

PATIENT AND CONSUMER COALITION

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**Statement at the FDA Meeting on
Risk Management of Prescription Drugs**

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The general public believes that FDA determines whether a drug is safe and effective. As consumers, we like to think of the FDA as a watchdog and a gatekeeper that protects us from unsafe medical products.

Of course, we realize that a prescription drug might be safe for almost everyone, and yet unsafe or potentially deadly for some individuals. Even so, we look to the FDA to make sure that those risks are outweighed by the benefits of a new drug. And by benefits, we don't mean the benefits to the company that makes the drug, but rather the benefits to patients and consumers.

In the decade since the passage of the Prescription Drug User Fee Act (PDUFA), the FDA has devoted disproportionate resources towards accelerating the new-drug approval process. To date, none of the additional revenue provided by prescription drug user fees have been devoted to improving the FDA's post-marketing surveillance and risk assessment programs. On the contrary, as more and more drugs have been approved more quickly, FDA staff and resources were less available for post-market safety programs for each newly approved drug.

Under PDUFA III, we expect increased resources for risk management. However, FDA's agreement to restrict the use of user fees for postmarket risk management will continue to undermine safety. For example, risk management is essential for all drugs, not only those approved in FY 2003 or later, and these activities are essential for many years after approval, not just the first three years.

Minimizing Risks in the Real World

If we start with the assumption that there is no such thing as a risk-free drug, we have to consider how to minimize the risks that exist. Unless placed under a restrictive drug schedule (for example, schedule II drugs such as cocaine, morphine, and methadone), virtually all prescription drugs will be used "off label." That means they will be used for indications other than those approved by the FDA; used by patient subpopulations not originally deemed

appropriate for the drug; and used at doses and frequencies other than those that are “approved.”

These off label uses are a major reason why the **absolute level of risk** is important, in addition to the benefit-to-risk ratio. Risk management strategies must aim both to reduce the absolute level of risk and to maximize the benefit-to-risk ratio.

A low absolute level of risk is important because, unless a drug being considered for approval is to be placed in a restrictive drug schedule, the drug has the potential to be used by thousands or even millions of patients who will have little benefit from the drug. Meridia and other diet pills that are intended for very obese patients but are prescribed for patients who want to lose a few pounds illustrate how common that problem is.

A drug with a high benefit-to-risk ratio but also a high absolute level of risk (such as a psychotropic drug with potentially deadly side effects) should only be approved if its use can be limited to those individuals who are likely to benefit and if other, safer alternatives are not available.

Even the best risk management strategies will not always be successful. That’s why risk management efforts should not be used to justify placing more drugs with high absolute levels of risk on the market. It is safer and better for consumers to keep drugs with high levels of absolute risk off the market whenever possible, unless they meet a serious unmet health need.

Of course, some higher-risk drugs should be made available. People living with HIV who rely on antiretroviral therapies must choose among harmful prescription drugs with potentially debilitating side effects and toxicities in order to maintain optimum health and viral suppression. Risk management is essential for the health maintenance and outcomes of these and many other populations for whom safer, less toxic alternatives are not available.

Thalidomide is an example of a drug that was kept off the market for a long time, and not returned to the market until it had a use that was essential for some patients. In cases like that, effective post-marketing risk management strategies can be designed for a drug, because we had a great deal of information about the drug's adverse effects. In these situations, it is essential to have a thorough understanding of the mechanism of all major adverse effects; clearly defined subpopulations of patients who are at greatest risk for adverse events; clearly defined subpopulations of patients who are likely to benefit most; a comprehensive knowledge of what influences adverse reactions (such as gender, drug-drug interactions, age); documented outcomes of those suffering from severe adverse reactions; and an effective monitoring system for adverse reactions.

Practical Considerations

In the ideal world, we could develop ways to manage risk and communicate those risks to the public. In the real world, we have little evidence that this works.

- We have very little information about risk communication and risk management strategies that are generally effective. Those that have been evaluated – such as product labeling -- have been found wanting.
- FDA’s track record on risk management strategies is not inspiring: the most damning example is the product labels that every reasonable person agrees are almost impossible to read, and the “risk information” on direct-to-consumer advertisements, that are equally useless to most people.

These failures, acknowledged for years with no improvements made, make it difficult for patient and consumer groups to embrace FDA’s risk management mantra.

If the FDA is going to implement new risk communication and risk management strategies, it needs to prove that it is serious. It should thoroughly evaluate each new strategy for effectiveness and feasibility. The essential question is: are these strategies effective and do they safeguard patients’ health?

- Accutane is a drug with a high absolute level of risk but proven benefit for a narrowly-defined patient population. Thalidomide is another example. The FDA should thoroughly evaluate the effectiveness of the various risk management strategies for these drugs before employing those strategies for other high-risk medications.

Medication Guides

An important first step is for the FDA to provide information to consumers in plain, understandable English. The FDA should mandate Medication Guides written in plain and understandable language for all drugs as the first risk management and risk communication strategy to be implemented and evaluated.

The FDA can’t do it Alone

The effectiveness of various risk management strategies will rely at least in part on the willingness of pharmaceutical manufacturers to carry them out. In the past, pharmaceutical manufacturers have resisted efforts to institute stringent risk management programs. Industry may not be willing to support risk management strategies such as patient registries and special physician certification for prescribing high-risk drugs. If they don’t **prove** themselves willing to do so, then the FDA will need to be more restrictive in what they approve as “safe.” Products should be withdrawn from the market if the company does not follow through on required risk management commitments.

Enforcement Strategies

The FDA currently does not carefully monitor Phase IV trials and other post-market safety measures. Post-market safety efforts need to be improved before the FDA can rely on post-marketing risk management strategies. This problem is related to:

- Lack of FDA post-market staff and resources
- FDA's lack of the will to carefully examine drugs that are already approved
- FDA's lack of focus on long-term safety of drugs taken for chronic conditions

- FDA's lack of regulatory authority, such as the ability to impose civil monetary penalties on manufacturers who fail to institute required risk management programs.

Conclusions

The first line of defense for strengthening the safety of prescription drugs is a careful, scientifically-driven approval process. The FDA should not weaken its approval standards just because it is strengthening its risk management efforts. On the other hand, the current situation, where the approval process is the major focus and too few resources are available for post-market safeguards, is unacceptable. The FDA needs to implement a major overhaul of its efforts to evaluate and disseminate information about the risks and benefits of approved drugs, and to control and manage the risks that are inherent in the widespread availability and use of prescription drugs. To do that requires substantial additional staff and resources as well as a new focus on ensuring the effectiveness of safety programs and risk management efforts.

AIDS Action

Center for Medical Consumers

Consumer Federation of America

International Union, UAW

National Women's Health Network

National Center for Policy Research (CPR) for Women & Families

The Title II Community AIDS National Network