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Client Alert

FDA & Life Sciences Practice Group

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Responding to Unsolicited Requests for Off-Label Information

New FDA Draft Guidance

The Food and Drug Administration (FDA) issued a draft guidance on December 30, 2011 in response to stakeholder requests for clarification on how manufacturers and distributors of prescription drugs and medical devices, as well as animal drugs, can respond to unsolicited requests for information about unapproved or uncleared indications or conditions of use (off-label information).[1] The issuance of the draft guidance follows a public hearing held in November 2009 and a citizen petition, filed on behalf of seven prescription drug manufacturers in July 2011, seeking clarification on FDA's current policies.

Among multiple recommendations, the draft guidance addresses how firms should respond to requests for off-label information that occur in public forums, including the internet and electronic social media. The agency's positions also have potential implications for enforcement related to off-label promotion and advertising. The draft guidance states that if a firm responds to unsolicited requests in the manner described, the agency does not intend to use such responses "as evidence of the firm's intent that its product be used for an unapproved or uncleared use. In addition, such responses also would not be expected to comply with the disclosure requirements related to promotional labeling and advertising." Notably, however, in the draft guidance, FDA very narrowly construes what would constitute an "unsolicited" request. **The agency seeks comments on the draft guidance by March 29, 2012**.

This client alert highlights FDA's positions and recommendations on several major issues including:

- distinguishing solicited versus unsolicited requests,
- distinguishing non-public versus public requests and responses,
- responding to unsolicited requests made directly and privately, and
- ensuring that all responses to unsolicited public requests—including those encountered through emerging electronic media (*e.g.*, YouTube, Twitter)—are only made privately to individuals.

For more information, contact:

Edward Basile
+1 202 626 2903
ebasile@kslaw.com

Laurie Clarke
+1 202 626 2645
lclarke@kslaw.com

Beverly H. Lorell, MD
+1 202 383 8937
blorell@kslaw.com

Marian Lee
+1 202 661 7955
mlee@kslaw.com

Seth H. Lundy
+1 202 626 2924
slundy@kslaw.com

Christina Markus
+1 202 626 2926
cmarkus@kslaw.com

Nikki Reeves
+1 202 661 7850
nreeves@kslaw.com

Elaine Tseng
+1 415 318 1240
etseng@kslaw.com

King & Spalding
Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500
Fax: +1 202 626 3737

San Francisco
101 Second Street
Suite 2300
San Francisco, CA 94105
Tel: +1 415 318 1200
Fax: +1 415 318 1300

www.kslaw.com

Solicited versus Unsolicited Requests. Under the draft guidance, unsolicited requests are queries initiated by persons or entities that are completely independent of the firm. Thus, any connection to the firm, whether through a financial relationship or some type of prompt for the question by the firm (or its representatives), could result in a "solicited" request. The draft guidance clarifies that solicited requests are not limited to questions that follow the mention of an off-label use by a company sales representative. Though not exhaustive, the draft guidance provides several examples of situations FDA considers to be solicited requests for off-label information, including:

- **Medical liaisons and key opinion leaders acting on behalf of the firm.** FDA explicitly clarifies that solicited requests include those that follow the presentation of off-label information by a medical science liaison or a health care provider acting on behalf of the company as a "paid speaker (*e.g.*, a key opinion leader)" at a company-sponsored promotion event.
- **Clinical studies and investigational uses.** The draft guidance states that promotional pieces that cite clinical studies of "off-label" conditions and patients as well as commercial exhibits that read "Coming Soon, a new use for Product X" would be considered as solicitations for off-label information.
- **Uses of electronic media.** FDA provides multiple examples of activities by a firm that the agency interprets as solicitations of requests for off-label information including 1) provision of URLs and "alpha phrases" that implicate off-label information, 2) encouragement of users to post testimonials or videos of off-label uses (*e.g.*, YouTube), 3) communications that provoke discussion of off-label use on blogs, whether posted as comments to a third-party site or directed to the firm, 4) announcement of clinical study results about an off-label use via a microblogging service (*e.g.*, Twitter) in a manner that suggests such use is safe or effective, and 5) firm-generated websites that enable any prepared responses or use of search terms to provide information about an off-label use.

Non-public versus Public Unsolicited Requests and Responses.

- **Non-public**. FDA proposes that a non-public, unsolicited request is a query by an individual that is directed privately to a firm using a one-on-one approach, which is not visible to the public. Examples include a telephone call or email from an individual to the firm seeking information about an off-label use. Similarly, a non-public response is a firm's direct response to the individual that is not visible to the public.
- **Public.** Under the draft guidance, a public unsolicited request is any request made in a public forum, whether directed to a firm specifically or to a forum at large. A response conveyed to a public audience, rather than privately and one-on-one to an individual requestor, is considered a public response.

Responding to Non-Public Unsolicited Requests. FDA recommends that off-label information should be provided only to the individual making the request in a private one-on-one response.

- **Specificity of the response.** According to the draft guidance, the response should answer only the specific question(s) asked. The agency further advises that if an unsolicited question appears broad in nature, the firm should seek pertinent information from the requestor to understand the specific question being asked and appropriately "narrow the question."

- **Provision of non-biased information, including unpublished data.** In addition to the provision of data that is scientific in nature, FDA emphasizes that information that is provided should be "truthful, non-misleading, accurate, and balanced." The agency cautions that, "A response should provide non-biased information or data relating to the particular off-label use that is the subject of the request, including applicable data that are not supportive or that cast doubt on the safety or efficacy of that use." Although the response should include pertinent complete scientific reprints and technical literature, if available, the agency clarifies that, "The response can include unpublished data on file if they are responsive to the specific request (either supporting or casting doubt on the safety or efficacy of the off-label use)."
- **Referral of unsolicited requests to medical or scientific personnel.** Consistent with current practice of most firms, the draft guidance provides that responses to unsolicited requests should be carried out by medical or scientific personnel independent from sales or marketing functions. In addition, FDA advises that such personnel have specialized training, including training related to appropriately narrowing questions, providing specific and non-biased responses, and documenting responses to unsolicited requests.
- **The 5-point check list of information that should accompany the response to the individual.** In the draft guidance, FDA advises that all responses should be accompanied by five specific items:
    - a copy of the FDA-approved labeling, if any,
    - a prominent statement that "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 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 information disseminated in the response, including citations for data on file that is provided.

The 4-step Process for Responding Privately to Unsolicited Requests Made in Public Forums, including Electronic Media and Other Public Forums. Importantly, although FDA recognizes that firms are capable of responding to unsolicited requests – including requests made in public forums – about off-label uses of their own products in a truthful, non-misleading, and accurate manner, and that providing such information to requestors can be in the best interest of public health, FDA advises that firms should not *publicly* provide off-label information in response to public requests. The agency's rationale for inclusion of electronic media among public forums is that public information posted on websites and electronic forums is available to broad audiences and for an indefinite period, "FDA is concerned that firms may post detailed public online responses to questions about off-label uses of their products in such a way that they are communicating unapproved or uncleared uses of their products … to individuals who have not requested such information." Further, FDA opines that "communications to persons who have not requested information may promote a product for a use or condition for which FDA has not approved or cleared."

Accordingly, FDA recommends that firms who choose to respond to public unsolicited requests for off-label information follow four specific steps to ensure the provision of off-label information only to individuals in a private manner:

- Respond only if the request is specific to the firm's named product (and is not solely about a competitor's product or a non-specific query related to a disease condition);
- **Provide a public response that conveys that the question pertains to an unapproved or uncleared use of the product and state that individuals can contact the medical/scientific department with a specific request to obtain more information**;
    - Specific contact information should be provided for independent requests by individuals;
    - **The firm should only provide off-label information to individuals in private one-on-one responses to the specific request**;
- Provide a disclosure in this public response of the responder's involvement with the particular firm; and
- Ensure that this public response is not promotional in nature or tone. The public response that provides contact information for individual queries should also provide access to current FDA-approved labeling (*e.g.*, the package insert and FDA-approved patient labeling) but it should not include any other information, such as information about the firm, product, or third-party websites.

Implications for manufacturers. The expectations outlined in the draft guidance have major implications for the manner in which companies respond to unsolicited requests and communicate truthful and accurate off-label information about their products. In particular, the agency's interpretation of solicited versus unsolicited requests as well as the expectation for the provision of only private responses to public unsolicited queries, such as those occurring at promotional meetings and via the internet, may pose major operational challenges as well as enforcement risks. While this is only draft guidance, it is a strong indication of FDA's thinking on this volatile subject. In addition, since these draft guidelines are in many cases the first official guidance on these subjects, it is likely that other enforcement authorities, such as the Department of Justice, will begin to rely on the guidelines in prosecuting allegations of off-label promotion.

Please contact us if you have questions regarding the potential implications of the draft guidance or if you want assistance in preparing and submitting comments to the docket.

[1] 76 Fed. Reg. 82,303 (December 30, 2011). The draft guidance is accessible at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf