Center for Medical Consumers

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Comments Submitted to the Food and Drug Administration
Regarding Re-authorization of the Prescription Drug User Fee Act (PDUFA IV)
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The Center for Medical Consumers and the patient and consumer advocacy groups listed below urge the Food and Drug Administration to use the opportunity presented by the upcoming reauthorization of the Prescription Drug User Fee Act (PDUFA) to make meaningful and serious changes in this country's drug safety system. Repeated instances of the FDA's safety activities failing to protect the public health from dangerous drugs have come to light in recent years. Advocates, policy makers and drug safety experts, including the authors of the recent Institute of Medicine Report *The Future of Drug Safety – Promoting and Protecting the Health of the Public* have called for major reforms. Yet, the agency has negotiated a deal with the regulated industry for changes that will do little, if anything, to protect people's health and restore public confidence that the drugs prescribed for the cure and amelioration of illness are safe.

Funding for Safety Activities Remains Inadequate

On January 11, 2007, the FDA announced the proposed new measures to "strengthen drug safety" that it would like to be included in the upcoming reauthorization of the PDUFA by Congress. The fourth iteration of the user fee program (PDUFA IV) would, if Congress agrees, direct an estimated $392.8 million dollars in fee revenues from the industry to the agency. Of that amount, $29.3 million would go to fund what FDA describes as "activities to ensure the safety of medications after they are on the market."

We recognize that the proposed dedication of $29.3 million of user fee revenue to activities related to the safety surveillance of marketed drugs represents a break with past practice. However, we would suggest that the break is more symbolic than indicative of real change in the culture of FDA management which has steadfastly resisted putting safety on a par with efficacy. This resistance continues despite a growing body of evidence demonstrating that safety programs are not up to the task. The evidence includes a finding by the US General Accounting Office (GAO) that 51% of all approved drugs had a least 1 serious adverse drug reaction that was not recognized during the approval process [6] as well as the growing list of branded drugs with serious safety concerns including Vioxx, Bextra and Celebrex, Prozac, Paxil and similar antidepressants, Ritalin and other stimulant drugs and most recently Trasylol, Ketek and Zyprexa.

The first two iterations of PDUFA prohibited any application of user fee revenue to other than approval review activities, while PDUFA III allowed a meager $6 million for safety programs of limited scope. While the FDA's proposal for an almost five fold increase in user fees proposed for funding safety activities might be seen by some as indication that the agency is on the right track, it should be evaluated in a broader context. For example, of the $87.4 in additional user fee revenue FDA proposes that Congress authorize, $58.1 (66%) would be dedicated to uses *other* than improving post market safety. And, the allocation formula proposed for the almost $393 million total user fee revenue proposed in PDUFA IV allocates $13.50 to support approval reviews and some general expenses for every $1 allocated to post-market safety activities. We urge the FDA to increase the allocation of user fee revenues devoted to safety activities in annual increments so that by 2012, when PDUFA is again up for reauthorization, a

minimum of twenty-five percent of the total user fee revenue stream will be devoted to post market safety programs.

Some Needed Reforms Require Congressional Action

Some of the necessary changes for improved drug safety clearly require Congressional action to expand the FDA's authority. For example, drug companies often impede the timely adoption of critical labeling changes and risk management strategies by engaging in extended negotiations to postpone action to protect the public health. We hope the FDA will begin to speak out clearly about its need for such expanded authorities. But even without new legislative action to extend the agency's authority, there are opportunities through the reauthorization of PDUFA to make meaningful change that the agency/industry proposal fails to realize.

Public Accountability Lacking

The proposal ignores basic principle of evidence-based science and policy-making by failing to include any outcome evaluation or performance measurement activity of drug safety activities. The result is a proposal without any accountability for timely improvement in drug safety – accountability which Congress and the public have every right to demand.

Unfortunately, since the initial1992 passage of PDUFA, industry has shaped the metrics by which FDA's performance is measured. In fact, the Act stipulates that user fee revenues only become accessible to the agency if the time limits for priority and standard review are met. It is time to insist that, as a public health agency, the FDA should not be held accountable solely to the regulated industry. We strongly urge that PDUFA IV

include additional performance measures that track the agency's drug safety performance.

More Flexible Reviews Based on Science

We also recommend making the currently rigid time management review requirements more flexible. Review times, within reasonable parameters, should be determined by FDA scientists on an application by application basis – not a one size fits all standard. New drug reviews should be individualized to allow for the differing scientific complexity of each product under review and the adequate investigation of pre-approval signals of safety problems when they occur. **Transparency of Clinical Trials**

There is convincing evidence that sponsors too often cherry pick clinical trial results to favor their products. Publication bias that screens out trials with results unfavorable to a sponsor's product is also well documented as is the fact that important safety data may go unreported or unanalyzed. Therefore the FDA must increase its auditing of clinical data about a product to make sure that all results, whether favorable or unfavorable to the product, are disclosed. Increased oversight of proposed sponsor applications to ensure that study protocols are initially designed to maximize information about product safety should also be considered.

Pilot Programs to Increase Knowledge About Off-label Prescribing

A considerable proportion of prescribing is for "off-label" indications and there is often little or no scientific evidence to support it. Pediatric oncology serves as a model where doctors who treat children with cancer routinely prescribe oncologic drugs off-label, but the majority does so in a context where the clinical outcomes are captured. Such a model allows for development of an evidence base for the safety and efficacy of particular off-

label treatments and is a win-win for patients and for their clinicians. Creating similar clinical speciality cooperatives in other areas of medicine, requiring selective Phase IV studies or greater use of treatment IND's are all worth exploring as possible tools to address concerns about off-label prescribing.

Safety is a Public Good

We would be remiss not to point out that the passage of PDUFA in 1992 ended the long running arm's length transactional relationship between the FDA as regulator and the regulated industry. Many of us voiced concerns fifteen years ago when PDUFA was first discussed that such a breach could prove problematic and threaten the traditional high regard that was accorded the agency by the public over many decades. The evidence suggests that the public's trust has indeed eroded.

While we believe that the safety of medical and food products is a public good and should be funded out of general tax revenues, we recognize the realities of the current budget climate and the dependency that the agency has developed on the almost $400 million a year it receives in user fee revenues. In light of these budgetary constraints, reauthorization of the user fee program is inevitable, making the need to build drug safety improvements into PDUFA IV all the more critical. These reforms alone will not solve the fundamental problems with our drug safety system, but they can improve the process and also send a signal to the public, to policy makers and to the Congress that the FDA recognizes that its safety activities are flawed and it takes seriously its responsibility to establish a better balance between efficacy and safety to protect the public's lives and health.

More Meaningful Public Involvement

Finally, when PDUFA V is next considered in 2012, we believe it will be time that consumers and patients are invited to fully participate in the design of any future PDUFA legislation. Being asked to provide input through post-agreement meetings and informal consultations is no substitute for a seat at the negotiating table. The industry has one, and in the future the public that FDA is chartered to protect must as well.

Respectfully submitted by:

Center for Medical Consumers

Government Accountability Project

National Women's Health Network

The Title II Community AIDS National Network

United States Public Interest Research Group