

**Statement of Sidney M. Wolfe, MD and Larry D. Sasich, Pharm.D., MPH**  
**Public Citizen Health Research Group**  
**FDA Hearing on Risk Management of Prescription Drugs**  
**(docket number 02N-0115)**  
**May 22, 2002**

In order to more fully explore this important topic, we have broadened the discussion to include: (A) the processes of acquiring risk information by the FDA; (B) the processing the information by the agency to evaluate the nature of the risk as well as the process of deciding on the best risk management/risk prevention strategies; and (C) better dissemination of information about risk both to patients and health practitioners.

**A. Acquisition of information about risk**

1. Both in the pre and post approval phases of a drug's existence, there is a need to get much more complete and prompt data from the industry. To motivate the industry, there is the need for more criminal prosecution of reporting violations (Selacryn, Oraflex, Merital, Rezulin, Redux, Meridia).
2. Why are FDA epidemiologists not sent out to track down possible point source drug-induced epidemics as the Centers for Disease Control and Prevention's (CDC) Epidemiologic Intelligence Service officers are for point source infections. There also needs to be much better coordination with academic epidemiologists and clinicians doing such studies.
3. Risk needs to be put into much better context by requiring more head-to-head trials of efficacy so that benefit/risk balancing can be more accurate. Some of this could be accomplished by an FDA guidance and some may require a change in the law.
4. It is clear that if the reporting of adverse drug reactions to the FDA rose from the current estimated 10% of all that occur to 20%, it would take half as long to accumulate the number of reports of deaths or injuries necessary for a post-approval decision to ban or put a boxed warning on a drug. Despite successful experiments by the FDA and others which have shown such increases are possible, this concept has never been nationalized or even regionalized on an ongoing basis. In Rhode Island, for example, an FDA-funded project resulted in a 17-fold increase in adverse reaction reports submitted annually from Rhode Island to the FDA compared with the yearly average before the project. Similar increases were not experienced nationally.<sup>1</sup>

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## **B. Processing of Risk Information by the FDA: pre and post approval: risk prevention/risk management**

There must be a major effort to prevent risk management from becoming a device to rescue and salvage drugs that should be withdrawn (Lotronex, Meridia, Posicor, Rezulin, Duract, etc.). There have not been enough serious critiques of the previous failed risk management efforts that ultimately resulted in withdrawals.

1. One of the reasons the morale in Center for Drug Evaluation and Research (CDER) appears to be lower than in 30 years has to do with what Dr. Janet Woodcock has aptly described as the “sweat shop environment” created in the wake of Prescription Drug User Fee Act (PDUFA). In a survey by the FDA of CDER personnel last summer, intended to find out the reasons for the high rate of staff turnover, the problems found included the following: “About one-third of respondents did not feel comfortable expressing their differing scientific opinions.....over one-third felt that decisions such as holds, refuse-to-file actions, and non-approvals are stigmatized in the Agency. Over one-third felt that their work has more impact on a product’s labeling and marketability than it does on public health. A number of reviewers added comments stating that decisions should be based more on science and less on corporate wishes.”<sup>2</sup>

These results are similar to those of a survey we conducted in late 1998 of CDER medical officers which found that 27 times, medical officers stated that their decisions against approving drugs were overturned by their superiors. They also cited 14 instances in the past three years in which they had been instructed, usually by the Office Director, not to present their own opinion or data to an FDA Advisory Committee when to do so might have reduced the likelihood that a drug would be approved.<sup>3</sup>

2. There has been an historic split, and imbalance of power between drug review divisions and the postmarket surveillance (Office of Drug Safety) division; having an atmosphere not conducive to scientific inquiry and dispute results in esteemed epidemiologists such as Dr. Paul Stolley leaving the agency. Unless this poisoned atmosphere is changed, others will leave.

3. Failure to remove drugs thought too dangerous in other countries from the US market:

Drugs Approved in the U.S. since 1990 That Were Withdrawn in Other Countries for Safety Reasons that Remain on the Market in the U.S.				
Brand/Generic Name	Date Withdrawn in Another Country	Date Approved in the US	Reason for Withdrawal	Comment
Trovan/ Trovafoxin	6/99	12/97	Liver toxicity – 9 deaths or liver transplants	9th fluoroquinolone antibiotic approved since 1986. Liver toxicity was seen in clinical trials prior to the drug's approval.
Tasmar/ Tolcapone	11/98	1/98	Liver toxicity – 3 deaths	
Orlaam/ levomethadyl	4/01	7/93	QTc prolongation – 10 cases of life-threatening arrhythmias	

#### 4. Failure at any consistent policy for boxed warnings

##### Recent Bold Warning Changes Which Should Have Been Box Warnings

Diabetes Drugs Actos (pioglitazone) and Avandia (rosiglitazone) – Both Related to Rezulin (troglitazone):

New bolded warnings for heart failure and edema being caused by these drugs. This week we received an anonymous call from a GlaxoSmithKline physician this week who was alarmed at the failure of his company to require a black box warning concerning heart failure caused by Avandia. He maintained that the company currently has 450 reports of heart failure associated with the use of the drug and over 1200 reports of edema.

Antipsychotic Drug Geodon (ziprasidone, Pfizer):

This new Antipsychotic drug --with the serious problem of potential heart toxicity--probably should not have been approved. Despite the absence of a black box warning on this drug, there is a black box warning on six other drugs with prolongation of the QTc interval (an electrocardiograph abnormality that signals possible life-threatening ventricular arrhythmias. Although this is a dangerous inconsistency, it is somewhat predictable given the lack of clear FDA criteria for deciding on when a black box warning is necessary.

mesoridazine (SERENTIL)  
 thioridazine (MELLARIL)  
 arsenic trioxide (TRISENOX)  
 droperidol (INAPSINE)  
 levomethadyl acetate hydrochloride (ORLAAM)  
 itraconazole (SPORANOX)

## 5. Restricted distribution systems or IND experimental availability of drugs?

Risk management must be evaluated with well-designed studies for assessing outcomes. The oft-stated mantra of “all drugs have risks”, although true, does not mean that “the risks of all drugs are acceptable”. The FDA and the drug companies which increasingly fund it are causing the public to tolerate, as indicated above, many unacceptable risks.

### **C. What improvements are needed to enhance communication about safety issues for drugs?**

We assume that this question asks what improvements are need to enhance communication about the safety of drugs to consumers as well as physicians and pharmacists. Before addressing this question it is valuable to reflect on what has not worked over the past 20 years in informing patients about the risks of prescription drugs:

#### The Failure of Most Pharmacists and Physicians to Provide Useful Drug Information

##### 1. Verbal Information

The FDA conducted national telephone surveys in 1992, 1994, 1996, and 1998 to determine how much drug information, including risk information, is received by consumers.<sup>4</sup>

For orally provided drug information, the percentage of consumers who were counseled about at least one category of information has increased, although slowly. Consumers were told primarily about directions for use (how much to take and how often to take). In 1998, 24 percent of people were given both directions for use and risk information (precautions and adverse effects) at the doctor's office, and 14 percent of people were told both directions and risk information at the pharmacy.

The Office of Inspector General found in a 1997 report that the enforcement of Federal and State oral counseling laws requiring pharmacists to provide verbal drug information has been minimal.<sup>5</sup> Pharmacist are qualified to provide high quality information to patients, however they practice in an economic environment that does not allow the reliable provision of accurate and useful risk information about prescription drugs to patients.

##### 2. Written Information

An analysis of the types of written information consumers received with prescription drugs found that in 1998, 70 percent of Americans received written information that was longer than a brief sticker on the medicine container. This

figure compares with 67 percent in 1996, 54 percent in 1994, and 24 percent in 1992. These percentages do not reflect the quality or usefulness, or lack of quality and usefulness of this information prepared by unregulated commercial information vendors.

Public Citizen petitioned the FDA in June 1998 to ban the distribution of written drug information provided by pharmacists produced by unregulated information vendors because of its misleading nature that renders it dangerous.<sup>6</sup>

In December 1999, the FDA revealed the findings of an eight state survey of the quality of written information voluntarily provided by pharmacists to prescription drug consumers.<sup>7</sup> The FDA drew no conclusion as to whether the information distributed by pharmacists met agreed upon quality guidelines because this survey was a pilot study. Our interpretation of the survey's findings was that the unregulated information being distributed by pharmacists failed to meet the minimum guidelines for being scientifically accurate and useful.

The topic of providing drug information to patients invariably ignites a petty turf war between trade groups representing pharmacists and physicians in which the safety of patients is forgotten.

#### Medication Guides

The single most important risk management strategy the FDA can undertake in the short-term to reduce the public's risk from preventable adverse drug reactions is to go forward as rapidly as possible with regulations that require pharmacists to distribute scientifically accurate, useful written drug information, or Medication Guides, approved by the agency. At the very least, this would provide consumers with a reliable source of information that they can use to protect themselves from preventable injury.

Unfortunately, the FDA has been blocked by trade groups representing pharmacists and physicians and the pharmaceutical industry for over 20 years to implement regulations that would place objective, scientifically accurate written risk information about prescription drugs in the hands of the public. This history can be found in the FDA's failed 1995 proposed rule for Medication Guides.<sup>8</sup> The FDA now only has limited authority to require the distribution of Medication Guides<sup>9</sup>, but this authority has only been used rarely.

Public Law 104-180, signed August 6, 1996, required the FDA to conduct a national survey assess the quality and quantity of written drug information for consumers voluntarily being distributed by pharmacists. If these quality and quantity standards are not met, consideration can once again be given to providing the public with useful and accurate information by regulation. This assessment was to have been completed by January 1, 2001. The failure to

meet the deadlines in the law without the FDA taking over the Medication Guide program constitutes a violation of the terms of the 1996 law.

#### Revised Format of Professional Product Labeling

The FDA proposed a rule in December 2000 to revise the format and content of the professional product labeling, or "package insert," of new and recently approved drugs.<sup>10</sup> In the likely event that the private sector is again successful in blocking regulations to require the distribution of Medication Guides to consumers, easier to use package inserts would be the next best option to reducing the risk of preventable adverse drug reactions to the public.

Several provisions of this proposed rule would, if used in patient information as well, provide the public with useful information that could be used for their protection:

□ A Highlights of Prescribing Information section. This section would appear at the beginning of the label and consist of selected information that is most important about the risks and benefits of the drug.

□ An inverted black triangle on the labeling of new drugs. This is similar to what has been done in the United Kingdom for a number of years. This symbol can be used to alert prescribers and patients to the need for intensive surveillance for new and unexpected adverse drug reactions not detected in clinical trials. The symbol would also alert patients that they may have been prescribed a new drug with which, by definition, prescribing experience in the U.S. is limited.

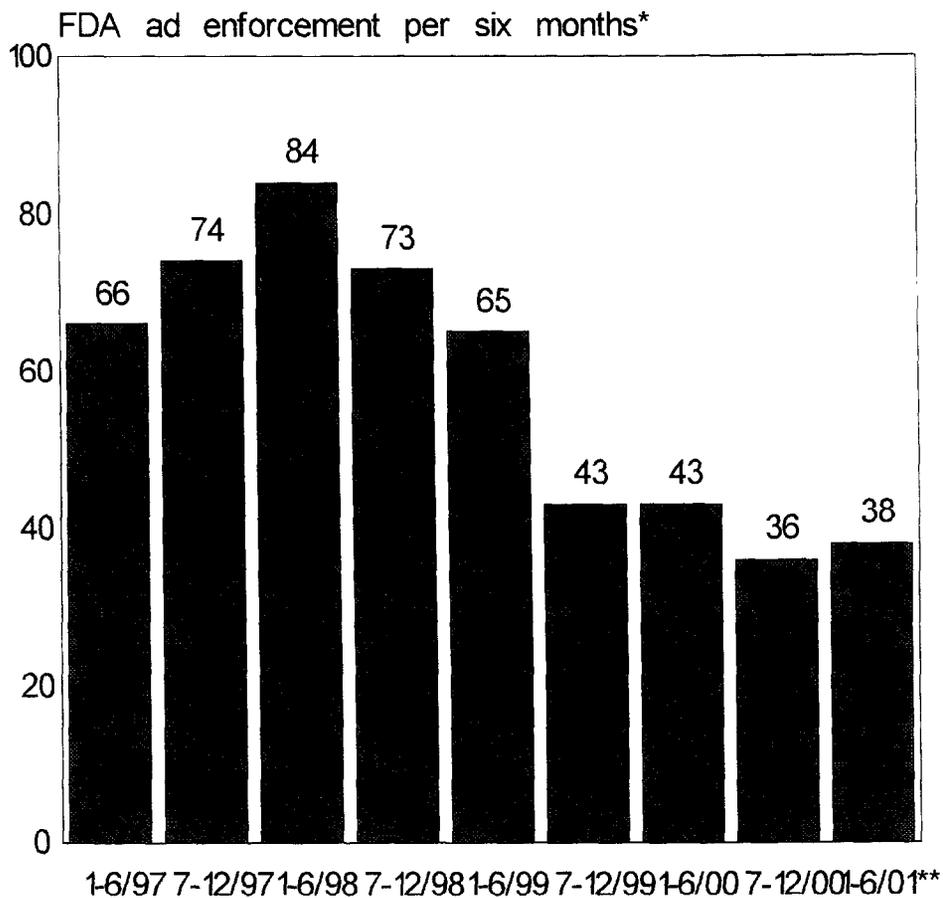
□ Indications and usage section. We suggest that the FDA, in the interest of clarity, change the name of this section to the Food and Drug Administration-Approved Uses section. The phrase "Indications and Usage" is regulatory jargon with a meaning that may not be clear to prescribers and is not understood by patients.

The new label would declare succinctly if evidence is available to support the safety and effectiveness of the drug only in a selected subgroup of the larger population of patients. If the evidence to support the FDA-approved use is based on surrogate endpoints or a post hoc sub-group analysis, the limitations of these data would also be described.

We also suggest that the FDA require a statement in the Food and Drug Administration- Approved Uses section of whether the drug was approved on the basis of placebo- or active-controlled trials. If active controls were used, the name(s) of these drugs and their results in the study should be stated. If there is no evidence that the new drug is any safer or effective than older drugs, this should be stated in both the professional and patient labeling.

In addition to the suggestions made above, are several others.

1. Much more active and well-staffed enforcement by the Division of Drug Marketing, Advertising, and Communications (DDMAC) to counter the often-false and misleading commercial advertising messages.



2. Finalize the long overdue direct-to-consumer advertising (DTC) regulations.
3. Expand the Freedom of Information Act/Federal Advisory Committee Act to require earlier public access to data, including prior to approval, so there can be more public input into FDA decisions. The public availability of AERS

adverse drug reaction data is hampered by the fact that, at present, the data are almost five months out of date.

4. Encourage, for Medicare and Medicaid, and other health service facilities, safer formularies that exclude the large number of recently-approved me-too drugs such as the Seattle-based Group Health Cooperative of Puget Sound has done.

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