

**Response to:  
“US Food and Drug Administration Docket No 2007N-0005:  
Prescription Drug User Fee Act; Public Meeting”**

**Submitted by the  
International Society for Pharmacoepidemiology (ISPE)  
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Introduction

The International Society for Pharmacoepidemiology (ISPE) is an international professional organization dedicated to advancing the health of the public by providing a forum for the open exchange of scientific information and for the development of policy, education, and advocacy for the field of pharmacoepidemiology, including pharmacovigilance, drug utilization research, and therapeutic risk management. ISPE’s more than 1000 members come from over 45 countries and work in academic institutions, the pharmaceutical industry, government agencies, and non-profit and for-profit private organizations.

On 16 January 2007, the US Food and Drug Administration (FDA) published proposed recommendations to the US Congress concerning extension of the Prescription Drug User Fee Act (PDUFA IV), and solicited public comment on these proposed recommendations (1). This document constitutes ISPE’s response to FDA’s proposed recommendations.

1. The recent Institute of Medicine (IOM) Report on the Future of Drug Safety (2) concluded that FDA is severely under-funded, and that within FDA, post-approval drug safety functions are particularly poorly funded. ISPE recommends a substantial increase in the funding for post-approval safety issues. Ideally, this increase in funding would not come from PDUFA but from additional appropriations. Given the current budgetary environment in the US, however, this increase in funding might only be achieved by even further increases in overall PDUFA funding beyond the requested \$29 million.
2. FDA’s proposed recommendations contain a number of very good ideas from a drug safety perspective, including the development of a five-year plan to enhance and modernize the drug safety system, earlier initiation of discussions with manufacturers about labeling and post-approval commitments, and the ability to use PDUFA revenue for post-approval safety activities beyond specific time limits. ISPE applauds these recommendations.
3. ISPE is concerned that the \$29 million proposed for 2008 in PDUFA IV to “modernize and transform” the US drug safety system will be grossly inadequate to achieve this goal, particularly since that sum will be divided over many activities that FDA has included within drug safety. These include funding an extramural study to determine the “best way to maximize the public health benefits” of spontaneous adverse event reporting; developing guidelines on epidemiologic best practices; maximizing the usefulness of tools for adverse event detection and risk assessment; performing signal detection from adverse event reports; obtaining access to epidemiologic databases and the staff to use those databases; implementing certain unspecified recommendations of the IOM report; conducting systematic reviews of one or two risk management programs and one risk management tool per year; strengthening the information technology infrastructure underlying FDA’s spontaneous reporting system; developing and updating a five-year plan to enhance and

modernize the drug safety system; implementing measures to reduce medication errors related to look-alike and sound-alike drugs; and developing industry guidance documents on drug name safety (1). Knowing how FDA intends to spend \$29 million over these activities would be very helpful. Regardless, it is useful to place this \$29 million in perspective. First, the \$29 million represents only 7.5% of the total anticipated PDUFA revenue in 2008 (1). Second, the \$29 million needs to be contrasted against the considerable total resources spent annually on medications and related activities. For example, \$188.5 *billion* was spent on prescription drugs US in 2004 (3). The IOM Report on the Future of Drug Safety observed that, within FDA, post-approval safety is particularly poorly funded, creating a “troubling imbalance” in the resources available for post-approval safety monitoring vs. pre-approval review (2). Devoting only 7.5% of PDUFA revenue to post-approval drug safety will not be adequate to “modernize and transform the drug safety system” and will perpetuate the “troubling imbalance” between FDA’s pre- and post-approval functions. Therefore, ISPE recommends that FDA devote a substantially larger proportion of revenue to post-approval drug safety functions.

4. An additional source of concern is that it appears that FDA is proposing no new PDUFA funds for extramural research to evaluate drug safety signals, even though such studies are clearly needed. Although FDA has some limited in-house capabilities to perform such research, hopefully to be expanded, there is a growing community of external pharmacoepidemiology investigators to whom FDA can turn as part of collaborative research projects. As noted by the IOM report, FDA’s extramural Epidemiology Contracts Program currently has a budget of < \$1 million per year over four extramural contract sites (2), which has proved inadequate to perform even a single major study of a safety signal with major public health importance: the cardiovascular safety of drugs used to treat attention deficit hyperactivity disorder. IOM estimates that at least ten such drug safety signals per year could be evaluated extramurally, at an annual cost of \$10-60 million (2). Therefore, ISPE recommends that substantial additional PDUFA resources be devoted to extramural training to increase the pharmacoepidemiology research capacity within and outside of FDA and to studies to evaluate drug safety signals.
5. ISPE supports the “development of a [regulatory] guidance document to delineate best practices.” ISPE hopes that the FDA will find useful the Society’s “Guidelines for Good Pharmacoepidemiology Practices” document (4) in developing such a regulatory guidance, and would welcome the opportunity to provide input into FDA’s process for developing this regulatory guidance document.

#### References

- (1) Prescription Drug User Fee Act; Public Meeting. Federal Register 2007; 72(9).
- (2) The future of drug safety: Promoting and protecting the health of the public. Washington, DC: The National Academies Press, 2006.
- (3) Prescription drug trends. 2006. Kaiser Family Foundation. <http://www.kff.org/rxdrugs/upload/3057-05.pdf>, accessed 24 January 2007
- (4) International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf* 2005; 14(8):589-595.