

American Medical Association

Physicians dedicated to the health of America



E. Ratcliffe Anderson, Jr., MD 515 North State Street 312464-5000
Executive Vice President, CEO Chicago, Illinois 60610 312464-4184 Fax

July 23, 1998

1 8 3 2 '98 JUL 23 P 1 :50

Dockets Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, Maryland 20857

RE: Dissemination of Information on Unapproved/New Uses for Marketed Drugs,
Biologics, and Devices [Docket No. 98N-0222]

Dear Sir or Madame:

The American Medical Association (AMA), representing approximately 300,000 physicians and physicians-in-training, is pleased to comment on the Food and Drug Administration's (FDA) Proposed Rule entitled, "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices." 63 Fed.Reg. 109, pp. 31143 – 31161. This Proposed Rule is intended to implement the provisions of Section 401 of the "Food and Drug Administration Modernization Act of 1997" [P.L. 105-399] (FDAMA). The AMA intends to limit its comments to Subparts 99.101 and 99.205 of the Proposed Rule.

Subpart 99.101

Section 401 of FDAMA was passed with strong bipartisan support and intends to balance two important objectives. First, this provision was intended to facilitate the dissemination of independently-derived scientific information by manufacturers, concerning the safety, effectiveness, or benefit of a use not described in the FDA-approved labeling of a drug, biologic, or device (off-label use). The second key objective of Section 401 was to ensure that important new research leading to new labeled uses is undertaken. This is accomplished by allowing manufacturers to disseminate off-label use information only if: 1) a supplemental application for such use has been submitted to the FDA; 2) the manufacturer agrees to submit a supplemental application within six months; or 3) the manufacturer submits a protocol and schedule for studies that will result in submission of a supplemental application within 36 months.

After reviewing proposed 99.101, particularly 99.101 (b)(1) and its description on pages 31146-31147, the AMA believes the FDA has discounted the intent, and possibly the actual statutory language, of Section 401 of FDAMA. In 99.101(b)(1) and its description on pages 31146-31147, the FDA proposes to severely restrict what journal articles or reference publications are acceptable for dissemination by imposing extremely rigorous requirements on what is a "scientifically sound clinical investigation."

While the randomized controlled clinical trial is the "gold standard" of such an investigation, we recognize that other studies can provide valuable information to physicians. It would be

98N-0222

c 23

difficult for many peer-reviewed journal articles, and impossible for reference textbooks, to meet the FDA's proposal for a comprehensive presentation of the study design and conduct, data presentation and analysis, summary of results, and conclusions of a clinical investigation. Excellent review articles, consensus statements, practice guidelines, case control studies and the like would be precluded from consideration. Thus, rather than facilitating the flow of independently-derived scientific information about off-label uses, the FDA essentially will retain the current limited flow of such information from manufacturers.

Regarding the dissemination of journal articles, Section 552(a)(1)(A) of Section 401 of FDAMA states that as long as an unabridged reprint or copy of the article is a clinical investigation that would be considered to be "scientifically sound" by those experts who are peer-reviewers for the journal, and the journal meets the requirements of Section 556(5), then the article is eligible for dissemination. The AMA believes that the FDA should follow the intent of the law and allow dissemination of journal articles that meet the requirements of Sections 552(a)(1)(A) and 556(5). The FDA has adequate other opportunities, both as described in Section 401 of the law and as proposed in 99.103 of this regulation, to exercise its oversight in ensuring that a manufacturer is not providing misleading or unbalanced information on an off-label use. Furthermore, by requiring the submission of a supplemental application in exchange for the privilege of disseminating information about off-label uses, the law provides a built-in mechanism to discourage manufacturers from frivolously disseminating journal articles under Section 401.

Under the FDA's proposal, it would be virtually impossible for a manufacturer to disseminate a reference textbook containing information about off-label uses because the FDA elected to impose the same rigorous requirements for a "scientifically sound clinical investigation" on reference publications as for journal articles. Rarely, if ever, would a reference textbook contain such detailed information. The FDA claims this problem has occurred because of the ambiguity of the term "reference publication," as used in Section 401 of FDAMA. The AMA appreciates the FDA's dilemma. However, Section 552(b) of Section 401 of FDAMA lists five criteria for a reference publication that are nearly identical to the FDA's own "Guidance for Industry Funded Dissemination of Reference Texts" (*Federal Register*, 1996;61 (196):52800-52801). Thus, the AMA believes it would be both practical and appropriate for the FDA to specifically allow dissemination of reference textbooks with off-label use information, provided the reference textbook meets the five criteria listed under Section 552(b).

Subpart 99.205

Under Section 554(d) of Section 401 of FDAMA, a manufacturer may apply for an exemption from meeting the requirements for a supplemental application if it is economically prohibitive to submit the application or it is unethical to conduct the necessary studies. The law gives the Secretary substantial discretion to define the circumstances when an exemption will be allowed.

As proposed in 99.205 and its accompanying description on pages 31148-31150, the FDA has taken the position that such exemptions should be granted rarely and the agency has proposed rigorous criteria that must be met by manufacturers to obtain such an exemption. Generally, the AMA concurs with the FDA that exemptions should be granted rarely under Section 401, especially when sought for economic reasons.

At its 1997 Annual Meeting, the AMA's House of Delegates adopted the recommendations of our Council on Scientific Affairs' (CSA) Report 3, "Unlabeled Indications of Food and Drug Administration-Approved Drugs" (enclosed). By adopting this report, AMA members made it

very clear that the AMA should "support the addition to FDA-approved labeling those uses of drugs for which safety and efficacy have been demonstrated." If manufacturers could easily obtain exemptions from meeting the requirements for a supplemental application under Section 401, the important research leading to new labeled uses would not be done.

Despite the above concerns about the granting of exemptions under Section 401, the AMA does support the need for an efficient supplemental application process. In the enclosed CSA report, a number of recommendations are put forward to achieve this goal. These include user fees, streamlining the review process, and legislation to provide extensions of marketing exclusivity for the product to manufacturers who submit and gain approval for efficacy supplements. While the AMA's recommendations go beyond the scope of the Proposed Rule being discussed in this letter, we hope you will find them useful and offered in the spirit of cooperation.

Section 554(d)(2)(b) of Section 401 of FDAMA instructs the Secretary, when determining whether to grant an exemption for ethical reasons, to consider "whether the new use involved is the standard of medical care for a health condition." The FDA includes this consideration in proposed 99.205 and, on page 31150 (column 1) of the Description, the FDA lists various sources that can be used to provide evidence that the new (off-label) use represents standard medical therapy. Generally, the AMA is supportive of this list; in particular, the FDA is encouraged to consult with relevant medical specialty societies regarding the status of the off-label use in medical practice.

As a footnote, regarding the use of current compendia for establishing the status of an off-label use as standard medical treatment, we would remind the FDA that the last edition of the AMA's *DRUG EVALUATIONS*, as a stand-alone product, was published in 1995. At that time, the AMA and the United States Pharmacopeial Convention, Inc. (USP) entered into a contractual alliance to merge the *DRUG EVALUATIONS* and the *USP Dispensing Information (USP-DI)* (Volume I) databases. However, the USP recently made a strategic decision to stop maintaining its database, and they have come to the AMA seeking to terminate the contract to merge the databases. Therefore, after 1998, neither the AMA's *DRUG EVALUATIONS* nor the *USP-DI* may be available.

In conclusion, the AMA believes that if the FDA adopts the recommendations outlined above, the dissemination of accurate, unbiased and balanced information about off-label uses of drugs, biologics, and devices will be facilitated and the supplemental approval process will be improved. The AMA appreciates the opportunity to comment on this important Proposed Rule and looks forward to continuing to work with the FDA on its successful implementation.

Sincerely,



E. Ratcliffe Anderson, Jr., MD

Enclosure

**THIS DOCUMENT IS NOT INCLUDED BECAUSE IT
CONTAINS COPYRIGHT MATERIALS**

**DOCKET
98N-0222**

**ON
FDAMA SECTION 401 DISSEMINATION OF INFORMATION ON UNAPPROVED/NEW USES**

Comment 23

**"3. UNLABELED INDICATIONS OF FOOD AND DRUG ADMINISTRATION-APPROVED DRUGS
(RESOLUTION 508, A-96) HOUSE ACTION: RECOMMENDATIONS ADOPTED AS FOLLOWS
IN LIEU OF RESOLUTION 508 (A-96) AND REMAINDER OF REPORT FILED;" Scientific
Affairs-3, June 1997, pp 403-413.**

THIS MATERIAL MAY BE OBTAINED BY:

VISITING THE PUBLIC ROOM AT:

**DOCKETS MANAGEMENT BRANCH
FOOD & DRUG ADMINISTRATION
12420 PARKLAWN DRIVE, ROOM 1-23
ROCKVILLE, MD 20857**