

# American Society of Clinical Oncology

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July 21, 1998

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Michael A. Friedman, M.D.  
Acting Commissioner  
Food and Drug Administration  
c/o Dockets Management Branch (HFA-305)  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20857

Re: Docket No. 98N-0222 -- Dissemination of  
Information on Unapproved/New Uses for  
Marketed Drugs, Biologicals, and Devices

Dear Dr. Friedman:

These comments are submitted by the American Society of Clinical Oncology (ASCO) in response to FDA's proposed rules to implement the dissemination provisions of the Food and Drug Administration Modernization Act, which were published in the Federal Register on June 8, 1998. ASCO is the national organization representing physicians who specialize in the treatment of cancer. We have previously written FDA regarding the agency's policy on dissemination of information on "off-label" uses of anticancer drugs, and we remain very interested in this issue.

## Background

Issues related to dissemination of information about new, off-label uses of FDA-regulated products have special significance to the cancer community:

- More than half of all cancer patients received anticancer drugs for off-label uses. These uses, which have not been reviewed by FDA, are the standard of care for most cancers.
- The labeling of anticancer products frequently presents an incomplete or even inaccurate picture of the current state of medical knowledge. For virtually every anticancer drug, appropriate medical usage differs from the terms of the product labeling.

1998

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- The most effective chemotherapy regimens are typically combinations of two or more approved drugs, yet combination regimens are not usually reviewed or approved by FDA, and the approved labeling therefore fails to provide useful guidance.
- Medically accepted off-label uses of approved anticancer products proliferate rapidly on the basis of data from the extensive clinical trials network for cancer

Oncologists are well aware of the inadequacies of the FDA-approved labeling as a guide to treatment, and we adapt our practice accordingly. Instead of relying on the approved labeling, we look to the peer-reviewed medical literature, continuing medical education programs, medical textbooks, and other reliable sources for information on cancer therapies. With so much useful data on off-label uses potentially available to practitioners, it is important to maximize the flow of reliable medical information.

Under the FDA Modernization Act passed by Congress last year, Congress relaxed somewhat the rules under which manufacturers of FDA-regulated products may distribute information related to new, unapproved uses of their products. Manufacturers may disseminate peer-reviewed journal articles and reference publications discussing off-label uses of their products under certain circumstances. In brief, the manufacturer must submit the textbook or journal article to FDA prior to distribution; the submission to FDA must be accompanied by other information known about the new use; FDA can require the manufacturer to distribute additional information, including a statement prepared by FDA; and the manufacturer must agree to submit a supplemental application for FDA approval of the new use within 36 months, unless the criteria for an exemption from this obligation are satisfied.

### **Analysis of the Proposed Regulations**

The legislation that FDA is implementing contains numerous restrictions on the distribution by product manufacturers of journal articles and textbooks discussing off-label uses of their products. Although the law itself is quite restrictive, ASCO believes that the proposed regulations go beyond the law's requirements by creating still further -- and inappropriate -- restrictions. The proposed rules thus fail to permit the desirable goal of increasing the flow of reliable scientific information to oncologists.

- **Eligibility of particular journal articles**

The principal criteria in the statute to determine whether a particular journal article discussing the off-label use of a product may be distributed by the product's manufacturer is whether the article was peer-reviewed by experts and whether the article is about a clinical investigation that would be considered scientifically sound by experts. The proposed regulations

impose rigorous requirements on the content of a journal article to qualify under this provision. Thus, in deciding whether the study was "scientifically sound," FDA would apparently insist on the same degree of rigor it would require in the case of a pivotal trial supporting an application for approval. To be eligible for dissemination, the journal article would need to demonstrate that the study --

- was prospectively planned;
- enrolled an appropriately defined and diagnosed patient population;
- accounted for all patients enrolled, including patients who discontinued therapy prematurely;
- utilized clinically meaningful endpoints, or surrogate endpoints that are reasonably likely to predict safety and effectiveness, with the endpoints assessed using well-established instruments and using appropriate measurement frequencies;
- used an appropriate control group or made reference to an appropriate historical control;
- collected and reported adequate information on adverse experiences and the need for dose reductions and treatment interruptions due to toxicity; and
- was analyzed in a scientifically appropriate manner, with results reported for patient subgroups if response is expected to differ among subgroups.

63 Fed. Reg. 31146-47.

ASCO has two objections to this extensive list of requirements. First, although a study meeting these criteria will certainly meet the test of being scientifically sound, there is no basis for FDA's implied assertion that a study that fails to comply with any of these requirements is scientifically of no value. A study must be judged in its entirety, and a study published in a peer-reviewed journal should not be disqualified from dissemination because it was less rigorous than it ideally might have been.

Second, ASCO is concerned that, under FDA's proposal, the study must not only have met all these requirements, but to be eligible for dissemination, the journal article must contain proof that all the requirements were met. Thus, for example, if a journal article fails to recite how the study drop-outs were handled, or fails to explain how information on adverse experiences was collected, or fails to reference an appropriate historical control, the study would

be considered not scientifically sound and the journal article would not qualify for dissemination. This requirement could be a major impediment to the dissemination of journal articles that the medical community would acknowledge to be descriptive of state-of-the-art medicine.

ASCO recommends that FDA substantially revise its proposed requirements. Articles about clinical trials that are published in peer-reviewed journals should be assessed as to their scientific soundness without resort to a checklist of requirements that must be met to avoid disqualification.

- **Textbooks and other reference publications**

The statute permits manufacturers to distribute certain independently published "reference publications" that are generally available in bookstores or other distribution channels where medical textbooks are sold. The publication may include information about an off-label use of the manufacturer's product if it is "information about a clinical investigation . . . that would be considered to be scientifically sound by experts . . ." We believe that this provision was intended by Congress to permit the distribution of standard medical textbooks, the major drug-use compendia such as the U.S. Pharmacopoeia -- Drug Information, and similar materials.

The proposed implementing regulation, however, makes this provision essentially worthless by declaring that it applies only when the textbook contains "detailed discussions" of the clinical investigation. 63 Fed. Reg. 31146. Apparently, a textbook must contain the same detailed discussion of the clinical trial that FDA would require for a journal article, as discussed above. FDA admits that this interpretation means "the majority of such publications would probably not meet the requirements" of the proposed regulations. Id.

ASCO believes that Congress intended to authorize the distribution of legitimate medical reference works, and FDA's admission that few if any textbooks would qualify under its proposed regulations demonstrates that a different approach is required. Since the law requires only that the information in the reference work be about a scientifically sound clinical investigation, we believe that this requirement would be satisfied if the information or conclusions in the reference work are based on scientifically sound clinical investigations. If a textbook states that Drug X has been found to be effective to treat Disease Y, and the textbook cites the report of a scientifically sound clinical study for that conclusion, the textbook's statement is "about a clinical investigation" and therefore qualifies under the statute. FDA's proposed requirement that the textbook discuss the clinical trial in rigorous detail is inconsistent with what Congress contemplated when it authorized the distribution of textbooks.

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- **Distribution of material to government agencies and insurance companies**

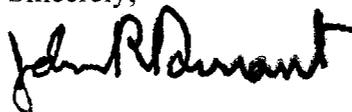
The provisions on dissemination of journal articles and reference publications in the FDA Modernization Act apply to material distributed to government agencies, insurance companies, and group health plans, as well as practitioners and pharmacy benefit managers. FDA should interpret the statute's application to government agencies, insurers, and group health plans in a manner that does not narrow rights that existed under pre-existing law.

Currently, pharmaceutical companies sometimes assist physicians and patients in obtaining reimbursement from Medicare, Medicaid, and private insurers by furnishing copies of journal articles and compendia references related to off-label uses to the insurer or government agency when reimbursement is denied on the ground that the use of the drug is experimental. Since such information is submitted solely for the purpose of helping the insurer or government program determine the drug's legal status under an insurance contract or program regulations -- and not to influence prescription or use of the drug -- it would not appear to constitute labeling subject to FDA's authority. FDA should make clear in its regulations that conduct such as this that was legal prior to the FDA Modernization Act did not become illegal as a result of Congress's attempt to liberalize the rules on dissemination of information on new uses. Such disseminations should not be subject to the provisions of the new law.

#### **Conclusion**

ASCO believes that the proposed regulations are unnecessarily restrictive. FDA should adopt regulations that permit the dissemination of reliable scientific information. As proposed, however, the regulations would have the effect of stifling such dissemination by severely limiting the conditions under which it could occur. We encourage FDA to review its approach to implementing the new law and seek to maximize the free flow of information to oncologists and other physicians who rely on published material as a substitute for the frequently inadequate FDA-approved labeling.

Sincerely,



John R. Durant, MD  
Executive Vice President

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