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

Re: Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices, Docket No. FDA–2014–D–0758, 79 Fed. Reg. 33569 (June 11, 2014)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to submit these comments in response to FDA's Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products (Draft Guidance). The Draft Guidance recommends practices for biopharmaceutical companies to follow in disseminating "new risk information" to healthcare professionals in the form of scientific and medical publications. The Draft Guidance defines "new risk information" as "information that becomes available after a drug is marketed that rebuts or mitigates information about a risk already identified in the approved labeling or otherwise refines risk information in the approved labeling in a way that does not indicate greater seriousness of the risk."[1] PhRMA is a voluntary, non-profit association that represents the country's leading pharmaceutical research and biotechnology companies. PhRMA members are dedicated to developing medicines that allow patients to live longer, healthier, and more productive lives. In 2013 alone, PhRMA's member companies invested an estimated $51.1 billion in the research and development of new medicines.

PhRMA and its member companies believe that FDA's regulation of medical communications – especially important safety communication – should adhere to principles intended to ensure that healthcare professionals may benefit from scientifically accurate, data-driven information from all sources including the companies that research and develop new medicines. Such high level principles, which we encourage FDA to adopt, include the following:

- All communication about medicines (including that of companies, payers, and the government) should be truthful and non-misleading in order to benefit patient care.

[1] Draft Guidance at 3.

Materials should be factually correct and should contain material benefit and risk information necessary for trained professionals to make informed treatment decisions.

- In order to enhance patient care, healthcare professionals deserve access to current, accurate, and comprehensive information about the benefits and risks of all medicines available for treatment. Any limitations on healthcare communications should be related to patient risk based on factors including the approval status of the medicine, general medical acceptance of the treatment (*e.g.*, appearance in compendia and/or clinical practice guidelines), and the level of scientific sophistication of the audience.

- Adequate disclosures regarding benefits and risks and the limitations of scientific understanding are preferable to prohibiting certain healthcare communications. Such disclosures can help ensure that medical communications are data-driven and transparent.

- Biopharmaceutical companies respect FDA's authoritative role in determining that medicines are safe and effective. Accordingly, companies recognize the need for incentives for sponsors to continue to seek supplemental indications for approved medicines and will work with FDA to create and maintain such incentives.

- Companies must be able to provide adequate directions for use of both approved and medically accepted alternative uses of approved medicines for patients.

PhRMA understands FDA's important role in evaluating the safety and efficacy of new medicines. At the same time, consistent with the above principles, we also must recognize the critical need for healthcare professionals to receive the most current, accurate, and comprehensive scientific information about both the benefits and risks of approved uses of medicines, especially when patients are being treated with such medicines. This information enables physicians to exercise sound independent medical judgment in determining the appropriate treatment option for their patients, which greatly benefits patient care. PhRMA also believes that its members can serve an important public health role and advance the interests of patients by providing truthful, non-misleading information to healthcare professionals about both the benefits and risks of their medicines. Any appropriate regulation by FDA in this area thus requires careful balancing of these interests, and, of course, cannot restrict truthful speech based on its content or the identity or viewpoint of the messenger.

PhRMA believes that the Draft Guidance in many respects reflects an appropriate balancing of the interests at stake. In particular, we commend FDA for its recognition that "the safety profile of a drug evolves throughout its lifecycle as the extent of exposure to the product increases," and that "it can be helpful for health care practitioners to receive significant new risk information about an approved product in a timely manner."[2] We further agree, most importantly, that "[t]he types of data that can contribute to further developing the safety profile of a drug include data from controlled trials intended to evaluate a specific safety endpoint,

[2] Draft Guidance at 2.

controlled and uncontrolled trials evaluating efficacy (e.g., new uses), pooled analyses of new and existing risk information from controlled trials, epidemiologic studies evaluating a particular safety endpoint or safety generally, registries, and analyses of post-marketing reports of adverse events obtained through active (e.g., Sentinel) or passive surveillance processes."[3]

PhRMA therefore supports FDA's focus on providing concrete guidance regarding the types of disclosures and other steps manufacturers should take in order to disseminate new risk information without risking regulatory or even criminal enforcement. We believe FDA should address this and other important topics by promulgating regulations through notice and comment rulemaking, rather than through the issuance of informal guidance documents that purport not to bind the agency.[4] But apart from that concern, we believe that FDA in the Draft Guidance identifies key safeguards that manufacturers should consider in disseminating new risk information to healthcare professionals. If new risk information is "published in an independent, peer-reviewed journal," accompanied by appropriate disclosures, and meets the other standards set out in the Draft Guidance,[5] there would be no basis for FDA to object to manufacturers disseminating such information.

We submit these comments primarily to urge FDA to apply the standards and levels of substantiation proposed in the Draft Guidance not only to manufacturers' dissemination of new information about *risk*, but also to the dissemination of new information about *efficacy*. In contrast to FDA's approach to new risk information in the Draft Guidance, the agency's regulations and guidance impermissibly restrict truthful and non-misleading communication to healthcare professionals about new efficacy information—information that would be beneficial to both physicians and patients—based on levels of evidence that FDA deems sufficient to support approval of a new drug. For the reasons described below, FDA's disparate treatment of speech about new information regarding risk and efficacy is neither compelled by the Federal Food, Drug, and Cosmetic Act (FDCA) nor consistent with the First Amendment.

I. Consistent with the First Amendment, FDA's Guidance Should Encourage and Facilitate, Rather Than Overburden, Manufacturers' Efforts to Provide Healthcare Professionals With Truthful, Non-Misleading Information

The Constitution's protection of an open and robust exchange of ideas—principles that are central to the meaning and purpose of the First Amendment—limits FDA's ability to regulate scientific communication. PhRMA respectfully submits that FDA should give additional consideration to these First Amendment limitations in issuing final guidance regarding biopharmaceutical companies' dissemination of new risk *and* efficacy information to healthcare

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[3] *Id.* at 5.

[4] *See id.* at 1 (asserting that even final guidance document "does not create or confer any rights for or on any person and does not operate to bind FDA or the public"); *id.* ("FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities.").

[5] *See id.* at 6-7.

professionals in the form of scientific or medial publications.[6] We agree with FDA that "[t]he types of data that can contribute to further developing the safety profile of a drug include data from controlled trials intended to evaluate a specific safety endpoint, controlled and uncontrolled trials evaluating efficacy (e.g., new uses), pooled analyses of new and existing risk information from controlled trials, epidemiologic studies evaluating a particular safety endpoint or safety generally, registries, and analyses of postmarketing reports of adverse events obtained through active (e.g., Sentinel) or passive surveillance processes."[7] To date, however, FDA has not taken a similarly flexible approach to dissemination of information about efficacy of approved products.[8] This divergent approach between risk and efficacy creates serious First Amendment concerns.

Overly restrictive FDA regulation of biopharmaceutical companies' sharing of scientific or medical publications based on the content of the communication or the viewpoint of the speaker is subject to heightened scrutiny under judicial review. Regulation of communications regarding risk based on different standards than regulation of communications regarding efficacy would not survive that test, thus unnecessarily jeopardizing FDA's ability to regulate labeling and advertising. In *Sorrell v. IMS Health*,[9] the Supreme Court applied heightened scrutiny to

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[6] "The First Amendment protects works which, taken as a whole, have serious literary, artistic, political, or scientific value, regardless of whether the government or a majority of the people approve of the ideas these works represent." *Miller v. California*, 413 U.S. 15, 34 (1973). The First Amendment accordingly "protects scientific expression and debate just as it protects political and artistic expression." *Bd. of Trs. of Leland Stanford Jr. Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991). In other words, scientific speech "reside[s] at the core of the First Amendment." *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 62 (D.D.C. 1998), *order vacated as moot sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). The Supreme Court has confirmed as much since FDA's publication of the 2009 Guidance. In *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), the Court reaffirmed that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Id.* at 2659. The Court further observed that the First Amendment serves a particularly critical function "in the fields of medicine and public health, where information can save lives." *Id.* at 2664.

[7] Draft Guidance at 5.

[8] *See, e.g.*, FDA Letter to Genentech, Inc. at 3 (Oct. 3, 2012) ("The data and subsequent claims presented in this sales aid were derived from a retrospective, exploratory subgroup analysis that does not provide substantial evidence to support the [company's] efficacy claims."); FDA Letter to Bristol-Myers Squibb at 2 (June 29, 2012) ("We note that stable disease, stable disease ≥6 months, and progressive disease were not pre-specified endpoints in the pivotal studies for Ixempra's monotherapy and combination therapy indications. Therefore, the pivotal studies do not provide substantial evidence to support these efficacy claims. We note pages five and 11 of the sales aid include the statement, '[s]table disease was a pre-specified analysis, not a pre-specified end point;' however, this statement does not mitigate the misleading implications made by the promotional claims in the sales aid."); FDA Letter to Teva Pharmaceuticals USA at 2 (Mar. 14, 2012) ("Promotional materials are misleading if they suggest that a drug is more effective or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience."); FDA Warning Letter to Forest Laboratories, Inc. at 4 (Aug. 28, 2008) ([I]t is misleading to imply that efficacy was demonstrated in [certain] subgroups when this has not been supported by substantial evidence or substantial clinical experience," since "none of the efficacy trials were specifically designed to evaluate patients [in those subgroups]."); FDA Letter to Allergan, Inc. at 2 (June 8, 2001) ("[Y]our sales aid is misleading because it suggests that Lumigan is superior to latanoprost and travoprost when such has not been demonstrated by substantial evidence.").

[9] 131 S. Ct. 2653 (2011).

strike down Vermont's content-based and speaker-based restrictions on speech by pharmaceutical companies. Following *Sorrell*, the Second Circuit in *United States v. Caronia*,[10] held that the First Amendment precludes a conviction for misbranding based on a pharmaceutical sales representative's truthful and non-misleading speech alone. Even analyzed under commercial speech doctrine, burdensome FDA restrictions on biopharmaceutical companies' truthful and non-misleading speech regarding new information about approved uses would fail, because the balance required when evaluating such restrictions favors a free flow of truthful and non-misleading scientific information.[11]

Thus, contrary to FDA's suggestion in the Draft Guidance,[12] any differences in the level of scientific evidence required to establish safety and efficacy for purposes of new drug approvals do not justify FDA's severe restriction on manufacturers' dissemination of truthful and non-misleading *post*-market information about only efficacy. While the FDCA establishes requirements for manufacturers to obtain new drug approval, including the general requirement to submit "substantial evidence" of a drug's efficacy for the indication at issue,[13] this statutory requirement does not purport to restrict manufacturers' speech about new information regarding an approved use outside of a drug's approved labeling. For these reasons, FDA should ensure that its guidance does not burden truthful speech regarding new information to a degree that would not withstand constitutional scrutiny.

II. FDA Should Apply a Consistent Standard With Respect to Data Sources That Can Serve as the Basis for Dissemination of New Information About Risk and Efficacy

PhRMA commends FDA for proposing to permit the dissemination of new risk information based on a range of data sources, including controlled trials, uncontrolled trials, pharmacoepidemiologic studies, and meta-analyses. In the Draft Guidance, FDA states that it does not intend to object to the distribution of new risk information that rebuts, mitigates, or refines risk information in a drug's approved labeling, provided certain standards are met,

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[10] 703 F.3d 149 (2d Cir. 2012).

[11] Courts have long expressed skepticism about regulation of mixed commercial and scientific speech. *See, e.g., Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d at 62 ("The resolution of this question is not an easy one, as the communications present one of those 'complex mixtures of commercial and non-commercial elements.'"). At a minimum, therefore, the government must establish that a restriction on commercial speech directly advances a substantial government interest that could not be served as well by a more limited restriction. *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980). This standard offers significant protection, particularly insofar as it disfavors paternalistic regulations targeted against particular speakers or messages. *See, e.g., Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002) (striking down federal statute prohibiting pharmacy compounding advertising under *Central Hudson* commercial speech test); *Virginia State Pharmacy Bd. v. Virginia Citizens Consumer Council*, 425 U.S. 748 (1976) (striking down state statute prohibiting pharmacy advertising of prescription drug prices).

[12] *See* Draft Guidance at 2 (indicating that the Draft Guidance addresses only new risk information in part because "there are differences in the purpose, nature, and reliability of the evidence used to determine the effectiveness of a drug (e.g., to support a new intended use) and the evidence that is the basis for the product's risk assessment").

[13] 21 U.S.C. § 355(d).

including that the study or analysis meets accepted design and other methodological standards, and that the study or analysis "should be at least as persuasive as the data sources that underlie the existing risk assessment."[14] The Draft Guidance further notes that, although randomized, controlled trials "would generally provide the most persuasive information," if the specified principles are satisfied, other types of data sources, including pharmacoepidemiologic studies or meta-analyses, could be relied on to rebut, mitigate, or refine risk information, although such data sources "will generally warrant more extensive discussions of their limitations."[15] PhRMA concurs with FDA's proposal, because it appropriately recognizes that there is scientific and public health value in communicating information based on those other data sources, as long as the speaker provides appropriate context about any limitations on the validity of the scientific data.

In contrast, FDA's March 3, 2014 Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses proposes an overly restrictive "adequate and well-controlled studies" standard for the dissemination of new efficacy information.[16] FDA has historically interpreted the adequate and well-controlled studies standard for "substantial evidence" as requiring statistically significant results demonstrated by meeting the standard of $p < 0.05$ with respect to pre-determined endpoints.[17] In proposing to adopt the "adequate and well-controlled studies" standard with respect to dissemination of new efficacy information, FDA seeks to exceed the scope of its statutory authority.

Under the FDCA, the "adequate and well-controlled studies" requirement serves as FDA's regulatory standard regarding studies that may serve as the basis for FDA *approval* of a new drug or a new use of an approved drug.[18] In fact, FDA's own implementing regulations specifically explain that reports of adequate and well-controlled studies provide the primary bases for determining whether there is substantial evidence "to support claims of effectiveness for new drugs."[19] The FDCA does not authorize FDA to extend the "adequate and well-controlled studies" limitation to the dissemination of new efficacy information when that information is not being used to support the approval of a new indication. Nor does the agency otherwise have authority to impose such a restriction. Indeed, restricting new efficacy information to dissemination of "adequate and well-controlled clinical investigations"

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[14] Draft Guidance at 6-7. The Draft Guidance explains that "a pharmacoepidemiologic study that is capable of reliably estimating the relative risk, or a rigorous meta-analysis of all relevant data from new and existing controlled trials," can be sufficiently persuasive data sources to rebut, mitigate, or refine existing risk information. *Id.*

[15] *Id.* at 7.

[16] *See also* Footnote 8 above, and letters cited therein.

[17] FDA has stated that "[a]lthough there is no statutory requirement for significance testing of any particular value, there are well-established conventions for assessing statistical significance to support the statutorily required conclusion that the well-controlled studies have demonstrated that a drug will have the effect it is represented to have." 57 Fed. Reg. at 58948.

[18] 21 U.S.C. § 355(d).

[19] 21 C.F.R. § 314.126

contravenes the First Amendment. It impedes a company's ability to provide clinically important information to healthcare professionals, thereby adversely impacting public health.

Thus, PhRMA recommends that the agency adopt a consistent standard in *both* guidances with respect to the data sources that can support new risk information and those that can support new efficacy information. Specifically, we recommend that the agency permit the dissemination of new efficacy information that is based on truthful, non-misleading information, with the requirement that the dissemination include appropriate important contextual information and disclosures regarding any limitations of the data sources. Such an approach would be consistent with the approach FDA proposes with respect to new risk information, and thus would not discriminate based on the content of the message in violation of *Sorrell*. By contrast, if FDA maintains the current proposal and allows different levels of substantiation for dissemination of new risk information as compared to dissemination of efficacy information, the divergent positions (based solely on the content of the message) would raise serious First Amendment concerns.

III. Conclusion

PhRMA and its member companies commend FDA for addressing the important issue of biopharmaceutical companies' dissemination of scientific or medical publications containing new risk information to healthcare professionals. A free flow of truthful, non-misleading scientific communication can be expected to benefit patients through the education of their healthcare professionals. We support the agency's efforts to provide a clear safe harbor regarding best practices for doing so without risking enforcement actions. PhRMA believes that FDA can further enhance patient care by applying the standards set forth in the Draft Guidance likewise to new information to healthcare professionals about the efficacy of a pharmaceutical product. This consistent approach to scientific and medical communications about new information would better conform to the First Amendment and would better promote healthy scientific debate and exchange of treatment information for the benefit of patients.

PhRMA appreciates the opportunity to submit these comments and would be happy to work with the agency to enhance the guidance in a manner that maximizes the flow of scientifically accurate, data-driven information to healthcare professionals for the purpose of benefiting patients.

Sincerely,

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