

American Medical Association

Physicians dedicated to the health of America



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July 29, 2002

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane – Room 1061
Rockville, MD 20852

RE: Request for Comment on First Amendment Issues [Docket No. 02N-0209]

On behalf of the American Medical Association (AMA), I am pleased to respond to the Food and Drug Administration's (FDA) Request for Comments on First Amendment issues, 67 Fed. Reg. 95, issued on May 16, 2002. The AMA would like to offer general comments on this subject, as well as specific comments on dietary supplements and on three issues associated with prescription drugs -- professional labeling, direct-to-consumer advertising (DTCA), and dissemination of information about off-label indications.

General Comments

The Food and Drug Administration (FDA) plays a critical role in protecting the public health of all Americans. As the principal federal agency that enforces the Food, Drug and Cosmetic Act (FDCA), the FDA has the responsibility to assure consumers and health professionals that foods, drugs, biologicals, medical devices, and cosmetics are safe and effective for their intended use and that all labeling is truthful, informative, and not deceptive. To carry out this enormous task, the FDA must have the necessary authority to adequately regulate the relevant industries that are involved in the manufacture and sale of this vast array of products.

At times, this may require the regulation of commercial speech by manufacturers of medical products to assure consumers and health professionals that the information provided about regulated products, including promotional materials, is accurate, truthful and not misleading, and sufficiently comprehensive to allow for appropriate use. If the FDA lacks this authority, the potential to improve health and/or minimize harm from medical products may be compromised. Thus, the AMA believes that, while case law must be taken into consideration, the FDA should not be deterred from regulating commercial speech of medical product manufacturers when this is necessary to protect the public health.

The AMA is concerned, however, when the FDA attempts to extend its regulatory authority to include the practices of physicians and other health professionals. Since 1990, the FDA has attempted to exert its regulatory authority on: 1) the content and conduct of continuing medical education (CME) programs; 2) the content and delivery of information about prescription drugs from health professionals to patients; 3) the compounding of drugs by pharmacists; and 4) which physicians can or cannot prescribe certain drug products under restricted distribution programs.

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The AMA does not believe the FDCA gives the FDA the authority to regulate medical practice and urges the Agency to avoid crossing this regulatory boundary. Furthermore, the AMA encourages the FDA to actively seek the input of physician organizations when its regulation of manufacturers of medical products is likely to significantly impact how physicians practice medicine.

Dietary Supplements

AMA's Overall View on Dietary Supplement Regulation:

The physician members of the AMA continue to be concerned about the quality, safety, and efficacy of dietary supplement products, especially herbal remedies. Do these products actually contain the active ingredient(s) and strengths that their manufacturers claim on the labeling? Are these products really as safe as the promotional materials of the manufacturers claim them to be? Does the degree of safety change in individuals who have pre-existing diseases and conditions, or in those individuals who are also taking prescription medications? Are the structure/function claims for these products accurate and based on good science? Are these products being used inappropriately to treat diseases or potentially delaying individuals with diseases from obtaining effective prescription medications? The AMA does not believe that the dietary supplement industry has provided satisfactory answers to these questions.

The AMA believes that the primary problem is that the Dietary Supplement Health and Education Act of 1994 (DSHEA) fails to provide for adequate FDA regulatory oversight of dietary supplements. The AMA has recommended that Congress modify DSHEA to require that dietary supplements and herbal remedies, including those products already in the marketplace, undergo FDA approval for evidence of safety and efficacy; meet standards established by the United States Pharmacopoeia (USP) for identity, strength, quality, purity, packaging, and labeling; and meet FDA postmarketing requirements to report adverse events, including drug interactions.

In the absence of modifications to the current federal law, the AMA believes that the FDA must aggressively regulate dietary supplements to the fullest extent possible, to fulfill its obligation to protect the health of the American public. The AMA has expressed this view to the FDA on numerous occasions through letters to the Commissioner and to various FDA Dockets (98N-0044 [three letters], 99N-1174, 00N-0598, 00N-0506, and 00N-1200).

AMA's views on Structure/Function Claims:

How FDA regulates structure/function claims and health claims for dietary supplements is particularly relevant to the issue of FDA regulation of commercial speech. The AMA believes it is imperative that consumers readily understand the differences between drug products and dietary supplements so each type of product is used appropriately. Drug products are used to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases. Drug products have a well-defined benefit/risk ratio based on rigorous scientific study and premarket regulatory review by the FDA. In contrast, dietary supplements can only make structure/function claims because knowledge about the benefit/risk ratio of these products is far less certain, and premarket regulatory review to support structure/function claims is not required by law.

The AMA supported the FDA's efforts to differentiate structure/function claims from disease claims, as described in its April 29, 1998 Proposed Rule. In particular, the detailed criteria for

identifying disease claims, as discussed in that Proposed Rule [101.93(g)(2)(i-x) with the accompanying introduction on pp. 23626-23628], would, to some degree, have clarified what structure/function claims could be made for a dietary supplement and, more important, significantly diminish the number of inappropriate disease claims for these types of products. The AMA also recommended that the FDA's proposed definition of a disease [101.93(g)(1)] be modified by adding the phrase, "or a state of health leading to such deviation, impairment, or interruption." The AMA expressed its deep concern and opposition when the FDA proposed to lower its proposed standards on structure/function claims (see 64 Fed. Reg. 130, pp. 36824-36826 [July 8, 1999]) as this would blur the distinction between a drug and a dietary supplement and result in confusion among consumers.

AMA's View on Disclaimers:

The DSHEA requires that a structure/function claim for a dietary supplement be followed by the disclaimer: "*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.*" At a minimum, the AMA believes this disclaimer should be required, without exception, on any dietary supplement product that makes a structure/function claim and have sufficient prominence on the label so that consumers can easily identify it. The AMA agrees with the FDA that dietary supplements bearing structure/function claims must comply with the notice, disclaimer, and other requirements of section 403(r)(6) of the FDCA. The AMA has opposed citizen petitions that ask the FDA to waive this requirement for some structure/function claims (e.g., those derived from nutritive value).

Although not required by the DSHEA, the AMA has proposed that the disclaimer for dietary supplements be expanded, as follows:

"This product has not been evaluated by the Food and Drug Administration and is not intended to diagnose, mitigate, treat, cure, or prevent disease. This product may have significant adverse side effects and/or interactions with medications and other dietary supplements; therefore, it is important that you inform your doctor that you are using this product."

The AMA believes there is ample evidence that some dietary supplements can cause adverse reactions in some patients and/or interact with certain drugs to diminish their effectiveness. Thus, there is a need to adequately inform consumers about these possibilities. Because specific side effects/precautions/warning information unfortunately is not required on the labeling of dietary supplements, an expanded disclaimer offers an alternative option to provide some, albeit general, information to consumers.

AMA's View on Health Claims:

Regarding health claims for dietary supplements, the AMA believes that the best regulatory approach for protecting and promoting public health is for FDA to mandate a single standard for health claims that would apply to both conventional foods and to dietary supplements. This type of standardization is needed to prevent confusion among consumers and to allow them to identify conventional food and dietary supplement products that may reduce the risk of certain diseases or health-related conditions.

In its April 8, 2000 Comments to Docket No. 00N-0598, the AMA suggested that the "significant scientific agreement standard," as described in the FDA's *Guidance for Industry*:

Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements (December 22, 1999), appeared adequate, provided a health claim only referred to reducing the risk of a disease or health-related condition in the general population or a significant subpopulation. For all other disease-related claims, the AMA believes that a dietary supplement should be considered a drug.

The AMA vigorously opposes a lesser standard for dietary supplement health claims. To allow health claims based on "preliminary or conflicting evidence" fails to adequately protect the health of the American people.

The AMA also strongly opposes the expansion of health claims for dietary supplements to include effects on an existing disease. The AMA believes to allow such claims would be in conflict with DSHEA's explicit distinction between a dietary supplement and a drug. To allow dietary supplements to make health claims relating to effects on existing diseases would confuse consumers and would not promote the public health.

Professional Labeling of Prescription Drugs

It is imperative that physicians have sufficient information about prescription drugs in order to prescribe these potent substances appropriately. The professional labeling (package insert) serves as a comprehensive, accurate and unbiased resource of information on a prescription drug product. While current professional product labeling is informative, the length and complexity of this document makes it very difficult for busy physicians to find specific and relevant information in a timely manner. In large part, this is because professional product labeling has become a legal document for liability protection of pharmaceutical manufacturers. Furthermore, the hard-copy professional product labeling that physicians most frequently access (e.g., from the *Physicians Desk Reference [PDR]*) may be dated, and there are no good mechanisms to communicate important changes in labeling to physicians in a timely manner.

For over a decade, the AMA has worked with the FDA to improve the content and format of professional product labeling to make it more useful and user-friendly to physicians. In December 2000, the FDA issued a Proposed Rule to change the requirements for the content and format of professional product labeling (65 Fed. Reg. 247, 81802-81131 [December 22, 2000]). Among the proposed changes are the addition of a "Highlights of Prescribing Information;" a reordering of prescribing information to give more prominence to those sections that are most important to physicians; the addition of an "Index" to cross-reference information in the Highlights section with information in the "Comprehensive Prescribing Information;" the elevation of "Drug Interactions" to major section status; the addition of a new section on "Most Recent Labeling Changes;" and contact information for FDA's MedWatch program.

The AMA continues to express its strong support for FDA's proposed changes in the content and format of professional product labeling. The AMA believes these changes will make the professional labeling substantially more useful and user-friendly for physicians. The AMA urges the FDA to issue a Final Rule as soon as possible to implement these changes.

The AMA also encourages the FDA to develop and make readily available (e.g., via the Internet) a computerized database of the most up-to-date professional labeling for all prescription drug products. This will allow physicians to have access to the most recent

labeling for all prescription drugs and to be aware of important changes to labeling (e.g., a new "Black Box Warning").

Direct-to-Consumer Advertising (DTCA) of Prescription Drugs

Generally, the AMA respects the right of pharmaceutical manufacturers and manufacturers of other medical products to promote their products, provided the promotional materials, including advertising, are not false or misleading and present a fair balance between the benefits and risks of the product. Promotional claims that go beyond what is in FDA-approved labeling should not be allowed. For prescription drugs, the AMA also supports the FDA's requirement that material facts about the product (e.g. side effects/precautions/warnings) be disclosed.

The AMA recognizes that DTCA is controversial because prescription drugs are only considered safe for use by consumers under the supervision of a practitioner (usually a physician) who is licensed to prescribe these drugs. The AMA's House of Delegates, its policy-making body, has adopted the following well-reasoned policy on DTCA, which we hope will be of assistance to the FDA as it considers this issue.

H-105.988 Direct-to-Consumer Advertising (DTCA) of Prescription Drugs

- (1) Our AMA considers acceptable those product-specific direct-to-consumer advertisements that follow the guidelines for such advertisements that were developed by the AMA, in consultation with the FDA, in 1993. These guidelines also apply to DTCA of FDA approved medical devices, and are as follows: (a) The advertisement should be disease-specific and enhance consumer education; (b) The ad should convey a clear, accurate and responsible health education message (i.e., information on the prevention or treatment of a disease, disorder, or condition); (c) In all cases, the ad should refer patients to their physicians for more information; (d) The ad should not encourage self-diagnosis and self-treatment, but should identify the consumer population at risk; (e). Discussion of the use of the drug product for the disease, disorder, or condition should exhibit fair balance; (f) Warnings, precautions, and potential adverse reactions associated with the drug product should be clearly explained so as to facilitate communication between physician and patient; (g) No comparative claims can be made for the product. In the interest of fair balance, alternative non-drug management options for the disease, disorder, or condition can be included; (h) The brief summary information should be presented in language that can be understood by the consumer; (i) The advertisement must comply with applicable FDA rules, regulations, policies and guidelines as provided by their Division of Drug Marketing, Advertising and Communications; (j) The ad should be part of a manufacturer's education program that would include collateral materials to educate both physician and consumer; and (k) The manufacturer should not run concurrent incentive programs for physician prescribing and pharmacist dispensing.
- (2) Our AMA opposes product-specific direct-to-consumer advertisements, regardless of medium, that do not follow the above AMA guidelines.

- (3) Our AMA encourages the FDA, other appropriate federal agencies, and the pharmaceutical industry to conduct or fund research on the effect of DTCA, focusing on its impact on the patient-physician relationship as well as overall health outcomes and cost benefit analyses; research results should be available to the public.
- (4) Our AMA supports the concept that when companies engage in DTCA, they assume an increased responsibility for the informational content, an increased duty to warn consumers, and they may lose an element of protection normally accorded under the learned intermediary doctrine.
- (5) Our AMA encourages physicians to be familiar with the above AMA guidelines for product-specific DTCA and with the Council on Ethical and Judicial Affairs (CEJA) Ethical Opinion E-5.015 and to adhere to the ethical guidance provided in that Opinion.
- (6) Our AMA continues to monitor DTCA, including new research findings, and work with the FDA and the pharmaceutical industry to make policy changes regarding DTCA, as necessary.
- (7) Our AMA advocates that direct-to-consumer prescription drug and medical device advertisements contain the disclaimer "Your physician may recommend other, appropriate treatments." (BOT Rep. 38 and Sub. Res. 513, A-99; Reaffirmed: CMS Rep. 9, Amended: Res. 509, and Reaffirmation, I-99; Appended & Reaffirmed: Sub. Res. 503, A-01)

The AMA is concerned about the paucity of high quality research, available in the public domain, on the impact of DTCA. A number of consumer surveys have been done and suggest DTCA increases: physician office visits; new diagnoses; informed discussion between physician and patient about conditions and treatments; and unfortunately in some cases, demand for a specific advertised prescription drug product. However, most of these consumer surveys have not been published in the peer-reviewed literature and, therefore, physicians often are skeptical of the conclusions.

The AMA believes there is a clear need for high quality research that objectively assesses how DTCA affects the physician-patient relationship, whether DTCA provides educational value to consumers, how DTCA affects consumers' perceptions of the risks of prescription drugs, and whether DTCA results in cost-effective health outcomes. Public policy decisions on DTCA need to be driven by evidence-based research rather than emotion. As such, the AMA eagerly awaits the results of the FDA survey of physicians' experiences with DTCA.

Dissemination of Information About Off-Label Indications

The AMA strongly believes that physicians can lawfully prescribe a FDA-approved drug or medical device for an off-label indication when such use is based upon sound scientific evidence and sound medical opinion. In the past, the AMA has informed the FDA that there should be an increased reliance on accredited continuing medical education as one avenue for the responsible dissemination of information about off-label uses of approved drugs and medical devices to practicing physicians. In addition, the AMA has suggested that the FDA explore further with medical societies, medical schools, and the pharmaceutical industry other avenues for the dissemination of accurate and unbiased information about off-label uses.

Regarding the dissemination of information about off-label indications of drugs and medical devices by manufacturers (sponsors), the AMA has adopted a position that balances the need for objective information by physicians with the need to maintain the integrity of the FDA's supplemental approval process for new indications.

The AMA supported Section 401 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (P.L. 105-399) (now Subchapter D of the FDCA). The AMA believes that allowing manufacturers to disseminate copies of peer-reviewed journal articles or referenced textbooks will increase physician access to independently derived information about off-label indications. The AMA believes this can be accomplished without compromising the supplemental approval process for new indications or the health of the public. Physicians who receive journal articles on off-label indications from sponsors will evaluate the study with more scrutiny than if the article had been personally retrieved from the journal.

However, the AMA does not believe that elimination of FDA oversight over the promotion of off-label uses is appropriate, as this would permit the dissemination of biased and inaccurate information to physicians and to the public. Furthermore, physicians ultimately want new indications to appear in FDA-approved labeling, and the physician community will continue to pressure manufacturers to file supplemental applications for new indications.

The AMA has opposed *both* the FDA and the Washington Legal Foundation's extreme positions on dissemination of information on off-label indications to physicians. In a July 1998 letter to FDA Docket No. 98N-0222 (63 Fed. Reg. 109), the AMA stated its concern that the FDA had discounted the intent, and possibly the actual statutory language of Section 401 of FDAMA, by imposing extremely rigorous requirements on the definition of a "scientifically sound clinical investigation." Under the FDA's proposed regulation, the number of peer-reviewed journal articles that could be disseminated with off-label use information would be severely restricted and the dissemination of reference textbooks would be virtually impossible. The AMA continues to urge the FDA to implement Section 401 of FDAMA as it was intended by Congress.

In contrast, in a 1995 letter to FDA in response to Docket No. 92N-0434 (November 18, 1994), the AMA did not support the Washington Legal Foundation's petition to remove all "non-labeling" promotion of off-label uses by manufacturers from FDA regulatory authority. This proposed action is unnecessary and unwarranted. As noted above, elimination of all oversight of promotion of off-label uses would permit the dissemination of biased and inaccurate information to physicians and the public. Also, manufacturers may lack the incentive to file supplemental applications for new indications if they can readily promote off-label uses.

Citizen Petitions Related to Nicotine Containing Products

On December 18, 2001, the AMA joined the Campaign for Tobacco-Free Kids, the American Cancer Society, the American College of Preventive Medicine, the American Thoracic Society, the American Society of Clinical Oncologists, the American Society of Addiction Medicine and a number of other national organizations in submitting four Citizen Petitions to the FDA. These petitions ask the agency to regulate Ariva Tobacco Lozenges, OMNI and Advance "low carcinogen" cigarettes, Eclipse, and Nicotine Water. Although the Supreme Court held that the FDA does not have jurisdiction over traditional tobacco products, the Court

left undisturbed the agency's jurisdiction over nicotine-containing products other than traditional tobacco products (e.g., mint-flavored nicotine lozenges) and traditional tobacco products that make drug claims (e.g. "low carcinogen"). Nonetheless, the manufacturers of these products did not submit them to the FDA or any other government agency before marketing them, and the manufacturers claim they are exempt from any review because the products contain tobacco. We continue to urge the FDA to classify and regulate the products as drugs, just as it has done with nicotine patches, gum, and inhalers. The AMA is also very pleased that the FDA recently banned the sale of nicotine lollipops and nicotine water unless and until new drug applications for these products are submitted and approved.

The AMA appreciates this opportunity to respond to your request for comments. The AMA hopes that its insight into these issues proves helpful for the agency, and we look forward to working with the agency as it moves forward in these areas. Please feel free to contact Sandy Marks at (202) 789-4585 at AMA's Washington Office with questions regarding these or any other concerns.

Sincerely,

A handwritten signature in black ink, appearing to read "M D Maves". The signature is fluid and cursive, written over a light blue grid background.

Michael D. Maves, MD, MBA

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