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IMPROVING FDA REGULATION OF PRESCRIPTION DRUGS

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A Policy Monograph of the
American College of Physicians

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Executive Summary

Prescription drugs are vital to preventing and treating illness and helping to avoid costlier health problems. The Food and Drug Administration (FDA) is charged with the mammoth and complex task of regulating the safety and effectiveness of new and approved drugs. Unfortunately, over the years the Agency's ability to approve and monitor new drugs has been compromised by chronic underfunding, limited regulatory authority, and insufficient organizational structure. The College offers the following recommendations to support and strengthen the FDA's capacity to regulate prescription drugs:

Recommendation 1: Improve the FDA's ability to approve and monitor prescription drugs through increased funding.

Recommendation 2: Increase the FDA's capacity to regulate drugs manufactured outside the U.S. through both appropriations and user fees.

Recommendation 3: The FDA's regulatory authority should be expanded and more clearly exercised in the design of preapproval trials and studies. Design of preapproval trials should include at least the following:

- A sample size large enough to reflect an appropriate distribution of age and comorbidity among subjects.
- Similar priority given to evaluating both drug safety and efficacy.
- Use of scientific and technological tools (such as pharmacogenetics and computer simulations) to provide earlier warnings about drug toxicities and potential harm.
- Mandatory registration and public reporting of all clinical trial results.

Recommendation 4: Bundling of drugs to limit marketability and availability should be prohibited.

Recommendation 5: Improve the adverse events reporting system.

Recommendation 6: Grant the FDA the authority to require that newly approved drugs have a special symbol on their labels to help increase public awareness that they are new, and limit direct-to-consumer (DTC) advertising for the first 2 years after approval.

Background

Prescription drugs are vital to preventing and treating illness and helping to avoid more costly health problems. The Food and Drug Administration (FDA) is charged with the mammoth and complex task of regulating the safety and effectiveness of new and approved drugs. The FDA reviews proposals for conducting clinical drug trials, evaluates drug applications and proposed drug labeling, and monitors drugs once they are approved and marketed. Recently, the FDA has been under increased scrutiny after several high-profile drugs were withdrawn from the market. The FDA approved Vioxx in May 1999 for several indications, including osteoarthritis, rheumatoid arthritis, acute pain in adults, and menstrual symptoms. However, in 2004, the manufacturer, Merck & Co., removed the drug from the market after a long-term study found an increased risk for serious cardiovascular events among study patients taking the drug compared with patients receiving placebo. Such incidents have caused the medical, science, legislative, and public health communities to question whether the current prescription drug regulation system is optimally designed to determine both the safety and efficacy of prescription drugs and adequately protect the public's health. Despite increased scrutiny and efforts to reform the agency, the Government Accountability Office (GAO) added the FDA's oversight authority to its list of government programs that were "high-risk." The GAO stated that the agency had to improve its foreign manufacturing inspection activities, drug and device promotional material review process, and oversight of clinical trials (1).

Preapproval

The current system of drug safety monitoring includes preclinical testing followed by three phases of clinical studies. Before any new drug can be tested on humans, the drug sponsor must submit a proposal outlining the plan for how the drug will be tested, the measures investigators will take to protect clinical trial participants, and the criteria for exclusion of participants. Although the FDA does provide guidance to manufacturers on the design of clinical trials, ultimately the owner of a drug has the legal right to design preapproval studies as the company sees fit, even if such studies are not optimally designed to serve the needs of prescribers, patients, payers, and science. Preapproval of study design can determine the form in which a new drug will be approved, how it can be manufactured and marketed, and how physicians will ultimately be able to prescribe it for their patients. It can also limit the knowledge gained about a new therapeutic approach to how it works with just one of many potentially beneficial combination therapies.

To obtain approval for marketing a drug in the U.S., drug sponsors must submit a new drug application (NDA) that details the completed clinical drug trials and includes data on safety and effectiveness, pharmacology, toxicology, chemistry, manufacturing information, and proposed labeling language. The NDAs are evaluated by FDA reviewers and other experts who help the FDA determine whether to approve a drug for marketing. The Prescription Drug User Fee Act (PDUFA), enacted in 1992, dramatically reduced the review time for NDAs by allowing industry to pay the FDA to cover the costs of additional staff and other resources needed to approve drugs quickly. After PDUFA went into effect, total median review time for new drugs and biologics decreased from 23 to 12 months (2). The FDA's Center for Drug Evaluation and Research (CDER) staff who review the new drug applications must strike a delicate balance when judging a drug's increased risks and benefits and decide whether the need for more study to increase certainty before approval warrants delaying release of the drug into the market.

Postmarketing

Until recently, once a drug was approved, the FDA was severely limited in its authority to take further regulatory action. The agency could only require post-market studies as a condition for accelerated approval of new drugs for serious or life-threatening conditions (also known as subpart H drugs) or drugs for which safe use in children needed to be determined or more clearly defined. However, the FDA Amendments Act (FDAAA) of 2007 increased both funding and regulatory authority for postmarket surveillance activities, with financing provided through allocation of user fees. The FDAAA grants the FDA new authority to require postmarketing testing to identify or assess potential serious risks. The measure also allows the agency to initiate timely label changes or new postmarketing studies in response to new safety information about marketed drugs. Failure to complete a postmarketing study or label change may result in a penalty of \$250,000 for each violation, up to \$10 million for an ongoing violation. Prior to enactment of the FDAAA, the Agency's postapproval authority was limited to requesting changes on drug labels, negotiating with manufacturers about restrictions on distribution, or petitioning for withdrawal of the drug (3).

Recommendations

In 2005, the FDA requested that the Institute of Medicine (IOM) convene a committee to assess the U.S. drug safety system and make recommendations to improve risk assessment surveillance and the safe use of drugs. The committee concluded that the FDA's ability to approve and monitor drug safety and efficacy had been impaired by a lack of regulatory authority, long-standing underfunding, organizational problems, and an alarming lack of postmarketing data on the effectiveness and safety of drugs (4). Since then, the FDA has taken some steps to improve its capacity for prescription drug approval and regulation. In addition, the FDAAA incorporates several of the IOM's recommendations regarding postmarket activities. However, the agency is still severely underfunded and the systems for ensuring the safety of prescription drugs remain inadequate (5, 6).

Recommendation 1: Improve the FDA's ability to approve and monitor prescription drugs through increased funding.

Over the years, the demands on the FDA have increased exponentially because of scientific advancement, an increase in the complexity and number of new products submitted for premarket review and approval, the emergence of challenging safety problems, and the globalization of the industries regulated by the FDA. Unfortunately, its resources have not increased in proportion to the demands. The number of federally appropriated personnel authorized for the FDA decreased from 9167 in 1994 to 7856 in 2007. Since January 2008, the Center for Drug Evaluation and Research has hired 657 new staff (7). Similarly, the FDA has insufficient access to data and cannot effectively regulate products based on new science because of the lack of a supportive information technology (IT) infrastructure. A Report of the FDA Subcommittee on Science and Technology, issued in November 2007, found that 80% of the Agency's computer servers are more than 5 years old, clinical trial records are stored on paper in warehouses (largely inaccessible for analysis), and the IT budget is about 40% of that for other public health agencies (8). As a result, the scientific demands on the Agency far exceed its capacity to respond, which compromises the integrity of the prescription drug regulatory system.

Ultimately, the FDA will require reorganization and an increase in resources to improve the process for ensuring drug safety and effectiveness.

Recommendation 2: Increase the FDA's capacity to regulate drugs manufactured outside the U.S. through both appropriations and user fees.

An increasing number of drugs marketed in the U.S. are manufactured in foreign countries. The FDA's responsibility for overseeing the safety and effectiveness of prescription drugs includes all that are marketed in the U.S., whether they are manufactured in foreign or domestic facilities. Foreign establishments that market their drugs in the U.S. must register with FDA, and the agency inspects foreign sites to ensure that they meet the same standards that are required of domestic ones. However, whereas all U.S. prescription drug manufacturing sites are inspected at least once every 2 years, there is no scheduled requirement for inspections of foreign facilities. The agency's foreign establishment inspection process was criticized in 2008 when a Chinese-manufactured batch of heparin sodium was discovered to have caused a number of adverse events. The Chinese plant that had produced the drug had never been inspected by the FDA. A 2008 study by the GAO found that the FDA is able to inspect only 8% of foreign establishments in any given year (9). At this rate, the study noted, it would take the FDA at least 13 years to conduct one inspection of all foreign establishments currently in operation. The difficulty in determining the actual number of foreign establishment inspections is attributed to the FDA's flawed and inaccurate databases (10). In addition, the success of the foreign drug inspection program is hindered by a lack of resources (including staff and translators) and an inability to conduct unannounced inspections of foreign drug manufacturers, as the agency sometimes does with domestic manufacturers. The GAO recommended that the agency conduct more inspections of foreign facilities, enforce requirements that manufacturers update annual registration information, establish methods to verify such information, conduct timely inspections of facilities that have received warnings from the agency, and facilitate integration of inspection information stored on all agency databases (11).

On January 28, 2009, Rep. John Dingell (D-MI), Frank Pallone Jr. (D-NJ), and Bart Stupak (D-MI) of the House Energy and Commerce Committee, introduced legislation that would create a user fee on importers of food and drugs to strengthen the U.S. system for ensuring import safety (12). The funds generated from the user fees would help strengthen the agency's ability to manage the foreign drug inspection program and ensure that foreign-made drugs are appropriately examined and deemed safe. The bill would also establish dedicated staff to inspect foreign manufacturers. In June 2008, U.S. Department of Health and Human Services amended its budget request for fiscal year 2009 to include an additional \$275 million for the FDA. The additional funding is intended to help the Agency improve import safety by establishing the FDA's presence in five countries or regions and implementing other measures that will help ensure greater foreign compliance with FDA standards, modernize the FDA's information technology infrastructure, and increase inspections of foreign production facilities.

Recommendation 3: The FDA's regulatory authority should be expanded and more clearly exercised in the design of preapproval trials and studies. Design of preapproval trials should include at least the following:

- A sample size large enough to reflect an appropriate distribution of age and comorbidity among subjects (13).
- High priority given to evaluating both drug safety and efficacy.
- Use of scientific and technological tools (such as pharmacogenetics and computer simulations) to provide earlier warnings about drug toxicities and potential harm.
- Mandatory registration and public reporting of all clinical trial results.

The FDA provides general guidance to industry on designing preclinical trials. However, the final decision regarding study design is determined by the company that funds much of the preapproval process through its payment of user fees. The FDA may not always use its influence in guiding clinical trial development to establish agendas that are patient and research-centered. Given the agency's focus on expediting product approval, the FDA's authority to ensure that clinical trials are constructed to give priority to drug safety and efficacy should be affirmed. This can be achieved by using the agency's authority (or granting such authority if needed) to require or compel drug manufacturers to conduct long-term trials, recruit adequate sample populations for the therapy being tested, and to use effective technologies to determine safety and effectiveness, among other things.

The present system is highly focused on rapid approval of new drugs and reducing delays in the availability of new therapies. As such, the FDA approves drugs on the basis of findings from studies of limited duration that include a relatively small number of patients who may not represent the target population. Preapproval trials include 500 to 3000 subjects. By the nature of their design, adverse events that occur in 1 of 100 patients will be reliably detected, but adverse reactions that occur in 1 in 1,000 patients or fewer may not be detected, even if the reactions are severe (14). As a result, when general safety and efficacy are determined and a drug is approved, little is known about the frequency of less common adverse reactions, effects of long-term exposures, effects in special populations, or efficacy in relation to other drugs. A study by the GAO concluded that 51% of all approved drugs had at least one serious adverse event that was not recognized during the approval process (15).

Some would argue that preapproval studies are necessarily limited to make potentially life-saving and life-altering therapies available to sick patients. However, rapid approval should not come at the expense of public safety. Currently, preapproval studies are not optimally designed to determine both drug efficacy and safety. As a result, 51% of drugs have label changes because of major safety issues discovered postmarketing, 20% of drugs receive black box warnings after marketing, and 3% to 4% of drugs are ultimately withdrawn for safety reasons (16, 17). Title VIII of the FDAAA law requires registration for all drug clinical trials beyond Phase 1 investigative studies (18). Although this is an important step to ensure that researchers, practitioners, and the public have access to critical information, the FDA's regulatory authority should be expanded and more clearly exercised in the design of preapproval trials and

studies to ensure that studies are designed to optimally evaluate both drug efficacy and safety. For example, drugs intended to treat chronic illnesses should be evaluated in long-term trials (19). In addition, clinical trials with larger samples sizes that include high-risk patients could be a cost-effective and efficient means of determining drug safety profiles (20). In commenting on the participation of elderly persons in clinical trials, the agency stressed that it expects medical officers to review the safety and efficacy of a drug in a new application for elderly persons; however, this expectation is not mentioned in agency guidance (21). The agency maintains that despite staffing and funding challenges, they continue to focus their efforts on effectively utilizing technology to detect and prevent adverse events as early as possible (22).

Recommendation 4: Bundling of drugs to limit marketability and availability should be prohibited.

Clinical trials should focus on a drug's safety, effectiveness, and clinical relevance rather than its marketability. Trials for bundled drugs can create patient safety and access problems and should be prohibited. For instance, in 2005 Pfizer submitted plans to the FDA to begin conducting large trials to test the cholesterol drug torcetrapib in combination with the popular and widely used statin Lipitor. Critics stated that Pfizer was putting profits before patients and that if the FDA approved the torcetrapib–Lipitor combination, it would preclude patients who can't afford or tolerate Lipitor from being able to use torcetrapib. Because only Lipitor and no other statin would be combined with torcetrapib, critics argued that the combination would unjustly insulate Lipitor from competition (23, 24). At least one physician reacted to the action by calling on other practitioners to boycott Pfizer products (25). Another blamed the FDA for permitting the trial design, saying, "It appears that Pfizer will avoid such antitrust prohibitions by having the FDA do its bundling for it. The FDA's acceptance of the proposed trial designs in effect acknowledges that since the new drug is Pfizer's intellectual property, the company's research plans are subject only to its own corporate prerogative" (26). Initially, Pfizer argued that patients would probably benefit most from the combined drug given their potentially complementary effects and that combining the two drugs, rather than comparing torcetrapib with other statins, would reduce ambiguity of results (27). Following the backlash, Pfizer indicated that it would market torcetrapib as a standalone product; however, the trials were terminated in December 2006 when evidence determined that torcetrapib elevated the risk for death (28, 29). The FDA should prohibit drug companies from conducting clinical trials of bundled products, especially when patient safety or access could be compromised. The FDA should also reaffirm the need to design trials that focus on a drug's safety, effectiveness, and clinical relevance.

Recommendation 5: Improve the adverse events reporting system.

Postmarketing surveillance is critical to determining the safety, long-term effects, and relative comparability of new drugs. According to Mark B. McClellan, MD, FACP, former FDA Commissioner, "One key reason drugs may be used for years by millions of patients before risks become evident is that the U.S. has no active drug surveillance system" (30). The FDA's primary source for identifying drug safety issues after marketing is the Adverse Event Reporting System (AERS), available through the online system MedWatch. MedWatch is intended to detect safety risk signals for prescription drugs, medical devices, and other medical products. FDA staff use reports from this system to conduct postmarketing surveillance, monitor compliance, and respond to outside requests for information. However, the FDA relies on drug manufacturers as the largest source of postmarket information on adverse drug events (ADEs). The FDA has the authority to require drug sponsors to report ADEs. Schedules for reporting vary on the basis of the seriousness of the event and whether the event has been previously identified and is included on a drug's label. Serious unlabeled events must be reported to the FDA within 15 days of learning about them. Others must be reported quarterly for 3 years, then annually. Despite these requirements, it has been estimated that only 1% of all ADEs and 10% of serious ADEs are reported (31).

Critics of the current system have pointed to the inherent conflict of interest in asking the industry to monitor its own drugs, an issue which is magnified by the intense direct-to-consumer advertising and promotional efforts directed toward physicians, especially during the initial and product launch phases (32). It is for this reason that the formation of an independent drug safety board, comprising consumer representatives and scientists with no industry ties or involvement in the approval process, has been suggested to oversee postmarket surveillance activities (33, 34). Physicians and consumers can also report adverse events voluntarily; however, most do not use the AERS system.

With passage of the FDAAA, the agency is now charged with establishing a stronger postmarket surveillance system that better monitors adverse events. The law requires the FDA to compile and publicize information regarding drugs that have received a significant number of adverse event reports. Further relevant changes include requiring the agency to conduct Risk Evaluation and Mitigation Strategy for drugs that exhibit an elevated safety concern to ensure that the drug's benefit outweighs its risk to consumers. Similarly, the agency is now able to require manufacturers to perform postmarket clinical trials. The Sentinel Initiative will enable agency personnel and researchers to query the system to determine whether a drug that exhibited problems during premarket studies has exhibited problems since reaching the market. The agency is working to compile data from Medicare, Veterans Administration, Department of Defense, and private insurers into a searchable database. However, the system will not be able to automatically monitor information on adverse events, which leaves the onus on researchers to search the database to determine potential safety problems (35).

Although the FDAAA requires the FDA to take significant steps to improve its efforts to monitor and report potentially unsafe drugs, the law does not require major changes to the current structure for reporting adverse events.

Efforts are needed to educate physicians on how and when to report an event that is potentially drug-related. In addition, streamlining reporting systems so that ADEs can easily be reported and ensuring anonymity may facilitate reporting by health care professionals. However, there also must be some means to ensure appropriate, unbiased reporting and to prevent erroneous reports by competitors or others with a self-interest in removing specific drugs from the marketplace.

Patients can also provide critical information about ADEs. One study found that patients reported ADEs earlier than health professionals, who are often overwhelmed by their patient load and administrative work (36). However, little is known about the unintended consequences of public reporting of adverse events. The system could potentially be overwhelmed with reports of minor symptoms and cases. This could be alleviated by developing explicit guidelines on the types of events to be reported and discouraging patients from reporting minor side effects already known to be associated with a given drug. There is also room for false alarms and biased reports from patients who may be influenced by news reports or other media sources (37). Pilot programs could provide useful information on the quality and effectiveness of patient reporting of ADEs.

The United Kingdom's Yellow Card Scheme is a potential model for an integrated approach to voluntary reporting. The system collects information from health professionals and consumers on *suspected* ADEs. It allows health care professionals and consumers to report online, by prepaid mail, and by phone. The system actively seeks reports and can be accessed in some form in almost any relevant care delivery setting, including pharmacies and physician offices (38). Although the system has existed since 1964, national patient reporting was not incorporated until 2005, after several years of local pilot programs. Currently, physician and patient reports are maintained in two separate but parallel systems (39).

Recommendation 6: Grant the FDA the authority to require that newly approved drugs have a special symbol on their labels to help increase public awareness that they are new and limit direct-to-consumer (DTC) advertising for the first 2 years after approval.

The drug label is the principle means of communication about a drug's risks and benefits. A redesigned drug label could provide physicians and patients with information about the drug's newly approved status as well as any new pertinent information uncovered during postmarket surveillance. In the UK, newly approved prescription drugs are marked with a black triangle while the Medicines and Healthcare Products Regulatory Agency and the Commission on Human Medicines intensively monitor the drug's risks and benefits. The black triangle is not removed until the safety of the drug is well established (40). The IOM recommended that the labels for all newly approved drugs in the U.S. contain a special symbol to help increase public awareness of the nature of newly approved therapies. The symbol would remain on the drug label for 2 years, during which time it would be subject to heightened postmarketing surveillance and limits on DTC advertising (41). Under FDAAA, the agency is permitted to require label changes if it has concerns that patient safety could be compromised.

Direct-to-consumer advertising is often used to promote newly approved medications. Advertising campaigns for 17 of the 20 drugs with the highest DTC advertising expenditures in 2005 commenced 1 year after FDA approval of the drug (42). Direct-to consumer advertising can dramatically increase uptake of a newly approved drug and in some cases may expose larger numbers of people to a drug with undocumented safety concerns.

The FDAAA requires that published DTC advertisements include a statement that encourages consumers to contact the FDA's MedWatch system and report any adverse events related to the advertised drug. The law also requires the agency to conduct a study on whether a similar statement should be included in televised advertisements as well as a study to determine the effect of DTC advertisements on consumer health literacy. The statute also establishes a program in which drug companies can voluntarily submit DTC television advertisements to the FDA for review prior to broadcasting and permits the FDA to require drug companies to submit DTC television advertisements for review if the agency has concerns regarding content. Although these steps are encouraging, at a minimum DTC advertising during the 2 years following a drug's approval should include explicit notice that the data related to risks and benefits associated with the product are less extensive than those related to alternative products that have been in use for a longer period and should include a caution to speak to one's health care provider about alternatives.

A possible consequence of requiring a special symbol on labels for newly approved drugs could be reduced patient adherence in taking physician-prescribed medications. Consequently, the design and implementation of the special symbol should consider this possible unintended consequence. Stronger clinical trials prior to approval for marketing is another alternative to reduce postmarketing ADEs.

Summary

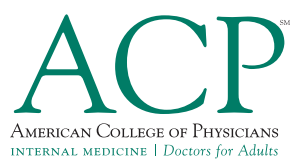
Health care providers and patients expect that the medications they prescribe and use as indicated and directed will generally have beneficial effects and not cause them significant harm. The FDA plays a crucial role in ensuring that approved prescription drugs are both safe and effective. Unfortunately, over the years the Agency's ability to approve and monitor new drugs has been compromised by chronic underfunding, limited regulatory authority, and insufficient organizational structure. The College's recommendations are intended to support and strengthen the FDA's capacity to regulate prescription drugs.

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