Pain is a common medical problem, and relief of pain is an important therapeutic goal. Although nonpharmacologic approaches to treating pain (e.g., behavioral techniques) show promise for certain

A Difficult Balance — Pain Management, Drug Safety, and the FDA
Janet Woodcock, M.D.

conditions, pain is most commonly treated with analgesics. Over the past decade, there have been growing concerns about the harm — abuse and addiction, as well as serious injury and death — caused by the use of prescription and over-the-counter analgesics. These concerns have emerged in parallel with the evolving understanding of the importance of pain management in medical care. We at the Food and Drug Administration (FDA) have been engaging physicians, pharmacy groups, patients, and other stakeholders in an ongoing effort to strike the right balance between two important goals: on the one hand, providing access to pain medications for those who need them, and on the other hand, managing the variety of risks posed by analgesic drugs. Recent FDA advisory committee meetings and actions reflect this effort.

Acetaminophen is one of the most commonly used analgesics. In 2008, approximately 25 billion doses were sold in the United States. Acetaminophen is marketed as a single-ingredient drug but can also be found in a multitude of over-the-counter combination products, such as cough and cold medicines, as well as in prescription opioid–acetaminophen combination products (e.g., Vicodin [Abbott], Percocet [Endo Pharmaceuticals], and Darvocet [AAIPharma]). Although acetaminophen, when used as labeled, is generally safe, the ubiquity of the drug and its relatively narrow therapeutic index create the potential for serious harm from both inadvertent and intentional overdoses (for related emergency department visits, see bar graph).

Approximately 30,000 hospitalizations are associated with acetaminophen overdose in the United States annually — approximately half of them resulting from unintentional overdose. Acetaminophen is also a leading cause of acute liver failure in the United States.

In June 2009, the FDA held a 2-day public advisory committee meeting to discuss acetaminophen toxicity. The FDA presented multiple options for improving the management of acetaminophen-related risk. The top three recommendations of the committee were to reduce the maximum single dose of over-the-counter acetaminophen from 1000 mg to
650 mg or switch the 1000-mg single dose to prescription status, to standardize the range of over-the-counter liquid concentrations (to reduce dosing confusion), and to eliminate prescription acetaminophen combinations or require a boxed warning on the labels of these products. The first and third recommendations, in particular, could have a considerable effect on the use and availability of acetaminophen-containing products. The agency is currently considering its next steps.

Opioid analgesics have also been the subject of FDA action. In February 2009, the agency announced that it was initiating a process under the FDA Amendments Act (FDAAA) that would require manufacturers of high-potency opioids to institute risk-evaluation and mitigation strategies (REMS) to address the risks of abuse, misuse, and the exposure of persons who are not opioid-tolerant. In one month in 2007, an estimated 5.2 million people 12 years of age or older used prescription pain relievers nonmedically. In 2006, there were approximately 57,000 emergency department visits for nonmedical use of hydrocodone or hydrocodone combinations, 65,000 for nonmedical use of oxycodone or oxycodone combinations, and 45,000 for nonmedical use of methadone (for admissions, see line graph). An analysis of poison-control data from 2003 through 2006 identified 9179 children who were inadvertently exposed to prescription opioids. The median age of the children was 2 years, and 92% of the poisonings occurred in the child’s home. Such data highlight the need for additional measures to limit the abuse and misuse of prescription opioids and prevent the accidental exposure of children.

As part of the process involved in developing REMS, the FDA has met with health care professionals, patient-advocacy groups, and representatives from the pharmaceutical industry. A public meeting on this topic was held in May 2009. Discussions have focused on ways to curb abuse and accidental harm while not limiting access for treatment of pain.

Meanwhile, the FDA will continue to take steps to manage the risks associated with new and existing products. For example, on July 16, 2009, the FDA approved Onsolis (BioDelivery Sciences), a fentanyl buccal soluble film used for the management of breakthrough pain in patients 18 years of age or older who have cancer and are already using another opioid. Given the significant risk posed by Onsolis if taken by someone who is not opioid-tolerant, the agency called for the institution of a REMS called the Full Ongoing Commitment to User Safety, or FOCUS, program to manage these risks and to reduce the likelihood of misuse and abuse.

In January 2009, the FDA convened an advisory committee meeting to discuss the safety and continued marketing of propoxyphene products. Propoxyphene, a low-potency opioid indicated for mild-to-moderate pain, has been on the U.S. market since 1957. A number of questions had surfaced regarding the safety and usefulness of propoxyphene in today’s armamentarium. In July 2009, the FDA made public its decision to require the makers of propoxyphene-containing products to make changes in safety labeling, including adding a boxed warning and a medication guide to address the risks of overdose, both accidental and intentional. The agency is initiating additional studies of propoxyphene safety.

Although the risks of serious or fatal gastrointestinal bleeding from nonsteroidal antiinflammatory drugs (NSAIDs) have long been recognized, additional safety concerns have also emerged about these agents. In April 2005, the FDA implemented the recommendation of an advisory committee to require a boxed warning on the labels of NSAIDs (except aspirin) about the risk of excess myocardial ischemia, particularly in patients with preexisting heart disease.

Despite increased awareness of the harm resulting from the use of NSAIDs, acetaminophen, opioids, and other drugs for pain, it is likely that extensive prescribing and use of these drugs will continue. Given this reality, there is a need for more vigorous risk-management efforts by the FDA and other stakeholders in the health care system. The FDA cannot address these risks on its own; prescribers and users of analgesics must also participate in this effort. Any risk-manage-
ment option must be considered in the light of its potential effect on the use of other analgesics, given that most analgesic drugs have substantial liabilities. The unintended consequences of shifting use from one drug class to another, for example, must be considered carefully.

The FDA has been implementing strategies to reduce preventable harm from suboptimal use, misuse, and abuse of analgesics. Although these strategies are intended to ensure that risks are better managed, their effectiveness in reducing harm will require ongoing evaluation. For products that requiring REMS, metrics and procedures for tracking outcomes and the effectiveness of the interventions must be identified. The FDAAA requires each REMS to contain a timetable for its assessment that is unique to that drug. If risks are not adequately mitigated, then additional steps can be taken.

Although management of the risks posed by the current armamentarium will be a predominant theme for the foreseeable future, the FDA is also exploring ways to improve analgesic-drug development, primarily through research into better designs for pain trials, in the hope that highly effective drugs with more easily managed risks may be developed.

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Getting to the Real Issues in Health Care Reform

Paul B. Ginsburg, Ph.D.

No issue has dominated the health care reform debate as much as whether the U.S. government should offer a health insurance plan to compete with private insurers — the so-called public option. Congress has discussed two approaches to the public option, one of which would have the public plan pay providers at rates close to Medicare rates (generally, substantially below those of private insurers). Opposition by insurers, providers, and the business community, as well as fears that such a payment structure would lead to a single-payer system, has pushed this “robust” public option off the table. Instead, both the House bill and, presumably, a final Sen-

![Figure: Number of Primary Admissions for Treatment of Abuse of Nonheroin Opiates or Synthetic Substances by Persons 12 Years of Age or Older, 1997 through 2007.](image-url)