

Dated: November 1, 2011.

George H. Sheldon,

Acting Assistant Secretary for Children and Families.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0912]

Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing the establishment of a docket to assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and information related to scientific exchange. FDA is interested in obtaining comments and information regarding scientific exchange about both unapproved new uses of products already legally marketed (“off-label” use) and use of products not yet legally marketed for any use.

DATES: Submit either electronic or written information and comments by March 27, 2012.

ADDRESSES: Submit electronic information and comments to <http://www.regulations.gov>. Submit written information and comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane Rm. 1061, Rockville, MD 20852. Identify both electronic and written comments and any supporting documents with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

For the Center for Drug Evaluation and Research

Nicole Mueller, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, Rm. 6312, Silver Spring, MD 20993-0002, (301) 796-3601.

For the Center for Biologics Evaluation and Research

Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, (301) 827-6210.

For the Center for Devices and Radiological Health

Deborah Wolf, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 66, Rm. 3414, Silver Spring, MD 20993-0002, (301) 796-5732.

SUPPLEMENTARY INFORMATION:

I. Background

On July 5, 2011, a citizen petition was submitted by Ropes & Gray and Sidley Austin LLP on behalf of seven product manufacturers (Petitioners): Allergan, Inc.; Eli Lilly and Co.; Johnson & Johnson; Novartis Pharmaceuticals Corp.; Novo Nordisk, Inc.; Pfizer, Inc.; and sanofi-aventis U.S. LLC under 21 CFR 10.30. The citizen petition requested that FDA clarify its policies for drug products and devices governing certain communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use.¹ Specifically, the 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
4. Dissemination of third-party clinical practice guidelines.

For some time, FDA has been considering these issues and is currently evaluating our policies on sponsor or investigator communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. We have been considering what actions to take in the areas specified by the petitioners with respect to manufacturer responses to unsolicited requests; interactions with formulary committees, payors, and similar entities; and the dissemination of third-party clinical practice guidelines. To assist with our evaluation of our policies on communications and activities related to off-label uses of marketed products, as well as communications and activities related to use of products that are not yet legally marketed for any use, we would like to obtain comments and

information related to scientific exchange.

Under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and the Public Health Service Act (PHS Act), any person who wishes to introduce or deliver for introduction into interstate commerce any new drug (including a biological drug product) must demonstrate that the product is safe and effective for its intended uses (see sections 505(a) and 512(a) of the FD&C Act (21 U.S.C. 355(a) and 360b(a)) and section 351 of the PHS Act (42 U.S.C. 262)). Any person who wishes to introduce or deliver for introduction into interstate commerce a new medical device (including a biological device product) must either demonstrate that the device has a reasonable assurance of safety and effectiveness for its intended uses or that it is substantially equivalent to a legally marketed predicate device (see sections 510(k), 513(f), and 515(a) of the FD&C Act (21 U.S.C. 360(k), 360c(f), 360e(a)) and section 351 of the PHS Act (42 U.S.C. 262)).

The demonstrations of product safety and efficacy usually consist of data and information derived from clinical investigations and presented as part of a marketing application. The marketing application also contains information regarding the product’s intended uses, the patient population (including any special conditions, restrictions, or limitations for segments of the population, such as children, pregnant women, or the elderly), potential adverse events associated with the product’s use, and technical information about the product (see, e.g., 21 CFR 314.50, 514.1, 601.25, and 814.20). If FDA agrees that a product is safe and effective for its intended uses, as reflected in the marketing application, it approves the application and certain required product labeling. For devices subject to clearance through the 510(k) process, the clearance establishes the intended use(s) for which it is legal to market the product. The uses that are approved or cleared by the Agency are sometimes referred to as “labeled” uses because they appear in the product’s required labeling. Uses that do not appear in the labeling and are not approved or cleared by the Agency are referred to as “unapproved,” “unlabeled,” “off-label,” or “extra-label” uses.

As explained previously in this document, under section 505 of the FD&C Act, a new drug (which includes a marketed drug intended for a new use) may not be introduced or delivered for introduction into interstate commerce without approval by FDA, but FDA is authorized to create regulations

¹ See Docket No. FDA-2011-P-0512 at <http://www.regulations.gov> for a copy of the citizen petition.

exempting from this requirement drugs intended for use in investigations to examine their safety or effectiveness (21 U.S.C. 355(i)). Under this authority, current FDA regulations in part 312 (21 CFR part 312) require submission of an investigational new drug application (IND) to FDA and set the other requirements for exemption. Regulations at §§ 312.22 and 312.23 contain the general principles underlying the IND submission and the general requirements for an IND's content and format. Drugs under investigation are subject to certain requirements in order to meet the terms of the exemption from approval prior to introduction into interstate commerce. One such requirement is a limitation on promotional activity, set forth in § 312.7. However, this regulation expressly states that it is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

There is a similar statutory and regulatory framework for investigational devices. Section 520(g) of the FD&C Act (21 U.S.C. 360j(g)) establishes the program by which sponsors may apply for investigational device exemptions (IDE), which allow for the investigational use of devices by experts qualified by scientific training and experience to investigate the safety and effectiveness of those devices and exempt the devices subject to approved IDEs from the statutory requirement that devices not otherwise exempt from premarket notification under section 510(k) of the FD&C Act be approved or cleared via premarket approval or premarket notification submissions. Regulations at 21 CFR 812.7 provide in relevant part that: "A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:" (1) "Promote or test market an investigational device, until after FDA has approved the device for commercial distribution" or (2) "Represent that an investigational device is safe or effective for the purposes for which it is being investigated."

FDA has made prior statements regarding scientific exchange about investigational products. For example, in the **Federal Register** of May 22, 1987 (52 FR 19466), the Agency published a final rule entitled "Investigational New

Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale" that provided for ways in which investigational new drugs could be made available to desperately ill patients prior to general marketing and that addressed charging for investigational drugs. In the preamble to that rule, FDA stated: "FDA's understanding of commercial promotion does not place limits on the free exchange of scientific information [regarding investigational drugs] (e.g., publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences). However, responses by sponsors or investigators to unsolicited media inquiries or statements made in the exchange of scientific information should (1) Make clear that a drug is investigational; (2) make no claims that a drug has been proven to be safe or effective; and (3) be truthful and non-misleading when measured against available information on the drug—and fairly represent available information—as set forth in materials such as investigators' brochures and patients' informed consent sheets." (52 FR 19466 at 19475).

II. FDA Is Seeking Comments on Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed

Interested persons are invited to provide detailed comment on all aspects of scientific exchange communications and activities related to off-label uses of marketed drugs, biologics, and devices and use of products that are not yet legally marketed. FDA is particularly interested in responses to the following questions.

- How should FDA define scientific exchange?
- What types of activities fall under scientific exchange?
- What types of activities do not fall under scientific exchange?
- Are there particular types and quality of data that may indicate that an activity is, or is not, scientific exchange?
- In what types of forums does scientific exchange typically occur? Should the use of certain forums be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which forums?
- What are the distinctions between scientific exchange and promotion? What are the boundaries between scientific exchange and promotion?
- Generally, who are the speakers involved in scientific exchange, and

who is the audience for their communications?

- Should the identity of the participants (either speakers or audience) be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which participants would be indicative of scientific exchange and which would be indicative of promotion?

- How do companies generally separate scientific roles and promotional roles within their corporate structures?

- How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices? Please address whether there should be any distinctions between communications regarding uses under FDA-regulated investigation (to support potential approval) and communications regarding uses that are not under express FDA-regulated investigation.

- How should the Agency treat scientific exchange concerning use of products that are not yet legally marketed (that is, products that cannot be legally distributed for any use outside of an FDA- or institutional review board (IRB)-approved clinical trial)?

- Should investigational new drugs and investigational devices be treated the same with respect to scientific exchange? Why or why not?

- Under 21 CFR 812.7(b), an investigational device is considered to be "commercialized" if the price charged for it is more than is necessary to recover the costs of manufacture, research, development, and handling. Similarly, FDA considers charging a price for an investigational drug that exceeds that permitted under its regulations (generally limited to cost recovery) to constitute "commercialization" of the drug (see 74 FR 40872 at 40890, August 13, 2009; 52 FR 19466 at 19467). What other actions indicate the commercialization of drug and/or device products? If there are differences in the steps taken to commercialize drug products and the steps taken to commercialize device products, either before or after approval, please explain these differences.

III. Submission of Information and Comments

Interested persons may submit information and comments to the Division of Dockets Management (see **ADDRESSES**) in electronic or written form. It is only necessary to send one set of comments. Identify comments with

the docket number found in brackets in the heading of this document. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 21, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0652]

Draft Guidance for Industry and Food and Drug Administration Staff; the 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the draft guidance entitled “Draft Guidance for Industry and Food and Drug Administration Staff; The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)].” FDA developed this draft guidance document to provide a contemporary perspective on how FDA reviews premarket notification (510(k)) submissions as well as on the Special and Abbreviated 510(k) programs. This guidance addresses the major aspects of the 510(k) decision-making process and updates FDA’s policies with respect to the Special and Abbreviated 510(k) programs. This draft guidance is not final nor is it in effect at this time.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by April 26, 2012.

ADDRESSES: Submit written requests for single copies of the draft guidance document entitled “Draft Guidance for Industry and Food and Drug Administration Staff; The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]” to the Division of Small Manufacturers, International, and

Consumer Assistance, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4613, Silver Spring, MD 20993-0002 or to the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your request, or fax your request to (301) 847-8149. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

Jonette Foy, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1676, Silver Spring, MD 20993-0002, (301) 796-6328;

or

Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852, (301) 827-6210.

SUPPLEMENTARY INFORMATION

I. Background

This draft guidance serves to update FDA’s perspective on the Agency’s approach to the 510(k) program, which began in 1976. Since that time, FDA has periodically published guidance that described its approach and any changes therein, to the 510(k) program. On June 30, 1986, FDA published a Blue Book Memorandum titled “Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum #K86-3,” a document which discussed general points regarding the process of determining substantial equivalence between a new device and a predicate device. On March 20, 1998, FDA published another guidance document titled “The New 510(k) Paradigm—Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications.” This guidance introduced two new 510(k) programs—the Special 510(k) and the Abbreviated 510(k)—as optional approaches available to device manufacturers. This

guidance also renamed the original 510(k) program that had been in place since 1976 to the “Traditional 510(k).” Traditional, Special, and Abbreviated 510(k)s differ with respect to the scope and content of information that are included within the submission. The Special 510(k) is an option for a manufacturer who has made certain changes to a medical device that was previously found substantially equivalent. With this option, the manufacturer relies on conformance with design controls under the Quality System Regulation (21 CFR 820.30) to support substantial equivalence. The Abbreviated 510(k) is an option for manufacturers who rely on guidance documents, special controls, and/or recognized consensus standards to support substantial equivalence. These alternate approaches were intended to streamline FDA’s review process and simplify for manufacturers the preparation of a 510(k) that was eligible for these programs. It is noted that the 1986 guidance was issued as final guidance prior to the February 27, 1997, implementation of FDA’s Good Guidance Practices (GGPs). Neither guidance has been updated since its initial publication. Upon its issuance as a final guidance document, this new guidance will replace both of those guidances.

In recent years, concerns have been raised both within and outside of FDA about whether the 510(k) program optimally achieves its intended goals. In September 2009, FDA’s Center for Devices and Radiological Health (CDRH) convened an internal 510(k) Working Group to conduct a comprehensive assessment of the 510(k) process. The 510(k) Working Group evaluated the 510(k) program with the goal of strengthening the program and improving the predictability, consistency, and transparency of the Agency’s decision-making process. On February 18, 2010, the 510(k) Working Group held a public meeting to solicit comments from the public regarding the strengths and challenges associated with the 510(k) program. In August 2010, CDRH published two documents in consideration of the comments made at the public meeting and the Agency’s preliminary assessment of the program. These documents are titled “CDRH Preliminary Internal Evaluations—Volume I: 510(k) Working Group Preliminary Report and Recommendations” and “CDRH Preliminary Internal Evaluations—Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and