February 23, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD, 20852

RE: Docket number 2007N-0005 (Prescription Drug User Fee Act; Public Meeting)

The Centers for Education & Research on Therapeutics (CERTs) principal investigators appreciate the opportunity to comment on the proposed recommendations of the U.S. Food and Drug Administration (FDA) to Congress concerning the reauthorization of the Prescription Drug User Fee Act (PDUFA).

The CERTs program is a national initiative to conduct research and provide education that advances the optimal use of drugs, medical devices, and biological products (therapeutics). The program, which consists of eleven research centers and a coordinating center, is administered as a cooperative agreement by the Agency for Healthcare Research and Quality (AHRQ), in consultation with the FDA. The CERTs program was created under the Food and Drug Administration Modernization Act of 1997, and reauthorized under the Healthcare Research and Quality Act of 1999, with the following major aims:

1. To increase awareness of both the uses and risks of new drugs and drug combinations, biological products, and devices, as well as of mechanisms to improve their safe and effective use.
2. To provide clinical information to patients and consumers; health care providers; pharmacists, pharmacy benefit managers, and purchasers; health maintenance organizations (HMOs) and health care delivery systems; insurers; and government agencies.
3. To improve quality while reducing cost of care by increasing the appropriate use of drugs, biological products, and devices and by preventing their adverse effects and consequences of these effects (such as unnecessary hospitalizations).

Our comments are shaped by our experience studying risks, benefits and appropriate use of therapeutics, as well as educating consumers, health care providers and other decision-makers so they can make decisions to improve the health of patients on an individual and population level. As the CERTs mandate is focused on marketed products, our comments are directed at proposed postmarket activities.

In general we support the proposed recommendations related to modernizing and transforming the postmarket drug safety system, as well as the recommendations for review of Direct-To-Consumer (DTC) advertising. We commend the FDA for trying to balance a number of considerations and perspectives in developing new activities to enhance our understanding of the risks and benefits of drugs and to support their safe and appropriate use.

User Fees – Relation to FDA Budget

We are concerned that too large a proportion of FDA's budget may come from user fees, which could create conflicting interest for FDA with regard to its obligations to the regulated industry vs. the American people. The recent Institute of Medicine (IOM) Report on the Future of Drug Safety (1) concluded that FDA is severely under-funded, and that within FDA, post-approval drug safety functions are particularly poorly funded. We would prefer that the federal budget designated for postmarket safety enhancements matched the proposed user fees so that the user fees do not continue to overshadow the federal contribution to FDA's mission. However, given the current U.S. budgetary environment, and the need for increased FDA funding to support postmarket safety activities, we do not recommend a reduction in PDUFA funding.

User Fees – Relation to Postmarket Needs

We are concerned that the $29 million proposed in 2008 to "modernize and transform" the U.S. drug safety system will be grossly inadequate to achieve this goal. This $29 million is only 7.5% of the total anticipated PDUFA revenue in 2008 (2). Even that sum will be divided over many activities that FDA has included within drug safety, such as 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 (2).

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 by considering the $188.5 *billion* spent on prescription drugs and $11.9 *billion* spent on pharmaceutical advertising in the U.S. 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 (1). Devoting only 7.5% of PDUFA revenue to post-approval drug safety will be wholly inadequate to "modernize and transform the drug safety system" and will perpetuate the "troubling imbalance" between FDA's pre- and post-approval functions. Therefore, we recommend that FDA devote a substantially larger proportion of revenue to post-approval drug safety functions.

New Drug Safety Initiatives

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. While the proposed activities represent a good first step in enhancing our knowledge of drug risks and the appropriate use of medications given their risks and benefits, we would encourage the FDA to more aggressively pursue the evaluation of risk management and risk communication strategies and tools. The FDA should consider contracting directly or through another HHS agency, such as AHRQ, for the evaluation of these tools on a more aggressive schedule than 1-2 per year. The value of better understanding the impact of risk communication and risk management strategies can have a significant effect on patients' ability to receive the most benefit and avoid potential harm from their medications.

Pharmacovigilance

We applaud the proposed activities to modernize and identify best practices associated with pharmacovigilance. CERTs investigators are experienced at using a variety of methods, including the use of large automated administrative and clinical databases, to study the risks and benefits of drugs and drug combinations, and would welcome the opportunity to work with the FDA on the proposed activities to identify and study potential adverse reactions.

We support the development a regulatory guidance document to delineate epidemiology best practices. The International Society for Pharmacoepidemiology (ISPE) has developed a "Good Pharmacoepidemiology Practices" document (4) which will be useful in developing such a guidance document. We would also welcome the opportunity to provide input into FDA's process for developing this document.

Extramural Research

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, there is a growing community of external pharmacoepidemiology investigators, including CERTs investigators, to whom FDA can turn as part of collaborative research projects. The CERTs were initially authorized under the Food and Drug Administration Modernization Act of 1997 (FDAMA), in part, to conduct this type of research.

We agree the agency should increase its internal expertise and access to databases. However, a strategy of expanding collaborations with outside organizations with access to epidemiologic databases and the expertise to use those databases would seem to offer the FDA greater access to expertise, databases and tools needed to assess signals in various situations, than would building duplicative internal resources.

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 (1), 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 (1). Therefore, we recommend that substantial additional PDUFA resources be devoted to extramural studies to evaluate drug safety signals.

Direct-To-Consumer (DTC) Advertising

Consumers and patients need accurate and fairly balanced information about medications they take or are considering taking. Television advertising has become one of the most visible sources of information. As such, it is important that the FDA have sufficient staff to review television advertisements before they are shown to the public to ensure they are accurate, balanced and evidence-based. Given the FDA budget situation, we agree with the proposed program to assess fees for advisory reviews of DTC television advertisements.

References

(1) The future of drug safety: Promoting and protecting the health of the public. Washington, DC: The National Academies Press, 2006.
(2) Prescription Drug User Fee Act; Public Meeting. Federal Register 2007; 72(9).
(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.

We appreciate the opportunity to comment on the proposed recommendations for PDUFA IV aimed at improving the FDA's ability to monitor and respond to emerging drug safety issues.

Sincerely,

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