

April 19, 2017

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

**Re: Medical Product Communications That Are Consistent With the  
FDA-Required Labeling—Questions and Answers; Draft Guidance  
for Industry; Availability (Docket No. FDA-2016-D-2285)**

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (“PhRMA”) is pleased to provide comments on the Food and Drug Administration’s (“FDA’s” or “the Agency’s”) draft guidance entitled “Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers” (“Draft Guidance”).<sup>1</sup> PhRMA represents the country’s leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than half a trillion dollars in the search for new treatments and cures, including an estimated \$58.8 billion in 2015 alone.

PhRMA appreciates FDA’s issuance of the Draft Guidance and the Agency’s recognition of the medical product communications covered by the Draft Guidance as a critical channel for providing information about these products beyond the FDA-approved labeling, including to help inform the prescribing decisions of health care professionals. We also commend FDA for holding a public hearing entitled “Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products”<sup>2</sup> and issuing separate draft guidance on manufacturer communications with payors, formulary committees, and similar entities.<sup>3</sup> In addition to this comment letter, we are simultaneously submitting two additional comment letters. One responds to the hearing notice and FDA’s accompanying Memorandum titled “Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products,”<sup>4</sup> and the other responds to the

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<sup>1</sup> 82 Fed. Reg. 6575 (Jan. 19, 2017); FDA, *Draft Guidance for Industry – Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers* (Jan. 2017).

<sup>2</sup> See 81 Fed. Reg. 60299 (Sept. 1, 2016).

<sup>3</sup> See FDA, *Draft Guidance, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers* (Jan. 2017).

<sup>4</sup> FDA, *Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products* (Jan. 2017).

draft guidance on manufacturer communications with payors, formulary committees, and similar entities.

In each of these contexts, FDA regulation of manufacturer communications should adhere to principles that ensure sophisticated audiences will benefit from accurate, data-driven information from all sources, including the companies that research and develop new medicines. In July 2016, PhRMA and the Biotechnology Innovation Organization (“BIO”) jointly published such principles, which state that communications should be based on analyses using scientifically- and statistically-sound methodologies, should clearly disclose appropriate contextual information, and should be tailored to the sophistication level of the intended audience.<sup>5</sup> Consistent with the PhRMA-BIO Principles and the First Amendment, FDA’s new draft guidances take meaningful steps to broaden the ability of manufacturers to undertake appropriate communications about their drugs and thereby enhance informed prescribing and payor decision-making. Undue limitations on manufacturer communications remain, however, and require further FDA review and action.

With respect to consistent with labeling communications, the Draft Guidance takes an important step towards helping firms understand how FDA evaluates whether communications about a medical product are consistent with the approved labeling and otherwise permitted. Portions of the Draft Guidance helpfully indicate that there is additional flexibility for appropriate firm communications regarding information that is not contained in the approved labeling but that relates to an approved use. This approach is consistent with the concepts in the PhRMA-BIO Principles and the First Amendment rights of firms to communicate truthful and non-misleading information.

At the same time, however, the Draft Guidance leaves considerable confusion about key issues for medical product communications that are consistent with a product’s labeling—including, in particular, the required evidentiary support and the standards that FDA will apply to determine whether communications are truthful and non-misleading. PhRMA urges FDA to revise the Draft Guidance to provide important additional clarity on these points and to address other issues discussed in the specific comments below, as well as to amend the Agency’s regulations to harmonize them more clearly with the Draft Guidance.

## **I. Scope of the Draft Guidance**

The Draft Guidance states that it “provides information for firms about how FDA evaluates firms’ medical product communications, *including* promotional materials” for consistency with the FDA-required labeling.<sup>6</sup> The use of “including” could be read to suggest that FDA requires non-promotional medical product communications to be consistent with the FDA-approved labeling and otherwise to meet the provisions of the Draft Guidance. However, FDA’s long-

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<sup>5</sup> See PhRMA and BIO, Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals and Payers (2016) [hereinafter “PhRMA-BIO Principles”].

<sup>6</sup> Draft Guidance at Lines 17-20 (emphasis added and footnotes omitted).

standing policy has been that non-promotional scientific exchange is not subject to FDA's requirements for promotional labeling or advertising, and is not evidence of a firm's intended use of a product. PhRMA strongly recommends that FDA amend the Draft Guidance to clarify its scope as limited to promotional communications.

FDA has long taken the position that scientific exchange is distinct from promotional communications and falls outside FDA's regulatory scheme for product promotion. For example, FDA's regulation governing investigational drugs prohibits preapproval promotion but distinguishes these communications from scientific exchange:

A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. *This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.*<sup>7</sup>

FDA has also distinguished between promotional activities and scientific exchange in other contexts, recognizing that “the constraints on advertising and labeling, when applied to scientific and educational activities, can restrict the freedom of participants to discuss their data or express their views.”<sup>8</sup> As an example, the Agency has stated:

If a firm responds to unsolicited requests for off-label information in the manner described in this draft guidance, FDA does not intend to use such responses as evidence of the firm's intent that the product be used for an unapproved or uncleared use. Such responses would also not be expected to comply with the disclosure requirements related to promotional labeling and advertising.<sup>9</sup>

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<sup>7</sup> 21 C.F.R. § 312.7(a) (emphasis added).

<sup>8</sup> FDA, *Guidance for Industry – Industry-Supported Scientific and Educational Activities*, 62 Fed. Reg. 64074, 64093-94 (Dec. 3, 1997) (footnote omitted).

<sup>9</sup> FDA, Revised Draft Guidance for Industry -- Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011), at lines 92-95. *See also* FDA, Revised Draft Guidance for Industry – Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (Feb. 2014), at lines 146-49 (“Consistent with longstanding FDA policy and practice, if manufacturers distribute scientific or medical publications as recommended in this guidance, FDA does not intend to use such distribution as evidence of the manufacturer's intent that the product be used for an unapproved new use.”); FDA Memorandum -- Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Jan. 2017), at lines 554-57 (“it has long been FDA policy not to consider a firm's presentation of truthful and non-misleading scientific information about unapproved uses (continued...)”).

Given FDA’s own policy that non-promotional scientific exchange falls outside its purview of regulation, scientific exchange should fall outside the scope of the Draft Guidance. Scientific exchange may relate to wholly unapproved uses of a drug, and the concept of “consistent with labeling” is not applicable to scientific exchange. FDA should make this clear by revising the Draft Guidance to apply only to promotional materials. To the extent FDA wishes to establish policies to clarify its approach to non-promotional scientific exchange, PhRMA recommends that the Agency do so by establishing a robust framework via a separate rulemaking or guidance.

## **II. Factors for Determining Whether a Firm’s Communication About a Medical Product Is Consistent With the FDA-Required Labeling for That Product**

PhRMA appreciates FDA’s efforts in Q.2/A.2 of the Draft Guidance to clarify the general framework FDA applies to determine whether a particular communication is consistent with the product’s approved labeling. In FDA’s framework, Factor 1 in particular—which considers “how the information in the communication compares to the information” in the product’s labeling for the indication, patient population, limitations and directions for handling/use, and dosing/administration<sup>10</sup>—appropriately captures the core components of a drug’s approved conditions of use. Factors 2 and 3 in FDA’s framework seem largely redundant with Factor 1 and therefore unnecessary. If FDA retains those additional factors, we suggest clarifying certain issues, as follows.

Factor 2 creates ambiguity that could cause the factor to be interpreted too broadly, discouraging medical product communications that would otherwise be considered consistent with a product’s labeling. Factor 2 asks “[w]hether the representations/suggestions in the communication increase the potential for harm to health relative to the information reflected in the FDA-required labeling.”<sup>11</sup> The Draft Guidance then recommends that firms consider whether a medical product communication “alters the benefit-risk profile of a product in a way that may result in increased harm to health” relative to the information reflected in the approved labeling.<sup>12</sup> PhRMA is concerned that this standard is vague and potentially overbroad, and thus may have a chilling effect on communications that are otherwise permissible.

Specifically, the language “increase the potential for harm to health” (Lines 120 to 121) establishes a subjective standard that could be read as sweeping in and deterring communications for which the impact on the product’s benefit-risk profile is attenuated at best. Similarly, the reference (Lines 134 to 135) to communications that “alter[] the benefit-risk profile of a product in a way that *may result in an increased harm to health*” also introduces ambiguity that could make the scope of communications covered by Factor 2 overly expansive. If retained, we recommend that FDA amend this factor starting on Line 120 to read instead: “Whether the

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at medical or scientific conferences to be evidence of intended use when the presentation is made in non-promotional settings and not accompanied by promotional materials”).

<sup>10</sup> Draft Guidance at Lines 101-119.

<sup>11</sup> *Id.* at Lines 120-122.

<sup>12</sup> *Id.* at Lines 134-135.

representations/ suggestions in the communication materially alter the product’s benefit-risk profile,” and revise the paragraph that follows accordingly.

### **III. Examples of the Kinds of Information That Could Be Consistent With the FDA-Required Labeling for a Product**

The examples in Q.4/A.4 of the Draft Guidance, which describe information that could be considered consistent with a product’s labeling, provide helpful illustrations of the overarching principles articulated by FDA. For some of the examples the Office of Prescription Drug Promotion (“OPDP”) and its predecessor, the Division of Drug Marketing, Advertising, and Communications (“DDMAC”), have previously issued enforcement letters citing certain promotional communications as violative that presented information similar to some of the Draft Guidance’s examples.<sup>13</sup> The Draft Guidance appropriately permits these categories of information described in Q.4/A.4 to be included in medical product communications, provided that the communications are presented in a truthful and non-misleading manner. The availability of this information serves an important public health objective by helping to advise health care professionals on their prescribing decisions, which in turn helps improve patient outcomes.

These important public health objectives would be further served by additional guidance on product convenience claims FDA would consider to be consistent with the FDA-required labeling. PhRMA agrees with FDA that product convenience claims relating to duration of effect (Lines 221-224) may be consistent with the FDA-required labeling. Given the variety of types of product convenience claims, PhRMA requests that FDA include additional examples in the final guidance of product convenience claims the agency would consider consistent with the FDA-required labeling.

### **IV. Evidentiary Support for Communications That Are Consistent With the FDA-Required Labeling**

The Draft Guidance states that “[a]ny data, studies, or analyses relied on” in a communication “should be scientifically appropriate and statistically sound to support the representations or suggestions made in the communication.”<sup>14</sup> The Agency goes on to say that representations or suggestions in a communication that are consistent with the FDA-required labeling will not be considered false or misleading “based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard”<sup>15</sup>—that is, in the case of a prescription drug, there need not be evidence rising to the approval standard of “substantial evidence.” This position is consistent with the PhRMA-BIO Principles, and PhRMA generally agrees with the approach.

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<sup>13</sup> See, e.g., OPDP Warning Letter to Teva Pharmaceuticals USA (March 14, 2012) (citing presentation of long-term safety and efficacy data based on open-label extension study where clinical trials in labeling were three years in duration); DDMAC Warning Letter to Salix Pharmaceuticals, Inc. (Mar. 19, 2010) (citing convenience claims for orally disintegrating tablet).

<sup>14</sup> *Id.* at Lines 286-288.

<sup>15</sup> *Id.* at Lines 300-301.

The Draft Guidance’s further discussion of the evidentiary standard for medical product communications creates significant uncertainty and confusion, however, and would benefit from clarification in several respects. First, the Draft Guidance appears to distinguish between, on the one hand, information that is presented in a factual manner with a disclosure of its limitations and, on the other, making a direct or indirect “representation” or “suggestion.” The discussion in the Draft Guidance leaves considerable confusion regarding this distinction. Q.6/A.6 of the Draft Guidance cautions against making “false or misleading” representations or suggestions, directly or indirectly, based on analyses of data from a pivotal trial that was not controlled for a Type 1 error.<sup>16</sup> The Draft Guidance also states elsewhere in Q.6/A.6 that “disclosure of the material limitations of [a] study does not correct the misleading message conveyed by the communication.”<sup>17</sup> Together, these statements could be read as imposing a substantial evidence standard for medical product communications, at least for “representations or suggestions” about data. In contrast, Example 2 of Q.10/A.10 describes a situation in which a clinical trial includes data on the treatment effects of Drug A and Drug B but is not designed to evaluate the superiority or non-inferiority of the two drugs.<sup>18</sup> The Draft Guidance then goes on to explain that a communication regarding these data would be considered both consistent with the drug’s labeling and truthful and non-misleading if it presents the data without making a representation or suggestion comparing the two drugs, along with a prominent disclosure of the data’s limitations.<sup>19</sup>

PhRMA recommends that FDA clarify the Draft Guidance to provide that the presentation of information consistent with a product’s labeling will not be considered to be false or misleading, as long as this information is presented based on scientifically appropriate and statistically sound data, and accompanied by the appropriate disclosure of contextual information such as the data’s limitations. For example, a sponsor may obtain data relating to subgroups in a clinical study for which the endpoint was not pre-specified, or data on secondary endpoints that were not controlled statistically for multiplicity. A sponsor’s communication of these subgroup or secondary endpoint data—if collected in a scientifically appropriate and sound manner, and presented with contextual information concerning the limitations on the data—is not false or misleading and should be permitted. Similarly, it should be permitted for manufacturers to share information generated from payor claims data, or from other sources of real world evidence, even if not rising to the level of substantial evidence, provided that high quality methods are used and the findings are appropriately presented.

Second, PhRMA would also appreciate greater clarity from FDA regarding the level of evidentiary support that the Agency considers sufficient for comparative claims. PhRMA recommends that FDA clarify, in express terms, that support from two head-to-head studies is not necessary to support a representation or suggestion comparing one product to another. This would be consistent with Q.4/A.4 in the Draft Guidance, which provides that it

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<sup>16</sup> *Id.* at Lines 310-319.

<sup>17</sup> *Id.* at Lines 292-293.

<sup>18</sup> *Id.* at Lines 492-504.

<sup>19</sup> *Id.* at Lines 525-533.

would be permissible to present comparative information (that is otherwise consistent with the FDA-required labeling) from “a” head-to-head study demonstrating that one drug is superior to another in treating high blood pressure.<sup>20</sup>

Third, although PhRMA agrees generally with the standard in the Draft Guidance that communications must be supported by evidence that is “scientifically appropriate and statistically sound,” it would be helpful for FDA to provide greater guidance on the sorts of data that would meet this standard in recognition that, because it is a new standard (i.e., not otherwise defined by statute, in case law, or in other regulatory constructs), it is challenging to interpret and apply the standard in a precise manner.

In particular, PhRMA recommends that FDA clarify that medical product communications supported by competent and reliable scientific evidence will satisfy the evidentiary standard described in the Draft Guidance. The “competent and reliable scientific evidence” standard—which FDA clarifies in the Agency’s separate proposed guidance on communications with payors, formulary committees, and similar entities—is based on principles and considerations that parallel the “scientifically appropriate and statistically sound” standard. This language has also been used extensively in the regulatory context, so stakeholders and sophisticated audiences are already familiar with its parameters.

It would also be helpful for FDA to call out examples of data other than primary endpoints from randomized, controlled clinical trials that may be eligible for use if collected in a scientifically appropriate and statistically sound manner. Prominent examples could include post-hoc analyses of clinical trial results, including subpopulation analyses; observational data; pooled analysis/integrated data; and real-world evidence. Consistent with the PhRMA-BIO Principles, these are all examples of potentially useful data that ought to be able to be communicated if collected in a scientifically appropriate and statistically sound manner and presented appropriately. We also note that any further guidance on the evidentiary standard should account for the different levels or types of evidence sufficient to support different types of information. For example, the level of evidence that is “scientifically appropriate and statistically sound” to support a comparative claim generally would be qualitatively and quantitatively different from the evidence required for a claim that merely clarifies a product’s mechanism of action.

Finally, there is some question as to how the flexible approach FDA has rightfully set out in the Draft Guidance to provide greater flexibility for manufacturer communications about “consistent with labeling” information syncs with FDA’s existing regulations. This creates potential confusion, which FDA ought to remedy by (1) revising the Draft Guidance to state clearly that FDA will deem promotional communications that satisfy the standard set forth in the Draft Guidance as compliant with its regulations; and (2) amending the relevant regulations to bring them more clearly into harmony with the Draft Guidance and a Final Guidance. The principal issues arise under 21 C.F.R. § 202.1(e)(6), which provides that advertisements are “false, lacking in fair balance, or otherwise misleading” if they, among other things, represent or suggest that a drug is safer or more effective “than has been demonstrated by substantial evidence or

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<sup>20</sup> *Id.* at Lines 188-191.

substantial clinical experience,”<sup>21</sup> or contains a comparison of safety or efficacy with another drug “when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.”<sup>22</sup> FDA should address this issue by, at the least, explaining in the Final Guidance how manufacturers can communicate information supported by less than substantial evidence consistent with all applicable FDA regulations.

#### **V. Considerations When Developing Communications That Are Consistent with FDA-Required Labeling to Help Ensure the Presentation of Information Does Not Render the Communication False or Misleading**

The Draft Guidance offers “high-level recommendations”<sup>23</sup> in Q.8/A.8 for firms to consider when developing their presentations of information to help ensure that the communications will not be considered misleading. One of these recommendations is to “clearly and prominently disclose[]” the “material aspects of study design and methodology for any studies relied on . . . to allow audiences to accurately interpret the information.”<sup>24</sup> Examples of this contextual information include the type of study, study objectives, product dosage/use regimens, controls used, and the patient population studied.<sup>25</sup> The Draft Guidance also recommends that “material limitations related to the study design, methodology, and results” be disclosed in a “clear and prominent manner.”<sup>26</sup> In order to facilitate compliance with this recommendation, PhRMA asks FDA to clarify, using examples, what the Agency considers to rise to the level of “material limitations.”

Any standard for material contextual information should balance the objective of making this information available to promote accurate interpretation of the information with the concern that extensive disclosures may have the inadvertent effect of obscuring the information being communicated and confusing the recipient. Moreover, although the disclosures proposed in the Draft Guidance seem to focus on static and written communications, different levels and types of disclosures and context may be more or less appropriate depending on the media in which information is being communicated. Accordingly, PhRMA asks FDA to clarify that implementation of the suggested disclosures may vary widely depending upon the audience, media type, and other applicable constraints.

#### **VI. Communication of Information About Unapproved Uses of Approved Medical Products**

The Draft Guidance refers firms with questions about information that is not consistent with a product’s approved labeling to previously issued FDA guidance documents, including two

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<sup>21</sup> 21 C.F.R. 202.1(e)(6)(i).

<sup>22</sup> 21 C.F.R. 202.1(e)(6)(ii).

<sup>23</sup> Draft Guidance at Line 344.

<sup>24</sup> *Id.* at Lines 350-352.

<sup>25</sup> *Id.* at Lines 352-354.

<sup>26</sup> *Id.* at Lines 354-355.

guidances still in draft form, on unsolicited requests for off-label information, good reprint practices, and distributing scientific and medical publications on unapproved uses.<sup>27</sup> Although PhRMA appreciates the guidance FDA has promulgated to date, we urge FDA to provide greater insight into the Agency’s current thinking on appropriate mechanisms for communications concerning unapproved uses of an approved drug. As the Agency’s Federal Register notice announcing the November 2016 public hearing explained, “FDA is currently engaged in a comprehensive review of the regulatory framework related to firms’ communications about unapproved uses of approved/cleared products,” and this review has been ongoing since the Agency first announced it in 2014.<sup>28</sup> Further Agency guidance is needed.

PhRMA strongly believes that truthful and non-misleading communications about FDA-approved drugs provide important information to physicians, payors, and population-based healthcare decision makers; can improve patient outcomes; and are protected by the First Amendment. This includes, in particular, communications about medically accepted but unapproved uses of a drug. Our comments on FDA’s docket for the public hearing discuss the specific contours of PhRMA’s views about firm communications regarding unapproved uses of approved drugs in greater detail.<sup>29</sup> As set out in those PhRMA comments, PhRMA urges FDA to adopt changes to its current restrictions on communications about unapproved uses of approved drugs, in addition to issuing final guidance on consistent with labeling communications and communications with payors, formulary committees, and similar entities, and updating its regulations.

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PhRMA looks forward to continued collaboration with FDA on the Agency’s regulatory policy regarding manufacturer communications that are consistent with a product’s approved labeling. We would welcome the opportunity to discuss these comments further.

Respectfully submitted,

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/s/  
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/s/  
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<sup>27</sup> See *id.* at Lines 539-545 n.14-16.

<sup>28</sup> 81 Fed. Reg. at 60300.

<sup>29</sup> See Docket No. FDA-2016-N-1149. In its comments, PhRMA discusses two narrow circumstances in which a prohibition on off-label communications would directly advance the government’s legitimate interest in preserving incentives for innovation and no less restrictive alternative would be available. See PhRMA Comments to Docket No. FDA-2016-N-1149, Section III.G (Apr. 19, 2017).