

**FOR FURTHER INFORMATION CONTACT:**

Kristiana Brugger, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6262, Silver Spring, MD 20993-0002, (301) 796-3601.

**SUPPLEMENTARY INFORMATION:** In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, and HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, are the subject of NDA 05-213, held by Endo Pharmaceuticals, and initially approved on March 23, 1943. In 1982, a Drug Efficacy Study Implementation

review concluded that HYCODAN syrup, tablets, and powder were effective "for the symptomatic relief of cough." (47 FR 23809, June 1, 1982). Subsequently, the sponsor submitted an NDA for HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, and HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, which was approved on July 26, 1988. HYCODAN is indicated for the symptomatic relief of cough in adults and children 6 years of age and older.

In a letter dated January 4, 2008, Endo Pharmaceuticals notified FDA that HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, were being discontinued, and FDA moved the drug product to the "Discontinued Drug Product List" section of the Orange Book. Vintage Pharmaceutical, Inc., submitted a citizen petition dated October 15, 2008 (Docket No. FDA-2008-P-0555), under 21 CFR 10.30, requesting that the Agency determine whether HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, were withdrawn from sale for reasons of safety or effectiveness. Although the citizen petition did not request it, FDA has determined, on its own initiative, whether the oral solution dosage form was withdrawn for safety or effectiveness reasons.

After considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, and HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, were not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, or HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, were withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, and HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse

events. We have found no information that would indicate that these products were withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, and HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to HYCODAN (hydrocodone bitartrate and homatropine methylbromide) tablets, 5 mg/1.5 mg, or HYCODAN (hydrocodone bitartrate and homatropine methylbromide) oral solution, 5 mg/5 mL and 1.5 mg/5 mL, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: December 22, 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-0868]

#### **Draft Guidance for Industry on Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices." This draft guidance responds to stakeholder requests for specific guidance on FDA's current views on how manufacturers and distributors (firms) of prescription human and animal drug products and

medical devices can respond to unsolicited requests for information about unapproved or unclear indications or conditions of use (off-label information) related to their FDA-approved or cleared products. This draft guidance updates and clarifies FDA's policies on unsolicited requests for off-label information, including those that firms may encounter through emerging electronic media.

**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 comments 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 March 29, 2012. Submit written comments on the proposed collection of information by February 28, 2012.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Office of Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002; to the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448; to the Communications Staff, Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl. (HFV-12), Rockville, MD 20855; or to the Division of Small Manufacturers, International and Consumer Assistance, Office of Communication, Education and Radiation Programs, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 4613, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

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.

#### **FOR FURTHER INFORMATION CONTACT:**

*Regarding human prescription drugs:* Jean-Ah Kang, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993, (301) 796-1200.

*Regarding prescription human biological products:* 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.

*Regarding animal prescription drugs:* Dorothy McAdams, Center for Veterinary Medicine (HFV-216), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, (240) 276-9300.

*Regarding medical devices:* Deborah Wolf, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Silver Spring, MD 20993, (301) 796-5732.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

FDA is announcing the availability of a draft guidance for industry entitled "Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices." In July 2011, FDA received a citizen petition, filed on behalf of seven prescription drug manufacturers, seeking additional clarification on several areas of FDA policy regarding distribution of information about prescription drugs. One of the areas was how to respond to unsolicited requests from health care professionals or consumers for information about off-label uses of approved products.

In addition, on November 12 and 13, 2009, FDA held a Part 15 public hearing on "Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools" to provide an opportunity for broad public participation and comment on the following questions that relate specifically to promotional issues: (1) For what online communications are manufacturers, packers, or distributors accountable? (2) How can manufacturers, packers, or distributors fulfill regulatory requirements (e.g., fair balance, disclosure of indication and risk information, post-marketing submission requirements) in their internet and social media promotion, particularly when using tools that are associated with space limitations and tools that allow for real-time communications (e.g., microblogs, mobile technology)? (3) What parameters should apply to the posting of corrective information on Web sites controlled by third parties? (4) When is the use of links appropriate? Subsequent to the live testimony heard at the Part 15 public hearing, FDA received 72 comments to the docket. This draft guidance is the first of multiple draft

guidances the Agency plans to publish that address questions and issues related to emerging electronic media.

This draft guidance provides FDA's recommendations to firms wishing to respond to unsolicited requests for off-label information about their products, including both requests made directly and privately to firms and requests made in public forums, including through emerging electronic media. This draft guidance discusses the difference between unsolicited and solicited requests and presents a number of examples of both types of requests. If a firm responds to unsolicited requests for off-label information in the manner described in this draft guidance, FDA does not intend to use such responses as evidence of the firm's intent that its product be used for an unapproved or unclear use. Such responses also would not be expected to comply with the disclosure requirements related to promotional labeling and advertising. Firms may choose to respond to unsolicited requests for information about off-label uses of their approved or cleared products in a manner other than that recommended in this draft guidance. Such activity would not constitute a per se violation of the law, but could potentially be introduced as evidence of a new intended use.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on responding to unsolicited requests for off-label information about prescription drugs and medical devices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

##### **II. The Paperwork Reduction Act of 1995**

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information

before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of information collected on the respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

**Title:** Industry Responses to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices.

**Description of Respondents:** Respondents to this collection of information are manufacturers and distributors (firms) of prescription human and animal drug products or medical devices.

**Burden Estimate:** The draft guidance pertains to the dissemination of scientific or medical information about off-label uses for approved or cleared products by FDA-regulated industry when it responds to (1) non-public unsolicited requests for off-label information made directly and privately to them, or (2) public unsolicited requests for off-label information, including those that firms may encounter through emerging electronic media.

The draft guidance explains that FDA's current policy position is that, regardless of whether the initial unsolicited request for off-label information was made in a non-public or public forum, FDA does not intend to use the firm's actions as evidence of a new intended use, nor expect distributed materials to conform to existing regulatory requirements for promotional labeling or advertising, if the firm responds in the manner outlined in the guidance. Specifically, the draft guidance recommends that a firm that chooses to respond to an unsolicited request for off-label information provide the final response containing the requested off-label information about its product only to the specific individual who requested the information as a private, one-on-one communication. FDA also recommends

that information distributed in response to an unsolicited request be truthful, non-misleading, accurate, balanced, and non-promotional scientific or medical information that is tailored to answer only the specific question asked, even if responding to the request requires the firm to provide information regarding unapproved or unclear indications or conditions of use. To meet this standard, the draft guidance recommends that firms disclose certain information to others when responding to their unsolicited requests. This "third-party disclosure" constitutes a "collection of information" under the PRA. In addition, the PRA is triggered because the draft guidance also recommends that firms maintain certain records related to this disclosure.

#### *Non-Public Responses*

When providing *non-public* responses to unsolicited requests for information about unapproved or unclear indications or conditions of use, the draft guidance recommends the following:

- 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. For example, when conclusions of articles or texts that are disseminated have been specifically called into question by other articles or texts, a firm should disseminate representative publications that reach contrary or different conclusions regarding the use at issue. The response should include complete copies of scientific reprints, technical literature, or other scientific and medical information responsive to the request, not just summary documents or abstracts prepared by the firm. The response may 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). However, to the greatest extent possible, a firm should rely on published peer-reviewed journal articles, medical texts, or data derived from independent sources. To the extent the response consists of published reprints from journals, those reprints should be from journals that have a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization.

In addition to responsive materials as described previously in this document,

the guidance recommends that the following information be provided to the requestor:

1. A copy of the FDA-required labeling, if any, for the product (*e.g.*, FDA-approved package insert and, if the response is for a consumer, FDA-approved patient labeling or, for new animal drugs, FDA-approved client information sheet).
2. A prominent statement notifying the recipient that FDA has not approved or cleared the product as safe and effective for the use addressed in the materials provided.
3. A prominent statement disclosing the indication(s) for which FDA has approved or cleared the product.
4. A prominent statement providing all relevant safety information including, if applicable, any boxed warning for the product.

5. 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, for summary documents, or for abstracts).

Finally, the draft guidance recommends that a firm maintain the following related records:

1. The nature of the request for information, including the name, address, and affiliation of the requestor.
2. Records regarding the information provided to the requestor.
3. Any followup inquiries or questions from the requestor.

#### *Public Responses*

When providing *public* responses to unsolicited requests for information about unapproved or unclear indications or conditions of use, the draft guidance recommends that the following information be disclosed to the requestor:

1. A firm's public response to public unsolicited requests for off-label information about its named product should convey that the question pertains to an unapproved or unclear use of the product and be limited to providing the firm's contact information for the medical or scientific personnel or department so that individuals can follow up independently with the firm to obtain specific information about the off-label use of the product through a non-public, one-on-one communication. After an individual has privately contacted the firm for more information regarding an off-label use of the firm's product, the firm should provide a detailed response and maintain records following the parameters outlined in Section V of the draft guidance (and summarized previously in this

document for non-public responses to unsolicited requests).

2. Representatives who provide public responses to unsolicited requests for off-label information should clearly disclose their involvement with a particular firm.

3. Public responses to public unsolicited requests for off-label information should not be promotional in nature or tone and should include a mechanism for providing readily accessible FDA-required labeling, if any,

for the product (e.g., FDA-approved package insert and, if the response is for a consumer, FDA-approved patient labeling or, for new animal drugs, FDA-approved client information sheet).

FDA estimates that approximately 400 firms respond annually to approximately 40,000 non-public unsolicited requests for off-label information made directly and privately to them as well as to public unsolicited requests for off-label information, including those that firms may

encounter on emerging electronic media. FDA estimates that it will take firms approximately 4 hours to provide responses to each unsolicited request for off-label information as recommended in the draft guidance.

FDA also estimates that approximately 40,000 records will be maintained for all responses to non-public and public unsolicited requests for off-label information, and that each record will take approximately 15 minutes to prepare and maintain.

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN <sup>1</sup>

Draft guidance on responding to unsolicited requests for off-label information	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Responses to non-public and public unsolicited requests .....	400	100	40,000	4	160,000

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2—ESTIMATED ANNUAL RECORDKEEPING BURDEN <sup>1</sup>

Draft guidance on responding to unsolicited requests for off-label information	Number of recordkeepers	Number of records per recordkeeper	Total annual records	Average burden per recordkeeping	Total hours
Records related to responses to non-public and public unsolicited requests .....	400	100	40,000	.25	10,000

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

### III. Comments

Interested persons can submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

### IV. Electronic Access

Persons with access to the Internet may obtain the document at either

<http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/default.htm>,

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>,

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>,

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm>, or <http://www.regulations.gov>.

Dated: December 27, 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-0872]

#### Draft Guidance for Industry on Use of Histology in Biomarker Qualification Studies; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Use of Histology in Biomarker Qualification Studies.” This guidance is intended to assist sponsors that conduct biomarker qualification studies for which histology is a reference standard. This guidance discusses the processes that should be considered to ensure the quality and integrity of histology data in biomarker studies, and outlines the scientific standards for histology used in

biomarker characterization and qualification. The recommendations in this guidance are intended for studies in biomarker qualification designated to justify the proposed context of use, where scientifically rigorous evaluation of biomarker performance in relation to histologic changes is essential. The principles outlined in this guidance are also applicable to exploratory biomarker studies.

**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 March 29, 2012.

Submit either electronic or written comments concerning the proposed collection of information by February 28, 2012.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY**