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New FDA Guidance Largely Affirms Prior Policy on Off-Label Responses but Distinguishes Between Public and Nonpublic Requests

On December 27, 2011, the U.S. Food and Drug Administration (FDA) released a draft guidance (Draft Guidance) on how pharmaceutical and medical device manufacturers should respond to unsolicited requests for information about unapproved (or uncleared) indications or conditions of use related to their FDA-approved or cleared products.[1] The Draft Guidance largely reaffirms the agency's view that companies can respond to unsolicited requests for information about FDA-regulated products by providing truthful, nonmisleading scientific or medical information that is responsive to the specific request even if such information relates to an unapproved or uncleared indication or condition of use. The FDA says it issued the Draft Guidance in response to "[t]he rapid growth of the Internet, including social media tools and other emerging technologies, [that] has made it easier for both consumers and health care professionals to quickly seek information about medical conditions and treatments." The FDA has opened a docket to receive comments regarding communications related to off-label uses, and interested persons have until March 27, 2012, to submit comments to the FDA.

Top-Line Summary

- Draft Guidance largely affirms prior agency policy on company responses to off-label questions, which has allowed companies to provide responsive, nonpromotional information in response to unsolicited requests for off-label information.
- Draft Guidance distinguishes between public and nonpublic off-label questions and recommends that companies handle public questions by providing one-on-one responses — as opposed to responding to the question in the presence of a group.
- By largely affirming its prior approach and arguably tightening recommendations on how to handle responses to public off-label questions, the FDA appears to be unmoved by recent First Amendment challenges to its ability to regulate the dissemination of truthful, nonmisleading off-label information.

Background

The Federal Food, Drug, and Cosmetic Act (FDCA) and the FDA's implementing regulations prohibit manufacturers and distributors from introducing new drugs and most Class III medical devices into interstate commerce for any intended use that the FDA has not determined to be safe and effective.[2] The FDA long has taken the position that

1 "Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices," U.S. Food and Drug Administration, December 2011, *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf.

2 The FDCA and related implementing regulations also prohibit device firms subject to premarket notification requirements under Section 510(k), which include most Class II and some Class I devices, from introducing such devices into interstate commerce for any intended use that is outside the FDA's substantial equivalence determination (clearance) for such devices.

statements that promote a drug or medical device for uses other than those approved or cleared by the FDA may be used as evidence of a new intended use. Introducing a product into commerce for such a new intended use without FDA approval or clearance would, under these requirements, generally violate the law. However, once a drug or medical device has been approved or cleared by the FDA, health care professionals can generally use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling. The Draft Guidance recognizes that such "off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care."

What Is an Unsolicited Request?

The Draft Guidance defines "unsolicited requests" as those "initiated by persons or entities that are completely independent of the relevant manufacturer or distributor" and may include "many health care professionals, health care organizations, members of the academic community, and formulary committees, as well as consumers such as patients and caregivers." Requests that are prompted in any way by a manufacturer or its representatives, in contrast, are not unsolicited requests.

Two Types of Unsolicited Requests: Public and Nonpublic

While the Draft Guidance is generally consistent with prior agency comments on the proper response to unsolicited requests for off-label information, it codifies a distinction between public and nonpublic requests. According to the Draft Guidance:

> **Nonpublic request**: A nonpublic unsolicited request is an unsolicited request that is directed privately to a firm using a one-on-one communication approach. An example of a nonpublic request would be where an individual calls or e-mails the medical information staff at a manufacturer seeking information about an off-label use. In this case, neither the request nor the response would be visible to the public.
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> **Public request**: A public unsolicited request is an unsolicited request made in a public forum, whether directed to a firm specifically or to a forum at large. An example of a public request is a situation where, during a live presentation, an individual asks a question regarding an off-label use of a specific product to a company representative in the presence of other attendees. This is a public request. A response by the firm that is conveyed to the same audience would be considered a public response.

By distinguishing between nonpublic and public requests, the FDA is attempting to limit the extent to which one person's off-label question can become a platform for a firm to provide off-label information to a broader group.

Recommendations for How Companies Should Respond to Public and Nonpublic Requests

Nonpublic Requests

With respect to nonpublic requests, the FDA reiterates its existing policy that firms should provide information in response to such a request only to the individual making the request. Further, FDA reiterates that the communication should be tailored to answer only the specific question(s) asked. The Draft Guidance also advises firms to include the following with the response:

- a copy of the FDA-required labeling, if any, for the product;
- a prominent statement notifying the recipient that the FDA has not approved or cleared the product as safe and effective for the use addressed in the materials provided;
- a prominent statement disclosing the indication(s) for which the FDA has approved or cleared the product;
- a prominent statement providing all important safety information including, if applicable, any boxed warning for the product; and
- a complete list of references for all of the information disseminated in the response (*e.g.*, a bibliography of publications in peer-reviewed medical journals or in medical or scientific texts; citations for data on file, summary documents or abstracts).

The Draft Guidance also recommends that firms maintain records for such responses that include:

- the nature of the request for information, including the name, address and affiliation of the requestor;
- records regarding the information provided to the requestor; and
- any follow-up inquiries or questions from the requestor.

Public Responses

Where the request is made in a public forum (as described above), the Draft Guidance recommends that the company "respond only when the request pertains specifically to its own named product (and is not solely about a competitor's product)." Where the request is about a company's product, the FDA recommends that the public response "be limited to providing the firm's contact information and should ***not*** include any off-label information." (Emphasis in original). The Draft Guidance further advises that a company's "public response should convey that the question pertains to an unapproved or uncleared use of the product and state that individuals can contact the medical/scientific representative or medical affairs department with the specific unsolicited request to obtain more information" and should provide specific contact information for such a one-on-one communication. Off-label information provided in response to such a one-on-one follow-up request should be consistent with the recommendations for nonpublic responses.

Responses Should Be Handled by Medical or Scientific Affairs Departments

Notably, although not stating so expressly, the Draft Guidance envisions that responses to unsolicited requests for off-label information will be handled by a company's medical or scientific personnel or department. The Draft Guidance provides several scenarios in which off-label requests are directed to commercial personnel. In each of those examples, the agency recommends that the response be forwarded to medical or scientific personnel; in no instance does the agency recommend that commercial personnel handle a response. A fair reading of the Draft Guidance is that the FDA disfavors the practice of allowing commercial personnel to respond to unsolicited requests for off-label information.

Implications for Pharmaceutical and Medical Device Manufacturers

Current industry practice varies with respect to the handling of unsolicited requests for information. While some companies permit commercial personnel to respond to a specific request for off-label information, others require all such requests to be handled by a company's medical affairs personnel.

The range of practices with respect to questions posed in public settings is equally broad. Some companies allow company personnel or representatives to respond to off-label questions in public settings (such as in a speaker's program), while other companies prohibit such public responses in favor of one-on-one discussions following the conclusion of the public session. Others simply instruct personnel to provide information on how to contact the company's medical information department for follow-up. This is not surprising given the diverse nature of company product portfolios, regulatory and enforcement history, and risk tolerance. Nevertheless, companies should consider reviewing their policies and practices in light of the Draft Guidance to consider the following:

- To what extent do our policies and practices align with the Draft Guidance? To the extent they do not, have we adequately assessed the risks and benefits of our current approach?
- Do our responses to unsolicited requests for off-label information include the information recommended in the Draft Guidance?
- Do we maintain adequate documentation of such requests as recommended in the Draft Guidance?
- Do we provide training to all affected components of the organization (including commercial personnel, medical affairs personnel and outside speakers) that ensures they know the company's policies pertaining to the handling of off-label questions?

Interestingly, the Draft Guidance acknowledges (albeit in a footnote) that "receiving an unsolicited request is not the only way a [manufacturer or distributor] can disseminate information about unapproved uses of its FDA-regulated products without such dissemination being used as evidence of the firm's intent that the product be used for an unapproved use". In so conceding, the FDA cites, by way of example, the agency's January 2009 Good Reprint Guidance.[3] But the Draft Guidance cites no other examples of the agency countenancing such dissemination and largely ignores the recent First Amendment challenges to the agency's broad prohibition on the dissemination of truthful, nonmisleading off-label information. Given the current Supreme Court's broad reading of the First Amendment's prohibition on limits to free speech generally and commercial speech in particular, the implicit restrictions contained in the Draft Guidance are less likely to survive eventual Supreme Court review. These regulations illustrate the difficulties in formulating clear regulations designed to limit speech that is in other contexts lawful. Clients should carefully consider their First Amendment rights when commenting on these regulations.

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3 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, U.S. Food and Drug Administration, a*vailable at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm.