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Conflicts of Interest in Medicine
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Thank you for the opportunity to address the Medwatcher Conference. I am honoured to be here.

My talk will first describe the varieties of conflict of interest. Among these, I will examine four, focusing on Public Citizen's own activities: those in research, clinical practice, medical education and public advisory committees. Then I will discuss the differences between financial and intellectual conflicts of interest. After that, I will present a framework for developing approaches to conflict of interest, which I will apply to each of the types of conflicts of interest I've previously described. Finally, I will offer some conclusions.

I. Varieties of conflict of interest

a. Research

Conflicts of interest in medical research are very common. A recent survey (response rate: 88%) asked research administrators at each U.S. medical school whether they found certain contractual arrangements acceptable. Sixty-two percent each thought keeping the terms of the contract and allowing the sponsor to alter the study design was acceptable. Twenty-four percent would allow sponsors to include their own statistical analyses, 50% would allow the sponsor to write the first draft of the resultant publication and 80% would allow sponsors to own the data. Only 1% would allow the sponsor to prevent publication.[1]

We have identified many examples of biased data reporting in published medical journal articles, of which I shall name but two. An article on alosetron (Lotronex), a now-discredited drug for irritable bowel syndrome, used a variety of graphic techniques including emphasis on relative (vs. absolute) changes in the outcome and failure to show the full x- and y-axes to exaggerate drug efficacy.[2] In another, the dangers of salmeterol (Advair) were diluted by including additional data from an informal follow-up period (a violation of the original protocol).[3]

Relying on disclosure as the cure-all for conflicts of interest is particularly problematic when non-disclosure is common. In a recent meta-analysis of statin clinical trials,

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[1] Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical-trial agreements with industry. N*ew England Journal of Medicine 2005;352:2160-2.*

[2] Barbehenn E, Lurie P, Wolfe SM. Alosetron for irritable bowel syndrome (letter). *Lancet.* 2000;356:2009-10.

[3] Lurie P, Wolfe SM. Misleading data analyses in salmeterol (SMART) study (letter). *Lancet* 2005;366:1261-2.

published between 1999 and 2005, 37 percent had no conflict-of-interest disclosures.[4] In another striking example, an article in *Neuropsychopharmacology* reviewing the vagus nerve stimulation device had nine authors, one of whom worked for the manufacturer. The remaining authors disclosed no conflicts of interest, even though all were consultants to the company. The first author was actually the editor of the journal, and so he was in an especially good position to know that its policies required disclosure of such conflicts; he was forced to resign.[5]

Disclosure as an approach to conflict of interest does have a role to play and can be effective in certain circumstances. In a controlled trial, members of the British Medical Association were sent the identical paper to review, but were randomized to receive or not receive conflict-of-interest declarations.[6] Those who received the declarations rated the paper statistically significantly lower with respect to Importance, Relevance, Validity and Believability than those not receiving the declarations.

b. Clinical practice

Conflicts of interest involving physicians in practice are also common. A survey of U.S. physicians[7] (weighted response rate: 58%) showed the following prevalences of interactions with the pharmaceutical industry in the previous year: samples (78%), food (83%), tickets to cultural or sporting events (7%), meetings (35%), consulting agreements (18%) and public speaking (16%). The prevalence of any interactions was 94%.

The American College of Physicians suggests the following as one of the criteria for deciding whether to accept a gift from the pharmaceutical industry: "What would my patients think about this arrangement? What would the public think? How would I feel if the relationship was disclosed through the media?"[8] Making such payments public is a way of putting this question to the test.

We conducted a study of disclosures of payments by pharmaceutical companies to physicians in Vermont and Minnesota, the first states to make such disclosures public.[9]

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[4] Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug-drug comparisons: why some statins appear more efficacious than others. *PloS Medicine* 2007'4:e184.

[5] Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology, 2006;31:1345-55.

[6] Schroter S, Morris J, Chaudhry S, Smith R, Barratt H. Does the type of competing interest statement affect readers' perceptions of the credibility of research? Randomised trial. *British Medical Journal*. 2004;328:742-743.

[7] Campbell EG, Gruen RL, Mountford J, Miller LG, Cleary PD, Blumenthal D. A national survey of physician-industry relationships. *New England Journal of Medicine* 2007;356:1742-50.

[8] Coyle SL; Ethics and Human Rights Committee, American College of Physicians-American Society of Internal Medicine. Physician-industry relations. Part 1: individual physicians. *Annals of Internal Medicine* 2002;136:396-402.

[9] Ross J, Lackner J, Lurie P, Gross C, Wolfe SM, Krumholz H. Pharmaceutical company payments to physicians: early experiences with disclosure laws in Vermont and Minnesota. *Journal of the American Medical Association.* 2007;297:1216-23.

Although there is significant underreporting, large volumes of gifts were disclosed: $1.01 million in Vermont over two years and $22.4 million in Minnesota over three years. By numbers of payments, the predominant category was education, although by dollar value it was for speakers.

There remain significant deficiencies in the reporting processes in these two states. As noted, there are high rates of underreporting, with companies that report millions of dollars one year, yet nothing the next. The submissions are nonstandardized with much aggregation by both physician and gift, limiting the ability to analyze the data adequately. Exemptions to the reporting requirements are common (e.g., samples and research studies) and public access is limited. In Vermont, we had to file a lawsuit to get access to the data and a personal trip to Minneapolis was necessary to obtain the Minnesota data.

c. Education

We used data published in the industry magazine Medical Marketing and Media that described companies known as Medical Education and Services Suppliers (MESSs).[10] The magazine identified 123 MESSs of whom 80 (65 percent) responded to the survey; only 42 of these (53 percent of respondents or 34 percent of known MESSs) provided financial data. Nonetheless, these companies reported $643 million in revenue in 1999, including $115 million for organizing grand rounds, $114 million for medical symposia and $60 million in publications-related activities. Seventy-six percent of the MESSs' clients were drug companies. These data emphasize the degree to which medical education and continuing medical education activities can be driven by corporate interests.

d. Public advisory committees

In this example, I'd like to emphasize the way we conceptualized conflict of interest and the analytic tools we applied to the problem. We tried to go beyond simply describing the prevalence of conflicts of interest, which is what most of the research in this area does, to investigate the relationship between the conflict and actual behavior.

In 1997, the Food and Drug Administration Modernization Act required more extensive public disclosure of conflicts of interest by Food and Drug Administration (FDA) advisory committee members. In September 2001, we realized that the FDA had not complied with the law and threatened the FDA with a lawsuit. As a consequence, in January 2002, the FDA issued a draft guidance that required more detailed disclosures. In March 2007, the FDA made available a new draft guidance that takes an approach that goes beyond mere disclosure. It recuses (dismisses for the meeting with the conflict) members with total conflicts that exceed $50,000, and members with conflicts below

[10] Ross J, Lurie P, Wolfe SM. Medical Education Services Suppliers: A Threat to Physician Education. Public Citizen's Health Research Group, July 19, 2000. Available at: http://www.citizen.org/publications/release.cfm?ID=7142.

$50,000 can attend but not vote. In the Autumn of 2007, Congress passed a bill that requires a 5 percent annual reduction in the prevalence of conflicts of interest in the advisory committees.

This brief history sheds light on the frequently heard claim that it is impossible to find adequate numbers of unconflicted experts to serve on advisory panels (or to act as journal reviewers). Every time the FDA reconsidered its policy, this argument was raised and yet the policy has become successively stronger, in effect negating the argument when it was previously raised. As a Lancet editorial stated, "Defenders of FDA policy say that it is difficult to find experts free of conflicts of interest. But it is hard to believe that in a country with 125 medical schools—not to mention the pool of international experts—the FDA cannot find experts who do not have financial ties with companies whose products are under review."[11]

The study[12] I am going to describe was conducted between the time of the two FDA draft guidances. It examined the disclosed conflict rate at FDA drug advisory committee meetings between 2001 and 2004. The study showed that conflicts were common: at least one person had a conflict in 73 percent of meetings and, overall, 28 percent of members had a conflict. Importantly, there was no difference in the rate of disclosure of conflicts before and after the 2002 draft guidance, so the enhanced disclosure requirement had no apparent impact upon conflict rates, merely upon the detail in which these conflicts were disclosed. The recusal rate was only 1 percent, so many members served and voted despite large conflicts.

In this study we also tried to assess the link between the predictor variable (the financial conflict of interest) and a concrete outcome (in this case, the votes of advisory committee members). We looked at this question in six different ways, divided into two categories. The last two analyses, the Mantel-Haenszel and the Monte Carlo, looked at this relationship from the perspective of the individual. The underlying premise is that a particular individual, having received funding from industry, might go on to vote in some particular way as a consequence. The analyses of "index conflict" (those with the company producing the drug under discussion at the meeting) were limited by small sample sizes. In the Mantel-Haenszel analysis, we did find positive relationships between voting in favor of the drug and having "any conflict" (with the index drug's manufacturer or a competitor) and, somewhat paradoxically, with competitor conflict. The Monte Carlo simulation found a relationship only with "competitor conflict."

The first four analyses took a different approach: instead of looking at the individual perspective, they consider a group-level perspective. In other words, "Did the conflicts have an impact upon the overall voting behavior of the committee?" In the first

[11] Anon. No place for conflict of interest. *The Lancet*. 2005;365:1664.

[12] Lurie P, Almeida C, Stine N, Stine A, Wolfe SM. Financial conflict of interest disclosure and voting patterns at Food and Drug Administration drug advisory committee meetings. *Journal of the American Medical Association.* 2006;295:1921-8.

("continuous outcome"), we asked whether there was a relationship between the fraction of people voting in favor of the index drug and the fraction of people who had conflicts of the three kinds. In the second ("dichotomous outcome"), we tried to address the possibility that voting behavior is nonlinear – when members of a committee come to realize that there is a growing consensus in favor of one particular point of view, they start to drift towards that point of view. In this scenario, voting behavior would be most likely to be influenced by a conflict when the vote was close to 50-50, so we used a dichotomous outcome variable – whether the vote was in favor/against the index drug. (In fact, many advisory committees are unanimous, or close to unanimous, usually in favor of drug approval.) None of these analyses yielded a statistically significant finding.

We then looked at whether or not excluding advisory committee members with the various conflicts would have led to a less favorable vote for the drug being considered. In each case, we found that it did: in 64 percent of meetings for index conflict, 77 percent of meetings for competitor conflict and 72 percent of meetings for any conflict, the vote became less favorable toward the drug. Finally, we looked at whether or not excluding people with conflicts of interest would have changed the overall vote outcome of the meeting. Regardless of the conflict type, we found no such meeting.

I would like to point out, however, that there has been at least one example where exclusions would have affected the vote outcome.[13],[14] At the Cox-2 inhibitor advisory committee meeting, which occurred in 2005 and was therefore outside the data frame for our study, the committee examined Vioxx, which had already been taken off the market, and the other two Cox-2s, Celebrex and Bextra, and voted in favor of all three drugs. However, of the members who had consulted with industry, 93 percent voted in favor of the drugs in the various votes, whereas only 56 percent of non-consultants did so. Had those conflicted members been excluded, Vioxx would not have been recommended for a return to the market (the FDA didn't allow it to return anyway) and Bextra would not have been recommended for continued marketing (it was later removed from the market despite the advisory committee vote).

II. Financial vs. intellectual conflicts of interest

Frequently, one hears that there are both financial and intellectual conflicts of interest; somehow this argument is offered as evidence to downplay the importance of the financial conflicts. While intellectual conflicts are important, they can readily be distinguished from financial ones. Financial conflicts of interest are extrinsic to the scientific endeavor, whereas intellectual conflict is the very way science moves forward. Financial conflicts can occur at variable levels – some people have them, some people don't – and they can be quantified, whereas intellectual conflicts are ubiquitous and not susceptible to quantification in the same way. Moreover, in the context of debate on an

[13] Harris G, Berenson A. 10 voters on panel backing pain pills had industry ties. *The New York Times*. Feb. 25, 2005.

[14] Steinbrook R. Financial conflicts of interest and the Food and Drug Administration's advisory committees. *The New England Journal of Medicine*. 2005; 353:2.

advisory committee, for example, it is unlikely that the financial conflict information will naturally emerge, whereas it is likely that any relevant intellectual one will. There are relatively straight-forward methods to alleviate financial conflicts, whereas it's not nearly as clear how one should approach intellectual conflicts. Finally, our legal system has long recognized the distinctions between the two.

III. Framework for addressing conflict of interest

The framework begins with the potential conflict. One has three general options to address this: legal restrictions, policy restrictions or disclosure. An alternative, somewhat overlapping, formulation of this framework might be ban, manage or disclose conflicts of interest.

The advantage of legal restrictions is that they tend to be straightforward and can be very effective in that they can eliminate the conflict of interest entirely. In some circumstances, they will be particularly cost-effective. However, the modern trend in conflict of interest seems to lean heavily toward disclosure as a remedy, sometimes the only remedy. While disclosure certainly has its place (and may be the only option in some instances), if used exclusively it can amount to an evasion of responsibility. In effect, disclosure transfers responsibility to the consumer of the information, who is then expected to understand what it means for an author, committee member or clinician to have an equity interest of $50,000 in some pharmaceutical company.

Thus, the question is: What is the correct mixture of the three remedies in particular circumstances?

I will now revisit each of the four categories I have described to show how we have approached each issue.

Turning to research payment to physicians, I would agree that legal restrictions in this area are probably not desirable and they're certainly not feasible. A policy restriction, dating back to the late 1970s when it was proposed by U.S. Senator Gaylord Nelson, is to take all the money that would go toward research, put it in a single fund, and then establish a group of researchers whose job it is to conduct, analyze and report results in a completely unbiased fashion. Politically, this idea does not seem to have much traction at the present time. Instead what we have is disclosure by some journals, some of the time, and at some scientific presentations, some of the time.

Next, I consider non-research payments to physicians. (The same general issues apply to MESSs, so these are not discussed separately.) Here legal restrictions have limited political feasibility, although I will point out that in Minnesota there actually is a ban on any gift to physicians exceeding $50. In the policy arena, we are starting to see a small number of universities and health care systems that are putting various policy restrictions in place, such as banning samples or restricting pharmaceutical company representative access to clinics. In the disclosure category, there are now bills in the U.S. House and

Senate that would create a national database of pharmaceutical company payments to physicians.

Regarding FDA advisory committees, it is notable that the approach has evolved from disclosure to regulation to legislation as discomfort rose over the preceding approach. Thus, the FDA initially had a disclosure policy as the cornerstone of its approach, but there were very few recusals from the meetings. The quality of these disclosures was improved by regulation. Subsequently, an additional guidance was adopted that should result in considerably more recusals. But now the Congress has stepped in and required incremental annual decreases in the conflict levels.

In sum, the particular mix of approaches that one adopts is highly dependent on the particular conflict-of-interest problem one is addressing.

IV. Conclusions

- There is limited research actually linking the conflicts with the outcomes of interest; this committee could play a helpful role in delineating how future research should be conducted
- Financial conflicts are of particular concern and merit specific attention; the existence of intellectual conflicts of interest should not be used to distract from the more-remediable problem of financial conflicts
- In general, committees/reviewers with low or no conflicts can be assembled if sufficient effort is made
- Disclosure is no substitute for prevention of conflicts when this is feasible and legal