

**STATEMENT OF SIDNEY M. WOLFE, M.D.  
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BEFORE FDA SCIENCE BOARD HEARING ON  
CLINICAL INVESTIGATOR CONFLICT OF INTEREST  
SEPTEMBER 9, 1993**

**Introduction**

Twenty-one years ago, at a Senate hearing in July, 1972, I expressed serious concerns about the unaddressed problem of financial conflict of interest of clinical investigators. The incident which precipitated this was the clinical investigation of a soft contact lens, the Griffen lens, manufactured by Frigitonics. Because the company was too poor to offer clinical investigators cash, stock and/or stock options were given to investigators. These investigators, including members of the faculty of the University of Florida School of Medicine, were among the most optimistic about the potential of the lens and the stock rose in response to their optimism and the positive results of their clinical trials. Because most were already charging patients for the new lenses, they were already getting compensation for their labor.

I stated then that, "Not only is the investigator rewarded in the present [by the patient] but, much more insidiously, he is wedded to the future success of the company. How, under these circumstances, can objective scientific inquiry flourish?"

"The possible relationship between testing for safety and efficacy and conflict of interest must be examined in detail in the case of the "soft" lens. Why are practitioners now (compensated only by the patient, rather than by the patient and company, as before), reporting what appears to be a larger number and greater variety of adverse reactions than did their doubly-compensated counterparts during the pre-marketing investigational stage? "

In conclusion, I stated in the 1972 testimony that, "As long as investigators of the "Soft" lens or other new drugs continue to labor under the weight of conflict of interest, as long as the manufacturers, medical schools and the FDA continue to condone such practices, and as long as the FDA...allows drugs on the market without adequate pre-marketing tests, the American public will be the victims."

This was an example of apparent conflict-of-interest which seemed to have actually resulted in questionably reliable clinical investigations and there are surely more of this kind, the evidence for which has been buried. But, as recently stated in the AAMC (Association of American Medical Colleges) Guidelines on Conflict of Research, February 22, 1990, "The mere appearance of a conflict may be just as serious and potentially damaging as an actual

distortion of objectivity. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts."

But 20 years after the incident with the soft lens, HHS Inspector General Richard Kusserow wrote to HHS Assistant Secretary for Health, Dr. James Mason (June 26, 1991),

"To alert you to a serious programmatic deficiency relating to the financial relationships between clinical investigators and sponsors of research leading to FDA marketing approval of products."

"Recent investigation into a Medicare provider kickback scheme revealed that a firm made investment proposals to approximately 125 physicians, of which at least 100 were serving as clinical investigators to the firm in studies of new medical device designs. The conflict of interest created in this situation could potentially compromise the investigators' objectivity since FDA approval of the product could mean huge profits for the firm and its investors."

"There are no regulations to prevent conflict of interest situations created when investigators invest in firms which have selected them to participate in studies of products which the sponsor hopes to market."

In an April, 1993 letter from the Pharmaceutical Manufacturers' Association to the FDA, it was clear, based on a survey of PMA member companies, that the drug, device and biotech manufacturers were extraordinarily insensitive to the problem of conflict of interest. Among the findings (followed by our comments in parentheses) were:

1. "[N]one of the companies responding require financial disclosure by the investigator to the sponsor." (So, if the investigator owns a large chunk of company stock, the sponsor does not know about it.)

2. The majority conceded that if a study is not blinded and the investigator has an equity position related to study outcome, "[b]ias might be a possibility."

3. "The majority of respondents felt FDA should not require information on the financial interests of clinical investigators... the responsibility for both valid data and financial integrity was between the sponsor and the investigator, not the FDA and the investigator." (In light of #1, this is curious, because if none of the companies require financial disclosure by the investigator to the sponsor, how will this financial integrity be monitored?)

4. "The majority of respondents felt that there were no financial interests unacceptable for a clinical investigator because they created too great a bias potential, particularly if they were declared up front." (They don't say to whom.)

5. "The general tone of the responses was that FDA should limit its concerns to the quality of the data. FDA should not focus on financial arrangements between sponsor and investigator." (The quality of the data submitted tells very little. It is nearly impossible to perceive subtle bias in data submitted. Financial incentives may subtly affect the way the study is conducted, analyzed or reported.)

A similar amount of indifference to the problems of financial conflict was shown by the device trade association, HIMA (Health Industry Manufacturing Association) in a June, 1993 letter to FDA:

1. "[T]hat all financial arrangements between the sponsor of a clinical investigation and the clinical investigator involved in that investigation be fully disclosed to FDA."

2. "HIMA considers all legal business practices (including, but not limited to, fee-for-service compensation, stocks, royalties, ownership or part-ownership in a company) to be acceptable financial arrangements for clinical investigators, with the proviso that no payments should be in any way linked to obtaining a particular result (i.e. payment correlated with success or failure in demonstrating safety or effectiveness)."

3. "[T]hat financial disclosure should not include the actual value of such financial arrangements to the investigator."

#### **Recent Example of a More Rational Approach**

We have received the Conflict of Interest Guidelines for a multi-center trial of a Merck drug based at UCSF Medical Center (see attached), involving clinical studies at 16 different sites including the University of California, San Francisco, U.C. San Diego, the University of North Carolina, Johns Hopkins, the aforementioned University of Florida and other institutions. These guidelines, limited to clinical investigators not employed by Merck state that, "No FIT [Fracture Intervention Trial] investigators or their immediate families shall have any financial interest in Merck [the company sponsoring the clinical trials], including stock and stock options." The guidelines also require disclosure of grants, honoraria, and remuneration for consultation from Merck, to the trial Executive Committee; in advance if the amount exceeds \$1000.

There is no reason why this important issue should be left to being done only on a voluntary basis and we therefore advocate, as in the responses to the questions below, that no clinical investigation done to support FDA approval of any product be

allowed if the investigator has any such financial conflict of interest. We do have two disagreements with this proposal, however. First, there does not seem to be any limit on grants, honoraria or consultations with the company. There has to be a very, very low limit on these or they can have the same biasing effect as stock ownership. Second, there is a serious question about whether clinical trials being done by employees of companies manufacturing drugs, devices or other FDA-regulated products should be allowed.

### **Responses to Questions Asked of Presenters**

FDA is considering publication of a Notice of Proposed Rulemaking that will:

1. propose that sponsors certify that

a) they have not entered into financial arrangements in which the compensation received by the clinical investigator might be influenced by the outcome of the research. **We agree.**

b) no clinical investigator has any direct financial interest in the product being tested, such as a patent. **We agree.**

c) no clinical investigator's equity interest in the sponsoring company is more than 5 percent of total equity. **We disagree. There should be no equity interest allowed in the company. In addition, "[o]nce the investigator becomes involved in a research project for a company or knows that he or she might become involved in the research, he or she, as an individual, cannot ethically buy or sell the company's stock until the involvement ends and the results of the research are published or otherwise disseminated to the public."<sup>1</sup>**

2. in the absence of such certification, seek disclosure from the sponsor of the specific financial arrangements or interests involved and the steps that have been taken to minimize the potential for bias. **There should be no "absence of such certification," and this language should be stricken from any proposed rule. Any sponsor who can not certify to a), b), and c) above should be banned from participation in the clinical trial. In addition to the above, all sponsors should be required to disclose to the FDA the specific financial arrangements or interests between them and investigators and their immediate families (parents, children, spouses), whether they be in the form of royalties, honoraria, consultation fees, retainer agreements or other financial arrangements.**

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<sup>1</sup> Council on Scientific Affairs, Council on Ethical and Judicial Affairs. Conflicts of interest in medical center/industry research relationships. JAMA 1990;263:2790-93.

## Response to Questions Asked of the Science Board

1. Do financial interests of a clinical investigator in the product under study or the product sponsor have the potential to bias the outcome of studies undertaken by the sponsor? **YES.** Investigators should not gain financially from companies whose products they are evaluating. For FDA not to have a policy in this area is to invite investigator bias. "Financial interests may compromise the objectivity of researchers and cause them to downplay or suppress negative data while exaggerating favorable data .... Economic incentives may introduce subtle biases into the way research is conducted, analyzed, or reported, and these biases can escape detection by even careful peer review."<sup>2</sup> "The issue is not primarily one of honesty, but of unconscious bias, which may be subtle and difficult to detect."<sup>3</sup>

The basic purposes of conflict of interest rules are to maintain the objectivity of professional judgment and to maintain confidence in professional judgment.<sup>4</sup> In many areas of life, restrictions on conflicts of interest are the norm. For example, judges are expected to excuse themselves from cases involving companies in which they have an interest, not only to eliminate bias, but to eliminate the appearance of bias or partiality. The growing role of governments in regulating physician conflicts of interest, such as physician self-referrals to labs in which they have a financial interest, is in part a response to the failure of physicians and scholars to deal adequately with the problem.<sup>5</sup>

Is the potential for bias in this area sufficiently serious to warrant requiring disclosure of these interests to FDA in some or all cases? **YES.** Disclosure is warranted, in addition to certification. "Disclosure is, to be sure, necessary but [disclosure] does not mitigate the risks - it only announces that the risk is present."<sup>6</sup> "Perhaps the best mechanism available to assuage public and professional doubts about the propriety of a research arrangement is full disclosure."<sup>7</sup> Clinical researchers should therefore disclose all financial arrangements as well as any

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<sup>2</sup> *ibid.*

<sup>3</sup> Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. *N Engl J Med* 1993;329:570-1.

<sup>4</sup> Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993;329:573-6.

<sup>5</sup> Conflicts of interest, note 1.

<sup>6</sup> *ibid.*

<sup>7</sup> *ibid.*

ancillary ties to companies whose products they are investigating, such as educational activities supported by the companies, participation in other research projects funded by the companies, and consulting arrangements. Disclosure should be to the FDA, to the medical center where research is conducted, to organizations that are funding the research and to journals that publish.

Furthermore, financial disclosures ought to be made to FDA early in the review process, at the time of the IND or IDE application. We believe that there is enough risk to subjects and data integrity during the early stages that financial disclosure ought to be made at that time.

Investigators ought to have to disclose information about themselves and family members, such as parents, children and spouses.

2. Do certain types of financial interests pose a greater potential for bias (e.g., equity interests or other forms of compensation where the value of interest/compensation may be influenced by the outcome of the study)? **YES.** "Researchers who might benefit financially by distorting their work have a conflict of interest regardless of whether they actually distort their work....The circumstances determine whether there is a conflict of interest, not the outcome." <sup>8</sup> Associations with business which could affect outcome include direct employment and consultancy, stock ownership, and patent-licensing agreements.<sup>9</sup>

3. Apart from outcome-dependent interests, are there interests that should be of special concern to FDA (e.g., large retainer or consulting fees)? **YES** Of these, can a financial threshold be identified below which FDA may reasonably assume that such financial interests are unlikely to have influenced the outcome of the study? **It would be very difficult to set a safe threshold.**

4. If FDA were to require disclosure of specified financial interests held by investigators, what steps should FDA take to minimize the potential for bias resulting from such studies? Disclosure alone is not enough. **Researchers with outcome-dependent interests should be banned from taking part in studies. Any other payment by the company, if allowed at all, should be commensurate with actual efforts expended on behalf of the company, and should be disclosed to FDA.** FDA is already operating under an enormous statutory mandate and should not be responsible for minimizing the potential for bias resulting from financial interests.

a. Are there forms of compensation or financial interests that

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<sup>8</sup> Kassirer, note 3.

<sup>9</sup> *ibid.*

create a significant enough risk of biasing a study to cause FDA not to rely on the study? **YES.** When the sponsor and the investigator are the same person, or are closely related (business partners), as is the case with many start-up device and drug companies.

What could be the effects of such a determination on the development of drugs, biotech products and medical devices? **It may delay the approval of some drugs and devices, because the companies will be forced to repeat the studies.**

b. Are there methods of minimizing bias, e.g., blinding, independent assessments of study endpoints, participation of multiple investigators (most of whom have no financial interest) that are or could in some cases, be adequate to protect against the potential for biases created by an investigator's financial interests? Should utilization of such methods be required (or shown not to be needed) whenever an investigator holds an interest in the product or the sponsor? **NO.** FDA should not get involved in determining whether or not various methods employed by companies are adequate to sufficiently eliminate bias, or even whether such methods are needed. Rather, there should be a ban on such arrangements, and a disclosure requirement. "[I]t is safer and therefore ethically more responsible to decide in advance to remove insofar as possible factors that tend to distract [researchers] from concentrating on medical and scholarly goals."<sup>10</sup>

c. If FDA were to require disclosure of specified financial interests, should the FDA disclose these financial interests to the public? If so, what is the appropriate forum to release this information publicly? **Public disclosure of this information in some useful form is critical.** The FDA cannot always do its job alone. It is imperative that the public be able to play some policing function in this area. Our organization, and others, often examine data submitted to the FDA and bring problems to the public's and agency's attention. Public disclosure is a positive good in itself, and it has a way of preventing substantive abuses in the first place.

5. Should the clinical investigator's financial interests in the product under study or in the product's sponsor be disclosed during the informed consent process? **NO, but only if the investigator has:**

1. met the certification requirement, i.e., that a) any compensation received for the study is not outcome-dependant, b) he has no direct financial interest in the product being tested and c) he holds no equity interest in the company.

2. disclosed all other financial arrangements to the FDA.

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<sup>10</sup> Thompson, note 4.

**Conflict of Interest Guidelines for Investigators and Members of the Data and Safety Monitoring Board: Fracture Intervention Trial**

The following guidelines apply to investigators in the FIT trial, defined as any person receiving support from FIT who may participate as an author or co-author on any form of publication about FIT. These guidelines do not apply to full-time employees of Merck who may participate as authors or co-authors on FIT publications.

Financial interest in Merck

No FIT investigators or their immediate families shall have any financial interest in Merck, including stock and stock options. However, mutual funds and blind trusts that include Merck are not considered a conflict of interest.

Consultations, grants, and honoraria

FIT investigators may accept grants, contracts, honoraria, and remuneration for consultation from Merck. However, it is the responsibility of all FIT investigators to report all such activity to the FIT Executive Committee, including a description of the aims of studies, services provided, and amounts to be paid by Merck for these activities. Investigators and DSMB members are requested to notify the Executive Committee in advance before accepting honoraria and personal remuneration from Merck exceeding \$1000.

**Reporting Form**

FIT Investigator: \_\_\_\_\_

Report for the period January 1, 1993 through December 31, 1993:

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