



May 29, 1998

Peggy Dotzel
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Office of Policy
Food and Drug Administration
HF-13
5600 Fishers Lane
Rockville, MD 20857

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**Re: PhRMA Recommended Approach For Implementing
FDAMA §401 – Dissemination of Treatment Information**

Dear Ms. Dotzel:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents the country's leading research-based pharmaceutical and biotechnology companies, to provide industry input on Section 401 of the FDA Modernization Act of 1997 (FDAMA).

As you know, FDAMA §401 adds a new subchapter D to the Drugs and Devices Chapter V of the Federal Food, Drug, and Cosmetic Act to permit manufacturers to disseminate information to health care providers on unapproved uses of approved drugs, biological products, and devices, under certain conditions. This provision takes effect one year after enactment of FDAMA, November 21, 1998, or upon the issuance of implementing regulations, whichever first occurs. Section 401 represents a significant change from FDA's traditional prohibition on the dissemination of any off-label information. PhRMA's Dissemination Work Group prepared the attached comments to assist FDA in implementing this important provision. The Work Group is available at your convenience to discuss this recommended approach and answer any questions; we hope that you and others at FDA, and interested members of the public, find this input useful.

Sincerely yours,

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cc: Jane Axelrad, Associate Director for Policy, CDER/FDA

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May 29, 1998

*PhRMA Recommended Approach
FDAMA §401 -- Dissemination*

**PhRMA'S RECOMMENDED APPROACH TO THE IMPLEMENTATION OF
THE TREATMENT INFORMATION DISSEMINATION PROVISIONS OF THE
FDA MODERNIZATION ACT (§ 401)**

Section 401 of the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997), adds a new subchapter D to the Drugs and Devices Chapter V of the Federal Food, Drug & Cosmetic Act (FFDCA) to permit manufacturers to disseminate information on unapproved ("off-label") uses of approved drugs, biological products, and devices under certain conditions. Section 401 facilitates the sharing of important treatment information with health care providers to enable better patient care in accordance with current medical knowledge. At the same time, Section 401 places controls on the dissemination of information on unapproved uses and establishes requirements for manufacturers to conduct follow-up research and file supplemental product applications with FDA to include the new use(s) in product labeling. These provisions take effect on November 21, 1998, or upon the FDA's promulgating implementing regulations, whichever is earlier.

Section 401 represents a significant change from FDA's traditional prohibition on the dissemination of any off-label information. The conditions Congress imposed on the dissemination of such information are intended to protect the public health while facilitating the access of health care providers to valuable scientific information. *See* Joint Explanatory Statement of the Committee on Conference at 10; H. R. Rep. No. 105-43 at 60 (1997). Those conditions should not be interpreted so narrowly as to nullify the

reforms Congress intended in enacting the FDA Modernization Act. Indeed, Section 401 is the most detailed and lengthy provision in the FDA Modernization Act and embodies a careful compromise. When FDA promulgates regulations to implement Section 401, as required by the FDA Modernization Act, it must respect that compromise. Key issues that FDA should address in implementing Section 401 include: (1) clarifying important details of the basic requirements for disseminating off-label information; (2) streamlining the process for the review of reprints and adopting an appropriate definition of qualifying reference texts; (3) clarifying the content and timing of applicable reporting requirements; (4) ensuring that determinations regarding proposed study protocols are timely and delineating the obligations to submit progress reports on studies; and (5) providing for an appeal of determinations that supplements are inadequate.

1. Basic Requirements for Disseminating Off-Label Information

Section 401 provides that a manufacturer may disseminate information concerning the safety, effectiveness, or benefit of a product's use not described in the approved labeling of the product to a health care practitioner, a pharmacy benefit manager, a health insurance issuer, a group health plan, or a Federal or State governmental agency. FDCA § 551(a); 21 U.S.C. § 360aaa(a). In order to distribute off-label information to these audiences, the following basic conditions must be met:

- (1) the drug, biological product, or device must be approved;
- (2) the information must be in an approved form and not be false or misleading or pose a significant risk to the public health, as delineated further in a separate portion of Section 401;
- (3) the information must not be derived from research conducted by another manufacturer, except with its permission;

- (4) the manufacturer must submit the information to FDA 60 days before beginning distribution, together with any safety and effectiveness information from clinical trials and safety information from reports of clinical experience;
- (5) the manufacturer must comply with the requirements relating to the submission of a supplement covering the use in question; and
- (6) the manufacturer must include with the information to be disseminated a prominent statement that the use has not been approved, a copy of the approved labeling, disclosures relating to authorship and funding of the disseminated information, a bibliography of other articles published about the use of the product covered by the information disseminated, and a statement (if applicable) that other products or treatments have been approved for the use being discussed in the disseminated information.

FFDCA § 551(b); 21 U.S.C. § 360aaa(b). FDA may also require the manufacturer to disseminate additional safety and effectiveness information, if the Agency determines after giving notice and meeting with the manufacturer that such additional information is necessary to provide objectivity and balance. FFDCA § 551(c); 21 U.S.C. § 360aaa(c).¹

In order to implement these basic requirements in an efficient and sensible manner, FDA should clarify certain important details. First, when a manufacturer submits information to FDA as required by Section 401, it should submit the information to both the Division of Drug Marketing, Advertising and Communication (DDMAC) and the appropriate Reviewing Division. Second, FDA should provide that the method used to present the disclosures and documentation required to accompany the disseminated

¹ Information disseminated in accordance with these and the other requirements of Section 401 will not be considered product labeling and will not cause a product to be adulterated or misbranded, or be considered as evidence of a new intended use. FFDCA § 557(b); 21 U.S.C. § 360aaa-6(b). Disseminating information in violation of Section 401 is a prohibited act under the FFDCA. FFDCA § 301(z); 21 U.S.C. § 331(z).

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information may take a number of forms (*e.g.*, cover page, reprint carrier, etc.). Nothing in Section 401 requires that the disclosures be made in any specific manner, and FDA should provide manufacturers flexibility, provided that the disclosures and other information are clear and sufficiently conspicuous. Third, the manufacturer should not be required to identify the name of any particular product or treatment approved for the use which is the subject of the information being disseminated, as long as the manufacturer includes a statement that other products or treatments exist that have been approved for such use. Nothing more is required by Section 401, and confusion could be created if manufacturers were required to provide detailed information about the products of other manufacturers.

As FDA clarifies and implements these requirements, it should ensure that it reviews the information a manufacturer submits in order to disseminate material under Section 401 and resolves all pertinent issues (*e.g.*, the need for additional information) within the 60-day period prior to information dissemination. If FDA does not notify a manufacturer of problems with the planned dissemination of information within the 60-day review period, dissemination may proceed and the information is considered objective and balanced under FFDCA § 551(c) (21 U.S.C. § 360aaa(c)).

2. Information Authorized to be Disseminated

The only information that a manufacturer may distribute under Section 401 is (1) a “scientifically sound” unabridged reprint of a peer-reviewed article published in a

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Manufacturers remain free to respond to unsolicited requests for information. FFDCA § 557(a); 21 U.S.C. § 360aaa-6(a).

scientific or medical journal² about a clinical investigation, or (2) a reference publication containing similar information. FFDCA § 552(a); 21 U.S.C. § 360aaa-1(a). To qualify, a reference publication must not have been prepared at the manufacturer's request or significantly influenced or distributed solely by the manufacturer, and must not focus on a particular drug or device, or present materials that are false or misleading. FFDCA § 552(b); 21 U.S.C. § 360aaa-1(b). None of the information may be false or misleading or "pose a significant risk to the public health." FFDCA § 552(a); 21 U.S.C. § 360aaa-1(a).

In applying these requirements, FDA should accept for review final manuscripts or pre-prints of articles that have cleared the peer-review process (*i.e.*, have been accepted for publication or are to be published during the 60-day review period). This will prevent the dissemination of qualifying articles from being delayed by having to wait for actual publication before beginning the 60-day review period.

In addition, FDA should exercise prudence in construing the prohibition that a reference publication cannot focus primarily on new uses of a particular product. Provided that the discussion of the product is objective, a reference publication with a significant focus on a particular product provides valuable new clinical information in accordance with the purposes underlying Section 401.

² A scientific or medical journal under Section 401 is a journal that has an expert editorial board and policy requiring full disclosure by authors of conflicts of interest, requires that articles be peer-reviewed in accordance with regular procedures, is "generally recognized to be of national scope and reputation," is indexed in the Index Medicus, and is not in the form of a "special supplement" funded wholly or partly by one or more manufacturers. FFDCA § 556(5); 21 U.S.C. § 360aaa-5(5).

3. Recordkeeping and Reporting

A manufacturer must submit to FDA biannually a list of articles and reference publications distributed under Section 401 and a list identifying the categories of persons that received them. FFDCa § 553(a); 21 U.S.C. § 360aaa-2(a). A manufacturer must also maintain records to facilitate any corrective action that FDA might require. FFDCa § 553(b); 21 U.S.C. § 360aaa-2(b). In implementing these requirements, FDA should not require that a manufacturer maintain records of individual recipients of information disseminated under Section 401. Maintaining records of the categories of recipients of information is adequate to facilitate appropriate corrective action and avoids the heavy administrative burden of individual records. The required timing for the submission of reports to FDA should be determined by the date of the first dissemination of any information by the manufacturer.

4. Requirement of Submitting a Supplemental Application

In order to disseminate off-label information concerning a new use under Section 401, a manufacturer must have submitted to FDA a supplemental application covering the new use, certify that it will submit a supplement, or obtain an exemption from the supplement requirement. FFDCa § 554(a); 21 U.S.C. § 360aaa-3(a).³

³ When a manufacturer certifies that it will submit a supplement, it must either certify that it has completed the necessary studies and will submit the supplement within six months of the initial dissemination of off-label information (FFDCa § 554(b); 21 U.S.C. § 360aaa-3(b)), or submit a proposed protocol and schedule for the studies to FDA and commit to filing the supplement within 36 months (FFDCa § 554(c)(1); 21 U.S.C. § 360aaa-3(c)(1)). For proposed studies, FDA must make a determination that the proposed protocol is adequate and that the planned schedule is reasonable. FFDCa § 554(c)(1); 21 U.S.C. § 360aaa-3(c)(1). The manufacturer must also make periodic progress reports to FDA. FFDCa § 554(c)(2); 21 U.S.C. § 360aaa-3(c)(2). FDA can

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When a manufacturer certifies that it will submit a supplemental application within 36 months of disseminating information under Section 401 and submits a proposed protocol and schedule, FDA should determine the adequacy of the proposed protocol and schedule pursuant to FFDCa § 554(c)(1)(B) (21 U.S.C. § 360aaa-3(c)(1)(B)) and resolve any issues with the manufacturer within the 60-day time period prior to the start of information dissemination activities. If FDA does not notify the manufacturer otherwise during the 60-day period before dissemination, the proposed protocol and schedule should be deemed adequate. If FDA has any objection to the proposed protocol and schedule during the 60-day period before dissemination, it should immediately notify the manufacturer and provide the manufacturer an opportunity to meet and resolve the issue.

Progress reports on studies required under this section should be submitted in accordance with the standard IND/NDA reporting requirements.

When a manufacturer applies for an exemption from the supplement requirement, the 60-day period within which FDA must approve or deny the application should run from the date FDA receives the application. FDA should provide timely notice to the applicant of the date it received the application. As specified in Section 401, an exemption request will be deemed to be approved if FDA does not act on it within 60

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extend the 36-month period for up to 24 additional months if the manufacturer has acted with “due diligence.” FFDCa § 554(c)(3); 21 U.S.C. § 360aaa-3(c)(3).

A manufacturer can request an exemption from the supplement requirement if it would be “economically prohibitive” or “unethical” to conduct the studies and submit the supplement. FFDCa § 554(d); 21 U.S.C. § 360aaa-3(d).

days of receipt, although FDA can thereafter terminate the approval. FDCA § 554(d)(3); 21 U.S.C. § 360aaa-3(c)(3).

5. Corrective Actions

If FDA receives new information following the dissemination of information under Section 401 that indicates that the new use may not be effective or may present a “significant risk to public health,” the Agency may, after consulting with the manufacturer, take appropriate action, including ordering the manufacturer to cease dissemination of information concerning the new use. FDCA § 555(a); 21 U.S.C. § 360aaa-4(a). Manufacturers are required to report new safety and effectiveness information to FDA. FDCA § 555(a)(2); 21 U.S.C. § 360aaa-4(a)(2).⁴

Before FDA takes any corrective actions based on a determination that a supplement is inadequate for approval, the Agency should afford a manufacturer the opportunity (informally, or through available appeals procedures) to resolve outstanding issues to avoid unnecessary and burdensome corrective action. The manufacturer should be permitted to continue to disseminate the information related to such an application pending the outcome of any resolution or appeals process. FDA should only order corrective action when the dissemination of information concerning a new use presents a

⁴ FDA may also order a manufacturer to cease dissemination of information under Section 401 if FDA determines that the information being disseminated does not comply with the requirements of Section 401, the manufacturer has not submitted a supplement within six months as promised or has not acted with due diligence in the completion of studies and submission of a supplement, or FDA terminates a “deemed approved” exemption from the supplement requirement. FDCA § 555(b); 21 U.S.C. § 360aaa-4(b). When FDA orders a manufacturer to cease disseminating information, the Agency may also require the manufacturer to take action to correct information that has been disseminated. FDCA § 555(d); 21 U.S.C. § 360aaa-4(d).

significant risk. Corrective action will not be warranted in all cases where FDA does not approve a supplement, and FDA should use its authority under this provision judiciously.

A manufacturer should be able to satisfy its obligations to report new safety and effectiveness information to FDA by complying with the existing postmarketing reporting requirements related to adverse drug experiences (21 C.F.R. § 314.80) and annual reports (21 C.F.R. § 314.81). All significant information on safety and effectiveness is reported through these established mechanisms, and there should be no need to create an additional administrative obligation.

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Section 401 of the FDA Modernization Act provides an important new mechanism to share valuable medical information with health care providers. The detailed requirements already specified in Section 401 ensure that such information must be disseminated in an appropriate manner and that incentives exist to file supplemental product applications. When implementing Section 401, FDA should clarify certain important additional details related to the requirements of Section 401. At the same time, FDA should take care to preserve the compromises and balance already embodied in this significant statutory provision. FDA should not impede implementation of Section 401 by promulgating restrictive regulations where the statutory provisions themselves already provide adequate controls and specific restrictions on the dissemination of off-label information.