

# Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees

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Advisory committees to the Food and Drug Administration (FDA) help the agency make decisions about the approval of medications and medical devices, among other issues. Membership on these committees is subject to detailed policies and procedures for managing potential conflicts of interest and for balancing possible conflicts against the agency's need for advisers with relevant scientific expertise (see box).<sup>1,2</sup> Two recent high-profile meetings have raised questions about the agency's approach and whether it should change.

In February, the FDA convened a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the safety of cyclooxygenase-2 (COX-2) inhibitors. At the beginning of the meeting, an agency official read a conflict-of-interest statement indicating that in the FDA's

judgment the topics were "issues of broad applicability and there [were] no products being approved." Although the FDA acknowledged the possibility of conflicts of interest on the part of committee members, it declared that "because of the general nature of the discussions before the committee, these potential conflicts are mitigated." The agency issued general waivers to the members who required them in order to participate; no specific information was provided.

After the meeting, it was disclosed that 10 of the 32 voting panel members had financial associations with the manufacturers of COX-2 inhibitors, such as the receipt of speaking or consulting fees or research support.<sup>3,4</sup> Of the 30 votes cast by these 10 members on whether rofecoxib, celecoxib, and valdecoxib should continue to be marketed, 28 favored marketing the drugs. Of the 66

votes of the other 22 members, only 37 favored marketing the drugs. If the 10 panel members with the financial associations had not participated, the committee would have voted 12 to 8 that valdecoxib should be withdrawn and 14 to 8 that rofecoxib should not return to the market. With their votes included, the tally was 17 to 13 for keeping valdecoxib on the market and 17 to 15 for the return of rofecoxib.<sup>4</sup> Subsequently, the FDA announced that it had asked Pfizer, the manufacturer of valdecoxib, to withdraw it voluntarily from the market. Rofecoxib, which Merck voluntarily withdrew from the market in 2004, remains off the market.

According to Dr. Alastair J.J. Wood of Vanderbilt University Medical School, the chair of the joint meeting, the FDA made a "judgment error" when it decided to issue a general waiver and not to disclose specific information

### Managing Conflicts of Interest for FDA Advisory Panels

The FDA's management of conflicts of interest for its advisory committees is based on the Ethics Reform Act of 1989 and implementing regulations that were issued in 1996 by the Office of Government Ethics.<sup>1,2</sup> Voting members of FDA advisory committees are considered "special government employees." Before each meeting in which they may participate, these experts complete a detailed confidential financial disclosure report. The agency determines whether any of the reported relationships pose a potential conflict of interest, and some people are disqualified on this basis.

The FDA, like other federal agencies, is permitted to balance its needs for scientific expertise against the potential for a conflict and to grant a waiver when "the need for the individual's services outweighs the potential for a conflict of interest."<sup>1</sup> If the FDA determines that only general topics are being discussed, as at the meeting on cyclooxygenase-2 inhibitors, it takes a different approach from that used when it determines that approval of a specific product is being considered.

In reaching decisions, FDA officials use a detailed "waiver criteria document" that provides guidance and suggests an "expected action," which is defined as "the outcome that is anticipated in the majority of cases."<sup>1</sup> For example, when an advisory committee is considering approval of a specific product, stock holdings of greater than \$100,000 are expected to lead to exclusion, whereas smaller stock holdings lead to a decision by the agency. A limited waiver permits partial participation. The FDA may allow a member to participate in discussions and deliberations but not to vote.

After granting a waiver, the FDA balances the public's right to the information against the privacy of its advisory committee members. According to the agency, "information to be disclosed will adequately enable a reasonable person to understand the nature of the conflict and the degree to which it could be expected to influence the recommendations the [special government employee] will make."<sup>2</sup>

The disclosure is read into the record at the beginning of the meeting. The FDA usually does not provide specifics when it grants a general waiver. When it grants a specific waiver, it usually discloses the type of interest (such as stock, consulting, or contracts and grants) as well as the magnitude, which is expressed in terms of dollar ranges rather than as a specific amount. The disclosure notes whether the financial interest is related to the product under discussion or a competing product (without naming the competitor). The actual waiver statements are not released; they can be obtained only through a written request under the Freedom of Information Act.

about the potential conflicts of members of the committees. In an interview, Wood said: "Of all the FDA advisory committee meetings I have attended, there has

never been more money on the table. Some potential panel members had already been excluded because of conflicts. The people who were chosen had disclosed

their financial interests to the FDA, although it played out as though they had something to hide."

Concern about potential conflicts of interest arose again in April, when the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee met to consider the safety of silicone gel-filled breast implants made by Inamed and Mentor, both of Santa Barbara, California. Before the meeting, the FDA told a plastic surgeon from George Washington University School of Medicine and Health Sciences that the \$50,000 to \$100,000 in stock he owned in a company that is seeking to purchase Inamed did not disqualify him, and he was designated as one of 10 voting members of the panel. Days later, the agency said that he could participate but not vote; he declined a nonvoting seat. The remaining plastic surgeon on the panel had a major role in the development of an educational CD-ROM about breast-reconstruction surgery, a project that had received funding from Inamed. At the beginning of the meeting, an FDA official said that the surgeon "reported his institution's past and current involvement with firms at issue. In the absence of personal financial interests, the Agency has determined that he may participate fully in the Panel's deliberations." In the end, the panel made a split recommendation — approval of the implants made by Mentor and nonapproval of those made by Inamed.

In these recent cases, the FDA followed its standard procedures for managing conflicts of interest. The panel members with financial interests said that their ties did not influence their votes.

Nonetheless, the cases raise the specific concern that the agency's disclosure statements are opaque and lack detail. They also raise the general concern that waivers for potential conflicts are common and that the agency has paid insufficient attention to its — and the public's — interest in selecting scientific advisers who are independent of industry.

The FDA has 30 advisory committees and holds nearly 85 advisory committee meetings a year. Voting members of FDA advisory committees are considered “special government employees.” In 2003 and 2004, about 12 percent of the special government employees participating in these meetings were granted waivers related to the particular matter before their committee (an average of 194 waivers per year). In May, Dr. Steven Galson, acting director of the FDA's Center for Drug Evaluation and Research, said that the frequent waiver of these conflict-of-interest rules for advisory committees was “very controversial.”

The matter is complicated by the importance of the FDA's decisions for medical practice and public health, the agency's need for specialized expertise on specific topics, the huge amounts of money that are often at stake, and the extensive financial ties between leading medical researchers and industry. It is also complicated by the fact that the FDA has been without a permanent commissioner since March 2004. The FDA itself receives substantial financial support from the “user fees” that pharmaceutical compa-

nies pay the agency under the Prescription Drug User Fee Act of 1992 and that are used primarily to accelerate drug approvals.<sup>5</sup> As the *New York Times* noted in an editorial on March 4, 2005, “Unless the FDA makes a more aggressive effort to find unbiased experts or medical researchers start severing their ties with industry, a whiff of bias may taint the verdicts of many advisory panels.”

Some changes to the FDA's approach to financial conflicts of interest could probably be implemented by the agency or the Department of Health and Human Services. One possible approach would be for the FDA to publish the names and background information of proposed committee members in the *Federal Register* and on its Web site and to give the public several weeks to comment. The agency could then consider these comments before the roster of participants in an advisory meeting was made final. Such procedures for public comment are used by the National Academies and the Environmental Protection Agency. The FDA could also make public more complete financial disclosures for its outside advisers. A possible criticism of such a move is that potential advisers would be less willing to serve under these conditions. However, in recent years, detailed public disclosures have become widely accepted — for example, in articles in medical journals and in materials associated with continuing medical education activities.

Any fundamental change in the FDA's approach, such as ex-

cluding from advisory committees anyone who is a paid consultant to industry, would probably require new federal legislation. On June 8, 2005, the House of Representatives, by a vote of 218 to 210, attached a rider to the bill that includes appropriations for the FDA (H.R.2744). The amendment (H.AMDT.235), sponsored by Representative Maurice Hinchey (D-N.Y.), would prohibit the agency from using appropriated funds to grant waivers of its financial conflict-of-interest requirements to voting members of its advisory committees. As of early July, the measure was under consideration in the Senate, where Senator Richard Durbin (D-Ill.) is backing a similar amendment. If the amendment eventually becomes law, industry-connected scientists would be unable to serve on advisory committees during fiscal year 2006 (October 1, 2005, to September 30, 2006), the period covered by the appropriations bill.

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1. Food and Drug Administration. FDA guidance on conflict of interest for advisory committee members, consultants and experts. February 2000. (Accessed June 23, 2005, at <http://www.fda.gov/oc/advisory/conflictinterest/guidance.html>.)
2. *Idem*. Draft guidance on disclosure of conflicts of interest for special government employees participating in FDA product specific advisory committees. January 2002. (Accessed June 23, 2005, at <http://www.fda.gov/oc/guidance/advisorycommittee.html>.)
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4. Harris G, Berenson A. 10 Voters on panel backing pain pills had industry ties. *New York Times*. February 25, 2005:A1.
5. Okie S. What ails the FDA? *N Engl J Med* 2005;352:1063-6.