Did the FDA Miss the Chance to “Test Drive” Its Proposed Conflict-of-Interest Rules?

Leah A. Greene, J.D., LL.M. candidate

On March 21, 2007, the U.S. Food & Drug Administration (“FDA”) announced new guidelines to tighten conflict-of-interest rules for advisory committee members.1 The FDA is proposing to exclude participation by individuals whose financial interest in either the drug company seeking approval or a competitor has a combined value of greater than $50,000.2 If the combined value of the disqualifying interests is less that $50,000, the individual might be able to participate as a non-voting member.3 Disqualifying interests include, but are not limited to, stock ownership and research or consulting arrangements.4

A notable example of potential conflict of interest within the advisory process is the approval of Pfizer’s Bextra and Merck’s Vioxx. Ten of the 32 advisors who voted to allow Bextra to remain on the market and to return Vioxx to the market despite concerns about their safety had received money from the respective drug makers.5 Under the new rules, they would not have been allowed to vote, and the committee would have not approved returning the drugs to market.6 Ultimately, both drugs were taken off the market, but the FDA’s advisory process was scrutinized because of the questions raised by the financial ties of the advisory committee members.7

Pharmaceutical companies typically hire physicians as consultants for marketing and research.8 Under the FDA’s old rules, any advisor with $100,000 or more in stock in accompany requesting approval for a drug or device was prohibited from participating.9 The FDA, however, could waive almost any other financial conflict, even if the financial interest was valued in the tens of thousands of dollars.10 Although waivers will be possible under the new rules, only the commissioner will have the authority to approve them and presumably they will be rare.11

Herein lies the rub. The same physicians who are recruited by pharmaceutical companies to research new drugs are likely the best qualified to serve on the advisory panel to review the new drug, because of their familiarity with the development process. Yet under the old rules, they

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1 Press Release, FDA, FDA Proposes New, Tougher Procedures for Membership on Advisory Committees”, Mar. 21, 2007, available at http://www.fda.gov/bbs/topics/NEWS/2007/NEW01591.html. These proposed guidelines will not take effect until May 21 so individuals can make comments on the guidelines to the FDA.
2 Id.
3 Id.
4 Id.
6 Id.
7 Id.
8 Id.
9 Id.
10 Id.
11 Id.
might have been limited in their participation or barred altogether. On the other hand, physicians hired by competing drug companies were able to serve on the same advisory committee and have more than drug safety on their mind when they decided which drugs to approve for the market.

Despite the FDA’s decision to improve the credibility of its approval process, it allowed the approval process for Arcoxia, Merck’s most recent COX-2 inhibitor, to go forward under the old rules. Arcoxia is intended to relieve arthritis pain and belongs to the same class of drugs as Vioxx. Three of the advisory committee members who reviewed Arcoxia have ties to the drug industry. Dr. Robert Levine, a digestive system specialist, disclosed that he owned Merck stock worth between $25,001 and $50,000. Osteoporosis specialist Dr. Kenneth Saag disclosed that he received speaker and consulting fees from Merck on drug issues unrelated to Arcoxia, as well as consulting fees from two competitors. The total was less than $50,000 per year. The chairman of the meeting, Dr. Dennis Turk, a pain specialist, received fees of less than $10,000 a year from a competitor. These doctors were allowed to serve as voting members, but they had to disclose their conflicts and obtain an FDA waiver.

As many may remember from the first round of controversy surrounding COX-2 inhibitors, Vioxx was supposed to provide pain relief with less gastrointestinal irritation, calling Dr. Levine’s participation into question even more, as he is a digestive system specialist. Dr. Turk’s participation may seem benign at first glance, but it could be argued that the competing drug company could promise him greater consulting fees for his disapproval of the drug. Moreover, as chairman of the committee, he should be extremely sensitive to the appearance of his objectivity in light of his financial interests. It would be interesting to learn from which company Dr. Saag received consulting fees to evaluate whether those financial ties would play a role in his decision regarding Arcoxia.

Under the new rules, none of these physicians would be allowed to vote on Arcoxia. Peter Lurie, Deputy Director of the Health Research Group of Public Citizen, told the Los Angeles Times that the meeting about Arcoxia “[was] an ideal opportunity for the FDA to demonstrate its seriousness about the proposed rules and simply prevent these people from voting.”

Indeed, the FDA could have used the Arcoxia committee meeting to model how the new rules would work by asking the three physicians with financial ties to the drug industry to recuse themselves from voting. Even better, the physicians could have voluntarily recused themselves from the committee meeting. Their failure to recuse themselves is not atypical, however. In 2006, a study published in the Journal of the American Medical Association examined 221

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13 Id.
14 Id.
15 Id.
16 Id.
17 Id.
19 Alonso-Zaldivar supra note 12.
meetings held by 16 FDA Drug Advisory Committees between 2001 and 2004 to determine conflict rates, type and size.\textsuperscript{20} It concluded the following:

[i]n 73\% of the meetings, at least one advisory committee member or voting consultant disclosed a conflict. Only 1\% of those advisory committee members were recused. For advisory committee members and voting consultants combined, 28\% disclosed a conflict. The most commonly specified conflicts were consulting arrangements, contracts/grants, and investments. Nineteen percent of consulting arrangements involved over $10,000, 23\% of contract/grants exceeded $100,000, and 30\% of investments were over $25,000.\textsuperscript{21}

The study noted, however, that there was not a statistically significant relationship between conflict rate and voting patterns. It also revealed that excluding consulting and voting members with conflicts would have resulted in margins less favorable to the index drug in most of the meetings, but would not have changed the ultimate outcome.\textsuperscript{22}

Consumer groups recognize the tension in wanting knowledgeable physicians on these FDA committees, but excluding those whose participation could appear mercenary. Merrill Goozner of the Center for Science in Public Interest, a consumer group, told the \textit{Los Angeles Times}, “You want two things on this committee: completely objective people and a sufficient number of people skilled in sifting through the data to evaluate the risk.”\textsuperscript{23}

Rep. Maurice D. Hinchey (D-N.Y.) told the \textit{Los Angeles Times} that the FDA’s decision to go forward with the review of Arcoxia by a committee with three physicians with financial conflicts showed “insincerity” and cast doubt on the FDA's promises.\textsuperscript{24} Rep. Hinchey, who has sought stricter rules on financial interests, further explained, “They know they should be eliminating these conflicts, but nevertheless they continue to have people with conflicts on the panels.”\textsuperscript{25}

Rep. Hinchey summarized the concern over allowing financially conflicted individuals to serve on these committees. “That's not going to encourage consumer confidence in these decisions, or, ultimately, in the product itself.”\textsuperscript{26}

FDA spokeswoman Kimberly Rawlings said the agency is following its existing conflict-of-interest rules because the proposed ones are still being refined.\textsuperscript{27} An open-comment period on the new policy is in effect until May 21.\textsuperscript{28}

\textsuperscript{21} Id.
\textsuperscript{22} Id.
\textsuperscript{23} Alonso-Zaldivar supra note 12.
\textsuperscript{24} Id.
\textsuperscript{25} Id.
\textsuperscript{26} Id.
\textsuperscript{27} Id.
\textsuperscript{28} Id.
Dr. Saag explained, “The pending deliberation by the advisory committee represents a drug approval issue of significant public health importance that requires careful deliberation by a multi-disciplinary group of experts.”

Dr. Saag’s statement, while accurately describing one concern of these committees, does not address the ultimate concern: whether his financial ties played any role, consciously or unconsciously, in his decision regarding Arcoxia.

Ultimately, the FDA panel voted 20-1 against recommending approval of Arcoxia. While some may cite this decision as an example of how financial ties might not influence the ultimate decision-making of the committee members, questions remain. For instance, what if Merck influenced the two doctors with financial ties to it on the Arcoxia committee to vote against Arcoxia in attempt to illustrate the effectiveness of the current conflict-of-interest rules? What if the physician with financial ties to Merck’s competitor voted against it because he knows of that company’s plans to produce an arthritis drug in the same class as Arcoxia?

The sole recommending member of the Arcoxia panel was Dr. P. Jay Pasricha of the University of Texas Medical Branch and a member of the FDA’s Gastrointestinal Drugs Advisory Committee. He explained, “[I voted] yes, with the additional labeling that it be used for patients who can't tolerate existing traditional nonsteroidals and who are at low risk for cardiovascular events.”

The other physicians expressed difficulty in approving a drug so similar to Vioxx and Celebrex, another COX-2 inhibitor, even though it showed some signs of gastrointestinal safety, as there are other drugs on the market with nearly identical efficacy.

The FDA rejected approval of the drug in late April 2007. Arcoxia is still on the market in 63 countries, and FDA whistle-blower David Graham, part of the Office of Surveillance and Epidemiology, is working to take Arcoxia off the market in those countries. He claims it is “a potential public-health disaster” because it increases the risk of heart attacks and strokes.

Because many health consumers ascribe a great deal of trust to physicians, it is of utmost importance for them to do nothing to jeopardize that trust, including the very crucial job of approving new drugs. One can imagine that the physicians with smaller financial ties to a drug company believe they can vote on new drugs with absolutely no improper motivations. Despite that, the FDA’s new financial conflict-of-interest guidelines will likely improve the public’s trust of the drug approval process, especially in light of the Vioxx scandal.

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29 Id.
31 Because of the great cost of getting a drug to this stage of approval, this scenario is probably not likely.
32 Wood, supra, note 18.
33 Id.
The case of the Arcoxia approval process was an excellent opportunity for the FDA to show how the new rules would work to remove the appearance of financial impropriety from the drug-approval process. The FDA refused to take this opportunity to voluntarily “test drive” the new rules, however. Despite the fact that three of the physicians had financial conflicts that would have barred their participation under the new rules, the drug was denied approval.\textsuperscript{36} Hopefully, the new rules will increase physicians’ awareness of the importance of financial propriety when they serve on these committees in addition to increasing the public’s perception of the approval process. In addition, physicians interested in the drug-approval process will have to make a choice: either invest in drug companies and participate in their research or serve on an FDA advisory committee, but not both.

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\textsuperscript{36} Given the similarity of the concerns of Arcoxia and Vioxx, it could be argued that Arcoxia was not the ideal test situation for the new rules. This author, however, believes the FDA could have shown how serious it was about decreasing the appearance of financial conflicts by requesting voluntary compliance with the new rules during the approval process for Arcoxia.