nature biotechnology

Probity gone nuts

The thinking behind the US Food and Drug Administration's (FDA) draft guidance on financial conflicts of interest for outside experts is deeply flawed.

This month marks the end of the public consultation period for FDA's draft policy detailing procedures for determining the eligibility of individuals on advisory committees. The new guidance—issued following a period of widespread public and political criticism over the perceived influence of industry on the agency—introduces stringent new restrictions on the eligibility of outside experts with corporate ties to participate and vote on FDA panels. Agency officials claim the clampdown will ensure "that the public has confidence in the integrity of recommendations" made by its committees. A more likely consequence is that it will both undermine FDA's ability to recruit top researchers and compromise the quality of the scientific advice it receives.

Advisory committees provide FDA with independent, expert and objective advice on safety and efficacy of regulated products, the design and analysis of clinical trials, and policy. They also help the public better understand the factors weighed in approving drugs, pulling back the curtain on FDA decision making. Although their recommendations are usually followed by agency officials, the decisions are not binding—as illustrated last year by the case of the emergency contraceptive Plan B (see p. 495).

When FDA determines that advisory committee review is warranted, it recruits outside experts as voting members along with industry liaisons, patient representatives, guest experts and public citizens. Those who have competing interests of $100,000 or greater are prohibited from participation. Everyone else must complete a confidential financial disclosure report detailing their (and their spouse's) current investments, employment, patents, contracts, grants and cooperative research and development agreements as well as consulting, speaking and writing arrangements.

Advisors with serious conflicts can be asked to either recuse themselves from panel participation or divest their financial interests before the meeting. More commonly, if an outside researcher with industry ties is deemed to be particularly valuable to a committee's deliberation, FDA grants what is known as a 208(b)(3) waiver, occasionally allowing voting rights.

According to the draft advisory announced on March 15 (http://www.fda.gov/oc/advisory/waiver/coiguidedft.html), FDA now proposes to introduce a flowchart that would enable officials to determine the financial interests of outside experts in a systematic, stepwise manner. The system is intended to "reduce the likelihood that the process for recommending waivers would vary from meeting to meeting" and "provide greater clarity to the public regarding how FDA selects members."

The problem is that the threshold for disqualification has been slashed in half so that anyone with a financial interest >$50,000 will now be barred from sitting on a panel. Waivers will be granted to those with smaller financial interests only under exceptional circumstances, and even then experts will be forbidden from voting.

A cursory look at waivers from previous advisory committee meetings reveals that numerous scientific experts with international reputations who contributed as full voting members will now be excluded. Only three months ago, FDA Commissioner Andrew von Eschenbach reported that over a third of all the outside experts at the agency's Center for Drug Evaluation and Research received waivers between November 2005 and January 20007. Many of these have financial interests >$50,000.

If officials had no difficulty recruiting outside experts to their panels, this might not matter. But the reality is that FDA is finding it increasingly hard to find qualified experts 'untainted' by corporate ties or investments, a problem that will be exacerbated by the new cap. It doesn't help that there's little incentive for outside researchers to serve on the panels—a process likened by some to jury duty.

One might still make a case for tightening the rules if there were evidence that industry ties bias committee decisions. But there isn't.

The example routinely parroted is the February 2005 joint meeting of the Arthritis Drugs and the Drug Safety and Risk Management advisory committees on cyclooxygenase 2 (COX-2) inhibitors. Of the 32 advisors present at that meeting, 10 of those who voted that Vioxx, Bextra and Celebrex should be marketed had financial ties to one or more companies that manufactured COX-2 inhibitors. If these experts hadn't participated, critics argue, the committees would have voted 12 to 8 for Bextra to be withdrawn and 14 to 8 that Vioxx should not return to market. But this assumes that the 10 experts voted in favor of marketing the drugs solely on the basis of their industry ties, irrespective of their scientific judgment or integrity. Guilt by association, plain and simple.

A rather different picture is painted by a study in *JAMA* (**295**, 1921–1928, 2006) analyzing the votes of 76 FDA advisory committee meetings from 2001 to 2004. That research, carried out by the Washington-based consumer advocacy group Public Citizen, concludes that financial conflicts do not alter the overall outcome of voting. In an analysis of the same data, FDA concluded "advisory committee members with financial ties to companies tend to vote *against* [emphasis added] the financial interest of those companies."

In fact, according to FDA, the vast majority of conflicts disclosed are not due to experts' ties to firms sponsoring a product; they are due to links with competing companies. Thus, even if there were evidence of a bias (which there isn't), one could argue that it should have the opposite effect—coercing panels to turn down competitor's drugs, rather than approve them.

The new rules then are more about political expediency and public relations than correcting an advisory panel process corrupted by industry. But FDA is seriously mistaken if it believes purging the best minds from the advisory committee process because of financial ties will not have dire repercussions. It will make expert recruitment more difficult, resulting in delayed committee meetings and ultimately lengthened drug approval times. Worse still, it will encourage scientific mediocrity on panels. And settling for second best is simply not good enough for an agency charged with protecting the nation's health.