Addressing Improvements in Evaluating Drug Safety in the Prescription Drug Use Fee Act (PDUFA):

Providing The Right Tools for the Job

John H Powers, MD

Assistant Professor of Medicine

George Washington University School of Medicine

University of Maryland School of Medicine

House Energy and Commerce Committee, Subcommittee on Health

May 9, 2007

Good morning Mr. Chairman and members of the committee. My name is John Powers. I am a physician-scientist who worked at the Food and Drug Administration for the last 8 years. My background is that of a clinician in internal medicine and infectious diseases, an investigator and researcher in clinical trials, a scientist in the field of drug development, and a consultant for several drug sponsors. Perhaps most importantly, I have been a patient myself. I would like thank you for the opportunity to discuss with you today my perspective on the issues of evaluating the risks and benefits of medical interventions.

As the Institute of Medicine report on drug safety points out, the current reauthorization of the Prescription Drug User Fee Act is a golden opportunity to address long-overdue improvements with drug safety in order to adequately protect the public's health. **PDUFA should not be reauthorized without simultaneously addressing the important public health issues related to drug safety**. The standard we should use to judge proposed changes to the evaluation of drug safety should be: Would these changes prevent another drug safety episode like Vioxx or Ketek? Bringing medical interventions to patients in a timely way and appropriate post-approval evaluations of those same interventions are not mutually exclusive goals, and addressing post-approval drug safety need not slow bringing new medications to patients. Indeed, the FDA Critical Path initiative points out that better tools for pre-approval evaluation of potential safety issues may allow more efficient drug development, earlier cessation of drug development programs of drugs with toxicities before spending precious resources, and more focused evaluation of drug toxicities post-approval.

The passage of the Food, Drug and Cosmetic Act (FD&C) in 1938 shifted the burden of the evaluation of pre-approval safety of drugs from the government to drug sponsors. From that time forward there was no assumption that a drug was safe, and sponsors had to provide evidence of the potential adverse events associated with drug use. This reflected a notion that is clear today; no drug is completely safe in that all drugs are associated with some adverse events. In 1962, Congress amended the FD&C Act to require substantial evidence of effectiveness based on adequate and well-controlled trials, codifying the logic that there must be evidence of benefit in order to justify any risks of drugs, no matter how rare.

Both these provisions focused on the pre-approval evaluation of medical interventions, which was appropriate for that time. However, it is now clear that we need to focus on the entire life-cycle of medicines with a greater focus on post-approval evaluations. This is eminently sensible as we cannot learn all we need to know about medical interventions given the limited number and types of patients and the short time span in which drugs are studied pre-approval. The vast majority the life-cycle of a drug is spent post-approval, and it follows we can learn much about a drug during this time. FDA must play a crucial role in continuing to evaluate drugs once they are approved.

The need for regulation is two fold: first, regulation is needed when market forces tend to guide businesses in a way that may be contrary to public interest, and second, regulation

provides a uniform standard for public health and consistency and fairness for the regulated industry. In regards to the first point, there is little incentive for drug sponsors to rigorously evaluate potential safety issues with a drug once it is approved since from a business perspective this evaluation has the potential to decrease sales. This is in contrast to providing evidence of drug effectiveness prior to approval which is necessary both for FDA approval for marketing and to convince clinicians to use the drug. Many drug sponsors certainly do include protecting the public's health in their decision making. But as James Madison stated in the Federalist #51 in 1788, if all men were angels no government would be necessary. Even one sponsor who decides that profits trump public health is one too many and it is the FDA's job to ensure all sponsors are held to the same standard. This relates to the second point, which is that FDA is supposed to ensure a scientifically based and consistent standard of public health both for the sake of the public health, and out of fairness to drug sponsors so that every sponsor is subject to the same rules. This allows less uncertainty in drug development, and allows sponsors to plan their studies accordingly. The only way to ensure both protecting and advancing the public health and fairness to drug sponsors is to base laws and regulation upon the best science. Since science changes over time as we learn new things, regulations need to adapt as well. The prior focus on pre-approval evaluations is still needed, but we now need to focus our attention of post-approval evaluations as well.

One can view the issues related to addressing drug safety as divided into three categories: **inputs** of resources and authority *into* FDA, **internal** use of resources, science and

functioning *inside* **FDA**, and **outputs** of decisions and communications with the public *from* FDA.

I. Inputs into FDA

FDA staff need the resources in terms of funding, manpower, knowledge, data and authority to do its job properly.

1. **Congress should authorize adequate funding for FDA from general appropriations and PDUFA fees should have "no strings attached" and not be negotiated with regulated industry**: FDA has been severely under-funded for some time, even to do the job it already has to do. Indeed, the original intent of PDUFA in 1992 was to bring greater funding to FDA to provide it the resources it needed at that time. To address the larger issues of post-approval evaluations of drugs it will need greater funding. It seems logical that regulated industry should pay for a fee for licensing of drugs to defray the costs to the government, similar to how drivers pay a fee for their drivers' license of doctors pay a fee to State medical boards for a license to practice medicine. However, drivers and doctors do not negotiate the uses to which those fees are put with Division of Motor Vehicles or the State Medical Board. In addition to the obvious appearance of conflict of interest of allowing the regulated to help decide where the regulator appropriates funds, the long time frame between PDUFA negotiations – done only once every five years – does not allow FDA to adapt and shift resources to where they are most needed. Again, there is a need for regulation when there is no incentive for the regulated to address issues of public health, and previous

negotiations of PDUFA in which FDA was barred from applying fees to post-approval safety evaluations are evidence of a desire by some to avoid performing these evaluations.

2. **FDA needs adequate authority to ensure the public health including ability to assess sufficiently stringent civil monetary penalties for non-adherence and sufficient authority to ensure device effectiveness –** FDA needs the authority to require post-approval studies and ensure sponsors complete those studies**.** As noted previously, there is an obvious incentive for drug sponsors to submit data in support of drug effectiveness. Since there is less incentive to perform post-approval studies, FDA needs the ability to require studies and impose meaningful penalties on drug sponsors who do not fulfill their stated commitments. The Enhancing Drug Safety and Innovation Act (H.R. 1561) is a start in this direction by providing for more meaningful penalties beyond those that sponsors could just write off as the cost of doing business. Penalties need to be appropriate in order to provide an incentive to comply. In addition, the current legally mandated standards for effectiveness of devices are quite different for those from drugs. It is not clear from a scientific point of view why this should be so, as patients who receive devices should receive the same protection under the law as those who receive drugs. Recent approvals of some devices have left outstanding questions regarding their effectiveness, such as the vagal nerve stimulator for depression. This seems to contradict the basic principle that there needs to be substantial evidence of effectiveness in order to justify the risks of any intervention. Congress should address this by changing the law to hold devices to the same

standard of substantial evidence of effectiveness from adequate and well controlled trials as for drugs.

3. **FDA needs adequate data upon which to base decisions –** The use of modern databases to more efficiently gather information on drug use and potential adverse events is desperately needed. FDA cannot rely on the good graces of busy clinicians for spontaneous reports of adverse events. Many medical schools do not teach their trainees about the need to report adverse events, so there is a need for education as well. FDA always needs to stay in touch with practicing clinicians, but they cannot be the only source of information in evaluating medical interventions post-approval. In addition, for reasons discussed previously drug sponsors cannot be the sole source of information. There is little incentive for them to report adverse events and there are recent unfortunate examples in which important information was withheld from FDA. If FDA had independent sources of information this would be less of a concern.
4. **FDA needs to hire adequately trained staff –** It is important that FDA hire, train and keep staff who have a background and training in drug development and evaluation. It is sad to say that many in academic medicine view a career at FDA for their trainees as "a waste of time" and "unscientific". FDA needs to be on the same scientific par as the National Institutes of Health and the Centers for Disease Control and Prevention in terms of scientific reputation and in terms of appropriately applying science. The only way to accomplish this goal is if the scientific community has positive interactions with FDA staff, instead of the current "black box" that clinicians see as the current FDA.

5. **FDA needs close contact with the scientific community –** FDA has to have a symbiotic relationship with clinicians and scientists. As science is ever-changing, FDA staff need to keep abreast of the latest scientific developments. In addition, FDA staff have much to teach the scientific community about clinical trials and the pharmacoepidemiology, and much of the view that FDA is "unscientific" comes from a lack of understanding of the scientific principles upon which appropriate drug evaluation is based. This means that FDA staff need to be able to interact with scientist in their fields, an issue I will address in terms of outputs from FDA as well.

II. Science and Process Inside FDA

FDA has become too focused on "process" to the exclusion of the reason for why process is needed. The process as FDA should serve good science which in turn protects and advances the public health. Science should not serve process. Appropriate processes are needed in order to drug sponsors to submit data and for FDA staff to review this data in an orderly way. However, on the Center for Drug Evaluation and Research guidance page there are 53 guidances under the heading of "process" and 3 under the heading of "drug safety". Clearly this balance seems tilted in the wrong direction. FDA managers needs to treat the scientists and review staff with professionalism and the basis for decision making needs to be good scientific principles

1. **FDA managers need to treat staff with professionalism** – Science is based on the scientific method, and as such, any one who uses this method, from the medical student to the senior attending, can make equally valid analyses and draw

equally valid conclusions. As with school teachers, if most of their class fails the examination, they must take part of the blame. If FDA managers believe their staff is not using appropriate scientific analyses, then it is incumbent on these managers to train staff in these same principles and provide mentoring for them and career development paths. It is inappropriate and unprofessional to characterize scientists who raise scientific issues as "disgruntled" or to characterize a scientist work as "junk science". FDA managers need to realize that there are substantial issues with the relationships between managers are staff at FDA that need to be addressed. A Union of Concerned Scientists poll of FDA staff showed that 44% of FDA scientists did not respect their managers' integrity. A substantial shift in culture at FDA is needed, and this can be accomplished by making FDA place where people who follow the scientific method and who treat their peers with respect want to work and those who choose not to behave professionally don't want to work

2. **Joint authority of Office of New Drug and Office of Surveillance and Epidemiology regarding post-approval decision making**. It is part of the scientific method that data, analysis and conclusions undergo peer review and re-analysis by others to confirm the conclusions of a given set of scientists. Also, it is only human nature that when one makes an important decision that may affect the lives of thousands or million of persons it is very disheartening to learn that decision may have resulted in people being harmed. However, it is also part of science that we learn more as more evidence accumulates. Lastly, systems function best when there are checks and balances and no one person or group of

persons exerts absolute authority. The framers of the Constitution set up a bicameral legislature and three branches of government for exactly this purpose. For all these reasons there needs to be joint decision making authority between the Office that approves new drugs (the Office of New Drugs) and the Office responsible for evaluating drugs after approval (the Office of Surveillance and Epidemiology). The Enhancing Drug Safety and Innovation act could be strengthened by including provisions for this joint authority.

3. **Accountability for decision making and behavior at FDA and increase "whistleblower" protections** -There needs to be accountability for FDA managers who treat staff unprofessionally, both from within FDA by senior managers and from oversight from Congress to ensure that accountability takes place. Increased transparency of the operations at FDA would discourage some from inappropriate behavior, and all of FDA would benefit from changing the perception held by many clinicians, academics and those in industry that FDA is a "black box" in which operations, decision making and the scientific reasoning behind decision making seem unclear. There is no blind acceptance of data in science, and statements that "FDA cannot be second-guessed" do not take into account that "second –guessing" (also called peer review and confirmation of evidence) is part of science. One of the basic premises of the scientific method is we can never be sure we are correct, but we can always be proven wrong, so one needs to keep an open mind at all times. No one questions that FDA managers have the authority to render decisions, but with the authority comes responsibility. There is no such thing as "THE" FDA, as FDA is made of up individuals. It

would be best if no staff person at FDA ever has to "blow a whistle" on inappropriate use of science or failure to protect the public's health, but should this be necessary, FDA staff need to know they will not be risking their livelihood to protect patients. Therefore there needs to be increased whistle-blower protections such as those in the legislation proposed in the Swift Approval Full Evaluation act.

4. **Best Use of Science and Consistency of Decision Making within FDA and publication of guidance on risk-benefit analysis –** One of the major complaints of drugs sponsors is that they receive inconsistent advice from FDA. While in some cases advice can and should change as science advances during the course of drug development program, some sponsors feel that they do not receive consistent scientifically-based advice from Division to Division within FDA across similar drug development plans in different therapeutic areas. This would seem at odds with using appropriate scientific methods to make decisions. FDA needs to train staff on the scientific and legal bases for drug evaluation, especially in that there are legally mandated standards for drug effectiveness that must be followed in order to justify the potential adverse events of drugs. FDA needs to formulate guidance which explains the scientific decision making process of balancing risks and benefits. While there needs to be some flexibility to accommodate individual cases, there are some basic principles which would apply to all situations, such as evaluating the frequency, severity and seriousness of adverse events weighed against the nature and magnitude of the benefits of a medical intervention. FDA reviews need to explain the scientific as well as legal

basis for decision making and conclusions so that sponsors, clinicians and the public can understand the scientifically reasoning behind a decision. FDA reviews include a tremendous amount of data and analysis but is it not always clear how this data is synthesized into an overall decision.

III. Outputs from FDA

FDA serves the public and therefore needs to communicate with the scientific community, clinicians and patients as well as drug sponsors.

1. **Transparency of decision making and reviews at FDA** - The Belmont Report in 1979 on the protection of subjects in human research pointed out that research is the pursuit of generalizable knowledge. For research to be ethical the knowledge obtained must be generalizable in order to justify exposing subjects to the risk of the research. If research is not generalized, that is, shared with others in the scientific community then it is inherently unethical. Therefore it is incumbent upon FDA and drug sponsors to share the information from all clinical trials. A registry that includes a listing of all clinical trials including the results of these trials would allow knowledge to be generalized. The Enhancing Drug Safety and Innovation Act includes such a provision. It is important that data from earlier phase trials be included in such registries and databases as these earlier phase trials often form the basis for evaluation of further adverse events post-approval. In addition the results of these trials, not merely that fact that they are ongoing or completed, need to be included in any database in order for the results to be generalizable. FDA

reviews should be published on the FDA website within a reasonable period of time (no longer than a few weeks) in order for the scientific community to evaluate the basis for FDA decision making. This form of peer review is part of the scientific process.

2. **FDA staff should have a right to publish and participate in scientific meetings** – As noted previously, FDA reviewers need to keep current with the science in their field. This means FDA staffers need to share their knowledge with those outside FDA as well as gaining knowledge themselves from scientists outside FDA. FDA reviewers need to be able to share their analyses with the scientific community and the need to FDA managers to "make one decision" should not bar a scientific discussion among the scientific community. The Supreme Court "make one decision" and yet members of the Court still publish a minority as well as a majority explanation of their findings. Therefore, FDA should publish a Summary Basis of Approval (SBA) for each medical intervention which would include a discussion of any and all scientific differences during the review process and an explanation and scientific reasoning for the final conclusions.

Conclusion

The IOM report tells us that now is the time to address the important issues in evaluating drug safety that have needed to be addressed for some time. In order to address this urgent public health issue, we need to act now. Congress should include provisions for strengthening the evaluation of drug safety in any reauthorization of PDUFA. A recent

Harris poll showed that the public is losing confidence in FDA, and the only way to restore that confidence is by action, not merely by words or reshuffling of the structure of FDA and without new resources and authority. We can address the important issues in evaluating drug safety in an efficient way without slowing bringing important medical advances to patients. Safety and efficiency and not mutually exclusive goals and more focus on post-approval activities need not slow pre-approval evaluations. However, we need to learn from recent events and take action today to avoid another Vioxx or Ketek tomorrow. Congress can help FDA start down the road to being the foremost authorities on pharmacoepidemiology, to work closely with the scientific community to gather data and to develop new methods and analyses, to come up with cogent scientifically based approaches to evaluating the balance of risks and benefits of drugs, and help FDA achieve its stated mission of protecting and advancing the public health. Most FDA staffers are courageous public health servants. Please give them the tools they need to do their jobs for all of us.