DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

JUN 6 2014

Alan R. Bennett
Ropes & Gray LLP
One Metro Center
700 12th Street, NW
Washington, DC 20005

Joan McPhee
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600

Coleen Klasmeier
Paul E. Kalb
Sidley Austin LLP
1501 K Street, NW
Washington, DC 20005

Re: Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079

Dear Mr. Bennett, Ms. McPhee, Ms. Klasmeier, and Mr. Kalb:

This responds to your citizen petitions received by the Food and Drug Administration (FDA or the Agency) on July 5, 2011 (2011 Petition), and September 3, 2013 (2013 Petition), and submitted on behalf of members of the Medical Information Working Group (MIWG).[1] Your petitions request that the FDA clarify its regulations and policies governing certain communications and activities related to investigational new drugs and investigational devices and off-label uses of marketed drugs and devices. You maintain that currently there is a lack of clarity regarding the sharing of truthful and non-misleading scientific information about unapproved new uses of these products. Specifically, the 2011 Petition requests clarification in the following areas:

1. Manufacturer responses to unsolicited requests;
2. Scientific exchange;
3. Interactions with formulary committees, payors, and similar entities; and

[1] Collectively, the petitions were submitted on behalf of the following companies: Allergan, Inc.; Bayer Healthcare Pharmaceuticals Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline LLC; Johnson & Johnson; Novartis Pharmaceutical Corporation; Novo Nordisk, Inc.; Pfizer, Inc.; Purdue Pharma L.P.; and Sanofi US.

4. Dissemination of third-party clinical practice guidelines.

The 2013 Petition requests that FDA (1) respond fully and in a constitutionally permissible manner to the four specific requests in the 2011 Petition and (2) comprehensively review, and modify as necessary in view of constitutional and statutory limitations, the regulatory regime governing manufacturer communications to protect and promote public health.

FDA has carefully considered the information submitted in your petitions. For the reasons stated below, your petitions are granted to the extent that they seek greater regulatory clarity on the four specified topics and, more generally, that FDA engage in a comprehensive review of the regulatory regime governing communications about medical products.

I. DISCUSSION

You claim in both the 2011 and 2013 Petitions that there is a lack of clarity regarding truthful, non-misleading scientific communications and activities related to investigational new drugs and investigational devices and off-label uses of marketed drugs[2] and devices. In both petitions, you emphasize the constitutional implications of the Agency's regulation of the following four activities that you describe as involving medical and scientific communications:

1. Manufacturer responses to unsolicited requests;
2. Scientific exchange;
3. Interactions with formulary committees, payors, and similar entities; and
4. Dissemination of third-party clinical practice guidelines.

In the 2011 Petition, you contend that with uncertainty in these areas, manufacturers may develop policies that do not align with FDA's expectations (2011 Petition at 5). You request that FDA affirm and clarify the contours of its policies in regulations that are legally binding and offer comprehensive guidance consistent with FDA's mission to protect the public health (2011 Petition at 5).

The 2013 Petition recognizes that FDA has already taken action on some areas since the 2011 Petition and requests that we complete the policy development in these areas with some "mid-course correction" in recognition of the emerging case law, in particular the case law involving the First and Fifth Amendments of the United States Constitution (2013 Petition at 3). You request that the Agency "initiate notice-and-comment

[2] For purposes of this petition response, the term *drug* includes drugs regulated as biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262(a)).

rulemaking in the two areas in which FDA has not already taken action" — manufacturers' off-label communications with payors and similar entities, and manufacturer dissemination of third-party clinical practice guidelines that include information about off-label uses (2013 Petition at 4).

The 2013 Petition also contains several new requests. You request that we provide clear interpretations of key definitions to assure that our regulatory scheme better aligns with the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the limitations under the First and Fifth Amendments (2013 Petition at 12-19). You assert that the key constitutional principles reflected in recent case law involving the First and Fifth Amendments must inform the policies and foundations of our regulatory scheme governing manufacturer communications of off-label use information (2013 Petition at 12). This would include making changes to clarify the scope of (a) the definition of *labeling*, (b) the drug and medical device advertising provisions, and (c) the definition for *intended use* (2013 Petition at 12-19).

A. Background: Public Health and the FD&C Act Framework

Over more than a century, Congress has developed and amended the medical product provisions of the FD&C Act, and FDA has issued implementing regulations, to protect and promote the public health. From an initial reliance primarily on post-marketing enforcement, the governing legal authorities expanded first to require most drugs, and then many devices, to undergo premarket review and evaluation to ensure their safety and effectiveness for each of their intended uses,[3] as well as to ensure that the directions and warnings provided when they are distributed will enable their safe and effective use.

More specifically, the FD&C Act and FDA regulations collectively prohibit manufacturers from introducing new drugs into interstate commerce for any intended use that FDA has not determined to be safe and effective. A new drug, including a new drug approved for a specified use, that is accompanied by written, printed, or graphic matter that suggests an unapproved new use would be an unapproved new drug with respect to that use (see section 201(m) and (p) of the FD&C Act (21 U.S.C. 321(m) and (p)). Introducing an unapproved new drug into interstate commerce is prohibited (sections 505(a) and 301(d) of the FD&C Act (21 U.S.C. 355(a) and 331(d))). Furthermore, an approved prescription drug that is intended for an unapproved use (whether referenced in labeling or not) would be considered misbranded, because the drug does not meet the

[3] For both drugs and devices, a manufacturer's or distributor's intended use for the product can be established not only by the manufacturer's or distributor's subjective claims of intent, but also by objective evidence, which may include a variety of direct and circumstantial evidence. See, e.g., *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (observing that "it is well established that the 'intended use' of a product, within the meaning of the [FD&C] Act is determined from its label, accompanying labeling, promotional claims, advertising and any other relevant source").

regulatory exemptions from the requirement that its labeling bear "adequate directions for use" (see section 502(f) of the FD&C Act (21 U.S.C. 352(f)) and 21 CFR 201.5, 201.100(c)(1), and 201.115). Introduction of misbranded drugs into interstate commerce is prohibited (see sections 301(a) and 301(k) of the FD&C Act).

Similarly, the FD&C Act prohibits, in general, manufacturers from introducing medical devices into interstate commerce for intended uses for which FDA has not determined there to be a reasonable assurance of safety and effectiveness (see sections 301(a) 501(f)(1), 502(o), 510(k), 513, and 515 of the FD&C Act (21 U.S.C. 331(a), 351(f)(1), 352(o), 360, 360c, and 360e)). For devices subject to premarket approval (most class III devices), the FD&C Act requires that manufacturers obtain approval of a premarket approval application (PMA) before introducing a new device, or a new use of an approved device, into interstate commerce (see sections 501(f)(1), 513, and 515 of the FD&C Act (21 U.S.C. 351, 360c, and 360e) and 21 CFR 814.39). For devices subject to premarket notification requirements under section 510(k) of the FD&C Act, which includes most class II and certain class I devices, manufacturers must obtain FDA clearance of a premarket notification before introducing the device into interstate commerce, and before making a major change or modification in the intended use of a cleared device (see sections 502(o) and 510(k) of the FD&C Act (21 U.S.C. 352(o) and 360(k)) and 21 CFR 807.81(a)(3)(ii)).[4]

FDA also reviews and approves the labeling for inclusion on or within the package from which the drug is dispensed as part of the process for approving a new drug application (NDA) (section 505(b) of the FD&C Act). For devices subject to premarket approval, labeling is reviewed and approved by FDA as part of the PMA review (see 21 U.S.C. 360e(c)(1)(F)).[5]

Regardless of whether the product's labeling is subject to FDA premarket approval, all drug and device labeling, as well as advertising for prescription drugs and for restricted devices, is subject to the misbranding provisions of the FD&C Act. For example, a drug or device is considered misbranded if its labeling is "false or misleading in any particular" (section 502(a) of the FD&C Act). Similarly, a prescription drug or a

---

[4] Devices that are exempt from premarket notification requirements, generally because they are low risk, may be introduced into interstate commerce for the specifically exempt intended use(s) without obtaining FDA clearance (see sections 510(l) and (m) of the FD&C Act (21 U.S.C. 360(l) and (m))). Devices exempt from premarket review remain subject to labeling requirements and other postmarket provisions of the FD&C Act, however. Changing the intended use of such a device generally requires 510(k) clearance and may, in certain situations, require a PMA.

[5] For devices that are subject to premarket notification (510(k)) requirements, the 510(k) notification must contain the proposed labeling sufficient to describe the device, its intended use, and the directions for its use (21 CFR 807.87(e)). All devices, including those exempt from premarket review, are subject to applicable labeling requirements (see 21 CFR part 801).

restricted device is considered misbranded if its advertising fails to provide adequate information regarding the product's safety and effectiveness, or is otherwise false or misleading.[6] As noted previously, introducing misbranded drugs or devices into interstate commerce is prohibited (sections 301(a) and 301(k) of the FD&C Act).

In developing the statutory framework described above, Congress intended to curb the distribution of unsafe and ineffective medical products in the market, by requiring manufacturers to investigate and substantiate the safety and effectiveness of medical products for each intended use before offering the products for sale to the public.[7] One objective of the safety and efficacy requirements for drugs was to prevent manufacturers from evading the drug approval requirements by obtaining approval of a drug for one use, then promoting the drug for other, unapproved uses without first demonstrating through the approval process that the drug was safe and effective for each new use (see S. Rep. No. 87-1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884, 2901-2903 (if manufacturers were not required to demonstrate safety and effectiveness for new uses, "[t]he expectation would be that the initial claims would tend to be quite limited," and "[t]hereafter 'the sky would be the limit' and extreme claims of any kind could be made")). The requirement that safety and effectiveness for each intended use be established before introduction of the product into interstate commerce for that use came from experience showing that exclusive reliance on post-marketing remedies, such as enforcement actions for false or misleading labeling, was inadequate to protect the public health, as these remedies were not sufficient to deter manufacturers and distributors—who profit from each sale of their products for any use—from making unsubstantiated and misleading claims to encourage use of their products. As the Secretary of Health, Education, and Welfare told Congress, "[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a manufacturer can fool the public until the [FDA] finally catches up with him."[8]

Furthermore, FDA evaluates whether a drug is safe for a particular use by comparing the expected therapeutic gain against the risk associated with its use. Many drugs have potentially significant adverse side effects, and therefore may be deemed safe only with respect to particular uses that involve significant countervailing benefits. Information that emphasizes the drugs' claimed benefits, while minimizing the drugs' limitations and adverse effects, may inappropriately influence a physician's prescribing decisions in a manner that is not in the patient's best interest. Even widespread acceptance of an unapproved use in the medical community is no guarantee that the drug is safe or

---

[6] See section 502(n) of the FD&C Act, 21 CFR 202.1 (prescription drug advertising), and section 502(q) and (r) of the FD&C Act (restricted device advertising); see also section 201(n) of the FD&C Act.
[7] See section 505(a) and (d) of the FD&C Act; see also section 515(a) and (d) of the FD&C Act (requiring proof of safety and effectiveness for premarket approval of class III devices).
[8] *The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the Comm. on the Judiciary*, 87th Cong., 2d Sess. 173 (1962).

effective for that use, and is no substitute for the rigorous clinical trials, FDA-approved labeling, and careful scrutiny by FDA that the drug approval process requires.[9]

Likewise, premarket review of medical devices was a key feature of the Medical Device Amendments of 1976. In 1976, Congress overhauled the postmarket surveillance system put in place for devices by the 1938 FD&C Act, replacing it with a comprehensive framework that included premarket review. Among the reasons for the changes to the statute was Congress' concern about unsafe and ineffective marketed devices.[10]

B. Harmonizing First Amendment Interests in the Dissemination of Information with the Governmental Interest in Protecting the Public Health

The FD&C Act, its implementing regulations, and FDA policies must protect the public health – the fundamental interest underlying FDA's mission and the statutory framework – while harmonizing this goal with First Amendment interests in the dissemination of truthful, accurate, and non-misleading information regarding medical products. In pursuing this goal, it is important to remember that the current regulatory framework, including requirements described above, has been developed over time in response to public health tragedies, particularly those that occurred when manufacturers could distribute drugs and devices without independent review of scientific evidence of the products' safety and efficacy.[11] FDA plays an important role by conducting this safety and efficacy review; by helping to ensure that required labeling for a drug or

---

[9] See, e.g., Echt DS, Liebson PR, Mitchell LB et al., "Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial," New Eng. J. Med., 324(12): 781-88 (1991). The Cardiac Arrhythmia Suppression Trial (CAST) examined the widely held belief that treating minor rhythm abnormalities (frequent ventricular premature beats) with anti-arrhythmics after an acute myocardial infarction would improve survival. The well-controlled study (CAST) to test this belief, conducted by the National Institutes of Health, demonstrated that, although the drugs did indeed treat minor rhythm abnormalities, the patients who took those drugs had a 2 ½ fold increase in mortality.

[10] For Congressional history regarding the need for the Medical Device Amendments of 1976, see S. Rep. No. 94-33, at 2-6 (1975).

[11] The Food, Drug, and Cosmetic Act of 1938, which introduced the requirement that manufacturers demonstrate a drug product to be safe before being marketed, followed the deaths of approximately 100 people from ingesting "Elixir Sulfanilamide," in which diethylene glycol was used as a solvent. The manufacturer did not test this lethal solvent in advance, nor did the label reveal its presence. Similarly, the passage of the 1962 drug amendments was precipitated in part by the distribution of thalidomide, a sleeping pill that caused birth defects when taken by pregnant women. See Wallace F. Janssen, Outline of the History of U.S. Drug Regulation and Labeling, 36 FOOD DRUG COSM. L.J. 420 (1981). Significant problems with medical devices likewise preceded the Medical Device Amendments of 1976, including widespread and tragic problems reported with the Dalkon Shield intrauterine contraceptive device (IUD). By 1975, at least 16 deaths, 25 miscarriages, numerous cases of pelvic perforation and pelvic infection, removal of the IUD for medical reasons, and pregnancies due to IUD failure had been reported (H.R. Rep. No. 94-853, at 8 (1976)).

medical device is truthful, accurate, non-misleading, and balanced; and by monitoring the marketing of the drug or device to determine whether it continues to comply with applicable requirements. The FDA process for reviewing a manufacturer's clinical studies and approving product labeling[12] that conveys important information related to the safe and effective use of the product for its intended use, such as indications, dosage, precautions, warnings, and contraindications, is an effective tool to help ensure appropriate use of the product.

The Agency has recognized – and continues to recognize –that there can be utility in the dissemination of truthful and non-misleading scientific or medical information regarding off-label uses under appropriate circumstances. The premarket review and labeling and advertising provisions of the FD&C Act address the critical public health need to ensure that—at a general (population) level—the use of medical products is based on sound science, not mere anecdotal experience. At the same time, any individual patient may have characteristics and needs that deviate from the patient population for which a medical product is indicated. Thus, FDA's regulatory framework also recognizes the role that medical professionals play in making treatment decisions for individual patients; this recognition is embodied in FDA's long-standing recognition of the practice of medicine and in the device-specific "practice of medicine" provision of the FD&C Act, section 1006 (21 U.S.C. 396). In general, FDA does not seek to regulate the practice of medicine, including the off-label use of legally marketed drugs and devices for individual patients. Indeed, for some health conditions, off-label uses of medical products have made valuable contributions to patient care.

As we conduct our examination of our regulations, guidance, and policies, our goal is to harmonize:

- the FD&C Act's premarket review, labeling, and advertising provisions that apply to medical products;
- the important public health and safety interests these provisions serve;
- the utility of dissemination of information about medical products; and
- First and Fifth Amendment considerations.

[12] FDA regulatory processes not only help ensure that each intended use of drugs and many medical devices is supported by appropriate scientific evidence, but also that this scientific information is used to develop labeling to support the safe and effective use of those products (see section 502(f)(1) of the FD&C Act; see also, e.g., 21 CFR 201.100 and 801.109). Such labeling is in turn required to be provided with the product (Id.).

C. Agency Initiatives

We are granting your request for a review of FDA's regulations, guidance, and policies, and for more clarity on truthful, non-misleading scientific communications and activities related to investigational new drugs and investigational devices and off-label uses of marketed drugs and devices.[13] These tasks are part of FDA's more comprehensive review of its regulations and guidance documents in an effort to harmonize the goal of protecting the public health with First Amendment interests. Although we are aware that the draft guidance documents we have issued[14] do not as of yet provide a comprehensive answer to all of your questions and concerns, it is important to note that the issuance of Agency guidance can be accomplished in a prompt and efficient fashion, and provides an opportunity for comment that assists the Agency in understanding where questions remain. It is our judgment that issuing guidance initially to address industry questions is an effective first step to provide clarity to those who manufacture medical products and wish to disseminate scientific information about their products.[15] These initial steps should not be viewed as precluding further agency action in these areas, including issuing new or modified regulations.

The Agency initiative to evaluate our current regulations, guidance, and policies has already netted concrete progress. Since the submission of both your petitions, we have been engaged in extensive internal review of the Agency's approach to the dissemination of scientific information about off-label uses of approved products, and have issued draft guidance documents for comment as we seek to provide industry with more clarity about how it can share scientific information about off-label uses. In December 2011, we issued two documents providing information and soliciting public comment on the dissemination of scientific information. First, FDA made available for public comment the Unsolicited Requests Draft Guidance. We are in the process of reviewing and

---

[13] Your petitions do not include any requests regarding FDA's regulation of animal drugs. Nevertheless, our examination of our regulations, guidance, and policies will encompass those that apply to animal drugs.

[14] We have issued several draft guidance documents that pertain to the requests in your petitions, including *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices Practices* (Unsolicited Requests Draft Guidance) (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf) and *Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices* (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). This response references several FDA draft guidances. When finalized, these guidances will represent FDA's current thinking on the respective topics.

[15] Although guidance documents are not legally binding on the public or FDA, they provide industry with FDA's current thinking on a particular topic or on certain issues and we generally follow our final guidance documents when we decide whether or not to take action with respect to industry activities (21 CFR 10.115(d)).

analyzing the comments received on this guidance. The Unsolicited Requests Draft Guidance addresses the concerns you raise in your petitions regarding manufacturer responses to unsolicited requests. Second, in the *Federal Register* of December 28, 2011 (76 FR 81508), FDA published a notice seeking comment on various issues associated with scientific exchange (i.e., dissemination of scientific information) to help in our consideration of that subject.

In addition, in the *Federal Register* of March 3, 2014, FDA published a notice announcing the availability of the draft guidance for industry, *Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices* (Scientific and Medical Publications Draft Guidance).[16] This draft guidance revised FDA's 2009 Good Reprint Practices Guidance in response to stakeholder questions and comments. As a result, the 2014 Scientific and Medical Publications Draft Guidance includes revised Agency recommendations for the distribution of scientific and medical reference texts, and for the first time, includes recommendations for the distribution of third-party clinical practice guidelines, a specific area on which your petitions requested clarification. We are currently reviewing and evaluating the comments received on the Scientific and Medical Publications Draft Guidance.

FDA plans to issue guidance that addresses unsolicited requests, distributing scientific and medical information on unapproved new uses, and manufacturer discussions regarding scientific information more generally, by the end of the calendar year. FDA also plans to issue draft guidance documents that address your remaining requests involving health care economic information by year-end.

These documents represent an initial step resulting from our ongoing review of the regulatory regime governing manufacturer communications, as you requested. In addition, FDA is issuing a draft guidance that addresses the dissemination of risk information for approved prescription drugs and biological products. As always, when we issue a new draft guidance document, we will provide for public notice and opportunity for comment. We welcome your comments on the Agency's forthcoming guidance documents and will take the comments on these documents into consideration when drafting final guidance.

We believe that the guidances we have issued and plan to issue in the next year will provide the clarity you request in both petitions on those topics. In addition, in light of the importance of the public health issues and free speech and due process principles at stake, FDA is committed to examining its rules and policies for areas where it can refine

---

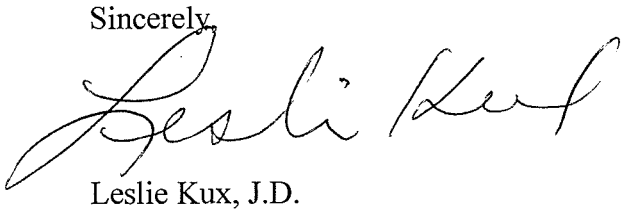
[16] The title of the 2009 guidance was *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2009 Good Reprint Practices Guidance).

and clarify the distinction between permissible and impermissible conduct. We recognize the evolving legal landscape in the area of the First Amendment, and we are reviewing and analyzing the Agency's policies, guidance, and regulations in this area more broadly. We will continue to evaluate the need for additional guidance and new or modified regulations as we engage in this comprehensive review.

II. CONCLUSION

For the reasons and in the manner described above, your petitions are granted.

Sincerely,



Leslie Kux, J.D.
Assistant Commissioner for Policy