

**The Future of Drug Safety:
Promoting and Protecting the Health of the Public**

Statement of

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Good morning, Mr. Chairman and members of the Committee. Thank you for the opportunity to come speak to you this morning. My name is Sheila Burke. I am Chair of the Institute of Medicine (IOM) Committee on the Assessment of the U.S. Drug Safety System.

The Institute of Medicine of the National Academies is an independent, non-governmental, non-profit organization operating under the 1863 congressional charter to the National Academy of Sciences. The Institute of Medicine has provided advice to the nation on matters of health and medicine for over 30 years. Early in 2005, the Food and Drug Administration (FDA) asked the Institute of Medicine to convene a committee of experts to conduct an independent assessment of the current system for evaluating and ensuring drug safety postmarketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs. In addition to FDA, the study was funded by the Centers for Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, the National Institutes of Health, and the U.S. Department of Veterans' Affairs. The Committee on the Assessment of the U.S. Drug Safety System met for the first time in June 2005. The committee's areas of expertise include public policy, statistics, health informatics, pharmacy, clinical medicine, health plan management, pharmacoepidemiology, economics, drug regulation, consumer concerns, law and ethics, and academic research. The committee met six times, and held several information gathering sessions that were open to the public and included presentations from industry representatives and a variety of patient, consumer, and professional organizations. Some committee members also made two site visits to FDA, and engaged in confidential conversations with more than 30 former and current staff and leaders

from FDA and especially its Center for Drug Evaluation and Research (CDER). The committee's report was released September 22, 2006.

First, let me speak briefly about what the report does and does not cover. The committee considered a wide array of issues, but there are several important topics that either fell outside the charge to the committee, or that the committee was unable to consider. For example, the committee did not undertake a systematic assessment of postmarketing safety concerns related to specific drugs that have captured the public's interest in recent years, such as the cox-2 inhibitors or the selective serotonin reuptake inhibitors. The report focuses on the postapproval period and therefore does not include a detailed examination of the preapproval process. The report also does not address over-the-counter drugs, or generics, nor does it treat at length the complex issues related to the conduct of clinical trials. The committee's focus was solely on prescription drugs and the drug safety system, in particular the functioning of FDA's Center for Drug Evaluation and Research, which is responsible for drug review, approval, and regulation.

The report recognized at the outset that it is impossible to think about safety independent of efficacy, and that the two must be considered together throughout the lifecycle of a drug. A drug's lifecycle begins at drug discovery and concludes at the end of useful product life. Drugs are approved after risk-benefit determinations made by FDA, but those determinations are made on the basis of clinical trials with carefully selected participants and under controlled conditions. The real-life use of drugs is often quite different—a drug tested in a few hundred or thousand people is prescribed and used by millions often for longer periods and in conjunction with other drugs or

supplements. That is why approval does not signify the end of uncertainty about a drug, and continued monitoring is necessary after approval. Most stakeholders in the drug safety system are aware of the need for continued attention to a drug's risk-benefit profile during the drug's lifecycle. However, the committee found an imbalance in the regulatory attention and resources available before and after a drug's approval. Staff and resources devoted to preapproval functions in CDER are substantially greater than those available for postapproval functions. The new drug review process involves sophisticated clinical trial design and execution; after approval, few high-quality studies are designed, conducted, and completed, and in general, the data available is quite limited. Before approval, regulatory authority is well-defined and robust; once a drug is marketed, FDA's ability to regulate and enforce becomes greatly diminished. Many of the committee's recommendations are intended to bring some of the strengths of the preapproval process to the postapproval process, to ensure ongoing attention to a drug's performance.

The committee made 25 recommendations in 5 topic areas: CDER organizational culture, science and scientific expertise, regulation, communication, and resources. A complete copy of the report is submitted for the record. Of the 25 recommendations, 11 are uniquely within Congressional purview or likely to be of interest to Congress. These include recommendations pertinent to expanding funding for the agency's mission, strengthening regulatory authority, stabilizing agency leadership, ensuring the credibility of regulatory science, and establishing a new advisory committee. More detailed discussion of key recommendations follows.

Research and the data it produces is in many ways the lifeblood of the drug safety system. The committee believes that CDER needs substantially increased resources to conduct and access better postmarketing safety research. The committee made a number of recommendations to increase the amount and quality of data that accrue after a drug is on the market. The committee recognized that it is not enough to have strong science backing up regulatory decisions about safety—safety science has to be credible. The committee made several recommendations intended to expand the expertise and research on drug safety at CDER. In addition, the committee recommended increased opportunities for appropriate review of drug safety issues by advisory committees, and transparency of the information accumulated about a drug (for example, the posting of structured field summaries and results of all efficacy and safety studies on a government Web site, and the posting of all NDA and sNDA packages on the FDA Web site). Other recommendations include: establishing a public-private partnership to prioritize, plan, and organize funding for confirmatory drug safety, efficacy, and effectiveness studies; demonstrating a commitment to research by appointing a Chief Scientist to oversee intramural and extramural research and by requesting and applying the necessary funding to support intramural research; and taking specific steps to increase the credibility of the advisory committee process.

FDA's regulatory authorities are derived from a statute that has been amended numerous times, yet requires some strengthening and clarification to allow the agency the flexibility to regulate increasingly complex drugs. In its discussion of FDA's ability to regulate, the committee was cognizant of the fact that the outcomes of regulation are not paper documents but the health of living, breathing patients. Delaying approval

until complete certainty is reached, or withdrawing a drug once safety problems arise are often not realistic options, yet they reflect the largely all-or-nothing nature of FDA regulatory authorities. The committee recommended that FDA be given a tool kit of regulatory options it can apply as appropriate and necessary at any time in the lifecycle of a drug, and clarified authority to enforce sponsor compliance with restrictions or limitations on marketing imposed at or after the time of approval. The committee also recommended that CDER establish a milestone moment at 5 years after the approval of a new molecular entity (NME) (roughly 20-25 are approved yearly) to review all accumulated safety and efficacy data related to that NME. This will ensure that there is a systematic look back at everything that has been learned about a truly novel drug after its launch and use in the “real world.” In another recommendation, the committee called for designating a special symbol to mark all new drugs, with the function of informing and educating the public that those products are placed under greater regulatory scrutiny and perhaps subject to stronger regulatory action (such as a moratorium on direct-to-consumer advertising during the period of time that the special symbol is in effect).

Anyone who has followed drug safety issues over the last several years has surely noticed that a theme that often surfaces is some type of management problem in CDER. Information has emerged—both in the media and in government reports (e.g., from the DHHS Office of the Inspector General, and the Government Accountability Office)—about scientific disagreement poorly handled, a lack of collaboration among divisions, an appearance of interdisciplinary tension, a perception of inappropriate management expectations, and so on. On the basis of that information and discussions

with present and former FDA staff and leaders, the committee has found that while CDER's staff work with great dedication and professionalism, the Center's organizational culture is, in some ways and at some times, dysfunctional. The report identified several factors that seem to shape organizational culture in CDER, and offered solutions to strengthening collaboration, improving stability and support of leadership's ability to effect organizational change, and addressing some of the challenges presented by a major force in FDA's external environment—the Prescription Drug User Fee Act. I'd like to draw your attention to two recommendations from the chapter on culture. The committee recommended that postmarketing safety staff have a formal role before approval and specific authority after approval. Although postmarketing staff, and specifically the staff of the Office of Drug Safety, now the Office of Surveillance and Epidemiology, are invited to some preapproval meetings, this does not occur consistently, it sometimes does not take place early enough in the preapproval process. Office of Surveillance and Epidemiology staff do not have a formal role before approval or authority after approval. This recommendation in the context of others in this report reflects the committee's view that keeping postmarketing safety activities closely linked with the drug approval process is crucial.

The committee also recommended a fixed-term for the FDA commissioner to stabilize the agency and promote a better integration of safety into the work of CDER. In the last 30 years, FDA has had eight commissioners and seven acting commissioners (including the current acting commissioner) or, when the post was vacant, an acting principal deputy commissioner. The eight commissioners have served an average of 2.5 years with a range of 2 months to 6.3 years. The committee believes that turnover and

instability in the commissioner's office leave the agency without effective leadership or the potential to emphasize safety as having high priority in the work of the agency. Without stable leadership strongly and visibly committed to drug safety, all other efforts to improve the effectiveness of the agency or position it effectively for the future will be seriously, if not fatally, compromised.

In the area of communication, the committee referred to and endorsed the sentiment behind recommendations made in the recent report of the Committee on Preventing Medication Errors, released July 2006. (The summary of that report is found in Appendix E of the Future of Drug Safety report.) The committee also recommended a new mechanism—an advisory committee with the requisite expertise and representation—for improving FDA's communication to and with patients and the general public.

The commitment of public servants, the concern of Congress, the advocacy of consumer organizations, the interest of industry, among others, is not enough to transform the drug safety system in the ways outlined by the committee's suite of recommendations. A substantial and sustained financial investment is needed. The suite of recommendations put forward in this report—to improve the culture in CDER, attract and retain highly qualified staff, improve technological capacity, obtain and benefit from access to data and innovative scientific partnerships and so on—is dependent on adequate resources. An agency whose crucial mission is to protect and advance the public's health should not have to go begging for resources to do its job. The committee has acknowledged that the user fee program has had many positive effects on drug approval. However, the committee gave several reasons why it prefers that the

additional funding required to implement the recommendations in the report for an improved drug safety system come entirely from appropriations. CDER's dependence on PDUFA funding with its associated restrictions may hurt FDA's credibility. If securing this additional funding entirely from appropriations proves impossible, the committee urges that restrictions on the use of PDUFA funds be curtailed.

The committee is grateful to have had the opportunity to be of assistance to FDA, and hopes that the agency and Congress find the report useful in moving ahead to strengthen drug safety.

Thank you for the opportunity to testify. I would be happy to address any questions the Committee might have.

[Attachment: *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, Institute of Medicine, 2006]