

FDA's Drug Approval Process: Up to the Challenge?

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Testimony

I appreciate the opportunity to testify on the important issues concerning the FDA's drug approval process. I have worked in this area as a public interest attorney, as a Congressional staffer, as an FDA official and now as an attorney in private practice. I have listened to criticisms that the FDA is too slow in approving prescription drugs and that it acts too quickly; that it approves too few drugs and that it approves too many; that it is too strict in controlling advertising and that it is too lax.

Today's hearing concerns important questions about drug safety that affect all patients who use prescription drugs. The recent studies about the safety of Vioxx and other COX-2 inhibitors have raised questions about whether the FDA is adequately carrying out its responsibility to protect patients from unsafe drugs. Essentially, the issues concern whether the FDA is doing a good job in: deciding whether to approve drugs; identifying drug safety issues that appear after a drug is approved; and monitoring drug advertising, particularly direct advertising to the consumer. Two other issues that I think should be added to this list are whether the FDA should devote more attention and resources towards informing and guiding physicians about how to use drugs; and informing the public about the safety of drugs. I now would like to address each of these issues.

A. THE DRUG APPROVAL PROCESS

Chronologically, the first question is whether there are serious flaws in the evaluation of applications to market new drugs, and in particular whether drugs such as Vioxx should have been approved in the first place. The same question could be asked of drugs such as Baycol, the cholesterol-lowering drug that was withdrawn after it caused more than 30 deaths and thousands of cases of severe muscle disease, and fenfluramine, one of the drugs that comprised the combination diet drug known as "Phen-Fen," which caused thousands of heart defects. The first point to make is that just because a drug was withdrawn for safety reasons does not mean that the FDA made a mistake in approving it. This is something that many patients do not understand.

The reason that we sometimes find out about safety risks after the drug has been marketed is explained by the necessary difference in the number of people on whom new drugs are tested and the number of people who ultimately use those prescription drugs. Typically, new drugs are studied in a population of about 3,000 people. Such a study can detect drug-related injuries that occur at a rate of between one in 500 and one in 1,000. Yet, if the drug is used by 200,000 people, a serious adverse event appearing in as few as one in 10,000 people is very significant, since it would occur 20 times. If the drug is used in 2 million patients, which is not uncommon, these serious, adverse events would occur 200 times. For this reason, rare adverse drug reactions often can be identified only after a

drug has been widely used. Common adverse reactions, such as the increase in heart attacks and strokes observed in the case of Vioxx, are even more difficult to detect during the clinical trials conducted during drug development.

On the question of whether the information learned about drugs that have been withdrawn over the last several years demonstrates that there are serious problems with the FDA drug approval process, my answer is that the case has not been made. Whenever a prescription drug causes death and serious injury, it is appropriate to ask whether the drug should have been approved in the first place. And it is appropriate to investigate that question. My point is that based on what we know today, I cannot identify any fundamental problems with the drug approval process at the FDA.

B. DRUG SAFETY AFTER APPROVAL

The important issue, in my view, is whether, with appropriate resources and regulatory authority, the FDA could do a better job in monitoring and regulating drugs after they are approved. At the outset, it must be acknowledged that the FDA is taking a number of steps to address the criticism of how drugs are evaluated after they enter the market. The most significant initiative relates to how information gathered by the agency's Office of Drug Safety should be evaluated and how decisions about the safety of marketed drugs should be made. At various times, it has been suggested that a separate drug safety agency should be established or that at least a separate drug safety center should be established within the FDA. This is a very tricky problem. On the one hand, the drug reviewers will have the greatest knowledge about the drug and the data reviewed in connection with its approval. On the other hand, any system must guard against the tendency of any decision-maker to defend his or her decisions. In other words, the charge that the reviewer who approved the drug will have a tendency to defend that decision must be taken seriously.

I do not believe that the best approach would be to completely separate the post-market function from the new drug application approval function. But it is important to elevate the post-market group in terms of resources and status and to create a mechanism so that an official who did not make the decision to approve the drug in the first place is charged with resolving disagreements. It seems to me that the agency's recent announcements about restructuring the decisionmaking on post-market issues are a step in the right direction. I do not know whether they go far enough. It is important that their implementation be closely monitored.

I am also aware that important steps are being taken to make studies of prescription drugs publicly available and to allow a public airing of opposing view before agency advisory committees.

I would now like to turn to other steps that should be considered to strengthen the agency's post-market program.

1. The FDA Should Initiate Programs to Educate Patients about the Inherent Risks of Drug and It Should Consider Restrictions on Direct Advertising to Consumers.

a. Educating Patients about the Inherent Risks of Drugs

The publicity around Vioxx and the other COX-2 inhibitors has highlighted the inherent risks of virtually all prescription drugs. In some cases, these risks are known when the drugs are approved, but the FDA has made a determination that the benefits of the drug (in terms of treating disease, for example) outweigh its risks. Everyone is aware of severe risks of chemotherapy drugs used to treat cancer. It has also been estimated that approximately 10-15,000 people die yearly from gastrointestinal complications caused by non-steroidal, anti-inflammatory pain medications (such as aspirin and the prescription alternatives to the COX-2 inhibitors). Many prescription drugs have documented risks. Other risks are not known, and in some cases the risks of a drug will never be identified because they simply cannot be detected. The FDA should take a leadership role in educating patients about the risks of drugs so that patients consider these risks when deciding whether to take prescription drugs. In particular, the FDA should take on the responsibility to remind physicians and patients about the additional risks of newly approved drugs and it should advise caution in taking drugs to which large numbers of patients have not yet been exposed.

b. Consider Limiting Direct Advertising to Consumers of Prescription Drugs

It is not uncommon for a drug to reach very high sales soon after entering the market. Often new drugs (with their inherently greater risks) are unnecessarily prescribed to patients. Until the mid-1990's, drug companies were effectively prohibited from advertising. Today the drug industry spends billions of dollars advertising directly to consumers, and it has been suggested that consumer advertising is an important factor in the increasing sales of prescription drugs, particularly new drugs entering the market place. This needs to be studied and limitations on consumer advertising should be considered.

One possibility is to ban consumer advertising for a period of time (one or two years) after a drug has been approved, as additional data are collected on the drug's safety. Another alternative is to require more explicit and more prominent disclosures about the safety of prescription drugs. In the case of new drugs, manufacturers could be required to include a standard disclosure about the inherent risks of new drugs.

2. The FDA Should Be Given the Resources and Authority to Establish an Effective Program for Monitoring Drugs After They Are Approved.

One unfortunate consequence of the Prescription Drug User Fee Act ("PDUFA") is that the FDA's program for monitoring drugs after approval has languished while the Center for Drugs focused its energies on meeting the Congressional directives regarding new drugs. Understandably, in recent years, the agency's focus has been on getting drugs reviewed, but in order to meet PDUFA targets that a certain portion of the drug approval process be funded with federal money, the agency has cut funds for post-market studies. Congress should consider sending the FDA a strong message that it expects the agency now to turn its attention to monitoring, identifying and controlling adverse reactions to drugs on the market. This can be done by giving the FDA the resources and legal authority it needs to devise an effective post-market program.

In terms of resources, the FY 2006 budget for the FDA's Center for Drugs is \$505 million, but only \$33 million is allocated for post-market activities, an increase of \$6 million over FY 2005. This funding level is insufficient to adequately monitor drugs after

they enter the market or to initiate studies if questions do arise. The resources could be made available through appropriations or by allowing the agency to use PDUFA funds for this purpose.

Congress should give the FDA adequate legal authority to act when it obtains information about a drug on the market. In essence, before a drug is approved, the company that has the burden of establishing safety and effectiveness. As a practical matter, the FDA has the upper hand in deciding whether to approve a drug and in deciding on the content of the drug's label. Once the drug enters the market, the dynamic changes. Now the company has the upper hand. Some of my suggestions are designed to give the agency more authority after the drug is approved and to make it clear that the company has the continuing obligation to demonstrate the safety and efficacy when new data become available raising questions about the safety of the drug.

a. Authority to Order Changes to the Drug Label Based on New Information

All known information about the safety of a drug is supposed to be included on the drug's label, and the FDA has sufficient leverage to require appropriate information at the time the drug is approved. The problem comes when new information is discovered after the drug is already on the market. When that occurs, there is no explicit authority for the FDA to order that the label be changed to include new information or new warnings. The FDA's only recourse is to withdraw the drug from the market or to bring a misbranding action. These options are usually inappropriate and cumbersome. Thus the FDA is left to negotiate labeling changes with the company and it does not have sufficient leverage to require the changes that it deems appropriate.

Congress give the FDA the authority to order appropriate changes in the labeling of prescription drugs. This authority could be used if the agency reaches an impasse in discussions with the drug manufacturer. This new authority should be accompanied by the opportunity for the affected company to appeal a decision with which it disagrees, administratively and in the courts, but ordinarily implementation of the changes should not be delayed while any appeal is pending. Finally, the agency should have authority to require the manufacturer to notify physicians of important labeling changes.

b. Authority to Require Manufacturers to Conduct Post-market Studies

When the FDA approves a drug, there are often unanswered questions that need to be studied. In other cases, these questions become apparent only after a drug is approved. Today, the FDA sometimes obtains commitments from companies to undertake post-market studies as a condition of approval, but often the companies do not fulfill those commitments, and the agency's legal authority to require the studies is questionable at best.

The FDA has the authority to require post-market surveillance of medical devices, but oddly it never has been given this authority for prescription drugs. The law should be amended to give the FDA the explicit authority to require companies to conduct post-market surveillance of prescription drugs, both at the time of approval and after the drug has been approved.

c. Authority to Address Misuse of Drugs by Physicians

The FDA should actively intervene when physicians misuse drugs. It is almost gospel at the FDA that the agency does not interfere with the "practice of medicine." This means that once a drug is approved for a single use, physicians are free under federal law to prescribe it for any use. Sometimes off-label uses are appropriate and represent good medical care. Other times, these unapproved uses can become widespread and dangerous. In some instances, physicians have ignored the FDA's directions, risking the health of their patients. For example, the FDA has approved the drug Accutane only for treating severe acne. Accutane is very effective, but it causes deformities in 25 percent of children born to women who take it during pregnancy, and strong warnings have not been enough to discourage physicians from limiting its use. For years, evidence has accumulated that physicians prescribe Accutane for moderate and mild forms of acne. The FDA should be given the legal authority to limit physicians' use of drugs when deviations from FDA-approved uses can lead to severe injuries. This should include explicit authority to limit the distribution of drugs to certain specialties. The authority to require physicians to follow important label directions also should be considered.

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As an observer and for a time as an insider, one thing that is clear to me is that The FDA listens very carefully to Congress. An excellent example of this is the Prescription Drug User Fee Act, first enacted in 1992. Before PDUFA, there were endless articles in newspapers and scientific journals accusing the FDA of denying sick people drugs that they desperately needed, while at the same time those drugs were available in Europe and other developed countries. According to these charges, the FDA was responsible for the "drug lag." Congress passed PDUFA because user fees were seen as the only realistic method of increasing the funds for reviewing prescription drugs, thus eliminating the delays that could be attributed to inadequate funding. As a result, drug review times have been cut in about half, so that today the FDA makes decisions on drugs that represent important advances in medical care in six months and on all drugs in 10 months. It can no longer be said that the United States is the last country to approve important prescription drugs; more often we are the first.

As with the drug lag, there is significant room for improvement in our system for monitoring drugs after they enter the market. With an appropriate direction from Congress in the form of adequate resources and legal authority, the FDA could make significant progress in identifying the risks of drugs after they enter the market. Thank you very much for the opportunity to testify. I would be happy to answer any questions.