Title

Financial Conflicts of Interest at FDA Drug Advisory Committee Meetings

Journal

Hastings Center Report, 48(2)

ISSN

0093-0334 1552-146X

Authors

Hayes, Michael J

Prasad, Vinay

Publication Date

2018-03-28

DOI

10.1002/hast.833

Peer reviewed

Financial Conflicts of Interest at FDA Drug Advisory Committee Meetings

BY MICHAEL J. HAYES AND VINAY PRASAD

The U.S. Food and Drug Administration's drug advisory committees provide expert assessments of the safety and efficacy of new therapies considered for approval. A committee hears from a variety of speakers, from six groups, including voting members of the committee, FDA staff members, employees of the pharmaceutical company seeking approval of a therapy, patient and consumer representatives, expert speakers invited by the company, and public participants. The committees convene at the request of the FDA when the risks and harms of novel products are not immediately clear, and their final decisions carry significant weight, as most therapies that receive advisory committee approval are subsequently approved by the FDA.[1]

In recent years, across a series of diverse publications, the financial conflicts of interest of each category of participants in the meetings have been investigated. Here, we summarize these findings and their ethical implications, focusing on the FDA Oncologic Drugs Advisory Committee, and we suggest ways to move toward more transparent and impartial advisory committee meetings.

Conflicts in All Speaker Categories

In all six of these groups that speak before an FDA drug advisory committee, some members have financial conflicts of interest: they are receiving money—or have previously received money—from the pharmaceutical company seeking to have its therapy approved. We focus on the Oncologic Drugs Advisory Committee because of our professional familiarity with oncology and because cancer drugs have tenuous risk-and-benefit balances, which makes impartiality in the approval process very important. The available data on conflicts of interest paint a sobering picture of ODAC. Conflict of interest within it is sizable.

Voting members. For ODAC, voting members are predominantly academic oncology professors at major universities or employees of the National Institutes of Health with expertise in cancer medicine, though not necessarily in the specific cancer type for which a drug product is under consideration. High-profile public cases in the late 1990s and early 2000s placed the FDA under scrutiny regarding the role of financial conflicts of interest among drug advisory committee voting members. An analysis of all drug advisory committee meetings held from 2001 to 2004 showed that, of 221 analyzed meetings, 73 percent included at least one voting member with a financial conflict of interest, and 28 percent of individual voting members had such a conflict.[2] Congress and the FDA recognized the seriousness of these findings, and subsequent guideline statements and legislation, such as the FDA Amendments Act of 2007, took significant steps to reduce the burden of such conflicts in these meetings. The rate of declared conflicts of interest at meetings of ODAC has declined over time, with only rare financial conflicts declared since 2007.[3]

Despite these changes, concern regarding the influence of financial bias remains. While the FDA publicly discloses current financial conflicts of interest, prior financial relationships between speakers and the drug companies are not routinely released to the public. A recently published analysis of advisory committee meetings following the above legislative changes shows that, while there were few active conflicts, there was at least one voting member with a prior financial tie present in 27 percent of 385 analyzed meetings.[4] The

Michael J. Hayes and Vinay Prasad, "Financial Conflicts of Interest at FDA Drug Advisory Committee Meetings," *Hastings Center Report* 48, no. 2 (2018): 10-13. DOI: 10.1002/hast.833

Former employees of the FDA should be required to have a cooling-off period—a period after departing from the agency when they cannot work for the pharmaceutical industry.

effect of this type of subtle bias may be most pronounced in fields such as oncology because therapies that are assessed by ODAC are frequently intended for treatment of orphan diseases and have been tested in clinical trials that are often either single arm or based on surrogate end points. In other words, many oncology drugs are judged based on gray evidence—findings from nonrandomized studies or from studies assessing only surrogate end points—leaving more room for judgment and raising the potential for bias.

Employees of the pharmaceutical company and experts hired by it. It is self-evident that employees of the company seeking approval for its product are conflicted. They argue in favor of drug approval in 100 percent of meetings. Recently, Austin Lammers and colleagues (including one of us, Vinay Prasad)[5] investigated the financial conflict among invited expert speakers in ODAC meetings and found that 92 percent of invited physician speakers over the last five years had significant financial ties to a pharmaceutical company. The median payment to the speakers was thirty-five thousand dollars, and 47.4 percent of the speakers had documented payments from the specific company whose product was being assessed. This percentage may be an underestimate, as the Sunshine Act disclosure provisions do not apply to companies that have no products on the U.S. market, which was the case for several of the companies.

Patient and consumer advocates. The analysis S. Scott Graham and colleagues conducted concerning advisory committee meetings held from 2009 to 2012 shows that 61 out of 315 patient and consumer representatives (19 percent) had financial conflicts of interest.[6] In 36 of the 61 conflicts of interest, Graham et al. were able to ascertain the value of the conflict, and they found that 35 were valued at fifty thousand dollars or more. Patient and consumer representatives are not required to disclose conflicts of interest, however, and thus these findings likely underrepresent the degree of conflict present among this group of participants.

Public participants. The prevalence of conflicts of interest among public members has been evaluated twice, to our knowledge. In an analysis of all advisory committee meetings from 2001 to 2004, Peter Lurie and colleagues identified 771 public speakers, 59 percent of whom included a disclosure statement, with 284 individuals (63 percent of those who disclosed) having a financial conflict of interest.[7] In a more recent study of ODAC meetings from 2009 to 2014, Matthew Abola and one of us (Prasad) found that, of the 103 public speakers they were able to identify, 31 (30 percent) reported financial ties to the companies seeking approvals.[8]

FDA employees. As government employees, the FDA employees at these meetings have the tightest restrictions on current financial relationships with any of the parties present, yet many of these employees leave the FDA to work for biopharmaceutical companies.[9] Of twenty-six identified former hematology-oncology FDA drug application medical reviewers who left the agency from 2001 to 2010, fifteen (58 percent) were found to have worked for or consulted for the biopharmaceutical industry after leaving the FDA. This employment pattern may raise concern that, although regulators intend to act always in the best interest of the public, the frequent opportunity for subsequent employment with the industry may serve to dissuade them from being too oppositional or critical. Even though FDA medical reviewers do not vote, the decision to approve a drug is ultimately theirs, as advisory committee votes do not bind the agency to a decision.

The Relevance of These Financial Ties

These findings bring us to two important questions: Does conflict of interest matter? Does having a financial conflict of interest directly affect a speaker's views or the advisory committee's final recommendations? The second of these is a much more challenging question to answer, as the only one of these groups for which the effect of such conflicts on judgment has been studied is that of voting members of the advisory committees. In one example, individuals with ties to the pharmaceutical companies seeking approvals voted disproportionately in favor of their medications.[10] Several larger studies of advisory committee meeting voting patterns also show an association between financial ties to the pharmaceutical company whose medication is being assessed and voting in favor of the proposed therapy,[11] with the most recent and largest study showing that the individual voting members are 1.49 times likelier to vote to approve the company's therapy when they are financially tied to the company than if they are not.[12]

Critics of these data will argue that the associations are merely that, that they are observational trends without any prospective studies showing direct causality. Our view is that the quality of evidence is limited, but that the ubiquity of financial conflict at the FDA, and in the United States' medical system in general, makes it nearly impossible for a

definitive study to be performed. Because the decisions are made in a system where conflict is ubiquitous, no one knows what the world would look like if those conflicts were absent. How would decisions otherwise be made? There is no natural experiment—a world without heavy financial ties—against which current decisions can be judged.

Furthermore, the findings summarized above are in line with a large body of literature about financial conflict of interest in medicine, which has consistently shown that financial ties between physicians and biopharmaceutical companies are associated with favorable clinical trial results,[13] with changes in physicians' published views on these trials,[14] and with alterations in physicians' prescribing patterns.[15] The unavoidable, and admittedly uncomfortable, conclusion is that physicians, like most human beings, are affected by financial incentives. Physicians with financial conflicts at FDA advisory committee meetings are almost certainly subject to this same prejudice.

While we do not have similar data to suggest that the views of public participants and patient representatives at FDA meetings are changed by financial ties to industry, it is reasonable to assume that individuals and patient advocacy groups who have not been trained to assess the merits of clinical trials would be equally, if not more, susceptible to the effects of financial benefits on evaluating the merit of new therapies. To understand how financial ties between public advocacy groups and pharmaceutical companies can affect the advocacy groups' actions, it is helpful to consider what pharmaceutical companies have openly shared for decades. Partnering with the public through patient advocacy organizations benefits the industry by helping spread the companies' messaging to larger groups of potential patients, strengthening their brand images and, ultimately, improving their chances of governmental drug approval.[16] Surveys of these patient advocacy organizations suggest that the degree of financial conflict is even greater than that observed at FDA meetings, with a majority of these powerful organizations receiving contributions from industry often valued in the millions of dollars and over one-third of them having an industry executive on their governing board.[17] In one recent survey, 7.7 percent of these organizations admitted to feeling pressure to conform their positions to those of their industry donors.[18]

These findings are not a new problem. Concerns over "disease mongering" and "astro turfing," whereby a pharmaceutical company uses patient advocacy organizations to disguise an advertising campaign as a spontaneous upwelling of public action or to broaden the scope of an illness to capture more potential patients, have persisted for over fifteen years.[19] The campaigns for the recently approved flibanserin[20] and eteplirsen[21] provide evidence of how pharmaceutical companies are continuing to leverage patients, families, and advocacy groups to gain approvals for new therapies with marginal, if any, real benefits.

With the most recent data available from different iterations of ODAC over roughly the last decade, we are coming to a fuller realization of the extent and scope of pharmaceutical investment in the drug approval process. The industry often funds patient advocacy groups, which spur public interest. The industry sponsors the drug trials, and pharmaceutical companies often have financial ties with key participants at advisory meetings that determine which drugs should be approved by the FDA. Even among public speakers, a large percentage self-report financial ties to the companies seeking approvals for their products.

These financial conflicts raise concerns over whether the discussion at other drug advisory committee meetings is always and only focused on the public interest or whether it may instead aim to expedite novel products to market even if they offer unfavorable risk-benefit profiles.

How Can the Situation Be Remedied?

We believe that three simple steps could do a lot to reorient the focus of drug advisory meetings. First, voting members should have no financial ties to the pharmaceutical company that is seeking approval at a meeting, and FDA policy should be changed to require that past financial ties be fully disclosed. Second, the public speaker portion of a meeting, which is dominated by participants with financial conflicts of interest, should no longer serve as the sole forum where voting members hear from patients. To provide representative patient testimony, video diaries could be collected in pivotal clinical trials and random selections played for the voting committee. This testimony could supplement the comments of the public, which are skewed toward positive statements.

Beyond hearing from clinical trial participants, policymakers should learn about the perspectives of diverse patients regarding their preferences for drug approval. Patients' opinions fall on a spectrum. Some patients desire more treatment options, even if those come with unclear adverse effects and uncertainty regarding efficacy, while others desire more information and certainty regarding approved drugs. The current narrative around drug approval disproportionately centers on patients who seek access to these agents—evidenced by the survey of public speakers showing that 92 percent favor approval—but many patients who desire greater knowledge and clinical trial data about new drugs may not be inclined to participate in advocacy groups or to travel to attend FDA functions. A broad, representative population-based survey of patients' desires, with a focus on rural or underserved areas, may provide a better foundation for patient-centered policymaking than the current system of engaging with the self-selected patients who choose to seek out national forums.

Third, former employees of the FDA should be required to have a cooling-off period—a period after departing from the FDA when they cannot work for the pharmaceutical industry. Former FDA commissioner Margaret Hamburg has suggested that such a period may be helpful, and she has placed such a restriction on herself.[22]

Collaboration between experienced physicians and pharmaceutical companies is essential for successful medical

innovation, but financial influence should be minimized when weighing the risks and benefits of drug approval. We applaud the FDA for the steps it has taken to limit financial conflicts of interest among voting committee members, but we believe that the evidence provided above shows ongoing and widespread conflict of interest at FDA advisory committee meetings. We call on policy-makers to consider the changes or alternatives proposed here to limit the effect of such conflicts of interest among all participants of drug advisory committee meetings.

1. A. S. Ciociola et al., "The Food and Drug Administration Advisory Committees and Panels: How They Are Applied to the Drug Regulatory Process," *American Journal of Gastroenterology* 109, no. 10 (2014): 1508-12.

2. P. Lurie et al., "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings," *Journal of American Medical Association* 295, no. 16 (2006): 1921-28.

3. A. Tibau et al. "Oncologic Drugs Advisory Committee Recommendations and Approval of Cancer Drugs by the US Food and Drug Administration," *Journal of American Medical Association Oncology* 2, no. 6 (2016): 744-50.

4. J. Xu et al., "Association of Appearance of Conflicts of Interest with Voting Behavior at FDA Advisory Committee Meetings: A Cross-sectional Study," *Journal of American Medical Association Internal Medicine* 177, no. 7 (2017): 1038-40.

5. A. Lammers et al., "Financial Conflict of Interest and Academic Influence among Expert Speakers on Behalf of the Pharmaceutical Industry at the U.S. Food and Drug Administration's Oncologic Drugs Advisory Committee Meetings," *Mayo Clinical Proceedings* 92, no. 7 (2017): 1164-66.

6. S. S. Graham et al., "Conflicts of Interest among Patient and Consumer Representatives to U.S. Food and Drug Administration Drug Advisory Committees," *Annals of Internal Medicine* 165, no. 8 (2016): 606-7.

7. P. Lurie et al., "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings," *Journal of American Medical Association* 295, no. 16 (2006): 1921-28.

8. M. V. Abola and V. Prasad, "Characteristics and Conflicts of Public Speakers at Meetings of the Oncologic Drugs Advisory Committee to the US Food and Drug Administration," *Journal of American Medical Association Internal Medicine* 176, no. 3 (2016): 389-91.

9. J. Bien and V. Prasad, "Future Jobs of FDA's Haematology-Oncology Reviewers," 354 *BMJ* (2016): i5055.

10. R. Steinbrook, "Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees," *New England Journal of Medicine* 353, no. 2 (2005): 116-18.

11. Lurie et al., "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings"; Tibau et al. "Oncologic Drugs Advisory Committee Recommendations and Approval of Cancer Drugs by the US Food and Drug Administration."

12. G. Pham-Kanter, "Revisiting Financial Conflicts of Interest in FDA Advisory Committees," *Milbank Quarterly* 92, no. 3 (2014): 446-70.

13. A. Lundh et al., "Industry Sponsorship and Research Outcome," *Cochrane Database of Systematic Reviews* 12 (2012): Mr000033; P. M. Ridker and J. Torres, "Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-For-Profit Organizations: 2000-2005," *Journal of American Medical Association* 295, no. 19 (2006): 2270-74; S. Sismondo, "Pharmaceutical Company Funding and Its Consequences: A Qualitative Systematic Review," *Contemporary Clinical Trials* 29, no. 2 (2008): 109-1.

14. A. Fugh-Berman et al., "Promotional Tone in Reviews of Menopausal Hormone Therapy after the Women's Health Initiative: An Analysis of Published Articles," *PLoS Medicine* 8, no. 3 (2011): e1000425; A. T. Wang et al, "Association between Industry Affiliation and Position on Cardiovascular Risk with Rosiglitazone: Cross Sectional Systematic Review," *BMJ* 340 (2010): c1344.

15. J. S. Hickman et al., "An Observational Study of the Safety Benefits of Electronic Logging Devices Using Carrier-Collected Data," *Traffic Injury Prevention* 18, no. 3 (2017): 312-17; W. Fleischman et al., "Association between Payments from Manufacturers of Pharmaceuticals to Physicians and Regional Prescribing: Cross Sectional Ecological Study," *BMJ* 354 (2016): i4189; C. Ornstein, M. Tigas, and R. G. Jones, "Now There's Proof: Docs Who Get Company Cash Tend to Prescribe More Brand-Name Meds," ProPublica, March 17, 2016, https://www.propublica.org/article/doctors-who-take-company-cash-tend-to-prescribe-more-brand-name-drugs.

16. B. Burton, "Drug Companies Told That Sponsoring Patients' Groups Might Help Win Approval for Their Products," *BMJ* 331, no. 7529 (2005): 1359; F. Buttle and J. Boldrini, "Customer Relationship Management in the Pharmaceutical Industry: The Role of the Patient Advocacy Group," *Journal of Medical Marketing* 1, no. 3 (2001): 203-14.

17. M. S. McCoy et al., "Conflicts of Interest for Patient-Advocacy Organizations," *New England Journal of Medicine* 376, no. 9 (2017): 880-85.

18. S. L. Rose et al., "Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest," *Journal of American Medical Association Internal Medicine* 177, no. 3 (2017): 344-50.

19. R. Moynihan, I. Heath, and D. Henry, "Selling Sickness: The Pharmaceutical Industry and Disease Mongering," *BMJ* 324, no. 7342 (2002): 886-891; D. C. Marshall et al., "Distribution and Patterns of Industry-Related Payments to Oncologists in 2014," *Journal of the National Cancer Institute* 108, no. 12 (2016), doi: 10.1093/jnci/djw163.

20. J. Z. Segal, "The Rhetoric of Female Sexual Dysfunction: Faux Feminism and the FDA," *Canadian Medical Association Journal* 187, no. 12 (2015): 915-16.

21. S. Pulliam and B. Mullins, "How the FDA Approved a $300,000-a-Year Drug Its Own Experts Didn't Believe Worked," *Wall Street Journal*, May 18, 2017.

22. R. Berke and S. Kaplan, "Former FDA Chief Margaret Hamburg Speaks Out about Califf, Cruz, and Congress," *STAT*, March 16, 2016.