PDUFA Reauthorization — Drug Safety's Golden Moment of Opportunity?

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"This [is] a golden moment of opportunity to improve fundamentally the way FDA regulation considers and responds to the evolving understanding of risks and benefits of drugs." So claims the September 2006 Institute of Medicine (IOM) report entitled *The Future of Drug Safety*, which paints a dismal picture of the U.S. system for ensuring the safety of drugs after they have been approved by the Food and Drug Administration (FDA).[1] Among the more easily remediable shortcomings identified by the IOM are the severe underfunding of the FDA, the particularly poor funding for postapproval monitoring of safety, and the "troubling imbalance" between these resources and those available for preapproval review.

This disparity is particularly disturbing because inherent limitations in the knowledge gained in the preapproval drug-testing process are responsible for the fact that 20% of drugs receive black-box warnings after approval[2] and that 4% of drugs are ultimately withdrawn from the market for safety reasons.[3] A principal goal of our postapproval drug-safety system should be to minimize the delay between approval and the discovery of these serious risks.

The IOM report suggests that we now face a "golden moment of opportunity" for improving the drug-safety system, since the Prescription Drug User Fee Act (PDUFA) comes up for reauthorization later this year amid increased national focus on drug safety. We believe that the FDA's January 16, 2007, recommendations to Congress for the reauthorization of PDUFA risk squandering this key opportunity by providing grossly inadequate PDUFA funds for postapproval drug safety in general and studies of specific drug-safety issues in particular.

Congress originally passed PDUFA in 1992 in an effort to streamline preapproval drug review by creating additional FDA staff positions funded by fees collected from drug companies. Although Congress initially barred the FDA from applying user-fee revenue to postapproval monitoring of safety — a prohibition that was not lifted until PDUFA's third authorization in 2002 — the FDA now applies about 5% of user-fee revenue to this function.[1]

For 2008, in response to increased concern about drug safety, the FDA is proposing many useful changes to PDUFA, including the development of a 5-year plan for enhancing and modernizing the drug-safety system, the earlier institution of discussions with manufacturers about labeling and postapproval commitments, and the expansion of permissible uses of user-fee revenue to include postapproval safety activities that occur after the current limit of 3 years.

However, despite the alarm expressed in the IOM report, the FDA is proposing to devote only $29.3 million — a mere 6.7% of the $437.8 million in user-fee revenue anticipated for 2008 — to modernizing and transforming the drug-safety system. It is useful to place this $29.3 million in perspective by considering the $188.5 billion that was spent on prescription drugs in the United States in 2004 and the $11.9 billion spent on pharmaceutical advertising in the same year.[4] Despite these vast sums, the FDA's extramural Epidemiology Contracts Program, for instance, has a budget of less than $1 million per year for all four extramural contract sites combined.[1] This funding has proved to be inadequate for performing even a single large study of one recently noted safety signal that has major public health importance — the indication of possible cardiovascular risk posed by drugs for attention deficit–hyperactivity disorder. The IOM estimates that at least 10 such safety signals per year could be evaluated extramurally at an annual cost of $10 million to $60 million.

Furthermore, the FDA proposes to spread the $29 million thinly across many divergent activities that are lumped together under the heading of drug safety. These activities include funding an extramural study on maximizing the public health benefits of the spontaneous reporting of adverse events, strengthening the information-technology infrastructure underlying the reporting system, developing guidelines on epide-

miologic best practices, and implementing measures to reduce medication errors related to look-alike and sound-alike drugs.[5] It is worrisome that the FDA has not specified how the $29 million will be divided among the myriad tasks on its agenda. And although the activities it proposes are all worthwhile, the agency's overall plan will fall far short of the goal of modernizing and transforming the drug-safety system and will perpetuate the "troubling imbalance" in resources decried by the IOM.

A potentially thorny issue is that the large infusion of cash from industry represented by user fees (amounting to 42% of the 2006 budget of the FDA's Center for Drug Evaluation and Research[1]) might result in a conflict of interest for the FDA by creating competing allegiances to pharmaceutical manufacturers and the American people. Although such a conflict would be of concern, it is difficult to tell whether it is actual or merely theoretical. Given this difficulty, it is unclear whether eliminating or reducing user fees, especially at a time of federal budget deficits, would ultimately benefit the U.S. population, and we are therefore reluctant to recommend doing so. In fact, we believe that relying on the pharmaceutical industry to perform all drug-safety studies creates a more severe conflict of interest — a conflict that could be most logically solved by giving the FDA sufficient resources to fund its own safety studies.

Major developments in drug regulation are often prompted by drug-safety disasters. For example, the 1938 U.S. Food, Drug, and Cosmetic Act was prompted by a series of deaths caused by sulfanilamide elixir containing diethylene glycol, and the 1962 passage of the Kefauver–Harris Amendment resulted directly from the thalidomide disaster of the early 1960s. More recent events that have captured the public's attention include the market withdrawals of troglitazone, cerivastatin, and rofecoxib. The IOM study on the drug-safety system was launched in response to such events, and the resulting report contains many useful suggestions that could be implemented as part of the upcoming renewal of PDUFA. Fortunately, Congress is not bound by the FDA's recommendation and should take advantage of this opportunity to provide a robust level of funding for postapproval drug safety so as to make full use of the current, transient "golden moment of opportunity."

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Dr. Hennessy reports receiving research funding from Pfizer and consulting fees from Johnson & Johnson, Wyeth, and Sanofi Pasteur and from law firms representing Bayer, Pfizer, and Eli Lilly and plaintiffs suing pharmaceutical manufacturers. Dr. Strom reports serving on the board of Medco Health Solutions; receiving grant support from Pfizer, Takeda, Amgen, Berlex, Merck, Novartis, and Wyeth; and receiving consulting fees from Abbott, Aetna, AstraZeneca, Berlex, Biogen Idec, Blue Cross Blue Shield Association, Bristol-Myers Squibb, Centocor, Cephalon, CV Therapeutics, Daiichi Sankyo, Oscient, GlaxoSmithKline, Johnson & Johnson, Eli Lilly, Novartis, Pfizer, Sanofi Pasteur, Schering-Plough, Shire, TAP, Warner-Lambert, and Wyeth and from law firms representing Bayer and plaintiffs suing pharmaceutical companies.

Drs. Hennessy and Strom are special government employees of the FDA, and Dr. Hennessy is a current member and Dr. Strom is a past member of the FDA's Drug Safety and Risk Management Advisory Committee. The views expressed in this article are those of the authors and do not necessarily reflect those of the FDA.

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