

American Medical Association

Physicians dedicated to the health of America



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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

**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:**

Resolution 508, introduced at the 1996 Annual Meeting by the Florida Delegation and referred to the Board of Trustees by the House of Delegates, asks:

That the American Medical Association seek to have the Food and Drug Administration (FDA) rescind any limits on **dissemination** of accurate information on off-label [unlabeled] therapies originating or referenced in quality peer-reviewed medical literature or otherwise validated by a peer panel of academic and community physicians of appropriate specialty expertise, and

That the AMA seek modification of FDA policies and procedures to expedite review of Supplemental New Drug Applications (**SNDAs**) regarding such **well-documented** off-label [unlabeled] indications to bring approved labeling rapidly into compliance with optimal medical practice; and

That the AMA seek modification of FDA policies and procedures to allow the approval process to accept evidence of safety **and** effectiveness developed through the approval process and accumulated clinical experience for the same therapies in other countries, and through independent evaluation and publication in the peer-reviewed scientific literature.

This Council on Scientific Affairs report responds to the above resolution by reviewing the subject of unlabeled (also called off-label) indications (uses) of FDA-approved drugs. While this report does not specifically consider unlabeled uses of medical devices, some of the recommendations at the end of the report are also applicable to **medical** devices. This report considers the FDA approval process for supplements to New Drug Applications (**NDAs**) that are submitted for new indications, including those for **uses** in special populations (e.g., pediatrics), because this is especially relevant to the unlabeled use issue. These supplements are called efficacy supplements or Supplemental New Drug Applications (**SNDAs**), and these terms will be used interchangeably throughout the report. However, the report neither addresses the FDA approval process globally nor does it address other FDA issues. Recent AMA Board of Trustees Reports 32-A-95 (**recommmendations** adopted), 45-A-95 (informational), 18-A-96 (recommendations adopted), and 3-I-96 (informational) have provided detailed considerations of the FDA approval process and other FDA issues.

LABELED AND UNLABELED USES: DEFINITIONS AND CLINICAL SIGNIFICANCE

As part of its regulatory function **in** approving drug products for marketing **in** the United States, the FDA also approves each drug product's labeling, i.e., container label, package insert, and certain advertising. This is referred to as FDA-approved **labeling**. Unlabeled uses are defined as the use of a drug product for **indications** or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling.

Under the federal Food, Drug, and Cosmetic (**FD&C**) Act, a drug approved by the FDA for marketing may be labeled, promoted and advertised by a manufacturer for only those uses for which the drug's safety and efficacy have been established. This requires submission of data by the manufacturer to the FDA demonstrating substantial evidence of efficacy and safety for each labeled indication. However, the **FD&C** Act does not limit the manner in which a physician may use an FDA-approved drug. A physician may choose to prescribe a drug for uses or in treatment regimens or patient populations that are not in approved labeling. This decision is made by the physician in light of **all** information available and in the **best** interests of the individual patient. Prescribing for an unlabeled use only requires the physician to use the **same** judgment and prudence as exercised in medical practice in general for it to conform to accepted professional standards.

The prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial. Historically, there are numerous examples of drugs for which FDA approval for a particular indication was sought and granted long after widespread **medical** acceptance. These include **propranolol** for angina and hypertension **lidocaine** for arrhythmias; **metronidazole** for **amebiasis**; **diazepam** for status epilepticus; and **amantadine** for **parkinsonism**.

In 1990, 88 drugs from nine chapters in the AMA's **Drug Evaluations** were reviewed to identify unlabeled uses. For the 88 drugs, 466 unlabeled **uses** were listed, and in 18 percent of these the drug was a preferred agent for the unlabeled indication.

Unlabeled indications are especially common in oncology, rare diseases, and pediatrics. For example, a U. S. General Accounting Office (GAO) survey of clinical oncologists showed that 56 percent of cancer patients were receiving at least one drug for an unlabeled use, and an audit conducted by the Association of Community Cancer Centers found that the majority of combination chemotherapy regimens, which are considered to be standard **medical** practice in oncology, included unlabeled uses for at least one of the agents. The National **Organization** for Rare Disorders (**NORD**) estimates that for those rare diseases that are treated with pharmaceuticals, approximately 90 percent of the usage is off-label. Similarly, the American Academy of Pediatrics (**AAP**) reports that only 20 percent of all marketed drug products in the United States have had clinical trials performed in children, that of the 80 drugs most frequently used to treat newborns and infants only 5 are labeled for use in children, and that of 28 new drugs approved in 1995 only 4 have pediatric labeling. In 1996, the AAP's Committee on Drugs published a review and policy statement on unlabeled uses.

Given the prevalence of unlabeled uses and the fact that in many clinical situations such use may represent the most appropriate treatment, the prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care. Therefore, the AMA's policy is:

That a physician may lawfully use an FDA approved drug product for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion (Policy 120.988).

The need for physicians to prescribe drugs for unlabeled uses is unchallenged. The position of the **FDA** on physician prescribing of unlabeled uses essentially supports that of the AMA. The FDA's published statement that **addresses** the appropriateness and legality of prescribing FDA-approved drugs for unlabeled uses includes *the* following:

The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

COVERAGE AND REIMBURSEMENT FOR FDA-APPROVED DRUGS PRESCRIBED FOR UNLABELED USE

Medical practice is dynamic in nature, and the standards of practice for drug **therapies** are continually **evolving**. Thus, at any given point in time, unlabeled uses can range from well established and **preferred** to therapies of **uncertain** efficacy and/or safety, or even a contraindication, for a particular unlabeled use. This has become a practical **problem** from the **perspective** of coverage and **reimbursement** for drugs prescribed for unlabeled **uses**. **Third party payors** typically exclude **coverage** for experimental therapies, and payers **frequently** have denied **reimbursement** for drug **products** used for unlabeled uses because they considered them to be experimental. For example, the GAO survey of **oncologists** revealed that 50 percent of respondents had experienced a reimbursement denial for an unlabeled use in the **pre-**ceding 12 months, that 10 percent had altered therapies because of reimbursement problems, and that **over 60** percent had admitted patients into the hospital solely to circumvent restrictions imposed by reimbursement **policies**.

Physicians have expressed great concern about the failure of third party payers to reimburse for FDA-approved drugs that **are** prescribed appropriately for unlabeled uses. The AMA has adopted the following policy:

That when the prescription of a drug represents safe and effective therapy, third party payers should consider that drug as reasonable and necessary medical care, irrespective of labeling, and should fulfill their obligation to their beneficiaries by covering such therapy (Policy 120.988).

The AMA position is shared by a number of provider and consumer organizations, and both the national Blue Cross and Blue Shield Association of America (**BC/BS**) and the Health Insurance Association of America (**HIAA**) have agreed that reimbursement for drug products used for medically necessary unlabeled uses is appropriate.

A key issue in the debate on coverage and reimbursement for unlabeled uses is what can be relied upon to define a medically appropriate unlabeled indication. In that regard, the AMA has taken the following position:

That the AMA encourages the use of three compendia (AMA's Drug Evaluations, * United States Pharmacopeia-Drug Information, Volume I,* and American Hospital Formulary Service-Drug Information) and the peer-reviewed literature for determiningg the medical acceptability of **unlabeled** uses (Policy 165.8%, #15). (***These** two compendia currently are being merged as the result of an alliance between the AMA and the **United** States Pharmacopoeia.)

The above-named compendia were identified because they are authoritative, up-to-date, comprehensive and unbiased, and they rely on a process that includes the consideration of evidence-based literature and the input of a large body of outside expert consultants.

The AMA position has been included in two federal statutes, the Omnibus Budget Reconciliation Act of 1990 (**OBRA '90**), which requires use of the three compendia and the peer-reviewed literature for determiningg medically acceptable unlabeled uses of outpatient prescription drugs used in state **Medicaid** programs, and the Omnibus Budget Reconciliation Act of 1993 (**OBRA '93**), which requires use of these sources for coverage of unlabeled uses of **antineoplastic** drugs in the Medicare program. Various state statutes have included language similar to OBRA '90 for coverage of unlabeled uses, and the GAO and the HIAA have encouraged use of the compendia for reimbursement purposes.

DISSEMINATION OF INFORMATION ABOUT UNLABELED USES

It is imperative that physicians have access to accurate and unbiased information about unlabeled uses of prescription drugs. Currently, physicians obtain this information through a variety of sources, including the compendia, journal articles, continuing medical education symposia and professional meetings. **In** addition, physicians can obtain information about an unlabeled use from a pharmaceutical manufacturer, provided the physician makes a specific request (unsolicited by the manufacturer) for the information.

Under current FDA regulations, pharmaceutical manufacturers are prohibited from providing physicians with unrequested information about unlabeled uses or any other information relating to the dosing, safety, or effectiveness of their products that is inconsistent with FDA approved labeling. The FDA considers the provision of such information, regardless of the source, as promotion of the product. The FDA's rationale for its position is twofold. First, it contends that manufacturers will have no incentive to do the necessary research and file SNDAS for new indications if they can promote unlabeled uses. Second, the FDA cites selected examples (e.g., the use of **encainide** and **flecainide** to suppress ventricular premature complexes) for which promotion of an unlabeled use could have resulted in many unnecessary deaths.

On October 8, 1996, the FDA published two guidances to clarify its position on information dissemination. 'he FDA's "Guidance for Industry Funded Dissemination of Reference Texts" represented a step forward in improving

the dissemination of accurate and unbiased information about drugs, including unlabeled uses, to physicians. This guidance generally was acceptable to physician **organizations**, and the Council on Scientific Affairs has included criteria for the dissemination of complete textbooks by manufacturers, almost identical to the FDA's criteria, in the recommendations to this report. On the other hand, the FDA's "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data" was extremely narrow in that the FDA would allow industry sponsors to disseminate only those journal articles that report well controlled studies of effectiveness for uses or indications that already have been approved by the Agency.

Whether pharmaceutical manufacturers should be allowed to disseminate unsolicited information, particularly reprints of journal articles, about unlabeled uses to physicians continues to be one of the most contentious issues of FDA reform legislation. Generally, the FDA and a number of consumer groups have opposed this, and the pharmaceutical industry and a number of physician organizations, including the American Society of **Clinical Oncology (ASCO)** and the AMA, have supported some relaxation of current FDA policy.

There is evidence in the medical literature that physicians, despite believing they were prescribing based on objective scientific evidence, were actually prescribing inappropriately based on the influence of commercial sources. Thus, the Council on Scientific Affairs believes that there needs to be a distinction between what is independently derived scientific information and what is manufacturer-sponsored promotion. Continued FDA regulation of the latter is supportable to ensure that promotional information is not false or misleading.

On the other hand, many physicians may not have access to all of the latest, scientifically credible information about unlabeled uses. For example, the majority of clinical oncologists practice in nonacademic settings and may not have easy and timely access to potentially life-extending information about new cancer therapies. Thus, the Council also believes that educational value for physicians can be obtained if pharmaceutical manufacturers are allowed to disseminate reprints from journal articles, provided physicians can be assured that the information was independently derived, published in a reputable, peer-reviewed journal, and not altered by the manufacturer. In the recommendations to this report, the Council offers criteria for the dissemination of reprints from journal articles by manufacturers that can achieve these goals. These criteria essentially are identical to those submitted to the U.S. Congress by the AMA in response to FDA reform legislation (see Board of Trustees Report 18-A-96, adopted).

It also appears appropriate to **allow** pharmaceutical manufacturers to disseminate reprints of monographs or chapters from the compendia. As discussed earlier in this report, the U. S. Congress **specifically recognized** the compendia as resources to determine the **medical** acceptability of unlabeled uses for reimbursement purposes.

As noted above, physicians frequently learn about unlabeled uses of drugs from scientific meetings and continuing medical education (**CME**), and pharmaceutical manufacturers may sponsor these activities. **In 1992**, the FDA issued a draft policy statement on industry-sponsored scientific and educational activities, such as CME courses. In effect, the policy **recognized** the standards established for CME by the Accreditation Council for Continuing Medical Education (**ACCME**) and described categories of educational activities that may continue to be funded by industry and yet avoid regulation as advertising or promotional labeling. The FDA recognized the important **role** accrediting organizations played in ensuring that industry-supported accredited CME activities were independent **and** nonpromotional. Essentially, a policy of regulatory deference was put into place if educational activities were conducted by appropriately accredited sponsors of CME.

AMA policy reinforces the importance of the integrity of medical education and the process of accreditationⁿ in CME. Only accredited sponsors can designate CME activities for credit toward the AMA's Physician's **Recognition Award (AMA PRA)** and, if so designated, these activities must additionally be in compliance with all **AMA PRA** policies and the AMA Ethical Opinions on Continuing Medical Education (9.011) and on gifts to **Physicians** (8.061) (see AMA PRA Information Booklet, January 1997). In 1992, the AMA House of Delegates 'tom.mend~ the activities of all parties, including the FDA, who worked under the auspices of the National Task Force on **CME Provider-Industry Collaboration in CME**, to develop the guidelines and clear concepts of independence for **educational** activities supported by commercial companies" (Policy 300.965) Also in 1992, the AMA House of **Delegates**

endorsed the ACCME's Revised Standards for Commercial Support of CME and pledged "to give the standards the greatest publicity possible" (Policies 300.971, 300.972). In 1995, the AMA incorporated the recommendations of the National Task Force on CME Provider-Industry Collaboration and the ACCME's revised Standards for Commercial Support of CME into its Standards for Industry-Supported Multimedia Continuing Medical Education and other Communications, which was approved by the Council on Medical Education in June 1995.

The Council on Scientific Affairs believes that it is essential that the policies in the FDA Draft Policy Statement of 1992 be finalized, and that the private accreditation sector have the responsibility for monitoring the independence and overall quality of accredited CME activities.

It is important that physicians have access to both positive and negative information about unlabeled uses. For example, a recent report showed that the widespread practice of prescribing sublingual nifedipine capsules for hypertensive emergencies and pseudoemergencies can result in serious adverse events with little evidence that the drug is effective for this unlabeled use. This becomes especially problematic when the evidence showing lack of efficacy is unpublished and proprietary to the manufacturer. The Council believes that manufacturers should report this information to the FDA and share the information with the entire physician community in a timely manner. This is consistent with current AMA policy (Policy 100.999) that urges the FDA to set up mechanisms to release information on drugs that are harmful or ineffective.

IMPROVING THE SUPPLEMENTAL NEW DRUG APPLICATION (SNDA) PROCESS

Physicians should strongly support FDA approval of SNDAS for unlabeled uses so that these uses become part of the FDA-approved labeling. Potential problems associated with prescribing the drug correctly, reimbursement and malpractice liability are likely to be lessened if the use is included in FDA-approved labeling. For example, the pediatrician will have greater confidence that the correct dosage has been prescribed, and the oncologist will have greater assurance that the drug treatment will be covered by a third party payor. Therefore, the Council on Scientific Affairs believes that all interested parties, including the U. S. Congress, the FDA, pharmaceutical manufacturers, patient organizations and medical specialty societies have a responsibility to work together to improve the SNDA process.

The question must be asked, "Why are there currently so many medically accepted unlabeled uses of FDA-approved drugs?" The simple answer is that FDA-approved labeling does not necessarily reflect current medical practice. Under the 1962 amendments to the federal Food, Drug and Cosmetic (FD&C) Act, approved labeling is restricted to those uses for which the sponsor (usually the manufacturer) has provided adequate evidence to the FDA to substantiate the safety and efficacy of the product. However, manufacturers are not required to and may not seek FDA approval for all useful indications. A major reason is because the expense of regulatory compliance may be greater than the eventual revenues expected (e.g., if patent protection for the drug product has expired, or if the patient population affected by the new use is very small). A sponsor also may not seek FDA approval because of difficulties in conducting controlled clinical trials (e.g., for ethical reasons, or due to the inability to recruit patients). Finally, even when a sponsor does elect to seek approval for a new indication, the regulatory approval process for the required SNDA is expensive and may proceed very slowly.

Prior to implementation of the Prescription Drug User Fee Act of 1992 (PDUFA), the FDA's performance in approving efficacy supplements was poor. For example, evidence compiled by DiMasi, et al, shows that from 1984 to 1992, the mean review times for supplemental indications lagged behind the mean review times for the original indications for the drug products; the overall mean review time for SNDAS during this period was about 28 months versus 24 months for the original NDA. This observation is unexpected because the SNDA should be much simpler to review than the original NDA, and suggests the FDA gave much lower priority to the review of SNDAS.

The FDA's performance in reviewing efficacy supplements has improved considerably under PDUFA. Under this Act, the FDA must meet certain performance goals for action on efficacy supplements in the same way that

it is accountable for processing new drug applications. The GAO has reviewed the FDA's performance and reported the following approval times for efficacy supplements in months:

<u>Year of Submission</u>	<u>Number of Submissions</u>	<u>Percent Approved</u>	<u>Median Approval Time</u>	<u>Mean Approval Time</u>
1993	69	57	18	19
1994	67	63	14	14
1995	48	71	12	12

Current data indicate that FDA actions on both **NDA**s and **SNDAs** have become substantially more timely under PDUFA, most likely because the FDA has had the **necessary** resources from user fees to meet their review time deadlines. (See also Board of Trustees Report 3-I-96, informational.) Therefore, the Council believes user fee legislation should be reauthorized by Congress in 1997.

The FDA also has initiated steps to improve the SNDA process. For example, in December 1994 the Agency finalized a rule that would allow approval of pediatric uses based on adult efficacy studies where the course of the disease and the effects of the drug are sufficiently similar in both populations. The manufacturer would be required to provide some additional information for pediatric use, usually **pharmacokinetic** studies for determination of dosage. The American Academy of Pediatrics (**AAP**) has raised concerns that this regulation has not increased labeling for **children**, although the FDA has stated that there are indications that submissions under this regulation have already increased (Stuart L. Nightingale, MD, personal communication). Manufacturers should be encouraged to pursue pediatric labeling via this regulation.

In 1996, the FDA assembled an internal task force, the Supplemental Indications Working Group, to examine, in depth, the broad range of issues that influence whether a supplemental indication is incorporated into a product's labeling. Thus far, this Working Group has developed two "draft" guidances for industry, entitled Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, and FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products (the **latter** done in collaboration with the FDA's **Division** of Oncology Drug products). These "draft" guidances were released by the FDA for public comment on March 13, 1997. The **Council** on Scientific Affairs strongly supports efforts by the FDA to streamline the **SNDA** process to facilitate the inclusion of more medically accepted uses in the approved labeling.

The fundamental precept of drug regulation in the United States is that drug products must be proven safe and effective for their intended indications before they can be marketed. A controversial issue in the debate over FDA reform generally, and in expediting the review process for efficacy supplements, has been whether the **efficacy** standard should be lowered. Current AMA policy (Policies 100.986 and **100.992, #1**) supports that **drug** approvals be based on sound scientific evidence from controlled clinical trials. The **AMA**, with **full support** from the Council on Scientific Affairs, has raised concerns about weakening the efficacy standard because ineffective **drugs could** be marketed or already marketed drugs could be promoted for indications for which efficacy is lacking. The **Drug Efficacy Study Implementation (DESI) project** provides historical evidence that **this is likely to occur**. Of 3,443 drugs reviewed under DIM, 1,124 were withdrawn from the market because they were not effective (see Board of Trustees Report 18-A-%, **recommendations** adopted). Thus, for the purpose of obtaining FDA-approved **labeling**, the Council supports the current requirements for adequate and well-controlled clinical studies to prove the drug **is** effective for the proposed indication. With regard to unlabeled uses, adequate well-controlled clinical studies **may** already have been published in the peer-reviewed literature, **and the FDA may be able to make its review decision** based on published literature (so-called "paper" **SNDAs**).

A specific issue raised in referred Resolution 508 was the use of foreign data to support drug approvals (**NDA**s and **SNDAs**) by the FDA. The FDA has long been an advocate of international harmonization, and the Agency **does**

use foreign data for some approvals in the United States. The AMA is supportive of international harmonization efforts (Policy 100.994) and the use of foreign data by the FDA (Policy 100.993, #2) to increase efficiency and optimize resources (see also Board of Trustees Report 45-A-95, informational).

The process of updating a drug's labeling cannot be accomplished by the FDA alone. SNDAS cannot be acted upon if they are not **submitted**. Pharmaceutical manufacturers may be enticed to submit more supplemental applications if the FDA improves the review process. However, additional economic incentives probably will be necessary, especially for indications where the company's expected return on its investment will be low. The Orphan Drug Act of 1983 has been considered successful in making orphan drugs available because **its** 7-year marketing exclusivity provision is a powerful incentive to manufacturers. Similar legislation should be enacted to provide incentives for manufacturers to submit efficacy supplements. Such legislation should be fair in the sense that rewards are proportionate to the level of investment and the importance of the **indication** (e.g., treatment of a life-threatening disease for which there are no alternatives) and safeguards are included to prevent manufacturers from inappropriate use of the system (e.g., repeatedly obtaining **additional** marketing exclusivity for trivial new uses).

Drug products that are no longer under patent protection and for which generic versions are available pose a particular problem because manufacturers have little incentive to file efficacy supplements. The Council on Scientific Affairs believes that the FDA, the **pharmaceutical** industry, the United States **Pharmacopeia**, patient organizations and medical specialty societies must come together and **find** alternative mechanisms to submit and obtain approval for these SNDAs. Submission of petitions by nonprofit organizations, such as patient organizations or medical specialty societies, may be an option. However, when additional clinical trials are necessary, funding will have to come from industry, government or some private funding body.

ENCOURAGING CLINICAL RESEARCH IN PEDIATRICS

As discussed earlier **in** this report, unlabeled uses are especially common in pediatrics. The primary reason is that manufacturers usually do not conduct pediatric clinical research **studies** during the development of investigational drugs, despite a high likelihood that the drugs will be **useful** in children. The AAP has labeled children as "therapeutic orphans" and has presented a series of recommendations to Congress to improve pediatric labeling of drugs.

Current AMA policy (Policy 100.987) supports development **and** testing of drugs **in** pediatric age groups. The Council on Scientific Affairs is supportive of the **AAP** and believes that pharmaceutical manufacturers and the FDA must work with the **AAP** and experts in pediatric medicine to **identify** those investigational drugs that would have **pediatric** indications and setup a mechanism to ensure that necessary pediatric clinical studies are completed prior to submission of NDAs for approval of these drug products. If this can be accomplished, unlabeled uses in pediatrics would be markedly reduced.

As with orphan drugs, legislation should be enacted that would extend marketing **exclusivity** for products of manufacturers who complete pediatric studies that lead to pediatric labeling. This should provide the economic incentive for manufacture to do the necessary studies. Senator Nancy **Kassebaum** (R-KS) introduced a bill called the Better Pharmaceuticals for Children Act of 1994 (S.2010) that would accomplish this goal, but it has not been passed. This legislation was incorporated into the Senate FDA reform **bill** (S. 1477) and should be supported during the 1997 **congressional** session.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following statements be adopted as policy in lieu of Resolution 508 (A-96):

Prescribing and Reimbursement for FDA-Approved Drugs for Unlabeled Uses

1. That the American Medical Association reaffirm the following policies:

- a. That a physician may lawfully use an FDA-approved drug product for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion (Policy 120.988);
- b. That when the prescription of a drug represents safe and effective therapy, third party payors should consider that drug as reasonable and necessary medical care, irrespective of labeling, and should fulfill their obligation to their beneficiaries by covering such therapy (Policy 120.988); and
- c. That the AMA encourages the use of **three** compendia (AMA's Drug Evaluations, * United States Pharmacopeia-Drug Information, Volume I,* and American Hospital Formulary Service-Drug Information) and the peer-reviewed literature for determining the medical acceptability of unlabeled uses (Policy 165.896, #15). (*These two compendia currently are being merged as the result of an alliance between the American Medical Association and the United States Pharmacopeia.)

Dissemination of Information about Unlabeled Uses of Drugs by Manufacturers

2. That the AMA strongly support the important need for physicians to have access to accurate and unbiased information about unlabeled uses of drugs, while ensuring that manufacturer-sponsored promotions remain under the Food and Drug Administration (FDA) regulation.
3. That the AMA support the dissemination of independently derived scientific information about unlabeled uses by manufacturers to physicians, if the independent information is provided in its entirety, is not edited or altered by the manufacturer, and is **clearly** distinguished from manufacturer-sponsored materials. Dissemination of information by manufacturers to physicians about unlabeled uses can be supported under the following conditions:
 - a. Reprints of independently derived articles from reputable, peer-reviewed **journals** that meet the following criteria
 1. The article should be peer reviewed and published in accordance with the regular peer review procedure of the journal in which it is published.
 2. The reprint should be from a peer-reviewed journal that both has an editorial board and utilizes experts to review and objectively select, reject, or provide comments about proposed articles. Such experts should have demonstrated expertise in the subject of the article under review, and be independent from the journal.
 3. The journal is recognized to be of national scope and reputation, as defined by an advisory panel to the FDA. Among its members, this advisory panel should have representatives from national medical societies.
 4. The journal must be indexed in the Index Medicus of the National Library of Medicine.
 5. The journal must have and adhere to a publicly stated policy of full disclosure of any conflicts of interest or biases for all authors or **contributors**.
 6. When the subject of the article is an unlabeled use, or the article contains other information that is different from approved labeling, the industry sponsor disseminating the reprint must disclose that the reprint includes information that

has not been approved by the FDA and attach a copy of the FDA-approved professional labeling with the reprint.

7. If financial support for the study **and/or** the author(s) was provided by the industry sponsor disseminating the article, and this is not already stated in the article, then this information should be clearly disclosed with the reprint.
- b. Reprints of monographs or chapters from the three compendia (AMA's Drug Evaluations, United States Pharmacopeia-Drug Information, Volume I, and American Hospital Formulary Service-Drug Information) named in federal statutes for determining the medical acceptability of unlabeled uses, provided:
1. The monograph or chapter is reprinted in its entirety by the publisher of the compendia, and the reprints are then sent to the requesting industry sponsor.
 2. The reprints are not **altered** in any way by the **industry** sponsor.
 3. The industry sponsor **disseminating** the reprint **discloses** that the reprint includes information that has not been approved by the FDA and attaches a copy of the FDA-approved professional labeling with the reprint.
- c. Complete textbooks that meet the following criteria:
1. The reference text should not have been written, edited, excerpted, or published specifically for, or at the request of, a drug, device, or biologic firm. When financial support is provided by a drug, device, or biologic firm, it should be disclosed clearly in the textbook.
 2. The content of the reference text should not have been **edited** or significantly influenced by a drug, device, or biologic firm, or agent thereof.
 3. The reference text should be generally available for sale in bookstores or other distribution channels where similar books are normally available and should not be distributed only or primarily through drug, device, or biologic firms.
 4. The reference text should not focus primarily on any particular drug(s), device(s), or biologic(s) of the disseminating company, nor should it have a significant focus on unapproved **uses** of drug(s), device(s), or biologic(s) marketed or under investigation by the firm supporting the dissemination of the text.
 5. Specific product information (other than the approved package insert) should not be physically appended to the reference text.
- d. Manufacturers should report to the FDA and share with all physicians any proprietary information that a drug is ineffective or unsafe when used for a specific unlabeled indication.
- e. Continuing medical education (**CME**) activities:
1. The FDA should continue to support principles in the FDA Draft Policy Statement on Industry-Supported Scientific and Educational Activities (Federal

Register 1992; **57:56412-56414**), which acknowledges the importance of relying on the professional health care communities, rather than the Agency, to monitor independent provider activities.

2. The FDA should continue a policy of regulatory deference for **industry**-supported CME activities conducted by **organizations** accredited by the Accreditation Council for Continuing **Medical** Education (**ACCME**), state **medical** societies, specialty societies and the American Academy of Family Physicians that follow the Essentials and Standards of the **ACCME** and that may be certified for AMA PRA **credit** under the auspices of the American Medical Association Physician's Recognition Award program.
4. That physicians have the responsibility to interpret and put into context information **received from** any source, including pharmaceutical manufacturers, before making clinical decisions (e. g., prescribing a drug for an unlabeled use).

Improving the Supplemental New Drug Application (**SNDA**) Process

5. That the AMA strongly support the addition to FDA-approved labeling those **uses** of drugs for which safety and efficacy have been demonstrated.
6. That the AMA encourage the U. S. Congress, the FDA, pharmaceutical manufacturers, the United States Pharmacopeia, patient organizations and **medical** specialty societies to work together to ensure that Supplemental New Drug Applications (**SNDAs**) for new indications (efficacy supplements), including those for uses in special populations (e.g., pediatrics), are submitted and acted upon in a timely manner. Specific **recommendations** include
 - a. User fee legislation should be reauthorized to ensure that the FDA has the necessary resources to act on all efficacy supplements within 6 months of submission;
 - b. The SNDA process should be streamlined as much as possible (e.g., basing review decisions on already published literature), without compromising the requirements for substantial evidence of efficacy and safety;
 - c. Legislation should be enacted that provides extensions of marketing exclusivity for the product to manufacturers who submit and gain FDA approval of efficacy supplements, including mechanisms both to provide greater reward when the new indication is for a life-threatening disease (with limited or no alternatives), an **orphan** disease, or for a special population (e. g., pediatrics), and to prevent inappropriate use of the system by manufacturers (e. g., place a limit on total length of extended marketing exclusivity);
 - d. For dregs no longer under patent and for which generic versions are available, the FDA, other governmental agencies (e.g., the National Institutes of Health), the pharmaceutical industry, the United States Pharmacopoeia, patient organizations and **medical** specialty societies should **discuss** and mutually agree on alternative mechanisms to ensure that efficacy supplements will be submitted to and **acted** upon by the FDA in a timely **manner**; and
 - e. Pharmaceutical manufacturers are urged to seek FDA approval for pediatric uses through the FDA's 1994 regulation that allows approval of pediatric uses based on adult efficacy studies (where the course of the disease and the effects of the drug are sufficiently similar in both populations) and additional information for pediatric use, usually **pharmacokinetic** studies for determination of dosage (Federal Register 1994; **59:64240-64250**).

Encouraging Clinical Research in Pediatrics

7. That the AMA urge pharmaceutical manufacturers and the FDA to work with the American Academy of Pediatrics and experts in pediatric medicine to **identify** those investigational drugs that would have pediatric indications and set up a **mechanism** to ensure that necessary pediatric clinical studies are completed prior to submission of NDAs for approval of these drug products. Legislation should be enacted that provides extensions of marketing exclusivity for the product to manufacturers who complete pediatric studies that lead to pediatric labeling.

(References pertaining to Report 3 of the Council on Scientific Affairs are available from the Office of Science, Technology and Public Health Standards.)