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Joan Claybrook, President

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

RE: Financial Disclosure by Clinical Investigators; Docket No. 93N-0445.

On behalf of Public Citizen's Health Research Group, we offer the following comments regarding FDA's proposed rule to require the sponsor of any drug, biological product, or device to submit information to the FDA concerning financial interests of clinical investigators conducting its clinical studies.

First of all, the proposed rule is long overdue. Sidney Wolfe, M.D., Director of Public Citizen Health Research Group, testified at a Senate hearing 21 years ago, expressing serious concerns about the unaddressed problem of financial conflict of interest of clinical investigators. The incident that precipitated this hearing was the clinical investigation of a soft contact lens, the Griffin lens, manufactured by Frigitonics. The clinical investigators were paid in stock and stock options, rather than in cash, because the company was in a weak financial position. 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 result of their clinical trials. Dr Wolfe stated then,

Not only is the investigator rewarded in the present, but, much more insidiously, he is wedded to the future success of the company. How, under these circumstances, can objective scientific inquiry flourish? Why are practitioners now (compensated only by the patient, rather than by the patient and the 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-market investigational stage? [A]s long as the manufacturers, medical schools and the FDA continue to condone such practices...the American public will be the victims. Statement before Senate Small Business



Subcommittee Hearings on Soft Contact Lenses, July 6, 1972.

It is encouraging that the FDA has finally chosen to address this issue in the form of proposed regulations, and our comments related to specific sections are as follows:

"SIGNIFICANT EQUITY INTEREST" SHOULD BE DEFINED TO LIMIT AN INVESTIGATOR'S INTEREST TO A MAXIMUM MONETARY VALUE.

Section 54.2(b) of the proposed rules defines "significant equity interest in the applicant" as "any ownership interest [defined]...or any equity interest in a publicly traded corporation that exceeds 5 percent of total equity." We would add "not to exceed a value of \$25,000," to the end of this paragraph. In certain companies, 5 percent or less of total equity could provide a windfall for an investigator in the event that the applicant's drug or device were to become widely used in clinical practice. For example, 4 percent of equity in a company worth one hundred million dollars could net the investigator \$4,000,000. In order to avoid potential bias, there must be a maximum allowable value included within this definition.

"CLINICAL INVESTIGATOR" SHOULD BE DEFINED TO INCLUDE INVESTIGATOR'S PARENTS AS WELL AS SPOUSE AND CHILDREN

Proposed section 54.2(d)(ii) states that "for the purposes of the requirements of this part relating to financial interests, 'investigator' includes the spouse and each dependent child of the investigator. We would include the parents of the investigator in this definition as well, because, through inheritance, trusts, gifts, etc., an investigator could be the ultimate beneficiary of a parent's financial interest in the outcome of a study he or she is conducting, thus presenting the potential for bias in the conduct or analysis of the study.

"SIGNIFICANT PAYMENTS OF OTHER SORTS" SHOULD BE DEFINED TO LIMIT SUCH PAYMENTS TO A MAXIMUM MONETARY VALUE.

Section 54.2(f) of the proposed rule defines "significant payments of other sorts" (thus disclosable) as:

payments that exceed \$5,000 (e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) or that exceed 5 percent of the total equity in a publicly held and widely traded company.

In certain publicly held and widely traded companies, 5 percent or less of the total equity could provide a windfall for an investigator in the event that the applicant's drug or device were to become widely used in clinical practice. In order to avoid potential bias, there must be a maximum allowable value

included within this definition. We would add the clause "up to \$5,000 per year" to the end of the section.

DISCLOSURE OF A FINANCIAL ARRANGEMENT BETWEEN SPONSOR AND INVESTIGATOR IS NOT SUFFICIENT TO PROTECT AGAINST BIAS.

We support the requirement contained in proposed section 54.4(a)(1) whereby a sponsor/applicant must certify to the FDA that it "has not entered into any financial arrangement with any clinical investigator, whereby the value of compensation to the investigator to conduct the study could be affected by the outcome of the study," and that no investigator has a proprietary or significant equity interest or was the recipient of significant payments of other kinds. However, we do not support 54.4(a)(2), which allows the (a)(1) certification to cover less than all covered clinical data in the application, so long as the applicant lists all studies covered. The (a)(1) certification, to have any value, must apply to **all** covered clinical data in the application.

Similarly, we do not support (a)(3), which allows "financial arrangements....whereby the value of the compensation to the clinical investigator to conduct the study could be influenced by the outcome of the study;" significant payments of other sorts; a proprietary interest in the tested product held by any clinical investigator involved in a study; and any significant equity interest, so long as the applicant/sponsor submits a disclosure statement. The (a)(3) statement would merely describe the extent and nature of financial arrangements with the clinical investigator, and the steps taken by the sponsor to minimize the potential for bias.

Disclosure is warranted, but disclosure alone is not enough - it only announces that the risk of bias is present. Investigators should not gain financially from companies whose products they are evaluating. Rather than allowing disclosure to cure financial arrangements, **researchers with any outcome-dependent interests should be banned from owning an equity interest in a sponsor that exceeds a value of \$25,000, and should be banned from receiving significant payments of other sorts that exceed \$5,000 per year.**

Investigators may be unconsciously affected by an economic incentive, causing them to downplay negative data and exaggerate favorable data. A financial interest may affect the way the research is carried out, analyzed or reported. Any payment by a company to an investigator should be commensurate with actual efforts expended on behalf of the company, and should be disclosed to FDA.

The basic purposes of conflict of interest rules are to maintain the objectivity of professional judgment and to maintain

public confidence in professional judgment. In many areas of life, restrictions on conflicts of interest are the norm. For example, judges are expected to recuse 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. Similarly, important judgments about how to design, carry out and interpret the results of clinical trials should not be tainted.

18 U.S.C section 208 provides that federal government employees may not in their official capacities participate in matters in which they have a financial interest. 45 CFR section 73.735-801 (b) (1) states the following:

A financial interest is any interest of monetary value which may be directly and predictably affected by the official action of an employee. There is no minimum amount of value or control that constitutes a financial interest...i.e., [a]n employee owns a single share of stock in a widely-held corporation. If the corporation is likely to be affected by a matter in which the employee participates as a Government official, the employee may violate 18 U.S.C. 208.

If the employee believes that his interest is so remote and inconsequential that it would not affect the integrity of his or her official duties, he may, **in advance**, request a waiver, pursuant to 45 C.F.R. 73.735-804. The request must be in writing and go through administrative channels for approval. Only when the employee is informed in writing that he has been given a waiver may he participate in the matter in which he has the interest.

An instructive analogy can be drawn to rules enacted by Congress in 1989 and 1993 regulating the practice known as "self-referral" -- doctors referring patients to labs and services in which the doctors have a financial interest. Like conflicts of interest facing clinical investigators, self-referral involves health professionals with a personal financial stake in the outcome of activities aimed primarily at protecting or improving the public health, not the professional's personal gain. Prior to enacting legislation addressing self-referral, Congress considered requiring doctors merely to disclose to their patients any financial interest the doctor held in a facility to which the patient was being referred. Several states already required such disclosure in regulations or law, and it was initially supported by the American Medical Association (AMA) as well. However, Congress explicitly rejected this strategy in favor of legislation that now bans Medicare or Medicaid payments for self-referrals for a wide range of products and services. Even the AMA eventually agreed that self-referral should be prohibited, reflecting widespread agreement that disclosure was ineffective in ending the conflicts of interest created by the practice.

FDA DOES NOT HAVE SUFFICIENT RESOURCES TO EVALUATE FINANCIAL INTERESTS AND THEIR IMPACT ON STUDY DESIGN AND DATA RELIABILITY

Proposed section 54.5 states that the FDA will evaluate the information contained in the section 54.4(a)(3) disclosure statements and assess the impact of any disclosed financial interests on the reliability of the study, taking into account factors such as the design and purpose of the study. The agency may then take various actions to assure the reliability of data, such as audits, requests for further data analysis, requests for further studies, or refusal to treat the study in question as pivotal.

The FDA does not have the resources to micromanage clinical trials in this manner. The agency is already operating under an enormous statutory burden and should not be responsible for reducing the potential for bias resulting from financial interests. 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, a clinical investigator should be banned from owning an equity interest in a sponsor that exceeds a value of \$25,000, and should be banned from receiving significant payments of other sorts that exceed \$5,000 per year. All other arrangements, such as compensation from the sponsor to the investigator (or his/her institution) for conducting studies must be disclosed. It is safer and more responsible to decide **in advance** to remove factors that tend to distract researchers from concentrating on medical and scholarly goals. Furthermore, financial disclosures ought to be made to FDA early in the review process. 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.

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, this may create a significant enough risk of biasing a study to cause FDA not to rely on the study, and may delay the approval of some drugs and devices, because the companies will be forced to repeat the studies.

FDA MUST DISCLOSE FINANCIAL ARRANGEMENTS BETWEEN SPONSORS AND INVESTIGATORS TO THE PUBLIC

We support proposed section 54.6, which requires sponsors to retain records pertaining to their financial arrangements with clinical investigators. The regulation requires the sponsor to retain the records for two years after the date of approval or shipping of the application. We think that these records should be retained for five years, especially considering that the

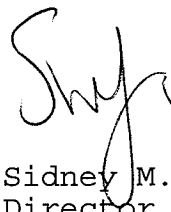
agency is occasionally unable to conduct scheduled inspections of facilities due to resource constraints.

We agree that the person maintaining the records should be required to permit an authorized officer or employee of FDA "to have access to and copy and verify these records." Unfortunately, the proposed rule contains no sections relating to public disclosure of financial arrangements and potential conflicts of interest. Public disclosure regarding all financial arrangements between sponsors and investigators in some useful form is critical. These include financial arrangements whereby the value of the compensation to the clinical investigator to conduct the study could be influenced by the outcome of the study, a significant equity interest, a proprietary interest in the tested product held by any clinical investigator involved in a study, significant payments of other sorts, and compensation to the investigator's institution. 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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