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

Re: Docket No. 2008-D-0053, Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Federal Register: February 20, 2008, Volume 73, Number 34, Page 9342)

Dear Sir/Madam,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comment on the Food and Drug Administration's (FDA's) *Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* ("Draft Guidance"). BIO represents more than 1,150 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.

General Comments

BIO supports 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. BIO agrees with FDA that the provision of truthful and non-misleading scientific and medical information to health care professionals has public

health value, and we note that the provision of such information also has constitutional protection under the First Amendment.

Information about new or potential new uses can be critical for physicians and their patients. As FDA recognizes in the Draft Guidance, many medical products are prescribed for unapproved uses, some of which may be an emerging standard of care, or perhaps already be the standard of care. This is often the case for products used off-label to treat cancer or other debilitating or life-threatening diseases where there are no approved treatment options, or where the off-label use is an advance in treatment. Information about new or potential new uses is also essential in many pediatric indications where labeled use frequently follows approval in adult populations and access to current information is essential to safe and effective medical use in children. Physicians should have unfettered access to all truthful and non-misleading information regarding potential medical options for their patients. FDA's Draft Guidance could further advance public health goals by facilitating the dissemination by industry of significant medical research to healthcare professionals.

We appreciate the Agency's focus on this issue, particularly in light of the sunset (September 30, 2006) of section 401 of the Food and Drug Administration Modernization Act (FDAMA) (previously, section 551 *et seq* of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 360aaa), as well as longstanding debate as to the scope of permissible dissemination by industry of truthful medical information about unapproved conditions of use. The FDAMA provision and its implementing regulation (21 CFR Part 99) described the conditions under which a drug or medical device manufacturer could disseminate certain medical and scientific information – specifically, reprints of scientific/medical journal articles and reference publications – discussing unapproved uses of approved drugs and cleared or approved medical devices.

The dissemination by manufacturers of scientific/medical journal articles and reference publications is supported by a considerable history of legal and regulatory determinations affirming such dissemination. FDA's regulation addressing investigational new drugs states that while an investigational product (or use) may not be promoted, this prohibition "is not intended to restrict the full exchange of scientific information concerning the drug" ¹ Prior to the 1997 enactment of FDAMA, FDA had issued several guidance documents setting forth the circumstances under which such dissemination was permissible, *e.g.* was not considered off-label promotion of a product, or violative of the FFDCA. ² These guidances, as well as the FDAMA section 401 provisions addressing "Dissemination of Information on New Uses" were reviewed in the Washington Legal Foundation (WLF) line of cases, which recognized the application of First Amendment Freedom of Speech principles to certain communications from manufacturers to health

¹ 21 C.F.R. section 312.7.

² See 1996 FDA Guidances on Enduring Materials (journal articles and textbooks).

care providers.³ FDA's February 2008 Draft Guidance is consistent with the recognized First Amendment protection of the right of manufacturers to provide truthful, non-misleading journal articles and reference texts to healthcare professionals and healthcare entities. These rights and FDA's policy of permitting non-promotional exchange of scientific information are also reflected in FDA's policies on continuing medical education⁴ and on manufacturer responses to unsolicited requests for information from health care providers. This additional guidance will help to further define and clarify off-label information dissemination policies for manufacturers.

BIO's specific comments on the Draft Guidance are as follows.

Specific Comments

1. Scope of the Draft Guidance

While we support FDA's initiative to describe its views regarding Good Reprint Practices, the Draft Guidance does not acknowledge the constitutional protection afforded to truthful and non-misleading speech, which may in some instances protect the distribution of medical information that does not meet the exact criteria in the Draft Guidance. We request that FDA acknowledge in the final Guidance that: (1) the Guidance is not intended to be exhaustive; (2) there may be other means of disseminating truthful and non-misleading information about unapproved conditions of use that are constitutionally protected, and (3) consistent with prior FDA practice, the Guidance is a safe harbor that does not prohibit dissemination of otherwise constitutionally protected free speech.

2. Compliance with the final guidance should provide a clearly defined Safe Harbor

BIO supports FDA's recognition that a clearly defined safe harbor should be an element of the final Guidance, by FDA's indication that specified compliant actions would not be used by government authorities "as evidence of intent by the manufacturer that the product be used for an unapproved use". FDA's intent to provide a clearly defined safe harbor appears to be further supported by the references in the Draft Guidance to FDAMA section 401 and the need for the guidance "in light of the statute's sunset". BIO believes that articulation of a clear safe harbor would advance the public health goals of the guidance.

However, we are concerned that the intent to provide a clearly defined safe harbor is directly undermined by the addition of the phrase "and there is no unlawful promotion of the product" (in Section V, the Summary). Under one reading of the draft guidance, a

³ WLF v. Friedman, 13 F. Supp. 2d 51 (D.D.C.1998); WLF v. Henney, 56 F.Supp. 2d 81 (D.D.C. 1989); WLF v. Henney, 202 F.3d 381 (D.C. Cir. 2000).

⁴ FDA Final Guidance on Industry-Supported Scientific and Educational Activities (December 3, 1997)

manufacturer that complies with every element of the draft guidance and yet fails to comply with any other element of lawful promotion of the product, even if completely unrelated to the reprint distributed, could find that reprint used as evidence of intent in a misbranding action. For example, a reprint otherwise disseminated in full compliance with the draft guidance could be used as evidence of intent in a misbranding action if there was also an unrelated technical violation of a fair balance requirement in a promotional piece disseminated by the same manufacturer.

This drafting construct undermines the public health objectives of the draft guidance, because manufacturers may rationally decide that distribution of reprints under this extraordinarily limited safe harbor is unduly risky. Accordingly, BIO recommends striking the phrase “and there is no unlawful promotion of the product” and aligning the safe harbor more closely to that articulated by FDA with respect to FDAMA 401⁵ by indicating that “FDA does not intend to use the distribution of such medical and scientific information as evidence that an approved product is intended for a new or unapproved use”.

3. Section IV-A. Types of Reprints/Articles/Reference Publications

- **“A scientific or medical reference publication that is distributed should not be ... edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer”.** BIO is concerned that this requirement could result in important studies and data on unapproved uses not being available to physicians. The Draft Guidance would preclude dissemination of many pivotal study results if they contain off-label content — a result that is not consistent with the public policy reasons recognized by the Agency that support issuance of the Draft Guidance. For example, a physician employed by a drug or device manufacturer may be instrumental in the design, development and conduct of critical or pivotal research trials and would, accordingly, be an author on a resulting publication. BIO believes that excluding a publication from the scope of the Guidance based upon involvement by a manufacturer in editing or funding of a publication is unnecessarily restrictive, and that disclosure — rather than prohibition — is the appropriate means of addressing this concern.

We suggest that FDA remove this statement and instead state in the Guidance that a scientific or medical reference publication should “fully disclose any editing or significant influence by a drug or device manufacturer or any individual having a financial relationship with the manufacturer”. Requiring the disclosure of a manufacturer’s role in the drafting or funding of a publication would be consistent

⁵ 65 Fed. Reg. 14286 (March 16, 2000) (“In sum, then, FDAMA and its implementing regulations constitute a “safe harbor” for a manufacturer that complies with them before and while disseminating journal articles and reference texts about “new uses” of approved products. If a manufacturer does not comply, FDA may bring an enforcement action under the FFDCA, and seek to use journal articles and reference texts disseminated by the manufacturer as evidence that an approved product is intended for a “new use.””)

with other FDA policies related to the assessment of the reliability of data. For example, FDA requires a study sponsor seeking approval of new drugs and medical devices to disclose financial relationships with investigators, and then evaluates whether the data may be unreliable due to bias or other reasons.⁶ It would be inconsistent for FDA to view data from such a study as reliable and useful in evaluating the safety or efficacy of the product for a new use⁷, while at the same time preventing the manufacturer from disseminating the results to physicians when included in medical journal articles or scientific or medical reference publications. The Draft Guidance should therefore require the disclosure of financial relationships and other information which might raise questions regarding the reliability of the study, rather than excluding a publication from the scope of the Draft Guidance merely because a manufacturer may be directly or indirectly involved with editing or funding of the publication. Physicians will then be equipped with the information to assess for themselves the potential impact of a manufacturer's involvement in a publication.

- **"The information contained. . . should address adequate and well-controlled clinical investigations . . ."**. Without additional FDA clarification, the Draft Guidance's reference to "adequate and well-controlled clinical investigations" could be too narrowly construed and may not recognize important and scientifically significant results obtained through other types of investigations. For example, studies involving oncology treatments for conditions such as brain tumors typically involve small patient populations with studies that may include fewer than 50 patients. Although the use of such studies is supported by the National Comprehensive Cancer Network (NCCN) Guidelines,⁸ under the Draft Guidance these studies may not qualify as "adequate". Further, these types of studies may not be considered "well-controlled" in that, due to the severity of the disease and small study population, it may be unethical to include a control group.

Accordingly, BIO recommends that FDA remove the qualification of "adequate and well-controlled" and instead provide additional clarification regarding the types of studies that constitute "clinical investigations". The guidance should clarify that historically controlled studies, retrospective analyses, open label studies, and meta-analyses can all constitute a "clinical investigation" if they test a specific clinical hypothesis (consistent with the preamble to the implementing regulations for FDAMA Section 401).⁹ For example:

⁶ 21 C.F.R. Part 54. This regulation does not prohibit investigators who have a significant financial interest from participating in clinical research; it requires only that these relationships be disclosed.

⁷ 21 C.F.R. Part 54.

⁸ http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf

⁹ In the preamble to the final implementing regulations, FDA stated that "it was the agency's intent that the definition [of "clinical investigation"] could include historically controlled studies, retrospective analyses, open label studies, and metaanalyses if they are testing a specific clinical hypothesis." 63 Fed. Reg. 64556, 64559 (Nov. 20, 1998).

”The information contained in the above scientific or medical journal article or reference publications 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, provided, however, that Phase II studies, historically controlled analyses, open label studies, and meta-analyses can constitute “clinical investigations” if they are testing a specific clinical hypothesis”.

- **“The information must not be false or misleading, such as a journal article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (e.g., where a significant number of other studies contradict the article or reference text’s conclusions) . . . ”.** We agree that information that is false or misleading should not be disseminated. However, it is important to recognize that a new study may contradict the previous weight of evidence and not be false and misleading — in fact it may represent the latest and best science. As science and medicine advance, newly published journal articles may well be inconsistent with earlier publications, but not false and misleading. Given that false and misleading is a subjective standard that cannot be precisely defined, we recommend that FDA not attempt to clarify “false and misleading”, but instead rely upon the large body of case law and existing regulations to define the term as needed.
4. IV-B. Manner in which to Disseminate Scientific and Medical Information
- **“Scientific or medical information that is distributed should . . . in cases where the conclusions of article or text to be disseminated have been specifically called into question by another article(s) or text(s), be disseminated with a representative publication that reaches contrary or different conclusions regarding the unapproved use”.** As discussed above in regard to FDA’s comments regarding “false and misleading” information, we agree that false and misleading information should not be disseminated and we request that FDA recognize that as science advances, credible journal articles may reach different conclusions. With regard to this provision of the Draft Guidance, we request clarification of the criteria FDA will employ in determining whether representative opposing publications have been provided. For example, we recommend that FDA clarify that if a publication with contrary or different conclusions is based on results from a flawed trial, that publication should not be provided. We also request that FDA clarify whether one representative, divergent publication would meet the intention of the Agency.
 - **Scientific or medical information that is distributed should . . . be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the**

subject of discussion between the sales representative and the physician during the sales visit.¹⁰ Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers programs.” BIO suggests that FDA’s direction regarding distribution of information in promotional exhibit halls be revised for purposes of consistency with the direction in the Draft Guidance regarding the conduct of a sales representative delivering a reprint to a physician in his or her office. We suggest the following language:

“Scientific or medical information that is distributed should:

...

- be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.⁵ Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed ~~in promotional exhibit halls or during promotional speakers’ programs,~~ and reprints distributed in promotional exhibit halls should not be physically attached to any promotional material that is used or delivered during the exhibit hall visit and should not be the subject of discussion during the exhibit hall visit.

Thank you again for the opportunity to comment. We would be pleased to provide further input or clarification of our comments, as needed.

Regards,

/s/

Sara Radcliffe
Vice President, Science and Regulatory Affairs
Biotechnology Industry Organization

¹⁰ This is Footnote 5 in the Draft Guidance, and it reads “To the extent that the recipients of such information have questions, the Agency recommends that the sales representative refer such questions to a medical/scientific officer or department, and that the officer or department to which the referral is made be separate from the sales and/or marketing department.”