whole, the Revised Draft Guidance provides helpful guidance for manufacturers about how FDA would view or interpret manufacturer sharing of truthful and non-misleading information that appears in medical reference texts and CPGs concerning unapproved new uses of approved products. As explained in more detail below, however, BIO is concerned that the Revised Draft Guidance may have the effect of restricting the lawful distribution of truthful and non-misleading scientific or medical information. Accordingly, we urge FDA to ensure that the Agency's proposed constraints in the Revised Draft Guidance are narrowly tailored to meet the Agency's public health goals, while not unnecessarily restricting truthful and non-misleading communication.

a. Background Section

BIO acknowledges FDA’s lengthy Background Section in the Revised Draft Guidance, and further appreciates FDA’s confirmation that, if manufacturers distribute scientific or medical publications, including CPGs, as recommended in the Revised Draft Guidance, FDA does not intend to use the distribution as evidence of the manufacturer’s intent to promote the product for an unapproved new use. Certainly this provides helpful information for manufacturers and may help guide their approach to the dissemination of scientific information, which has important public health benefits. As FDA acknowledges in the Revised Draft Guidance, “the public health may benefit when health care professionals receive truthful and non-misleading scientific or medical publications on unapproved new uses,” and we are pleased that FDA indicates “this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses.”

BIO notes, however, that in the 2009 Guidance, FDA more clearly emphasized the public health benefits of the dissemination of truthful and non-misleading articles or reference publications on unapproved uses of approved medicines, including a statement that “the public health may be advanced by healthcare professionals’ receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.” BIO encourages the Agency to return to, or more clearly endorse in this revision, its prior guidance statements on the importance of such communication.

We further note that 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 is truthful and not misleading, even if distributed in a manner that may be inconsistent with this Revised Draft Guidance, the speech itself should not be the basis of an enforcement action. As FDA is aware, the Federal Court of Appeals for the Second Circuit, in United States v. Caronia, held that “the government cannot prosecute pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.”

---

3 2009 Guidance, at 3.
4 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”).
In the Revised Draft Guidance, FDA does not directly acknowledge Caronia, although we note that nowhere in the Revised Draft Guidance does FDA indicate that manufacturer-distributed content outside of the parameters set forth in these guidelines may, by itself, constitute the basis of an enforcement action.

In this regard, BIO appreciates FDA’s confirmation that the Revised Draft Guidance does not impose a legally enforceable responsibility on manufacturers, and also that FDA’s use of “should not” in the Revised 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 Revised Draft Guidance is not in and of itself prohibited, and further that there may be other means of disseminating truthful and non-misleading information concerning unapproved new uses of products that are neither prohibited nor in FDA’s view evidence of an intended use. However, to the extent that FDA utilizes this Revised Draft Guidance, or a later issued final guidance, to restrict truthful and non-misleading communication, FDA should ensure that the recommendations are narrowly tailored to meet compelling public health goals.

Further, FDA states in the Revised Draft Guidance that “[d]istribution of scientific and medical publications regarding a medical product is not a substitute for the information contained in FDA-approved product labeling.” Certainly BIO supports the importance of the information contained in FDA-approved product labeling, and does not argue that the distribution of truthful and non-misleading medical or scientific 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.

b. ‘Edited or Significantly Influenced’

In each of the Revised Draft Guidance sections addressing the three types of publications that are the subject of this Revised Draft Guidance, FDA recommends the distributed publication should not “be edited or significantly influenced” by a manufacturer or individuals having a financial relationship with a manufacturer. This would seem to result in a broad restriction on the manufacturer distribution of publications, the authors or editors of which may be (or may have been) investigators on company sponsored trials or otherwise recipients of company research funds, among other potential financial relationships. BIO is concerned that this restrictive view could interfere with the distribution of important research, including publications in which the information on unapproved uses may be only a small part, potentially including the peer-reviewed articles of the Phase III pivotal trials upon which FDA bases approval decisions.
Further, if FDA is concerned about the consumer of such information being unaware of the potential for bias in the publication, the appropriate solution is the clear disclosure of author or editor financial interests, of which there are already ample avenues for health care professionals to consult. Such avenues include the FDA’s own disclosure recommendations contained in this Draft Guidance (discussed below), and journal and other publishers’ requirements for disclosure of financial interests, as well as forthcoming Physician Payment Sunshine Act disclosures.

c. “False or Misleading”

In the Revised Draft Guidance, FDA recommends that none of the publications covered by the guidance should be “false or misleading,” and with respect to journal articles, provides examples of articles (or their characterization) that the Agency would consider false or misleading. As stated elsewhere, BIO believes in the importance of distribution of truthful and non-misleading scientific and medical information. BIO, however, requests FDA should clarify its definition in this guidance of “false or misleading” information in scientific publications, reference texts, or CPGs. Specifically, Agency clarification should include an acknowledgement of the relevance of the specific characteristics of the intended recipients (sophisticated health care professionals or individuals at health care entities) of the various publications or communications and relevance of the overall context. In other words, FDA’s views on “false or misleading” in this context must take into account the intended recipient’s knowledge, training, and experience, and the importance of disclosures and qualifications accompanying such communications, the actual truth or falsity of the information, and the likelihood that the sophisticated recipient of such scientific information might in fact find the information to be misleading. We urge the Agency to exercise caution in restricting important, truthful and credible contributions to the ongoing medical community dialogue on the evolution of patient care.

d. Disclosure of Financial Interest

In each of the Revised Draft Guidance’s sections addressing the three types of publications that are the subject of this Guidance, FDA recommends the publication 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.

This financial disclosure recommendation referred to in multiple sections of the Revised Draft Guidance presents challenges for manufacturers in terms of compliance 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 recommends that the Agency consider instead a financial-disclosure approach in which a company declares 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.
II. Specific Comments on Recommended Practices

a. Scientific or Medical Journals

i. Acceptable Reprints/“Adequate and Well Controlled”

BIO recommends that the Agency return to providing examples of acceptable reprints for pharmaceuticals and medical devices, such as it did in the 2009 Guidance with examples including historically controlled studies, pharmacokinetics and pharmacodynamics studies, and meta-analyses if they are testing a specific clinical hypothesis. BIO’s members appreciated the inclusion of the examples in the 2009 Guidance because the examples provided helpful clarification about the Agency’s thinking on the types of studies that could be considered “adequate and well-controlled clinical investigations.”

Notably, the Revised Draft Guidance explicitly includes meta-analyses among the examples of the types of significant investigations appropriate for dissemination regarding medical devices, but no longer mentions their appropriateness for biopharmaceuticals. As currently written, the Revised Reprints Guidance indicates that journal articles should contain “information that describes and addresses adequate and well-controlled clinical investigations,” and provides no explanation for why other “significant investigations... such as meta-analyses... and journal articles discussing significant non-clinical research” may be consistent with the Revised Draft Guidance in the context of devices but not biopharmaceuticals. This appears to be a change from the Agency’s views expressed in the 2009 Guidance in which the Agency’s perspective on acceptable distribution of reprints and texts included pharmacokinetic (“PK”) and pharmacodynamic (“PD”) studies, as well as certain meta-analyses. This implied change could signify the potential view by FDA that drug manufacturers should no longer distribute reprints discussing meta-analyses, PK or PD studies and other significant non-clinical research.

BIO is concerned about this narrow requirement that the content of distributed journal articles contain only what FDA considers “adequate and well-controlled clinical investigations.” Although the “adequate and well-controlled studies” standard serves as the basis for FDA approval of a new drug or a new use of an approved drug, it should not be a measure of whether distribution of information about uses of medicines is truthful or non-misleading. FDA’s interpretation would appear to preclude biopharmaceutical manufacturers from distributing a wide variety of scientifically important, truthful and non-misleading information, including information that may represent the standard of care or lead to advances in patient care.

ii. Definition of Health Care Professionals and Health Care Entities

The Revised Draft Guidance expands the definition of health care professionals (HCPs) and health care entities (HCEs) from the previous guidance to include “pharmacy benefits managers,  

---

10 See 2009 Guidance, at 3 (“The information contained in the scientific or medical journal article or reference publication should address adequate and well controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device. These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis.”) (emphasis added).
health insurance issuers, and Federal or State governmental agencies involved in the provision of health care or health insurance,” which means FDA now includes payers in its guidance to manufacturers on distribution of information. The expanded definition of HCEs to include payer audiences creates a consequential need for further consideration of appropriate types of reprints that may be disseminated to this broader audience. Payer audiences often rely on research that focuses on pharmacoeconomics, cost-effectiveness, comparative effectiveness, quality of life, patient-reported end points, and similar outcomes that use real-world data from non-randomized controlled trials (non-RCTs). These non-RCT evidence types provide payers with relevant evidence and have been deemed important to the payer audience as demonstrated by the Academy of Managed Care Pharmacy in its guidelines. We encourage the Agency to extend the acceptable types of peer-reviewed articles for payer audiences to include comparative studies and non-RCTs, such as observational, registry, and real-world studies (including appropriate health economics and outcomes research studies), well-conducted systematic reviews, analyses of claims databases, and meta-analyses of existing evidence.

b. Scientific or Medical Reference Texts

BIO supports FDA’s efforts to specifically address scientific or medical reference texts in the Revised Draft Guidance, and provide guidance on the FDA’s views on manufacturer distribution of these important publications as having certain distinct characteristics from journal reprints. BIO appreciates and supports FDA’s recommendation that unabridged individual chapters or sections may be distributed by manufacturers, rather than the manufacturer needing to distribute the entirety of a lengthy publication with irrelevant sections. BIO believes it is appropriate that additional sections or chapters (unabridged) as may be required for appropriate context are included in the manufacturer’s distribution.

That said, BIO suggests the Agency remove the criterion that a manufacturer ensure that a scientific or medical reference text “be based on a systematic review of the existing evidence.” Authors and publishers often do not fully describe their methodology for creating content, making it difficult for a manufacturer to determine if a “systematic review” was conducted. Additionally, the information in a chapter bibliography does not always allow a company to determine if a systematic review was performed, as a mixture of review papers, clinical studies, and other disparate types of literature are often cited and authors rarely disclose any predefined criteria for data inclusion.

c. Clinical Practice Guidelines

BIO appreciates FDA’s inclusion of Clinical Practice Guidelines (CPGs) in the Revised Draft Guidance’s recommendations as a welcome expansion of the types of publications containing information about unapproved new uses that FDA views as suitable for distribution. As FDA notes, CPGs provide helpful information to health care professionals that may assist them in making patient care decisions, and may include information on therapies that are not indicated for a patient’s specific condition. Often CPGs represent the endorsement of relevant professional medical societies, and therefore may have particular relevance for healthcare professionals and individuals at health care entities as they evaluate and consider patient care options.
The Revised Draft Guidance recommends that CPGs or CPG sections disseminated to HCPs and HCEs that discuss unapproved new uses adhere to the Institute of Medicine’s (IOM’s) standards for CPG “trustworthiness,” and the Guidance provides an enumerated list of standards companies must consider at a minimum. However, it can be difficult to determine whether existing, well-accepted, and scientifically rigorous CPGs fully meet these standards. In fact, it may often be the case that well-accepted CPGs do not fully meet all of the IOM criteria.

BIO requests that the Agency provide clear and attainable standards for companies to consider when evaluating which CPGs to disseminate. We also encourage the Agency to provide examples of acceptable CPGs that meet these standards, such as those published by national clinical practice guidelines organizations (e.g., American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), American College of Chest Physicians (ACCP), American College of Rheumatology (ACR), American College of Cardiology (ACC), American Heart Association (AHA), National Heart Lung and Blood Institute (NHLBI), European League Against Rheumatism (EULAR), American Academy of Pediatrics (AAP)); as well as guidelines published by public health agencies, such as the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC).

### III. Response to Open Comment Request

In the Federal Register notice announcing the availability of, and soliciting comment on, the Revised Draft Guidance, FDA further explains that it is seeking public input on a variety of topics of interest to industry and others. Specifically, FDA solicits public input with respect to several related issues, including (1) further explaining “scientific exchange”; (2) manufacturer responses to unsolicited requests for information relating to unapproved or uncleared uses; and (3) considering draft guidance on industry interactions with formulary committees, payors, and similar entities.

As FDA stated in this notice, the Agency is already considering comments submitted in response to 2011 Agency proposals on the first two topics. With respect to FDA’s request here for input regarding industry interactions with formulary committees, payors and similar entities, FDA notes that it is considering the issuance of draft guidance that would include clarifying the Agency’s “interpretation of several terms included in section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA 114) and the Agency’s recommendations for evidentiary support for health care economic information included in promotional materials disseminated to formulary committees and similar entities.” BIO believes written guidance from FDA on this topic would be beneficial to the industry, and encourages FDA to expeditiously publish draft guidance for public input and response.

As noted above, payer audiences often rely on—and increasingly demand from manufacturers—research that focuses on pharmacoeconomics, cost-effectiveness, comparative effectiveness, quality of life, patient-reported end points, and similar outcomes that use real-world data from

---

non-RCTs. Yet the Agency’s lack of consistent guidance regarding FDAMA 114 serves as a barrier to the development and dissemination of this potentially valuable information. Indeed, given the uncertainty of the regulatory landscape in this area, manufacturers are effectively discouraged from developing these data, particularly given the potentially large upfront costs required to do so.

Specifically, FDA should clarify in written, published guidance the Agency’s views on recommended dissemination practices for healthcare economic information (HEI), including content and distribution practices that would not be subject to enforcement or regulatory action. In particular, BIO notes that there are key statutory terms or phrases in FDAMA 114 about which the industry seeks clarification, including “competent and reliable scientific evidence,” “directly related to an approved indication,” and “similar entity.”

First, consistent with our comments in Section I.a., above, BIO believes the distribution of truthful and non-misleading HEI should receive broad protection. Second, BIO requests FDA clarify what it will consider "competent and reliable scientific evidence," and specifically for FDA to note that this standard is not the same as, and is not as rigorous as, the clinical evidentiary standard necessary to demonstrate safety and efficacy. This different standard should apply to comparative statements regarding economic consequences or economic impacts of a therapy. FDA’s interpretation of the statute should consider that distribution of HEI discussing the comparative economic impact of a therapy should be based on sound (i.e., competent and reliable) economic analysis, and not on the same standard as required for assumptions about, or distribution of information concerning, clinical outcomes.

Further, FDA should explain its views on recommended practices regarding “directly related to an approved indication,” including guidance on the types of statements and HEI that it would view as “directly related.” In particular, FDA should permit distribution of HEI containing reasonable assumptions of health care consequences derived from, but not necessarily mentioned in, the approved indication.

Last, FDA should provide, in guidance, recommendations and examples of the entities to which FDA believes manufacturers may distribute or share such information, consistent with the statute. As noted, the law states that HEI meeting the statutory standard will not be considered false or misleading if provided to a formulary committee or other similar entity. At minimum the Agency should include in its understanding of “similar entity” those “health care entities” delineated in the Revised Draft Guidance, including pharmacy benefits managers, health insurance issuers, and Federal or State governmental agencies. More broadly, dissemination of competent and reliable HEI should be permitted to a variety of entities involved in decision making regarding biopharmaceutical reimbursement and coverage, whether public or private.

---

131 USC §352(a).
IV. Conclusion

BIO and its members are appreciative of FDA’s efforts and for FDA’s guidance for manufacturers concerning how FDA would view or interpret manufacturer sharing of scientific or medical information with health care professionals and health care entities concerning unapproved uses of approved products. As explained in detail in these comments, we urge FDA to ensure that any proposed constraints in the Revised 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.

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 Peters
Deputy General Counsel, Health
Biotechnology Industry Organization (BIO)