4160-01-P

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 [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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

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

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 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.

[FR Doc. 2011-33188 Filed 12/27/2011 at 8:45 am; Publication Date: 12/28/2011]