April 29, 1996

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Dr., rm 1-23
Rockville, MD 20857

RE:Financial Disclosure by Clinical Investigators: Reopening of Comment Period; Docket No. 93N-0445

I. Background

On behalf of Public Citizen's Health Research Group, we offer the following comments on the Food and Drug Administration's ("FDA") proposed rule on financial disclosure by clinical investigators. These comments supplement our earlier comments of January 4, 1995 on this same issue.

In the *Federal Register* of September 22, 1994, the FDA proposed regulations to require that the sponsor of any drug, biological product, or device submit certain information concerning the compensation to, and financial interests of any clinical investigator conducting clinical studies to determine whether that product meets the marketing requirements specified by the agency.

In the *Federal Register* of March 5, 1996, the FDA reopened the comment period concerning the proposed rule to obtain additional comments on particular aspects of the rule. In addition, the Science Board to the FDA, an FDA advisory committee, held an open committee meeting on March 29, 1996, to discuss the proposed rulemaking.

Public Citizen's Health Research Group submitted comments on the Proposed Rule during the original comment period, supporting the concept of financial disclosure, but adding that disclosure alone is not enough to reduce the risk of bias in clinical research. We urged that researchers with any outcome-dependent interest be banned from owning an equity interest in a sponsor that exceeds a value of $25,000, and be banned from receiving significant payments of other sorts that exceed $5,000 per year. (See Public Citizen's Health Research Group's January 4, 1995 comments on Financial Disclosure by Clinical Investigators, Docket No. 93N-0445). In today's submission, we will not repeat our earlier comments, but wish to address two additional issues: (1) the three questions posed by the FDA in the *Federal Register* notice, and (2) concerns about "burden," raised by the participants at the March 29, 1996 Science Board meeting, at which Public Citizen's Health Research Group was an invited guest.

II. Introduction

Public Citizen's Health Research Group's has long supported the idea of disclosure of the financial relationships between clinical investigators and the sponsors of the clinical research for products regulated by the FDA. The financial relationship between the researcher and the product

sponsor can have subtle and not-so-subtle effects on every aspect of the research endeavor, and in order to adequately assess the reliability of the clinical research, the FDA and the public should, *at a minimum*, be aware of the financial connections.

Over twenty-four years ago, Sidney M. Wolfe, M.D., Director of Public Citizen's Health Research Group, testified at a Senate hearing on the problems of financial conflict of interest of clinical investigators. In particular, he noted the case of the clinical investigation of the Griffin soft contact lens, manufactured by Frigitronics. The clinical investigators were paid in stock and stock options, rather than cash, and were among the most optimistic about the potential of the lens. The stock of the company rose in response to the positive clinical trials. Later, practitioners using the lens reported what appeared to be a larger number and greater variety of adverse effects than the "doubly-compensated" researchers had found during the pre-market investigational stage.

In another case, an ophthalmologist studied an experimental eye ointment while owning 530,000 shares of stock in the pharmaceutical company that marketed the product. Investigations revealed that the ophthalmologist made unauthorized modifications in the study design and minimized negative findings before selling his stock for a significant profit (Council Report, 1990).

Other financial conflicts of interest can arise from the sponsorship of clinical trials. In 1986, Davidson published a study analyzing the source of funding on the outcomes of clinical trials. In his research, Davidson reviewed all clinical trials published in 1984 that included a concurrent or cross-over control group in the following journals: the New England Journal of Medicine, Annals of Internal Medicine, the American Journal of Medicine, Archives of Internal Medicine, and the Lancet. Studies were classified as either favoring a new therapy or a traditional therapy, and as being supported by a pharmaceutical manufacturer or by another source. Davidson found a statistically significant association between the source of funding and the outcome of the study ($p=.002$) with studies supported by pharmaceutical manufacturers more often favoring new therapies as compared with studies supported by other funds (Davidson, 1986).

According the Council of Scientific Affairs and the Council on Ethical and Judicial Affairs of the American Medical Association, financial interactions between manufacturers and researchers "may compromise, or give the impression of compromising, the objectivity of researchers" (1990). As noted by this council,

> "[e]ven the most conscientious researchers have difficulty remaining totally unbiased about their work. For the clinical investigator who has an economic interest in the outcome of his or her research, objectivity is especially difficult. 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" (Council Report, 1990).

In order to avoid any chance of bias, the Post Coronary Artery Bypass Graft Surgery Clinical Trial, a multicenter, randomized, double-blind study of cholesterol levels and antithrombotic treatment on the development of atherosclerosis, adopted very stringent guidelines for investigators.

The guidelines prohibited investigators from buying, selling, or holding stock or stock options in the companies whose products were used in the study, prohibited investigators from serving as paid consultants to the companies, and required investigators to disclose all other financial involvement with the companies (Healy et al, 1989).

III. Response to Three Specific Questions

Public Citizen's Health Research Group would like to begin by stating that it urges the FDA to impose the most rigorous financial disclosure requirements possible. We are disheartened by the direction indicated by the three questions for discussion, for it clearly assumes a final rule that falls far short of what we urge. However, we would like to address each of the questions posed in the March 5, 1996 *Federal Register*.

(1) In proposing to require disclosure of any significant equity interest held by a clinical investigator in the sponsor, the agency has defined a significant equity interest as "any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in a publicly traded corporation that exceeds 5 percent of total equity." Is a 5 percent equity interest in a publicly traded corporation an appropriate threshold to trigger disclosure of financial information to FDA? Should a threshold dollar amount also be specified? If so, what might be a reasonable threshold amount?

Any equity interest held by an investigator in the sponsor should trigger the disclosure requirement. Such a relationship is a significant piece of information that should be available to the FDA as it analyzes the clinical research results. If a threshold for disclosure is set, a five percent equity interest, *without a threshold dollar amount*, is clearly inadequate to provide the necessary financial disclosure envisioned by this proposed rule. An investigator working for a large and financially well-off company could receive significant sums of money for conducting clinical research, and yet not be required to disclose it. For example, a four percent equity in a company worth $100 million could net the investigator $4 million, and, without a threshold, would not trigger the disclosure requirement. While we disagree with the idea of any threshold amount before disclosure is triggered, if such an amount is set, we would suggest a "trigger" threshold of $10,000 to be equitable with the disclosure requirements of other federal agencies. Although this amount is lower than the level we suggested in our previous submission, we believe that it is warranted because of the reduction in burden that will occur if all federal agencies use the same disclosure trigger level.

During the March 29, 1996 meeting of the Science Board, members of industry and the medical profession also recognized that five percent, without a dollar amount, could be a very large sum of money. (See, e.g., comments by Dr. Salvatore Giorgianni, Pharmaceutical Research and Manufacturing Association ("PhRMA"): "Certainly, for companies as large as most of the PhRMA companies, five percent equity interest from wherever it comes certainly would have the person in the position of being probably retired and not doing an awful lot of work." Transcript, p. 52; comments by Dr. James Allen, American Medical Association: "With regard to the five percent equity versus a

dollar amount, again it depends . . .on the size of the company, five percent being an enormous amount of a large, well-established pharmaceutical company or perhaps a relatively small amount at the outset. . .of a small biotech company or device manufacturer." (Transcript, pp. 60-61.)

(2). Are there financial arrangements that may be overlooked that could affect study outcome if FDA eliminates the provision entitled "significant payments of other sorts," from the proposed rule?

Yes; if this section of the regulations is eliminated, there will be a significant loophole. The purpose of the regulations is to make the FDA aware of financial factors that may affect the conduct of the investigator and the reliability of the data. The regulations have to contain a provision to capture information on the variety of ways in which sponsors and investigators can structure compensation schemes, otherwise, valuable and relevant information will not be disclosed.

Any type of economic tie between a sponsor and a clinical investigator carries the potential for conflict of interest and should be disclosed to the FDA. According the American Federation for Clinical Research Guidelines for Avoiding Conflict of Interest, the acceptance of payments such as grants to fund ongoing research, equipment, consulting fees, or honoraria has the potential for conflict of interest "because the motivation for continued support by the company may, in certain instances, depend on the degree to which the observations and pronouncements of the investigator are favorable toward a particular product" (American Federation for Clinical Research, 1990).

Furthermore, these other financial arrangements must be disclosed not because there may be questions of dishonesty, but because the receipt of any type of financial support may introduce unconscious bias, which may be quite subtle and difficult to detect. These biases may be invisible to an individual investigator or to a study sponsor, but may be readily apparent to an external reviewer such as the FDA.

(3). Does it help to narrow the scope of the provision "significant payments of other sorts" by raising the current payment level that would trigger disclosure from $5000 to $50,000 annually? Are there other options that allow retention of the provision but effectively narrow its scope?

We believe that *all* financial arrangements between clinical investigator and sponsor should be disclosed. The problem with establishing thresholds for disclosure is that the impact of particular sums will vary depending upon a variety of factors, including the financial circumstances of the investigator, etc. Further, the establishment of a threshold can result in changes to payment schemes in order to circumvent a particular threshold, and can make the disclosure process *more* burdensome because it requires analyzing which payments fall below and which rise above the threshold. The better approach is to require disclosure of all financial arrangements, and leave it to the FDA to assess the meaning or effect of the arrangement. If, however, the FDA does set a threshold, we are strongly opposed to raising it above the current proposal of $5,000 annually. To raise the threshold to $50,000, as suggested in this question, would allow arrangements involving significant sums of money to be entirely hidden from any outside scrutiny.

Further, if "significant payment of other sorts" includes an equity interest of more than five percent in a publicly held company -- as it does currently in the proposed regulation -- we urge full disclosure, or at least a threshold dollar amount of $5,000 to trigger disclosure, for the same reasons given in the answer to question 1, above. We do not support any options that would narrow the scope of this provision.

IV. Concerns raised during the Science Board Meeting of March 29, 1996 about the "burden" imposed by the proposed rule

During the discussion at the Science Board meeting, with invited guests from industry, academia, and the public, the notion of "burden" was a recurrent theme -- both the burden imposed on the investigator and/or sponsor by financial disclosure, and the burden imposed on the FDA if it receives "too much" information, or "useless information." We would like to address these two different concerns with "burden."

A. Burden on clinical investigators and/or sponsors

First, it should be noted that poor quality, inadequate or misleading clinical data that results in the approval of an ineffective or unsafe product imposes a large burden on patients and society, and this "burden" on patients and society must be kept in mind when discussing the proposed rule.

The financial disclosure rule will impose some "burden" on investigators and on sponsors in that it will require them to do something that today they are not required to do. Yet the burden need not be great. In our opinion, a clear, easy to follow rule that requires *all* financial arrangements between clinical investigator and sponsor to be disclosed would go far towards reducing the burden. Investigators would not have to analyze the various arrangements they may have with sponsors to determine which rise above various thresholds, nor would they have to make sure changes over time

do not trigger a threshold. Full disclosure has the benefit of ease of understanding.

Financial disclosure is a burden that most government and private institutions have already accepted. Many investigators already must make certain financial disclosures to the academic institutions with which they are affiliated. Professional societies, including the American Medical Association and the International Committee of Medical Journal Editors, have developed guidelines recommending financial disclosure of any material ties between investigators and companies whose products they are investigating (Council Report, 1990; Conflict of Interest, 1993). Several federal agencies, including the National Science Foundation and the National Institutes on Health require investigators to disclose significant financial interests prior to receiving research funding. Many medical journals including JAMA and the New England Journal of Medicine, require authors to list all affiliations with or financial involvements in any businesses that could be affected by their work. Any of these agencies or institutions could provide a model for a simple disclosure form that would reduce any minimal burden the rule might impose.

Finally, this rule can only be considered burdensome if it is viewed as restrictive. Recognition of sources of potential conflict and open information about these issues is necessary for complete evaluation of research (Elks, 1995). This type of openness strengthens clinical research by placing it above suspicion and thus frees physicians and researchers to concentrate more fully on their primary missions.

B. "Burden" on the FDA

The second concern over "burden" is the burden imposed on the FDA by "inundating" it with information that is not useful, or about financial arrangements which are insignificant. Again, we believe this concern is exaggerated. First, a simple disclosure form would go a long way towards reducing the amount of paper submitted in connection with this rule. Further, this is but a small element in the ultimate submission made by a sponsor in connection with marketing approval. One of the problems with trying to restrict the FDA's collection of information to only that information that it will use, is that the FDA may not know of a problem with a financial arrangements until it sees it. While some arrangements are clearly problematic from the start, other arrangements may be quite troublesome only in light of clinical results or other circumstances, but the FDA will not know when these occur unless they have the financial disclosure information.

The biggest burden on the FDA is the burden that will occur if the financial disclosure information is available only to the FDA, and not to the public. Public disclosure regarding all financial arrangements between sponsors and investigators in some useful form is critical so that those who would be affected, or who are otherwise in a good position to assess the risks, can access the information they need to make informed decisions.

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.

Sincerely,

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