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Joan Claybrook, President

Public Citizen's Health Research Group's Comments On:

Dissemination of Information on Unapproved/New Uses for Marketed
Drugs, Biologics, and Devices

[Docket No. 98N-0222]

Submitted - July 23, 1998

Since 1972, Public Citizen's Health Research Group has been promoting research-based, system-wide changes in health care policy, as well as advocating for the appropriate prescribing and use of prescription drugs. The Health Research Group testifies before Congress and petitions the Food and Drug Administration (FDA) on issues such as banning or relabeling of drugs and the misleading advertising of prescription and non-prescription drugs by their manufacturers. Our publications help consumers make informed decisions about the health care they receive and the drugs they are prescribed.

Section 401 of the so-called FDA Modernization Act of 1997 (FDAMA '97) allows drug companies for the first time to promote prescription drugs for FDA unapproved-new uses that have not been shown to be safe and effective directly to health professionals. Such uses are frequently referred to as "off-label" uses. As written, the FDA's proposed regulation implementing the off-label promotion provisions of FDAMA '97 provides dangerously inadequate protection for the American public from the substantial risks of unknowingly being prescribed drugs for off-label uses. Public Citizen recognizes the difficult task faced by the FDA in attempting to write an implementing regulation that provides some protection for the public within the context of legislation that was patently intended only to further the economic well-being of multi-national pharmaceutical companies. To provide a minimum level of protection for the American public from the risks of off-label prescribing, this regulation must require the following three critical safety elements:

1. Patient Labeling
 - a. Drug companies must be required to include labeling written specifically for patients as a part of the professional product labeling for each drug that a company chooses to promote for an off-label use.

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- b. Patient labeling for drugs promoted for off-label uses must clearly notify consumers that the drug has been promoted for an off-label use and indicate the FDA-approved uses for the drug.
 - c. Patient labeling must include information about the potential risks of the drug and meet the quality and content standards of the FDA's 1995 proposed Medication Guide rule.¹
2. Full Public Access to Submissions, Requests, and Applications
 - a. The regulations must require full public access to all drug company submissions, requests, and applications seeking permission to promote drugs for off-label uses whether or not the FDA approve the request. In addition, the regulations must require full public access to all submissions, requests, and applications made by drug companies seeking to promote their drugs for off-label use that have been denied by the FDA, including the reason for the denial.
 3. Full Public Access to Safety and Effectiveness Information
 - a. The regulations must require full public access to all information held by the FDA pertaining to the safety or effectiveness of drugs that will be promoted for off-label uses.

Each of these three critical safeguards are discussed below.

REQUIRED PATIENT LABELING

Section 401 of FDAMA '97 sanctions the use of Americans as unwitting human guinea pigs in large uncontrolled experiments in which no one is collecting data and the guinea pigs have been denied their right of informed consent. Unquestionably, a patient prescribed a drug for a use that has not been shown to be safe and effective is receiving that drug for an experimental purpose. International standards of ethical medical research require that potential experimental subjects be fully informed of potential risks and allowed to give their informed consent before undergoing experimentation.

Not surprisingly, the Congress that created FDAMA '97 for the benefit of multinational drug firms neglected the fundamental right of human subjects to give their informed consent. The FDA must correct this serious ethical omission by requiring

¹Department of Health and Human Services. Food and Drug Administration. Prescription Drug Product Labeling; Medication Guide Requirements. *Federal Register* Vol. 60, No. 164, pages 44182-44252, August 24, 1995.

patient labeling for all drugs promoted for off-label uses and require that this labeling be easily accessible to potential human subjects.

Patient labeling must be a part of the drug's FDA-approved professional product labeling, or package insert, for each drug that is promoted for an off-label use and clearly state that the drug has been promoted to health professionals for uses that have not been shown to be safe and effective. The patient labeling must also list the FDA approved uses for the drug and other drugs that are FDA-approved for the off-label use that is being promoted, if any. In addition, the patient labeling must contain other useful information about the drug, in particular, information that places the risks of taking the drug in a context that can be interpreted by consumers and also meet the content and quality guidelines outlined in the FDA's 1995 proposed Medication Guide Rule for patient information about prescription drugs. The FDA approved patient labeling must be in the commercial distribution chain at the level of the pharmacy before the promotion of an off-label use to health professionals can commence in order to ensure that consumers have access to it.

Public Citizen believes that, due to the serious public health risks associated with off-label prescribing, the FDA has the regulatory authority to mandate the distribution of patient labeling by pharmacists at the time of dispensing.

PUBLIC ACCESS TO SUBMISSIONS, REQUESTS, AND APPLICATIONS

Subpart C, *Manufacturer's Submission, Requests, and Applications*, of the proposed regulation requires that companies submit: (1) an identical copy of the promotional materials to be disseminated to health professionals; (2) any other information held by the manufacturer regarding the safety and effectiveness of the off-label use to be promoted; (3) an explanation of how the manufacturer selected articles to be disseminated to health professionals; (4) if the manufacturer has not submitted an application for approval of an off-label use and the manufacturer has completed studies needed for the submission of an application for approval of an off-label use a copy of the protocol for each study and certification that the manufacturer will submit the application no later than six months from the date of the initial dissemination of the promotional materials; and (5) if the manufacturer has submitted a supplemental application for the off-label use, a cross-reference to that application.

The regulation must provide that both the submissions, requests, and full applications whether they have been allowed or denied by the FDA be made accessible to the public at the time that the submission, request, and application is made or denied. For those denied, the documents indicating the reasons for the denial should also be accessible to the public.

PUBLIC ACCESS TO SAFETY OR EFFECTIVENESS INFORMATION HELD BY THE FDA

Subpart B, Section 99.103, of the proposed regulation states that information submitted to the FDA by a manufacturer, or a summary of such information, pertinent to an off-label use that can be made publicly available, must accompany the promotional materials distributed to health professionals. The FDA has expressed concern that federal confidentiality laws may prohibit the Agency from disclosing evidence that an off-label use is ineffective or unsafe. The following statement was made by the FDA before the Senate Committee on Labor and Human Resources in 1996:

What makes this situation even more troubling is that when we [the FDA] have evidence that a particular use is unsafe or ineffective, federal confidentiality laws frequently prohibit FDA from disseminating that information. Thus, there are off label uses about which positive studies appear in the literature and negative data are contained in our files. However, depending on its source, FDA may be unable to use that information to ensure that the medical community has all of the available facts on which to base treatment decisions.²

Even though effectiveness and safety information submitted by manufacturers when seeking new drug approval or approval for a new use are exempt from public disclosure under the Freedom of Information Act until approval by the FDA, all information held by the Agency pertaining to an off-label use that is being promoted must be made available to the public for safety reasons. If the FDA has evidence that an off-label use is ineffective or dangerous, this information must be distributed to health professionals in order to provide objective and balanced information.

The following comments concern specific sections of the proposed regulation.

Subpart A - General Information

Regarding proposed Section 99.3 (5), Public Citizen strongly agrees that special medical journal supplements about off-label uses that have been funded in whole or in part by one or more manufacturers are not acceptable for dissemination. The clear purpose of these supplements is to circumvent the peer review process and to mislead health professionals about the risks and benefits of drugs.

The FDA should not accept for review final manuscripts or pre-prints of articles that have been accepted for publication but have not yet been published about off-label uses. It may take months for these manuscripts to be published, and would preclude an important part of the peer-review process, that of independent critical comment by the medical community in the form of letters to the editor and other commentaries that

²Statement of William B. Schultz, Deputy Commissioner for Policy, Food and Drug Administration, Public Health Service, Department of Health and Human Services, before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

may appear at the time of, or shortly after, the publication of the study. Critical comment on a study in the published medical literature adds objectivity and balance to the study's.

Subpart B - Information to be Disseminated

As to proposed Section 99.101 (2)(ii) regarding the dissemination of an unabridged reference publication, Public Citizen does not believe that the dissemination of reference publications is consistent with the purpose of Section 401 of FDAMA '97, which is to permit the dissemination of information about a clinical investigation concerning a specific off-label use for a drug. By their nature, reference publications are considerably out-of-date at the time of their publication. Moreover, because the authors of reference publications, in general, do not report the methods used to assess the current scientific literature, reference publications should be considered as the author's opinion which may not be scientifically sound.

Regarding proposed Section 99.101 (5)(b)(1) Public Citizen strongly agrees with the FDA that letters to the editor, review abstracts, or abstracts of publications about off-label uses are not scientifically sound and do not qualify for dissemination to health professionals under Section 401 of FDAMA '97.

Regarding proposed Section 99.103, mandatory statements and information, Public Citizen strongly agrees with the FDA that mandatory statements must disclose: (1) that the promotional material concerns a use that has not been approved by the FDA; (2) that the promotional material is paid for by the drug company; and (3) the names of any authors of the study who are employees of, or consultants to, or have received compensation from the manufacturer, or have a financial interest in the company promoting the off-label use.

Proposed Section 99.103 (a) (iv) must also require that the names of other drugs that have been approved by the FDA for the use that is being promoted be disclosed to health professionals, rather than a simple statement that other drugs are approved for the off-label use being promoted.

Subpart C - Manufacturer's Submissions, Requests, and Applications

Regarding proposed Section 99.201(a)(2) Public Citizen strongly agrees that manufacturers must submit any clinical trial information that they have relating to the safety or effectiveness of the off-label use, any reports of clinical experience pertinent to the safety of the off-label use, and a summary of such information. This information must include, but is not limited to, published papers and abstracts, even if not intended for dissemination, and unpublished manuscripts, abstracts, and data analyses from completed or ongoing investigations. Also, case studies, retrospective reviews, epidemiological studies, adverse event reports, and any other material concerning adverse effects or risks reported for or associated information relating to the safety or

effectiveness of the off-label use must be submitted to the FDA. This important safety and effectiveness information is routinely accessible to the public in regard to approved uses in recognition of the fact that release of the information does not pose a likelihood of substantial competitive harm to the company. For the same reason, for off-label uses, such information cannot be considered confidential commercial information and must be made accessible to the public through Freedom of Information Act requests.

Regarding proposed Section 99.205, application for exemption from the requirement to file a supplemental application, Public Citizen cannot foresee any circumstances in which an exemption should be granted from the requirement to file a supplemental application for the off-label use with the FDA.

Subpart D - FDA Action on Submissions, Requests, and Applications

Under proposed Section 99.301, Agency Action on a Submission, the FDA may find it necessary to request additional information or documents to assist in determining whether the information to be disseminated about an off-label use is scientifically sound. Section 401 of FDAMA '97 allows the FDA 60-days to review the materials intended to be disseminated by manufacturers promoting an off-label use. If the FDA finds it necessary to request additional information from a manufacturer, the start of the 60-day review period must begin when the FDA is assured it has sufficient information to make a decision whether or not to allow dissemination of off-label promotional materials. Manufacturers will thus be prevented from submitting the requested information at the end of the 60-day review period, thereby compressing the review time of what may be critical information to an unacceptably short period of time.

Subpart E - Corrective Actions and Cessation of Dissemination

Congress, by not giving the FDA authority to levy civil monetary penalties against manufacturers who do not comply with the proposed regulation, by and large, renders Subpart E of this proposed regulation hollow and meaningless.

Regarding Section 99.401, Corrective Actions and Cessation of Dissemination of Information, of the proposed regulation, Public Citizen strongly disagrees that the FDA must first consult with a company before ordering the company to cease dissemination of off-label use promotional material for any reason. Because the promotion of off-label uses presents a significant risk to the public's health a company should not be permitted to continue to disseminate off-label use materials while a company and the FDA are resolving outstanding issues over those promotional materials.

OFF-LABEL PRESCRIBING HAS DEVASTATING CONSEQUENCES

During a presentation before the Senate Committee on Labor and Human Resources in 1996 the FDA expressed its grave concerns to Congress regarding allowing the wide-spread promotion of prescription drugs for uses that had not been

shown to be safe and effective:

FDA has serious concerns regarding the promotion of indications that have not been reviewed and approved by the Agency. Because promotional activities of drug companies and others are substantially motivated by profit and market expansion, the widespread promotion of prescription drugs and devices for uses that have not been determined to be safe and effective could be detrimental to the health and safety of the public. Permitting companies to promote drugs and devices for off label uses could have a number of devastating consequences for the quality of medical care in this country.³

This warning was prophetic. Off-label promotion by the diet clinic industry (although not by the drug industry) and profit-motivated diet doctors was at the root of the 1997 "fen/phen" disaster that resulted in the injuries and deaths of countless Americans, mostly women. This widely prescribed combination of fenfluramine (Pondimin) and phentermine (Ionamin) was never approved to be used together and these drugs alone were never approved to be taken for more than a few weeks by the FDA. Limiting the deaths and injuries from "fen/phen" was the law that prevented the makers of these two diet drugs from disseminating hundreds-of-thousands of copies of two peer-reviewed medical journal studies to doctors about the benefits of "fen/phen".⁴ Fenfluramine was withdrawn from the market on September 15, 1997 because of heart valve damage and primary pulmonary hypertension, a lung reaction that is fatal about 50 percent of the time.⁵ Congress shamelessly ignored the deaths and injuries from the off-label prescribing of "fen/phen" when it passed FDAMA '97 and President Clinton callously signed FDAMA '97 into law on November 21, 1997.

On June 22, 1998, the painkiller bromfenac (Duract) was withdrawn from the market because of off-label prescribing that resulted in cases of severe hepatitis and liver failure with some patients requiring liver transplants.⁶ Bromfenac was approved for the treatment of acute pain, to be used for 10 days or less, but it was being prescribed by doctors, off-label, for more than 10 days.

³Statement of William B. Schultz, Deputy Commissioner for Policy, Food and Drug Administration, Public Health Service, Department of Health and Human Services, before the Committee on Labor and Human Resources, United States Senate, February 22, 1996.

⁴Weintraub M, Hasday JD, Mushlin AI, Lockwood DH. A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. *Archives of Internal Medicine* 1984;144:1143-1148.

Weintraub M, Sundaresan PR, Madan M, et al. Long-term weight control study I (weeks 0 to 34): the enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. *Clinical Pharmacology and Therapeutics* 1992;51:586-594.

⁵Department of Health and Human Services, Food and Drug Administration. FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine, September 15, 1997.

⁶Department of Health and Human Services, Food and Drug Administration. FDA Talk Paper: Wyeth-Ayerst Laboratories Announces the Withdrawal of Duract from the Market, June 22, 1988.

THE FDA CAN NOT SAFELY IMPLEMENT THE OFF-LABEL PROMOTION PROVISION OF FDAMA '97

The pharmaceutical industry, through its hired representatives in the United States Congress, has systematically weakened the FDA during the 1990s culminating in passage of FDAMA '97. This special interest law places the economic well-being of multinational pharmaceutical manufactures above the health and safety of the American public and marks a low point in U.S. drug regulatory history by weakening law meant to protect the public from needless drug-induced injury. Congress, by continually adding new responsibilities to an overburdened FDA, while keeping the Agency's budget constant, in effect ties the hands of the FDA and deregulates the pharmaceutical industry at the expense of public safety.

Public Citizen does not believe that the FDA has sufficient resources to implement Section 401 of FDAMA '97 in a manner that can adequately protect the public's health from the substantial risks of off-label drug prescribing. The FDA Division of Drug Marketing, Advertising and Communications (DDMAC) will have the responsibility for reviewing off-label promotional materials intended for distribution by drug companies. DDMAC currently employs only 10 full-time staff to review all direct-to-doctor and direct-to-consumer print and broadcast advertising in the United States.⁷

FDA medical reviewers from the appropriate drug review divisions will share the responsibility with the understaffed DDMAC to review off-label use promotional materials submitted by manufacturers. These reviewers have already been placed under tremendous pressure by Congress to approve record numbers of new drugs. This pressure has already resulted in three drugs, that should not have been approved, reaching the market and subsequently being withdrawn for safety reasons. The reviewers, therefore, cannot adequately support DDMAC's staff.

CONCLUSION

The assertion by the pharmaceutical industry that Section 401 of FDAMA '97 is to provide for "the sharing of important treatment information with health care providers to enable better patient care in accordance with current medical knowledge"⁸ is blatantly false. Drug companies submitting selected off-label use information to a congressionally weakened FDA for review before being disseminated to health professionals will ensure that a drug's off-label benefits, if any, will be overstated and

⁷Comments made by Laurie B. Burke, R.Ph., Chief, Managed Care Outcomes and Labeling Staff, Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, at the Consumer Federation of America's Pharmaceutical Issues Seminar, Washington, DC, July 2, 1998.

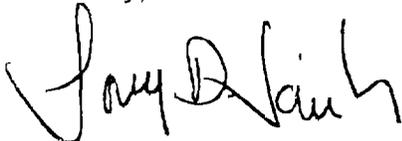
⁸Statement of Russel A. Bantham, Senior Vice President and General Counsel, Pharmaceutical Research and Manufacturers of America. Presentation on FDA's Proposed Rule, Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Washington, DC, July 8, 1998.

the risks of its off-label use dangerously minimized.

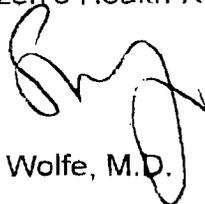
If, in fact, the pharmaceutical industry was truly interested in disseminating information about their drugs to "improve patient care," the industry would fully fund rigorous scientific reviews of their products, totally independent from their own influence, and then widely disseminate the results to health professionals and the public. Simply, Section 401 of FDAMA '97 provides for the promotion of prescription drugs for uses that have not been shown to be safe and effective. And Congress by permitting the promotion of such uses based on studies reported in medical journal articles or other texts that clearly are an inadequate basis for their approval by the FDA further undercuts the public's confidence in the Agency's ability to protect Americans from preventable drug-induced injury and death.

Section 401 of FDAMA '97 literally returns the American public to the unregulated marketplace reminiscent of the "snake oil" era that existed at the end of the 19th century, when drugs were sold without evidence of safety or effectiveness. Section 401 has forced the FDA to create a preposterous contradiction in these proposed regulations that would be laughable, if it were not so dangerous to the public's health. Section 401 requires that the information to be distributed by drug companies about off-label uses "is not false or misleading and does not pose a significant risk to public health." Any promotional material for an off-label use must be false or misleading if it contains insufficient evidence to gain FDA approval and thus by definition poses a significant risk to the public's health.

Sincerely,



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