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Joan Claybrook, President

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

Section 406(b) of the FDA Modernization Act of 1997

[Docket No. 98N-0339]

Submitted - September 16, 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. We testify before Congress and petition the Food and Drug Administration (FDA) on issues such as banning or relabeling of drugs and the misleading advertising of prescription and nonprescription drugs by their manufacturers. Our publications help consumers make informed decisions about the health care they receive and the drugs they are prescribed.

These comments are prompted by the so-called FDA Modernization Act of 1997 (FDAMA '97) that under Section 406(b) requires the FDA to consult with "appropriate scientific and academic experts, health care professionals, representatives of patient and consumer advocacy groups and the regulated industry" to discuss how the Agency can best meet its statutory obligations under the Federal Food, Drug, and Cosmetic Act (FFDCA), while meeting the mandates of FDAMA '97.

The irony in this request for comments lies in the fact that the purpose of the FFDCA was consumer protection, while the clear intent of FDAMA '97 is to further the economic well-being of multinational pharmaceutical and medical device companies at the expense of the public's safety. The FDA has been compelled by Congress to accept the drug industry as a "stakeholder" and has recast the Agency from the role of regulator and public protector to that of industry's "partner" in the marketing of record numbers of new drugs, a role that has already had, and will continue to have, serious consequences for the safety of the American public.

Public Citizen has no illusion that an FDA systematically weakened by Congress during this decade can fulfill one its most basic statutory responsibilities, that of

Ralph Nader, Founder
1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000 • www.citizen.org

protecting the public from dangerous prescription drugs. In its Message to FDA Stakeholders,[1] it is apparent that dedicated professionals within the Agency hold profound concerns that the FDA can no longer meet its important public safety responsibilities:

> Innovations and efficiencies alone, however, may not be sufficient to deal with the enormous growth in FDA's obligations that has been fueled by rapid technological developments, increased complexity of regulated products, and mushrooming global trade. As a result of these developments, FDA finds itself severely challenged to meet all of its statutory obligations.

Underscoring these concerns from within the Agency was the extraordinary display of courage and dedication to public safety by FDA medical review officer Robert I. Misbin, M.D. In a letter-to-the-editor appearing in the *Washington Post*, Dr. Misbin criticized the anti-regulatory political environment and the upper management of the FDA for the "linking of the productivity of FDA reviewers with approval of new products. . . even if the new drugs are not as good as what is available already".[2]

URGENT PUBLIC HEALTH PRIORITIES

Public Citizen strongly urges the FDA to set the following three points as its highest priorities for action:

1. A public investigation of the FDA's current defective drug approval process that now allows products on the market with known serious safety problems which should have prevented their approval.

2. Improveing the postmarketing safety surveillance system.

3. Ensure that the public has access to objective information written in non-technical language placing the risks and benefits of prescription drugs in a context that can be used by consumers to make informed decisions about their drug treatment and to protect themselves from preventable drug induced injury.

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[1]Food and Drug Administration. A Message to FDA Stakeholders. Posted on the FDA web site at http://www.fda.gov/oc/fdama/comm/message.htm.

[2]Letter to the Editor, Robert I. Misbin, M.D. A possible drug fix? *The Washington Post*, August 24, 1998.

INVESTIGATE THE DEFECTIVE DRUG APPROVAL PROCESS

Serious warning signals were raised with the withdrawals of dexfenfluramine (Redux)[3], mibefradil (Posicor)[4], and bromfenac (Duract)[5] for safety reasons in the brief nine month period between September 1997 and June 1998. This unprecedented number of safety withdrawals in such a short time places in serious question the FDA's current drug approval standards and ability to adequately protect the American public from needless drug induced injury and death. Chilling similarities surrounded the approval of each of these drugs: (1) serious safety problems were known before each of these drugs was approved; (2) none of these drugs could remotely be considered as therapeutic advances; and (3) multiple treatment options were available to patients and physicians for the same approved uses as these three new drugs.

Public Citizen has no confidence that the same Congress who wrote and passed FDAMA '97 will confess to its unprincipled act by holding public hearings to determine who was responsible for these senseless drug disasters. The FDA can no longer consider itself the world's gold standard for drug regulation unless it conducts its own public investigation into the reasons why dexfenfluramine, mibefradil, and bromfenac were cleared for marketing when serious safety problems were known before their approval and steps are taken to prevent more tragedies like these from occurring in the future. If there is no examination of the circumstances surrounding the approval of these drugs, Congress and the FDA will have cheapened the lives of the victims needlessly killed and injured by dexfenfluramine, mibefradil, and bromfenac.

IMPROVING POSTMARKETING SAFETY SURVEILLANCE

Adverse drug reactions are estimated to cause 100,000 deaths annually, ranking them as the fourth leading cause of death in the U.S.[6] We find it unacceptable that in the most technologically sophisticated medical system in the world that only estimates are possible of the number of people actually killed or injured by prescription drugs. Public Citizen strongly believes that an adequate postmarketing safety surveillance system would have the ability to provide incidence estimates of adverse drug reactions and also have the independent capability of more rapidly withdrawing dangerous drugs from the market.

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[3]U.S. Department of Health and Human Services, HHS News: FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine. September 15, 1997.

[4]U.S. Department of Health and Human Services, Food and Drug Administration. FDA Talk Paper: Roche Laboratories Announces Withdrawal of Posicor From the Market. June 8, 1998.

[5]U.S. Department 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, 1998.

[6]Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. *Journal of the American Medical Association* 1998; 279:1200-1205.

In light of the pressure exerted by the drug industry on the FDA, through its hired hands in Congress, there is no longer a balance between new drug approvals and postmarketing safety surveillance. The majority of the FDA's resources must go to approving record numbers of new drugs, while Congress refuses to appropriate the necessary resources that are needed for the safety surveillance system to keep pace with new drug approvals.

Public Citizen strongly supports the need to improve the FDA's postmarketing safety surveillance system, but not as a cover for the mistakes of the current defective drug approval process. For the public to be adequately protected, both the drug approval process and the postmarketing safety surveillance system must be improved.

Not only are drugs being approved that should not have been approved, but drugs have been withdrawn from foreign markets for safety reasons that remain on the market in the U.S. The dangerous sleeping pill triazolam (Halcion) was withdrawn in a number countries, including the United Kingdom (U.K.), but remains available in the U.S. Pemoline (Cylert in the U.S.), a drug used in hyperkinetic children, was withdrawn from the market by British authorities in 1997 because of serious liver toxicity.[7] The new diabetes drug troglitazone (Rezulin) was also withdrawn from the U.K. in 1997 because of serious liver toxicity.[8] In two of these cases, for pemoline and troglitazone, British authorities were using adverse drug reaction data obtained from the FDA and concluded that the risks of these drugs outweigh their benefits, yet both of these drugs remain on the market in the U.S.

Since 1960, the FDA has relied primarily on three approaches to postmarketing surveillance: (1) a combination of mandatory manufacturer reporting and spontaneous physician reporting; (2) record-linkage methods, where drug use and adverse clinical events are related using large external databases; and (3) postmarketing, or phase IV, safety studies. These approaches have worked at times, but there have been the failures mentioned above. The withdrawals of dexfenfluramine, mibefradil, and bromfenac where not successes of the safety surveillance system, but rather failures of the approval process.

There are other elements and approaches the FDA must consider to improve the existing postmarketing safety surveillance system. These are:

1. An innovative patient self-monitoring method of signaling possible adverse drug reactions that yields incidence estimates and relative risks pioneered by Seymour Fisher, Ph.D. and Stephen G. Bryant, Pharm.D. of the University of

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[7]Committee on Safety of Medicines. Volital (Pemoline) has been withdrawn. *Current Problems in Pharmacovigilance* 1997; 23:9-12.

[8]Committee on Safety of Medicines. Troglitazone (Romozin) withdrawn. *Current Problems in Pharmacovigilance* 1997; 23:13-16.

Texas Medical Branch, Galveston.[9,10,11]

2. Drug registries must be considered to identify rare but serious adverse drug reactions. For example, in Europe a register of patients with sickle cell disease treated with the drug hydroxyurea (Hydrea) has been established. Physicians will be able to submit data — demographic, clinical, laboratory, and outcome data, including details of adverse drug reactions -- by mail, fax and E-mail. A pilot study of 160 patients has reported four pregnancies, resulting in two normal births, one termination, and one stillbirth; malignancies in two patients; and other adverse effects, such as nail pigmentation in eight patients.[12]

3. A fundamental flaw in the FDA's present postmarketing safety surveillance system is that the decision to withdraw a drug from the market for safety reasons is in the hands of the same medical reviewers who approved the drug. This is an inherent conflict that can only corrected by establishing an independent authority within the FDA responsible for removing drugs from the market that have been found to be dangerous.

4. The FDA must critically examine its current policy on postmarketing, or Phase IV, safety studies. A 1996 Office of Inspector General report found that the FDA has "no formal standards and procedures for monitoring or for establishing whether a postmarketing commitment is met."[13]

   Public Citizen is deeply concerned that the FDA is agreeing to scientifically invalid Phase IV study protocols that cannot possibly answer important drug safety questions. The Phase IV study protocols for the drugs metformin (Glucophage) and dexfenfluramine (Redux) posted on the FDA's web site are examples of such poorly designed studies that the FDA should never have agreed to allow.

   Also, the FDA must consider if it is responsible public health policy to approve a

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[9] Fisher S, Bryant SG. Postmarketing surveillance of adverse drug reactions: patient self-monitoring. *Journal of the American Board of Family Practice* 1992; 5:17-25.

[10] Fisher S, Bryant SG, Kent TA. Postmarketing surveillance by patient self-monitoring: trazodone versus fluoxetine. *Journal of Clinical Psychopharmacology* 1993; 13:235-242.

[11] Fisher S, Kent TA, Bryant SG. Postmarketing surveillance by patient self-monitoring: preliminary data for sertraline versus fluoxetine. *Journal of Clinical Psychiatry* 1995; 56:288-296.

[12] Davies SC, Roberts-Harwood M. European register of patients with sickle cell disease treated with hydroxyurea is being set up. *British Medical Journal* 1998; 317:541-542[letter].

[13] Office of Inspector General. Postmarketing studies of prescription drugs, OEI-03-94-00760, May 1996.

new drug when there are enough serious safety questions that the drug company is requested to conduct a Phase IV study. If there are serious safety questions, these questions must be answered before, not after, approval, especially for the majority of drugs that are not therapeutic advances over existing drugs.

5. When serious safety problems have been found, including potentially life-threatening adverse reactions that require labeling changes, doctors and pharmacists are warned through Dear Health Professional letters from the drug companies, but the only group at risk of suffering a serious adverse effect, those taking the drug, are warned inadequately, if at all.

   The only warning that a patient may receive about a new and serious adverse effect of a drug they are taking may depend on luck. If on the day the FDA or drug company announces a safety problem with a drug, and it happens to be covered by the media, and if the patient happens to be tuned to the right TV or radio station at the right time or sees a newspaper article, then the patient is warned.

   The FDA must address the issue of adequately warning the public when new and serious adverse drug reactions are discovered.

THE PUBLIC'S DESPERATE NEED FOR OBJECTIVE DRUG INFORMATION

The single most important public safety initiative that the FDA must undertake in the short-term is to immediately provide consumers with access to the information necessary to make informed decisions about their drug treatment and to protect themselves from preventable drug induced injury and possible death.

Daily, the American public faces a fragmented, profit driven health care system where physicians influenced by drug company advertising prescribe inappropriate, needlessly dangerous drugs[14,15,16] and life-threatening combinations of drugs even after

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[14] Avorn J, Chen M, Hartley R. Scientific verses commercial sources of influence on the prescribing behavior of physicians. *American Journal of Medicine* 1982; 73:4-8.

[15] Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. *Journal of the American Medical Association* 1994; 272:292-296.

[16] Siegel D, Lopez J. Trends in antihypertensive drug use in the United States: do the JNC V recommendations affect prescribing? Fifth Joint National Commission on the Detection, Evaluation, and Treatment of High Blood Pressure. *Journal of the American Medical Association* 1997; 278:1745-1748.

being warned,[17,18] and in which pharmacists consistently fail to detect or warn the public[19,20] about serious drug interactions.

Increasing these risks has been drug company censorship of information that consumers need and have a right to in order to make informed decisions about their drugs. The drug industry and its allies have successfully blocked the FDA's efforts for 19 years to mandate the distribution of objective information, written in non-technical language, placing the risks and benefits of prescription drugs in a context that would allow consumers, along with their doctors, to make informed decisions about their drug treatments. While preventing the distribution of accurate and useful information, the drug industry bombards the public with misleading direct-to-consumer advertising and immorally claims that a 60 second TV commercial "empowers" consumers to make informed decisions about their drug therapy.

Pharmacists serve industry's censorship strategy by distributing unregulated patient information leaflets (PILs) produced by commercial information vendors. Some of these PILs have been found to be dangerously misleading by virtue of omitting important risk information and being out-of-date, thus giving the public a false sense of security about what is needed to take their drugs safely and effectively.[21] An estimated 1.8 billion unregulated PILs were distributed to the American public by pharmacists in 1997.

The FDA now provides drug information for consumers on its web site written by pharmacists from CDER's Drug Information Branch.[22] This web site provides information about drugs approved since January 1998 and a link to the FDA's approved professional product labeling, or package insert, for each new drug listed. However, the CDER prepared Consumer Drug Information Sheets fall short of meeting information quality guidelines suggested by the FDA in its 1995 proposed medication

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[17] Thompson D, Oster G. Use of terfenadine and contraindicated drugs. *Journal of the American Medical Association* 1996; 275:1339-1341.

[18] Carlson AM; Morris LS. Coprescription of terfenadine and erythromycin or ketoconazole: an assessment of potential harm. *Journal of the American Pharmaceutical Association* 1996; NS36:263-269.

[19] Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. *Journal of the American Medical Association* 1996; 275:1086-1087.

[20] Headden S. Danger at the drugstore. *U.S. News & World Report*, August 26, 1996.

[21] Public Citizen Health Research Group. Citizens' Petition to Immediately Stop the Distribution of Dangerously Misleading Prescription Drug Information to the Public, filed June 9, 1998.

[22] The FDA Consumer Drug Information page is located at http://www.fda.gov/cder/consumerinfo/default.htm.

guide rule[23] or the guidelines agreed to by representatives of pharmacy, medicine, commercial information vendors, and consumers that were accepted by the Secretary of the Department of Health and Human Services in early 1997.[24] In addition, this information, such as it is, is only available to those consumers with enough money to own a computer system. The FDA must continue its efforts to ensure that consumers have useful written drug information distributed at the time a new prescription is dispensed.

For example, the CDER drug information sheet for the new migraine drug rizatriptan (Maxalt) does provide a more meaningful organizational structure for consumers than does the patient labeling provided for this drug by Merck & Company, rizatriptan's manufacturer, as part of the drug's FDA approved professional product labeling. However, the CDER information sheet for rizatriptan fails to follow the FDA's own 1995 guidelines regarding risk information, the most important type of information for consumers:

> Warnings denoting serious or life-threatening effects, even if rare, should be expressly described. This information should not be combined with other information in a fashion that reduces communication of its significance. Additional contextual information should be provided to help patients understand these important risks.

Useful information for consumers must place the risks of rizatriptan in a meaningful context that allows consumers to make an informed decision about taking this drug. The following statement from the Warnings Section of rizatriptan's approved product labeling must be presented, along with other warnings, written in non-technical language:

> Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Because of the potential of this class of compounds (5-$HT_{1B/1D}$) to cause coronary vasospasm, MAXALT should not be give to patients with documented ischemic or vasospastic coronary artery disease. It is strongly recommended that rizatriptan not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best.

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[23]Department of Health and Human Services, Food and Drug Administration. Prescription Drug Product Labeling; Medication Guide Requirements. *Federal Register* 1995;Vol. 60, 164, Thursday, August 24, 1995, pages 44182-44252.

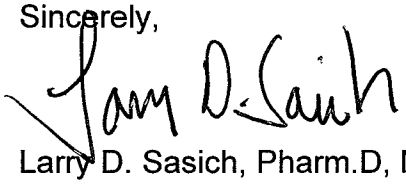
[24] Action Plan for the Provision of Useful Prescription Medicine Information presented to the Honorable Donna E. Shalala, Secretary of the Department of Health and Human Services by the Steering Committee for the Collaborative Development of a Long-Range Action Plan for the Provision of Useful Prescription Medicine Information, December 1996.

The FDA must continue and expand its important new endeavor to provide consumers with drug information, but for this information to be useful to consumers it must follow the format and guidelines first proposed by the Agency in 1995 and agreed to by the Secretary of the Department of Health and Human Services in 1997 and be handed out to consumers when a prescriptions are filled.

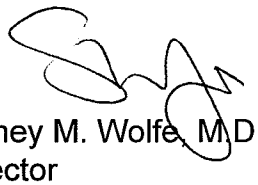
CONCLUSION

The FDA, by its own admission, can no longer fully meet its statutory obligations under the FFDCA. However, the Agency can and must provide the public with the means to protect themselves from a defective drug approval process and an under-funded postmarketing safety surveillance system: objective drug information, written specifically for the public, that is useful.

Sincerely,



Larry D. Sasich, Pharm.D, M.P.H., FASHP
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group