Ensuring Drug Safety: Where Do We Go From Here?
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Testimony

The American Medical Association (AMA) appreciates the opportunity to present its views on ways to ensure drug safety in this country and the implications for practicing physicians. We commend the Chairman and members of this Committee for holding this important hearing. The AMA shares a common goal with Congress and the Food and Drug Administration (FDA) to optimize the benefit/risk balance of drug therapy and minimize the risks of prescription drug and biologic products.

As our nation's drug regulatory agency, the FDA ensures that beneficial drug products are made available to the public with labels that contain adequate information about the product's risks and benefits, and protects the public from false claims. While the FDA's approval process is considered the "gold standard" around the world, the FDA's determination that a product is safe and effective is not meant to signal an absence of risk. Drug and biologic products, by their very nature, carry with them certain risks, some of which are discovered after approval. Pharmaceutical manufacturers, the FDA, physicians and patients all play essential roles in minimizing those risks and enhancing the benefits of prescription drugs and biologics.

The AMA supports the FDA's proposals to improve the format and content of the package insert, which is the portion of a drug product's labeling directed primarily to physicians. We have also been a proponent of more widespread use of the MedWatch program (FDA's adverse event reporting system) by encouraging physicians to participate. More recently, the AMA provided testimony and commentary on specific FDA initiatives related to the risk management of prescription drugs, including their concept paper on "Risk Management Programs" and their draft guidance for industry on the "Development and Use of Risk Minimization Action Plans" (Attachments 1 & 2).

This statement will focus on how FDA decisions impact practicing physicians through the drug approval process; postmarketing surveillance efforts; product labeling developed to guide physicians in the appropriate use of medications; policies on unlabeled uses; and risk management. In addition, we make recommendations to improve drug safety and minimize the impact on physicians' ability to practice medicine, including: more active approaches to post marketing surveillance; final FDA rules on the format and content of package inserts; the preservation of physicians' ability to prescribe medications for unlabeled uses; and collaboration between the FDA, pharmaceutical industry, and physicians to develop better risk communication tools.

FDA DECISIONS AFFECTING PHYSICIAN PRACTICE

Drug Approval

The FDA's decision to approve a prescription drug or biologic product for marketing moves that product from an investigational status to an approved product available for widespread use. Approving a prescription drug or biologic for marketing is the primary way in which the FDA affects physician practice. Over the years, the FDA approval process has resulted in access to a wide array of prescription drug and biologic products for use by physicians in the care of their patients.

Fifteen years ago, a primary complaint about the FDA was that the drug approval process was too slow. The problem was referred to as a "drug lag" because at the time, the United States stood well behind other industrialized countries in getting needed drugs to market. After numerous complaints, the government began to focus its attention on improving FDA drug review timelines. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), which authorized the FDA to collect user fees from companies that produce drug and biologic products. Under PDUFA, these fees were provided in exchange for an FDA agreement to meet drug-review performance goals, which emphasized timeliness. PDUFA was reauthorized by the Food and Drug Administration Modernization Act (FDAMA) of 1997 (PDUFA II) and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PDUFA III).

These acts required the FDA to: (1) speed agency review of New Drug Applications (NDAs) and Biologic Licensing Applications (BLAs); (2) improve the efficiency of drug development before submission of new drug or biologic applications; and (3) further improve the quality and efficiency of drug development, review, and risk management for newly approved products -- all without compromising safety. According to the FDA, before PDUFA, the agency approved about 40% of the new drugs introduced on the world market either first or within 1 year of their introduction in another country. After PDUFA and through 2002, this percentage had nearly doubled. Additionally, the median total review time for new drugs and biologics decreased from approximately 23 months to 12 months, with even shorter median approval times for drugs designated for priority review.

Concern has been expressed about the number of drugs approved under PDUFA that have been withdrawn for safety reasons. However, an FDA analysis showed the rate of withdrawal for safety reasons of "new molecular entities" pre-PDUFA was 2.7 percent, while the rate post-PDUFA was 2.5 percent. This is not a significant difference. Thus, it appears as if the FDA has met its obligations under PDUFA to increase the efficiency of the drug review process without compromising the safety of approved drug products. Therefore, the AMA and its physician members hope that any new efforts to improve drug safety can be accomplished without reversing the improvements that have occurred in the drug approval process.

Postmarketing Surveillance

If formal postmarketing studies are not conducted by manufacturers or clinical

investigators to obtain safety information, observational data collected by physicians, other health professionals, and patients are the cornerstone for evaluating and characterizing a drug's risk profile in actual clinical use. Currently, the FDA maintains an adverse event reporting system termed MedWatch, which incorporates both a mandatory adverse event reporting system for manufacturers subject to the Agency's postmarketing safety reporting regulations, and a voluntary, adverse event reporting system for health care professionals, consumers, and patients. MedWatch can be an effective tool for detecting signals suggesting that a drug may be associated with a rare, but serious, adverse event.

However, the MedWatch program is a passive system and it is limited by its reliance on voluntary reporting, which inevitably leads to under reporting. Under reporting and uncertainty about the actual extent of drug exposure, make it difficult to estimate true rates of occurrence of drug-induced adverse events. Because of their observational nature, spontaneous reports also are limited in their ability to establish causality. Given the limitations of spontaneous reporting systems, concerns have been raised about the FDA's ability to detect serious adverse events that occur during the postmarketing phase of a drug product's life cycle. Thus, as efforts are devoted to improving drug safety, attention should be directed toward enhancing postmarketing surveillance by using more active approaches. For example, well designed pharmacoepidemiologic studies on newly marketed drugs could enhance our ability to more accurately determine a drug's adverse event profile in a timely manner.

Recently, the FDA announced its intent to create an independent Drug Safety Oversight Board comprised of FDA staff as well as medical experts from other Department of Health and Human Services agencies and other government departments to oversee the management of important drug safety issues. The AMA has not taken a position on this issue.

In addition, the FDA pledged to "expand existing communication channels and create new ones to ensure that established and emerging drug safety data are quickly available to the public (and physicians) in an easily accessible form with the intent of enabling patients and their health care professional to make better-informed decisions about individual treatment options." One of these proposed channels would be a new "Drug Watch" Web page for emerging data and risk information, and the AMA applauds these efforts to enhance transparency. However, the FDA must provide clear advice when it disseminates emerging or preliminary information prior to taking regulatory action.

Product Labeling

Product labeling decisions are made by the FDA in collaboration with the drug sponsor, usually the manufacturer. The product labeling includes the materials and language that comprise the product's packaging, label and package insert. The package insert is that portion of the approved labeling that is directed primarily to physicians to inform them

about a product's risks and benefits, and to provide guidance on the conditions of appropriate use. However, today's package insert has become a barrier to effective risk communication, serving more as a legal document rather than a resource of useful information for practicing physicians. The FDA has recognized this problem and in December 2000, it issued a proposed rule to modify the format and content of the package insert with the goal of making the information more useful and user-friendly to physicians. Their recommendations included a more simplified, "Highlights of Prescribing Information" section within the package insert. The AMA continues to strongly support FDA efforts to make package inserts more useful and user-friendly for physicians and encourages the FDA to issue a final rule to that effect.

Unlabeled/Off-Label Uses

In an effort to strengthen drug safety, the FDA recently announced its commitment to sponsoring an Institute of Medicine study on drug safety systems with an emphasis on the postmarketing phase, including the study of unlabeled (also known as off-label) use. Unlabeled uses are defined as the use of a drug product for indications or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling. Under the federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved by the FDA for marketing may be labeled, promoted, and advertised by a manufacturer for only those uses for which the drug's safety and efficacy have been established. The manufacturer submits data to the FDA demonstrating substantial evidence of efficacy and safety for each labeled indication. Even though PDUFA has reduced the review time for efficacy supplements (i.e., Supplemental New Drug Applications or SNDAs), manufacturers are not required to and may choose not to seek FDA approval for all useful indications. One major reason for not submitting an SNDA is because the expense of regulatory compliance may be greater than the eventual revenues expected (e.g., if patent protection for the drug product has expired, or if the patient population affected by the new use is very small). A sponsor also may not seek FDA approval because of difficulties in conducting controlled clinical trials (e.g., for ethical reasons, or due to the inability to recruit patients).

A physician may choose to prescribe a drug for uses, in treatment regimens, or in patient populations that are not part of the FDA-approved labeling. The decision to prescribe a drug for an unlabeled use is made by the physician in light of all information available and in the best interest of the individual patient. Prescribing for an unlabeled use requires the physician to use the same judgment and prudence as exercised in medical practice for it to conform to accepted professional standards. Given the prevalence of unlabeled uses and the fact that in many clinical situations such use may represent the most appropriate treatment, the prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care. Therefore, the AMA has had longstanding policy:

"That a physician may lawfully use an FDA approved drug product for an unlabeled indication when such use is based upon sound scientific evidence and sound medical opinion (Policy 120.988, AMA Policy Compendium)."

The position of the FDA on physician prescribing of unlabeled uses supports that of the AMA. The FDA's published statement that addresses the appropriateness and legality of prescribing FDA-approved drugs for unlabeled uses includes the following:

"The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature (FDA Drug Bulletin. 1982; 12:4-5)."

It is important to emphasize that the AMA strongly supports the SNDA process to add new uses for drugs to FDA-approved labeling. However, given the disparity between the actual submission of SNDAs and the evolution of evidence-based medical practice, physician prescribing for unlabeled uses should not be impeded by any actions taken to improve drug safety.

Risk Management of Prescription Drug Products

In 1999, an FDA Task Force published "Managing the Risks from Medical Product Use." Subsequently, in the context of PDUFA III, the FDA agreed to provide guidance for the regulated industry on risk management activities for drug and biological products. In addition to conducting a Part 15 Hearing on risk management in 2002, the FDA issued three Concept Papers ("Premarketing Risk Assessment," "Risk Management Programs," and "Risk Assessment of Observational Data.") for comment in 2003, and then released three "draft" Guidances for Industry, ("Premarketing Risk Assessment, ""Development and Use of Risk Minimization Action Plans [RiskMAPs]," and "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment") in 2004. A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits.

Routine risk minimization measures include use and revision of the package insert, combined with postmarketing surveillance. These measures should constitute the risk management plan for the vast majority of drug and biologic products. The draft guidance on RiskMAPs identified several additional tools that could be considered in designing risk minimization plans when reliance on the package insert as the primary tool may be inadequate. These tools can generally be placed under the following three categories:

• Targeted education and outreach (e.g., physician letters; training programs for physicians or patients; medication guides);

• Reminder system, processes or forms (e.g., patient agreements or acknowledgement forms; certification programs for physicians; enrollment of physicians and/or patients in special educational programs; specialized systems or records that attest to safety measures having been satisfied); and

• Performance-linked access systems (e.g., prescription can be ordered only by specially certified physicians; use of compulsory fulfillment systems; product dispensing only to patients with evidence of lab tests results or other documentation).

Implications for Physicians. In government's efforts to improve drug safety, there may be a desire to use, more routinely, those risk minimization tools that extend beyond targeted education and outreach to include a more pervasive use of tools associated with reminder systems and/or performance-linked access systems. A number of these approaches would directly manage or restrict physician prescribing and may have unintended consequences.

These unintended consequences include:

1) preventing some patients (who would benefit from higher risk drugs) from having access to them because of added burdens on the prescriber;

2) prescribing of less effective, less studied, and even less safe alternative drugs that are not subject to restrictions because they are simply much easier to use;

3) employing multiple and complex risk management tools that may be confusing to both physician and patient and, potentially result in unintended medication errors;

4) creating administrative burdens for physicians that would likely result in the drug not being prescribed at all (unless the restricted drug is truly innovative); and

5) possibly adversely impacting pharmaceutical company research and development in promising areas where restrictive risk management of drugs is anticipated.

Rather than focus on restrictions, the AMA believes that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it and act on it when prescribing a drug. The AMA previously proposed potential ways to improve risk communication about drugs to physicians in its comment letters to FDA on risk management (see Attachments 1 & 2).

High level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk drug products with unique and important benefits on the market. The AMA encourages the FDA and the product sponsor to work with relevant physician organizations to assure that the minimum number and least intrusive RiskMAP tools are selected to achieve the risk minimization objective.

Recommendations

The AMA is pleased to offer the following recommendations to the Committee. We

believe these recommendations will both improve drug safety and not adversely impact how physicians practice medicine. The recommendations are as follows:

1. Improved postmarketing surveillance for potential adverse events can be achieved without slowing down the premarket drug approval process. The AMA supports the use of more active approaches to enhance postmarketing surveillance.

2. The FDA should issue a final rule, as soon as possible, implementing modifications to the format and content of the package insert with the goal of making the information more useful and user-friendly to physicians.

3. Physician prescribing for unlabeled uses should not be impeded because prescribing of FDA-approved drugs for unlabeled uses is often necessary for optimal patient care.

4. The package insert, combined with effective postmarketing surveillance, should constitute the risk management plan for the vast majority of drug and biologic products. When this is insufficient to ensure an appropriate level of drug safety, then effective risk communication to physicians should be the primary means to reduce risks of drugs. The AMA urges the FDA and the pharmaceutical industry to collaborate with physician organizations to develop better risk communication vehicles and approaches. High level risk minimization tools, such as performance-linked access systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

The AMA once again, commends the Committee for holding today's hearing, and we thank the chairman for the opportunity to present our views. We look forward to working together on this important issue.

Attachments

1. AMA Letter 7/6/04 to FDA RE: Draft Guidance for Industry on "Development and Use of Risk Minimization Action Plans" [Docket No. 2004D-0188]
2. AMA Letter 4/29/03 to FDA RE: Risk Management [Docket No. 02N-0528]