

May 15, 2007

The following comments for Docket No. 2007D-0101 are submitted on behalf of the following organizations:

**Center for Science in the Public Interest
Consumers Union
Government Accountability Project
National Women's Health Network**

“DRAFT GUIDANCE FOR THE PUBLIC, FDA ADVISORY COMMITTEE MEMBERS;
AND THE FDA STAFF ON PROCEDURES FOR DETERMINING CONFLICT OF
INTEREST AND ELIGIBILITY FOR PARTICIPATION IN FDA ADVISORY COMMITTEES

DOCKET NUMBER: 2007D-0101

Our organizations congratulate the Food and Drug Administration for acknowledging the public's concerns about the large number of scientists with conflicts of interest on its advisory committees. As the Draft Guidance points out, the public has high expectations for the advisory committee process. Any use of scientists with ties to companies with a stake in the outcome of a committee's deliberations undermines the public's faith in the fairness of the process. And, as happened at the February 2005 hearing on Cox-2 inhibitors where nearly a third of scientists on the panel had financial ties to Cox-2 makers, it can skew the outcome of a committee's deliberations. The proposed Guidance is long overdue.

While your Draft Guidance acknowledges the current process needs improvement, the proposal is at best a minimal first step toward developing a new committee formation process that will serve both the public interest and the FDA's ability to obtain the best available advice.

Reduced to its essence, the Draft Guidance:

1. Forbids the use of scientists with conflicts of interest if those financial arrangements amount to more than \$50,000 in the year prior to the meeting;
2. Prohibits any scientist who receives a waiver for lesser conflicts from voting at the conclusion of the meeting; and
3. Presumes there are cases where the need for an individual scientist's expertise outweighs any conflict of interest under \$50,000 because no one with comparable expertise can be found.

We have a number of objections to the Draft Guidance:

- As a practical matter, only about a tenth of scientists currently receiving waivers will be prohibited from serving on FDA advisory committees because of these

proposed guidelines. Of the 169 waivers granted at 41 meetings between September 2006 and May 2007, just 18 involved conflicts of interest greater than \$50,000, according to waiver documents available on the FDA website.

- By limiting the “look-back” period to one year, which may be shorter than the current look-back period, the number excluded may be even lower. A one-year look-back period is a completely inadequate standard for evaluating conflicts of interest. Many major medical journals consider conflicts of interest going back at least three for purposes of disclosure accompanying published articles. A recent guideline from Blackwell Publishing, which publishes over 800 journals, established a three-year look-back period as a minimum. We suggest the FDA do the same for the purposes of its guidance, whatever its final shape.
- The agency’s most recent report to Congress (“Fifth Report on FDA Efforts to Identify Qualified Persons for Appointment to FDA Advisory Committees,” Conference report 109-255, Jan. 31, 2007), showed that one in every four special government employees chosen for FDA advisory committees have been issued waivers. This proposal raises the possibility that a substantial fraction of some future advisory committees will be non-voting members, a circumstance that would further undermine the public’s confidence in the deliberations of the agency.
- Any cutoff (other than zero) will be very difficult if not impossible to implement. While it is fairly easy to measure the current value of stock in a publicly traded drug company owned by a committee member, how does one evaluate the current value of a January 2007 stock option given to the committee member by a drug company to buy a specified number of shares at a specified price at any time in the next five years? What is the current value of a two year contract signed in January 2007, renewable at the option of the drug company, that says the physician will be paid \$5,000 for each speech given to other physicians and that the number of such speeches will be jointly determined by the company and the physician? How does one evaluate a February 2007 contract between the drug company and the physician or scientist whereby the company agrees to pay \$500 per hour for each hour of consulting over the next three years? These are all situations where the advisory committee member could benefit substantially by his or her influence at the FDA meeting.

Our Proposal:

Because this Draft Guidance is aimed at the professional staff which creates and manages the advisory committees, we believe it should articulate a set of goals at its outset and outline a set of procedures that should be followed to achieve those goals. This Comment offers our proposed set of goals and procedures. Then the Comment proposes a limited circumstance that could justify the use of waivers, one that will insure the FDA can gain access to the best scientific advice that this nation has to offer in all instances.

Goal 1:

The Guidance should establish at its outset that it is the policy of the Food and Drug Administration to create outside advisory panels that are free from conflicts of interest.

We believe it is possible to establish expert advisory panels that do not have any scientists who require waivers of conflicts of interest. The experience of the National Institutes of Health (ANIH@) and several states indicates that there is no merit to the claim that the FDA must allow the participation of conflicted experts because they have a unique expertise. The Office of Medical Applications of Research (AOMAR@) within the NIH bars any conflicted scientist from serving on its panels that develop consensus statements on the implications of clinical trial evidence. OMAR panels require the same specialized expertise found on FDA advisory panels: biostatisticians expert in interpreting clinical trial data; clinicians expert in treating the disease, and scientists who understand the underlying biology.

As another example, consider the Center for Evidence-Based Policy (ACEBP@) at Oregon Health Sciences University. CEBP analyzes all clinical trial evidence in a field to determine which drugs, biologics, and devices provide the best medical outcomes; this evidence is then turned over to states for use in establishing what Medicaid will pay for. CEBP maintains a strict No conflicts-of-interest@ policy for its contractors.

Even your proposed guidance admits that the FDA can find experts to replace those with very large conflicts of interest. If qualified experts can be found to replace scientists with over \$50,000 a year in financial ties to industry, why can't the FDA find qualified experts to replace all those with any ties to industry? The time has come to end the participation of all scientists with conflicts of interest on FDA advisory committees, even in a non-voting capacity. Moreover, we believe the FDA should look back three years to determine if the member has a conflict of interest.

Finally, granting scientists with conflicts of interest waivers to serve on advisory committees can defeat the reason for excluding them in the first place, even if they don't have a vote. An analysis of voting patterns of FDA Advisory Committees between 1998 through 2005 reveals the consensus-building nature of the deliberations. Most votes are unanimous or nearly unanimous. Since many committee members are relatively inactive participants, one or two outspoken members of an Advisory Committee can have a disproportionate influence on the discussion as well as the outcome of the vote, even if they themselves don't get to vote. Indeed, busy professionals are unlikely to participate as non-voting members unless they believe they can influence the outcome through discussion. Having non-voting members who are actively trying to influence the outcome of the meeting would negate the policy of not allowing them to vote.

Goal 2:

The Guidance should require the staff to choose a range of scientists for each

advisory committee. It should include experts that can address all the issues of concern to both the agency and the public.

Many current advisory panels lack balance even though it is a requirement of the Federal Advisory Committee Act. Most advisory committees are biased towards physicians and academic physician-researchers who treat patients for the specific conditions that fall under the purview of the specific committee. The committees frequently lack experts in population health and public health protection. Those with expertise in biostatistics, pharmaco-epidemiology, epidemiology, pharmaco-vigilance, drug safety and risk management as well as non-physician health professionals are underrepresented.

Goal 3:

The Guidance should address transparency in the advisory committee process by creating mechanisms that give the public greater and more timely access to the information that is presented to the Food and Drug Administration's outside advisers.

There is substantial room for the FDA to improve the transparency of the advisory committee process. The advisory committee roster and any limited waivers (see below) should be released to the public at least 15 days before any advisory committee meeting. Briefing documents should be made available for public inspection at least one week before a meeting, not one day as is now the case. This will allow the public, patient advocates and independent researchers much-needed time to analyze this information before testifying at the public portion of the meeting.

Advisory committee meetings should be held for all new molecular entities, biologics, and devices. And the FDA should be given the power to levy civil and monetary penalties on any sponsor who withholds relevant information from the agency and public prior to an advisory committee, as recently happened with the Bayer/Trasylol case.

Procedure:

To find outside experts without conflicts of interest, the FDA staff should follow the following procedures (the algorithm).

1. Once a year, the staff should carry out a systematic informational and recruiting outreach campaign to identify scientists who may serve on its scientific advisory panels who do not have conflicts of interest. The letters should include a detailed description of the types of expertise needed on FDA advisory committees and the requirement that the scientists have no conflicts of interest. This outreach campaign should include letters of inquiry to:
 - a. medical, scientific and professional societies;
 - b. the deans of the nation's medical schools; pharmacy schools and schools of public health;

- c. the Office of Women's Health, the Office of Orphan Product Development, and the Office of Pediatric Therapeutics of the Food and Drug Administration;
 - d. the 27 heads of the institutes and centers at the National Institutes of Health;
 - e. the Centers for Disease Control; and
 - f. the Agency for Healthcare Research and Quality.
2. Once a year, the staff should carry out a systematic informational and recruiting outreach campaign to identify qualified members of patient organizations who could serve as patient representatives without conflicts of interest on advisory committees;
 3. The staff should follow up on those letters as necessary to compile a roster of experts without conflicts of interest who are available for and interested in serving on advisory committees. The staff should regularly communicate with members of this roster regarding the reasons for their inclusion on the list, including their lack of conflicts of interest, and provide them with regular updates on the likelihood of their being included in an upcoming advisory committee meeting.
 4. Upon being notified of an upcoming meeting, the staff should consult the roster and recruit non-conflicted experts as needed.
 5. Should a committee need a particular expertise not available on the roster generated by the initial outreach campaign, the staff should contact at least ten (10) institutions from the initial outreach list that have the greatest likelihood of housing a scientist with the required expertise and solicit participation.

The Limited Exemption:

If the staff believes an expert with conflicts of interest is necessary for a complete airing of all issues involving a particular new drug, biologic or device, it may hire that expert as a special government employee to provide expert testimony as long as that expert does not vote and does not participate in the intra-committee discussions prior to the vote.

If the above process has been exhausted and does not generate a sufficient number of experts for an advisory committee or has excluded an expert deemed vital to the deliberations of the committee, the staff may hire special government employee(s) with conflicts of interest to serve as a non-voting, non-discussant expert. This scientist can make a presentation to the committee and/or answer questions. This person(s) presentation should be distinct from and independent of either the sponsor's or FDA's presentation at the meeting.

Even if the staff has created an advisory committee without conflicts of interest with all the expertise required to render a judgment, nothing in this algorithm prevents the FDA staff from hiring a scientist with conflicts of interest to provide testimony and/or answer questions from the advisory committee if the staff believes that presentation will add value to the meeting.

In no case, however, shall a scientist with conflicts of interest hired in this capacity be

allowed to vote at the advisory committee meeting or be allowed to take part in discussions among members of the advisory committee prior to the vote.

Conclusion:

We, the undersigned, believe the time has come to end the participation of scientists with conflicts of interest on FDA advisory committees. In a nation with 125 medical schools and the world's premier medical research institution – the National Institutes of Health, the FDA should be able to find experts without ties to industry who can provide the agency with the best possible advice regarding the approval of new drugs, biologics and devices. We have outlined an algorithm for FDA staff to identify such experts. We have also outlined a limited exemption for the FDA to get that advice in those rare circumstances (an orphan disease or a rare pediatric condition, for instance) where someone with conflicts of interest has crucial knowledge for the committee.

Reforming the FDA advisory committee process along these lines will help restore the public's faith in the ability of the agency to carry out its mission.