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Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852
Docket No. 02N-0475

Re: Draft Guidance Document titled: *Financial Relationships and Interests in Research Involving Humans: Guidance for Human Subject Protection,* dated March 31, 2003.

These comments respond both to the changes between the January 10, 2001 Draft Interim Guidance Documents (DIGD-01) and the March 31, 2003 Draft Guidance Document (DGD-03), and also discusses the merits and deficiencies of the latter (most recent) guidance document.

The Draft Guidance Document issued Mar. 31, 2003 is superior to its predecessor (DIGD-01) in some respects, but falls short of it in others. The new document defines a conflicting financial interest in a manner that is not linked to the subjective determination of a "designated institutional official," as did its predecessor. The new definition of conflict of interest in DGD-03 (an interest that "will or may be reasonably be expected to create a bias") is superior to the operational definition used in DIGD-01 (whatever a "designated Institutional official(s) reasonably determines...").

Nevertheless, the new definition still falls prey to the consequentialist meaning of "conflict of interest." That is, the new definition claims that a financial conflict of interest exists when a potential or actual biasing effect on research exists. A financial conflict of interest should not be defined by the "effect of a relationship" but by the nature of the relationship. We would not say that a judge has a conflict of interest only when his financial interest in a case "may be reasonably expected to create a bias stemming from that financial interest." Generally, there is no empirical basis for an objective determination of what may "reasonably be expected to create a bias." Whether in law or science the financial conflict of interest is the *relationship* and not the *effect of the relationship*. These distinctions are discussed in detail in Andrew Stark, *Conflict of Interest in Public Life* (Harvard University Press, 2000) and in Sheldon Krimsky, *Science in the Private Interest* (Rowman-Littlefield, 2003). As Marcia Angell, editor emerita of the *New England Journal of Medicine*, aptly pointed out, conflict of interest is a function of the situation and not the investigator's response to it.

The second advance in DGD-03 over DIGD-01 is the former's emphasis on the rights and welfare of subjects. The California Supreme Court decision on the "Mo-Cell Line" [*Moore v. Regents of the University of California*, 793 P.2d 479, 271 Cal Rptr (1990)], as well as the Jesse Gelsinger case emphasize the rights of human subjects with regard to disclosing financial conflict of interest information. Someone who is

02N-0475 C8

considering volunteering as a human subject has a right to know all relevant information pertaining to the risks and benefits of that decision. The majority of the California Supreme Court wrote: "The possibility that an interest extraneous to the patient's health has affected the physician's judgment is something that a reasonable patient would want to know in deciding to consent to a proposed course of treatment" (Krimsky, 2003, 132). The disclosure of the clinical investigators', IRB's, or institution's, conflicts of interest is relevant to that determination and therefore becomes a fiduciary responsibility of those who engage in or oversee human subjects research.

The major limitation of DGD-03 is that it avoids making clear determinations about what should be prohibited, leaving it to individual institutions to work out their own ethical guidelines. Academic institutions are in intense competition to attract research funds and unless there are clear prohibitions of financial conflicts of interest, we will see a patchwork of responses, and eventually, there will be a regression to the "least ethical common denominator."

Institutional conflicts of interest are growing, as academic institutions—even the elite ones—invest in faculty-created companies. Institutional Review Boards (IRBs) are not trained or in a position to oversee the conflicts of interest of the institution to which they are accountable. The entire structure of DGD-03 depends on good will, at a time when commercialization has become rampant at universities, where "good will" is too easily compromised for the lure of research funds. It is unlikely that the establishment of "conflict of interest committees" unless they have norms to go by and the institutions they serve see the disadvantages and/or penalties of violating those norms, will contribute to preventing egregious conflicts of interest. Good will works to a large degree in protecting the integrity of science because violations in such areas as plagiarism and misconduct are perceived to have severe penalties to a violator's career. The same cannot be said of conflicts of interest.

DGD-03 gives no guidance on the most critical questions: When does the financial interest of researchers affect the rights and welfare of subjects? This question is left to each institution to work out. This is not even a question where empirical data can provide answers. DGD-03 recommends that investigators consider the potential effect that their financial relationship might have on the clinical trial. This is like asking an industrial polluter to assess the health impacts of their pollution. It must be assessed by third parties (as also suggested in DGD-03) but not strongly recommended. DGD-03 asks institutions, IRBs, and investigators to consider questions in their deliberations that are not empirically well defined. "What financial relationships and resulting financial interests cause potential or actual conflicts?" Without precise norms, who would know the answer to this question?

DIGD-01 and DGD-03 were written in different formats making a section-by-section comparison difficult. Appendix I is an attempt at such a comparison. In some respects DGD-03 relaxes the ethical responsibility and recommendations of DIGD-01. For example: compare the language of DIGD-02: "It is desirable sto avoid conflicts of interest wherever possible," with DGD-03: "Financial interests are not prohibited, and

not all financial interests cause conflicts of interest or harm to human subjects." Also, the recommendations about disclosing conflicts of interest (COIs) to human subjects is weaker in DGD-03 than in its predecessor. The earlier draft states that financial COIs that cannot be eliminated "should be disclosed in the consent document." The more recent draft recommends that the investigator consider whether to disclose the financial interest to the human subject.

In order for the federal government to help institutions secure the rights and welfare of subjects participating in clinical trials, it must establish clearer and more precise guidelines that set ethical standards, even boundaries, rather than allow those standards to be established in a marketplace of institutions competing for valuable research funds and commercial partnerships. The gold standard for protecting human subjects would prohibit certain egregious financial conflicts of interests for clinical investigators (equity ownership in a company that is poised to benefit from a positive outcome in a trial). The silver standard would *require* disclosure, while not suggesting that it be a discretionary decision to the individual institutions.

Respectfully submitted,

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APENDIX I
Comparison of DHHS Draft Guidance Documents on Financial Conflicts of Interest in Human Subject Research: Jan. 10, 2001 & Mar 31, 2003

[Compiled by Sheldon Krimsky, Tufts University]

Jan. 10, 2001 (Donna Shalala, Sec. DHHS)	March 31, 2003 (Tommy J. Thompson, Sec. DHHS)
Institutional Considerations	***Institutional Considerations***
A conflict of interest exists when a "designated Institutional official(s) reasonably determines that a Significant Financial Interest could directly and significantly affect the design, conduct or reporting of PHS-funded research."	"A financial interest related to a research study may be a conflicting financial interest if it will, or may be reasonably expected to, create a bias stemming from that financial interest." "...some financial interests in research may potentially or actually affect the rights and welfare of subjects..."
IRBs should be allowed to conduct their oversight in an autonomous manner, free from institutional pressures; and include broad participation from members outside the institution "who will have no interest in the outcome of the research of the business interests of the institution."	DHHS recommends that IRBs reviewing HHS conducted or supported human subjects research for FDA regulated human subjects research: "Determine whether methods being considered or used for management of financial interests of parties involved in the research adequately protect the rights and welfare of human subjects." Establish measures to foster the independence of IRBs and COICs . Include individuals from outside the institution in the review and oversight of financial interest in research.
"Accordingly, the institution should carefully consider whether a clinical trial to evaluate safety and efficacy should be performed at that site, and if it should, what special protections would be needed." "When institutions consider entering into such business agreements, they should consider establishing an independent advisory and oversight committee (institutional conflicts of interest committee), if one does not already exist, to determine whether the financial arrangements pose a conflict of interest, and if so, how those conflicts should be managed."	It is recommended that institutions engaged in federally conducted or supported human subjects research separate responsibilities for financial decision and research decisions; Establish conflict of interest committees (COICs); extend the responsibility of the COIC to address institutional financial interests in research or establish a separate COIC to address institutional financial interests in research; establish criteria to determine what constitutes an institutional conflict of interest; use independent organizations to hold or administer the institution's financial interest.
"Any financial relationships that the institution has with the commercial sponsor should be documented and the specific relationship submitted to the Chair/Staff of the IRB..."	"Financial interests are not prohibited, and not all financial interests cause conflicts of interest or harm to human subjects. HHS recognizes the complexity of the relationships between government, academia, industry and others, and recognizes that these relationships often legitimately include financial relationships. However, to the extent financial interests may affect the rights and welfare of human subjects in research, IRBs, institutions, and investigators need to consider what actions regarding financial interests may be necessary to protect those subjects."

"Any agreements between investigators and a sponsor should be reviewed by the Institution's Conflict of Interest Committee or equivalent body. It is desirable to avoid conflicts of interest wherever possible. If a potential conflict cannot be eliminated, the committee's determination of how the potential conflict is to be managed/reduced should be shared with the IRB for consideration during the discussion of the protocol.	DHHS recommends that Institutions (IRBs and investigators) consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects. "Financial interests are not prohibited, and not all financial interests cause conflict of interest or harm to human subjects."
Clinical Investigators	***Clinical Investigators***
If the clinical investigator has any conflicts of interest he or she should not be directly engaged in aspects of the trial that could be influenced inappropriately, including, designing of the trial, monitoring the trial, obtaining informed consent, adverse event reporting, or analyzing the data.	Recommends that investigators consider the potential effect that a financial relationship of any kind might have on a clinical trial and whether to include information on funding arrangements and COI of investigator or institution in the consent document; having a non-biased third party obtain consent, consider independent monitoring of the research
Disclosure to Human Subjects	***Disclosure to Human Subjects***
"If a financial conflict of interest on the part of the Institution and/or Clinical Investigator has not been or cannot be eliminated, what the financial arrangement is and how that conflict is being managed should be disclosed in the Consent document."	DHHS recommends that investigators consider whether to take the following actions: • Include information in the consent document such as source of funding and funding arrangements for the conduct and review of research or information about a financial arrangement of an institution or an investigator and how it is being managed. • Having a non-biased third party obtain consent; • Consider independent monitoring of the research.
Institutional Review Boards (IRBs)	***Institutional Review Boards (IRBs)***
IRBs should have a clear recusal policy. Its members should be recused from deliberating or voting on all protocols, where they have an actual or potential conflict of interest.	IRBs are responsible for ensuring that members who review research have no conflicting interest. IRBs should consider establishing policies and procedures addressing IRB member potential or actual conflicts of interest as part of its overall policies.
IRBs should consider including in the consent document for human subjects the source of funding and funding arrangements for performing the IRB review of the protocol.	Recommends that IRBs consider whether they should determine whether the methods being conducted or used to manage financial interests protect the rights and welfare of human subjects.
"IRBs should take steps to ensure that the potential research participants are apprised of the source of funding for the study and the payment arrangements for Investigators during the consent process and in the Consent form, whenever that information is considered material to the potential subject's decision-making process."	Recommends that IRBs consider whether they should determine the kind, amount, and level of detail of information to be provided to research subjects regarding the source of funding, funding arrangements, financial interests of parties involved in the research, and any financial interest management technique applied.