



Protecting the Health of the Public — Institute of Medicine Recommendations on Drug Safety

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Soon after rofecoxib had been withdrawn from the market in September 2004, hearings of the Senate Finance Committee and editorials in the lay and medical press raised serious questions about

drug safety in the United States. In response, the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) asked the Institute of Medicine (IOM) to assess the U.S. drug-safety system. The IOM assembled a diverse panel of experts without ostensible bias or conflict of interest, none of whom were pharmaceutical industry employees. The committee, on which we served, reviewed published literature, held open meetings, and received comments from the pharmaceutical industry, the FDA, and nonprofit groups. In September 2006, the IOM released the committee's findings and recommendations.¹

The drug-approval system

evolved over the past century in response to earlier drug disasters and advocacy by interest groups, including patients and industry. Currently, new drugs undergo serious evaluations of efficacy and safety before approval. The pre-marketing randomized clinical trials are generally small, short-term studies. CDER uses the information from these trials to make eventually a binary decision — to approve or not to approve.

The Prescription Drug User Fee Act of 1992 and its 1997 renewal helped to accelerate drug approval, but these acts also prohibited the FDA from applying user fees to improve post-marketing drug surveillance. In the absence of efforts to enhance drug safety, the

United States became increasingly the country of first launch, the public testing ground, for many new drugs. Although the 2002 reauthorization of user fees permitted their use for selected drug-safety activities, the negotiations between industry and the FDA about performance goals have contributed to the perception that the FDA's client is industry rather than the public.

Under the current model, drugs are rapidly evaluated before approval and are often aggressively marketed afterward. Direct-to-consumer advertising can rapidly expand the use of new drugs to include patient groups that were sparsely represented in pre-marketing evaluations. The centerpiece of the CDER post-approval safety system is the Adverse Event Reporting System (AERS); in this system, patients or health care professionals submit reports of adverse events thought to be related

to drug administration. Although this collection of voluntarily submitted case reports represents the weakest form of epidemiologic evidence, many drugs have been appropriately relabeled, sometimes with black-box warnings, or withdrawn from the market on the basis of AERS evidence.

CDER lacks a systematic approach to identifying possible pre-marketing drug-safety problems and translating them into high-quality post-marketing studies. Without an organized system to identify potential safety signals, the studies needed to resolve them may not be performed. The post-marketing commitments that are requested by the FDA are often hastily assembled by sponsors, who may not have a symmetric interest in safety and efficacy. Even so, once a drug is approved, CDER lacks the authority to force sponsors to complete agreed-upon post-marketing commitments or to require sponsors to initiate new studies. As a result, hundreds of agreed-upon studies remain “pending” in perpetuity. Since CDER

lacks the resources to conduct its own studies, when a new drug is launched, the current regulatory system creates “an evidence-free zone.”²

According to the 2003 report of the Office of Inspector General of the Department of Health and Human Services,³ a survey of CDER reviewers revealed that 66% lacked confidence in the FDA’s safety monitoring of marketed prescription drugs, and 18% had felt pressure to approve a drug despite reservations about its quality, efficacy, or safety. In 2006, the Government Accountability Office found that the “FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues.”⁴

On the basis of these reports and other evidence, the IOM committee identified a number of serious problems, including a lack of clear regulatory authority, chronic underfunding, organizational difficulties, and a scarcity of post-approval data. Contributing to an urgent need for cultural change in

the FDA are a suboptimal work environment, a lack of consistency among CDER review divisions, polarization between the offices responsible for the pre-marketing review and post-marketing surveillance, CDER management’s disregard and disrespect for scientific disagreement, and politicization and a lack of stability in the office of the FDA commissioner.

According to the committee’s vision (see box), the FDA must embrace a culture of safety in which the risks and benefits of medications are examined during their entire market life. This so-called life-cycle approach would entail evaluating risks in the context of benefits, sustaining attention to both efficacy and safety after approval, and advancing and protecting the health of the public. Risk–benefit analyses would highlight key areas of uncertainty. The careful design and conduct of post-marketing studies would help to resolve uncertainties as drug use expanded. The committee’s recommendations focus on the central theme of an ongoing effort to

Toward a New Vision of Drug Safety

The increasingly complex interface between innovation and regulation has been characterized by binary opposites: speed versus safety, tight preapproval regulation versus loose postapproval regulation, active collection of data before approval versus passive surveillance after approval, and an abundance of clinical efficacy data before approval compared with much less safety data after approval. The polarity of approach and emphasis is inconsistent with the widely accepted notions that risk must be considered in the context of benefits, that understanding of the risks and benefits associated with a drug changes over a drug’s lifecycle, and that the attention paid to safety and efficacy before approval must therefore be sustained as a drug enters and diffuses through the market and is used by a growing number and diversity of patients. Timely approval and attention to safety can become complementary rather than antithetical goals as postapproval surveillance becomes more effective, and regulatory authority and its exercise are commensurate with how a drug performs in real-life conditions over its lifecycle.

The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug — preapproval clinical trials do not obviate continuing formal evaluations after approval. However, the approval decision is a critical juncture in a product’s lifecycle because it releases a drug to the market, where the public will gain broad exposure to it. In a strengthened drug safety system, that juncture should mark the beginning of another important stage in the lifecycle, when regulators, sponsors, health insurers, health care providers, and independent researchers actively pursue and manage emerging knowledge about risk–benefit relationships and uncertainty and they communicate that knowledge to patients, health care providers, and health care organizations in a timely manner.

Excerpt from “The Future of Drug Safety: Promoting and Protecting the Health of the Public.”¹

acquire, integrate, and communicate information that will allow physicians and patients to use drugs wisely and well.

The committee sees its recommendations as an integrated package — not a menu of options. The recommendations that focus on science include, for instance, a thorough scientific review of the AERS system, an increase in FDA access to large administrative databases, a systematic approach to risk–benefit assessments, the development of an intramural research capacity, an advisory committee review of all new molecular entities, limitations on the proportion of advisory committee members who are given waivers of conflicts of interest, clinical trial registration, the reporting of summary results from all trials, and the development of a public–private partnership for prioritizing, designing, and funding confirmatory studies of public health importance.

The committee also recommended new attention to communication with patients; new authorities and enforcement tools that enable the FDA to require various post-marketing actions from drug companies in a timely fashion; the use of a new symbol, such as a black triangle, on product labels for up to 2 years after approval to signify the uncertainty associated with new drugs; a moratorium on direct-to-consumer advertising during that period; and a re-review of the risk–benefit status of new drugs 5 years after approval.

According to the committee, the FDA commissioner should be appointed for a fixed term of 6 years, and the appointee should have “appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire,

and a proven commitment to public health, scientific integrity, transparency, and communication.” An external management advisory board, noted the committee, could help to transform the agency’s culture and develop a comprehensive strategy for sustained cultural change. The committee recommended an interdisciplinary-team approach to the ongoing evaluation of drugs and joint authority on the part of the Office of New Drugs and the Office of Surveillance and Epidemiology for post-approval regulatory actions related to safety.

To accomplish these changes, the FDA needs a substantial increase in resources. The committee expressed a preference for these resources to come from general appropriations, because the understanding of a drug’s risks and benefits is a public good. If this approach is not practicable, then the current restrictions on the use of users’ fees should be greatly reduced. New safety-related performance goals, in addition to rapid-approval goals, should be developed.

The current system, in which the binary decision regarding approval essentially signals the end of information gathering, imposes a huge responsibility on CDER to make the right decision about new drugs. New post-marketing regulatory powers would provide the FDA with additional opportunities to act in a timely fashion. Scientific disagreements also tend to occur in the face of uncertainty. An ongoing systematic effort to identify safety signals, translate them into high-quality studies, and communicate the findings to patients and physicians can facilitate cultural change and foster productive scientific debate.

Post-marketing evaluations of

drugs can benefit all parties, including industry. For statin drugs, for instance, large, long-term trials have provided high-quality evidence about health benefits, extended the indications for use, and increased market share. For some drugs, new black-box warnings and occasional drug withdrawals are unavoidable. The timely identification, confirmation, and communication of risks and benefits are the best measure of regulatory success. With additional resources, new regulatory powers, and cultural changes, the FDA can link regulatory actions to new data in imaginative ways in an effort to improve the health of the public as well as industry.

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1. Committee on the Assessment of the US Drug Safety System, Baciu A, Stratton K, Burke SP, eds. *The future of drug safety: promoting and protecting the health of the public*. Washington, DC: National Academies Press, 2006. (Accessed October 5, 2006, at <http://www.iom.edu/CMS/3793/26341/37329.aspx>.)
2. Gale EA. Lessons from the glitazones: a story of drug development. *Lancet* 2001; 357:1870-5.
3. FDA’s review process for new drug applications: a management review. Washington, DC: Department of Health and Human Services, 2003. (Publication no. OEI-01-01-00590.)
4. Drug safety: improvement needed in FDA’s postmarket decision-making and oversight process. Washington, DC: Government Accountability Office, March 2006. (Report no. GAO-06-402.)

A list of IOM committee members and staff is included in the report brief, “The Future of Drug Safety: Action Steps for Congress” at www.iom.edu/CMS/3793/26341/37329/37331.aspx.