February 23rd 2007

Ann Sullivan
Office of Policy and Planning (HFP-20)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD. 20857

Dear Ms. Sullivan:

Please accept these comments regarding the Food and Drug Administration (FDA) proposed revisions to the Prescription Drug User Fee Act (PDUFA) as published in the Federal Register on January 16th, 2007.

We offer these comments in a spirit of cooperation, seeking to work with FDA to address issues raised by scientists within FDA as recorded in a survey conducted jointly by our organization and Public Employees for Environmental Responsibility (PEER) in 2006 and attached to this email.

As part of that survey, FDA scientists were given the opportunity to write an essay response to the question "The integrity of the scientific work produced by FDA could best be improved by…" Many of the essay responses highlighted the challenges which past iterations of PDUFA have imposed on FDA (the complete set of essay responses may be viewed online at www.ucsusa.org/scientific_integrity/interference/survey-summaries.html). The scientists' comments paint a disturbing picture of an agency in which the quality of science has been undermined by regulatory deadlines and industry pressure, with potentially serious consequences for public health.

Although the revisions proposed to be incorporated in PDUFA IV are a first step in the direction of addressing some of the scientists' concerns, particularly on the need for greatly expanded post-market surveillance and the need to incorporate epidemiological as well as clinical data in such studies, the proposed revisions completely fail to address the undermining of the scientific infrastructure and culture essential to FDA's mission as a "science-based" agency. Unless and until these issues are addressed through increased accountability and transparency, FDA scientists will remain disempowered and public confidence in the agency will continue to erode.

We provide below more details, together with recommendations which, if incorporated in PDUFA IV, will help FDA more effectively accomplish its mission of protecting public health.

REBUILDING THE SCIENTIFIC INFRASTRUCTURE AND CULTURE ESSENTIAL TO FDA'S MISSION AS A "SCIENCE-BASED" AGENCY.

The UCS/PEER survey results demonstrate a decline in the morale of scientists at FDA, with two in five (40%) reporting their morale as poor or extremely poor and many noting an exodus of well-respected and senior scientists coupled with difficulty in attracting new scientific staff. In order to retain and recruit the scientific workforce needed to meet its ever-expanding responsibilities, FDA has much work to do in rebuilding the support infrastructure and culture of respect in which good science can flourish.

Survey respondents identified three key needs:

- The need for additional funding for mission-related research. As one agency employee said "work being done by FDA scientists is work important to public health that would never be done by academia (NIH and universities) or by industry".
- Increasing opportunities for professional development, including encouraging scientists to participate in scientific meetings, trainings and site visits and encouraging them to publish their work.
- Opportunities for advancement based on scientific expertise. A recurring theme of the survey was frustration with a perceived two-tier system in which the only real opportunities for promotion lie in the management track, not the scientific track, and dismay that scientists are rewarded only for speedy drug approval and not for the quality of their reviews.
- An extramural research program to enhance and support intramural research objectives as well as to increase the numbers of trained scientists able to support the FDA mission.

We believe that the following are critical:

- Establishing performance standards for drug safety
- Establishing performance standards for scientific accomplishments of reviewers
- Rewarding managers for the scientific accomplishments of their staff in PDUFA IV will help engender a cultural change in the agency that will support these future reforms in funding and the staff reward system;

The Overall Problem: Decisions Driven by Deadlines, Not Data

Respondents to the UCS/PEER survey overwhelmingly noted the challenges posed by implementation of PDUFA. Almost uniformly they complained not only of an "overwhelming workload" but of the pressure to review volumes of "poorly-organized, worthless data" by "arbitrary deadlines". Because PDUFA contains binding deadlines for the timeliness of new drug review and approval, but no corresponding performance measures for drug safety, scientists expressed frustration with the skewed personnel policies that resulted. They reported that promotions and rewards went to those reviewers who recommended the approval of the most drugs, with no regard for the quality of review work or whether the reviewers considered drug safety. Indeed, several

respondents reported that if a reviewer recommended disapproval of a drug this would lead to a negative performance evaluation. The inevitable consequence, as one CDER reviewer wrote, is that "it is easier to ignore what could be a potential problem in an application". The rush to approval provides significant profits for the pharmaceutical industry but has potentially deadly consequences for consumers. As one respondent wrote: "the public should not be guinea pigs just to provide industry with revenue".

The solution is obvious: in the words of one scientist, what is needed is "less emphasis on adhering to PDUFA timelines and more emphasis on the quality of review". This can be accomplished by devising performance measures for drug safety such as measuring the percentage of approved drugs that show no adverse reactions within a five-year period from approval. Such performance measures will in turn drive a shift in personnel policies so as to "reward those who are not afraid to demand the information needed to adequately review products" and "those who identify safety and effectiveness concerns." The effect will be to "assure [employees] that job security does not depend on compromising scientific integrity".

Restoring Scientific Credibility to the Drug Review Process

Perhaps the greatest need identified by respondents to the UCS/PEER survey was for a clear "policy of science-based decision-making". Almost one in five (18 percent) responded, "I have been asked, for non-scientific reasons, to inappropriately exclude or alter technical information or my conclusions in an FDA scientific document" and more than three in five (61 percent) knew of cases in which "Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions." As one reviewer noted: "by the time the most senior review is completed, many (most) of the initial concerns are obfuscated". Many spoke of "non-scientific, non-supportable decisions by managers with minimal scientific training" overturning the recommendations of scientific reviewers. The end-result is an agency stamp of approval that sweeps aside scientists' concerns about drug safety and effectiveness.

The increased user fees and expanded testing programs recommended by FDA for PDUFA IV will do little to improve public health if agency decisions are not based on the best available science. In order for FDA reviews to represent the "gold standard" of testing and evaluation, scientists must have access to the necessary data and must be able to engage in the scientific discourse through which scientific understanding evolves. In addition as much of this data as possible needs to be publicly available as early in the review process as possible. Instead, FDA scientists report that the agency lacks the "regulatory authority to obtain data" from applicants, and speak repeatedly of the need for the agency to encourage, not suppress, scientific discourse and disagreement. One stated: "Scientific discourse is strongly discouraged where it may jeopardize an approval…Whenever safety or efficacy concerns are raised on scientific grounds…these concerns are not treated seriously"

We recommend that in reauthorizing PDUFA, FDA include legislative language that will enable reviewers to access the full suite of clinical data pertaining to drug approval. We further recommend that FDA examine mechanisms to encourage scientific discourse, such as encouraging scientists to participate in cross-program scientific discussions and external scientific meetings. In addition, we urge FDA to review its policies to ensure that scientists are aware of their first amendment rights to speak on matters of interest to them, and to ensure that scientists who believe their scientific analysis has been distorted or suppressed have access to dispute resolution procedures and an agency ombudsman charged with investigating such incidents.

A critical component of ensuring scientific credibility is providing for peer review by advisory panels of scientific experts, but only if such panels are provided full information and composed of true experts with fully disclosed conflicts of interest – at a minimum. The UCS/PEER survey documents the frustration of agency scientists who observe panels composed largely of scientists with ties to drug manufacturers. We urge FDA to include language in PDUFA IV authorizing the creation of a registry of experts free of ties to drug manufacturers and requiring that list registrants comprise a majority on science advisory panels.

Protecting the Public Interest by Increasing Transparency of Decision-Making

The single best way for FDA to demonstrate its commitment to "science-based" decision-making is to provide full documentation of the decisions made at each stage of the review process and the evidence upon which those decisions are made. The FDA scientists surveyed report widespread overturning of scientific recommendations by managers and political appointees. Particular concern is expressed over "secret" meetings between FDA managers and representatives of the pharmaceutical industry, meetings from which scientific reviewers are excluded. Three in five (60 percent) survey respondents knew of cases "where commercial interests have inappropriately induced or attempted to induce the reversal, withdrawal or modification of FDA determinations or actions." Fifty percent also felt that non-governmental interests (such as advocacy groups) had induced or attempted to induce such changes.

While decision-makers enjoy the prerogative of basing policy on factors other than science, the rationale for such decisions should be made clear and the decision should not be represented as "science-based". We urge FDA, as part of the PDUFA reauthorization process, to institute documentation procedures that make publicly available the scientific opinions and safety concerns of FDA staff at each stage of approval, the rationale for decision-making at every level, and sign-off procedures providing scientists with a "right of last review" of decisions that purport to be science-based.

In summary, PDUFA must support the ability of the FDA to do the following:

- Hire staff with adequate expertise in clinical areas and clinical acumen, as well as training in clinical trials and epidemiology;
- Have adequate data to make scientific decisions from adequate databases;
- Systematically rethink spontaneous reporting of drug adverse events
- Provide personnel with contact with clinical and research world to stay in touch with issues in order to avoid over reliance on company paid academic experts
- And finally provide adequate resources to accomplish tasks.

We believe that PDUFA IV offers a tremendous opportunity to re-align agency practices with its science-based mission, and we look forward to working with you to help advance some of these ideas through the legislative process.

Sincerely,

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Scientific Integrity Program