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U.S. Food & Drug Administration
Dockets Management Branch
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD, 20852

Re: FDA Docket No. 02N-0475
"Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection"

Dear Sir or Madam:

Thank you for the opportunity to comment on the Department of Health and Human Service's ("Department" or "HHS") Draft Guidance entitled *"Financial Relationships and Interests in Research Involving Human Subjects,"* published in the Federal Register on March 31, 2003.[1] Pfizer submits these comments based on its experience sponsoring thousands of clinical trials, and working with investigators, institutions, institutional review boards ("IRBs") and government officials in the United States and abroad.[2] Pfizer appreciates the role and efforts of HHS and the Food and Drug Administration ("FDA") in protecting the integrity of human research, and recognizes the appropriateness of using institutional policies and procedures as the primary mechanisms for managing conflicts of interests.

Clinical research is a highly regulated process. An extensive array of laws and guidelines already governs the conduct of clinical trials generally, and the relationships between sponsors and researchers particularly. For example, research-based pharmaceutical companies such as Pfizer comply with FDA regulations,[3] state informed consent laws and other state requirements,

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[1] 68 Fed. Reg. 15,456 *et seq.* (Mar. 31. 2003).

[2] This year, Pfizer will spend approximately $20 million on research every business day (or approximately $7 billion annually) on a research program that includes over 200 projects, involving more than 100 new molecular entities.

[3] *See* 21 C.F.R. Part 54. Pursuant to these regulations, research sponsors must disclose to the FDA certain interests of the investigators whose research they financially support when applying for marketing approval of a

and industry guidelines, including the recently issued *PhRMA Principles on Conduct of Clinical Trials and Communication of Study Results* (the "*PhRMA Principles*").[4]

What is needed now is a guidance document that consolidates and renders consistent these various sources of law, regulation and guidelines (including the *PhRMA Principles*), and that provides a more definitive and specific roadmap for institutions, IRBs, investigators, and others to follow in identifying and managing conflicts of interest in research.[5] The Department's Draft Guidance identifies areas of concern relating to conflicts of interest, but does not explain how to identify and manage conflicts. The document instead presents a compilation of suggestions that institutions "may elect to include ... in their deliberations." This compilation is likely to increase the administrative complexity of research oversight at institutions, and, ultimately, will yield less effective and less predictable approaches to conflicts of interest in research. Pfizer therefore suggests that, in the Final Guidance, HHS should specify explicitly how institutions should proceed to identify and manage the conflicts, so that the research community can comply with the standards expected by federal authorities. In other words, a simple, clearly defined approach is needed to assist institutions in determining what procedures are required to meet the government's expectations for conflict of interest management.

The tasks of consolidation and policy development (*i.e.*, defining how to identify and manage conflicts) should not be left to individual research institutions to design. Not only is the research community not trained to undertake these responsibilities, but leaving these responsibilities to the research community will lead to a fragmented and piecemeal conflict of interest infrastructure. The failure to articulate specific recommendations for identifying and managing conflicts of interest will result in varying treatment of conflicts even within the same institution, since few institutions now have a comprehensive research conflicts of interest process.

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particular drug or device. The FDA may review any reported financial arrangements between the sponsor and investigators, and may audit data, request further analyses, request independent studies, or reject data where there is a serious question as to the data's integrity. *Id.* at § 54.5(c).

[4] http://www.phrma.org/publications/policy/2002-06-24.430.pdf

[5] Most research sponsored by the U.S. government or regulated by the FDA must comply with the Federal Policy for the Protection of Human Subjects (45 C.F.R. Part 46, also known as the Common Rule), and parallel FDA regulations (21 C.F.R. Parts 50 and 56). However, it has been reported that at least 69 federal departments and agencies are not covered by the Common Rule, and that there are numerous variations in federal requirements. *See* National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, Vol. I (Aug. 2001) at 5, 9, posted at http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.html ("NBAC Report"). *See, also*, W. J. Burman et al., "Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards," *Annals of Internal Medicine*, 134:2 (Jan. 16, 2001) at 152-7 (recommending a "thorough overhaul of the system, in which the parts that monopolize resources and do not contribute to patient safety are modified or eliminated"), posted at http://www.annals.org/issues/v134n2/full/200101160-00016.html; R. Snyderman & E. W. Holmes, "Oversight Mechanisms for Clinical Research," *Science*, 287:5453 (Jan. 28, 2000) at 595-7 (discussing approaches to developing an effective, simplified system that "...is understandable, that works, and that is adaptable to change"), posted at http://www.sciencemag.org/cgi/content/full/287/5453/595.

In the Final Guidance, any failure to articulate specific recommendations or to reconcile the varying standards embedded in current law would create inconsistency, ambiguous responsibilities, and confusion. Such a result in no way serves the purposes of assuring research integrity or protecting human subjects.

We offer the following supplemental comments and recommendations, which derive from our core recommendation that the Department develop and make available to the research community an integrated, consistent and specific guidance for addressing conflicts of interest in research.

Provide Clear Recommendations, Not "Points to Consider"

Instead of discussing "general approaches" and "points to consider," the Final Guidance should put forth a clear and comprehensive roadmap for the research community to follow in dealing with conflicts of interest. This roadmap should include the following:[6]

- Concise definitions of the various types of conflicts of interest that arise in research (*i.e.*, investigator, IRB, institutional);
- A description of the nature of these various conflicts of interest, including the point at which they become significant and hence reportable and/or requiring review;
- Instructions for IRBs and institutions on how to develop a conflict of interest infrastructure that addresses each type of conflict of interest.

Financial and Non-Financial Interests Subject to the Oversight Process

Specific guidance is required regarding the processes for identifying and managing conflicts, both financial and non-financial. Instead, the Draft Guidance simply raises the question: "[w]hat financial relationships and resulting financial interests cause potential or actual conflicts?" Pfizer recommends that, in regard to financial interests of researchers, only incentives that rise to a specific level of significance should be reported. This approach is consistent with Public Health Service (PHS) and FDA requirements, which both set specific financial thresholds of significance below which reporting is not required. The thresholds established by these laws reflect the premise that the mere presence of a financial investment or relationship does not necessarily result in a meaningful or significant conflict of interest that must be managed. The purpose of a conflict of interest process is to identify and manage those incentives that are *likely* to result in bias (or *likely* to suggest bias to a reasonable observer), not to require the disclosure of all incentives no matter how trivial or attenuated. For all of these

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[6] Most of these points have, in fact, already been considered in great detail by various government and professional groups, including the National Bioethics Advisory Commission, National Human Research Protections Advisory Committee, the HHS Office of Inspector General, the U.S. General Accounting Office, the Institute of Medicine, the Association of American Medical Colleges, the American Medical Association, the Association for the Accreditation of Human Research Protection, and the World Health Organization, among others. Although Pfizer may disagree with some of the specific suggestions made by these groups, their recommendations at least have the benefit of being more specific in many cases than the Draft Guidance.

reasons, including the need to make the conflict of interest process as efficient and effective as possible (which could not happen if every dollar of financial interest were examined), some specific level of significance should be specified before a financial interest merits consideration in a conflict of interest process.

Pfizer recommends that the Department adopt a single threshold for identifying significant financial conflicts of interest, using the current FDA threshold rule for such disclosures ($25,000 in annual income from a sponsor, or $50,000 in investment in a sponsor) rather than the PHS' lower limit ($10,000). This would simplify the administrative review of conflicts of interests by institutions that are engaged in both FDA regulated and government sponsored research. Yearly interests under the FDA thresholds are very unlikely to cause bias or lead a physician researcher consciously or unconsciously to jeopardize subject welfare and personal standards of integrity. The lack of impact is especially true in the case of equity interests in publicly-traded corporations sponsoring research, in which even large personal equity investments are unlikely to create any significant bias. Since these publicly-traded companies are large and complicated organizations, with multiple products sold and under development in multiple clinical trials, the equity interests of any shareholder would tend to be quite attenuated from the results of any one investigator's contributions to a single clinical trial. In any case, the FDA thresholds have for several years been deemed adequate to alert the FDA to any potential bias of investigators, and therefore should be sufficient to inform institutions and IRBs of potential bias as well.

Finally, it is important to note that financial conflicts of interest (though they are often the focus of attention in the lay press) are not the only type of research conflict of interest.[7] By way of example, non-financial interests include the prestige of publishing the results of a successful study, peer recognition, the ability to attract additional research grants, and the opportunities that successful research projects can have on career advancement, promotion, and tenure.[8] IRB and institutional conflicts of interest, including both non-financial and financial interests, similarly can influence research and are difficult to identify and manage.[9] However, from a human subject

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[7] *See, e.g.,* Committee on Assessing the System for Protecting Human Research Participants of the Institute of Medicine, *Responsible Research* (National Academy Press 2003) at 186:

> Every successful investigator has some degree of self interest in the research ... [and] nonfinancial interests are more common and potentially more dangerous to participants [e.g., patients] and to the integrity of the research itself.

See also, Nathan Levinsky, "Nonfinancial Conflicts of Interest in Research," *New England Journal of Medicine*, Volume 347, No. 10 (Sept. 5, 2003) at 759-76 (describing the dual motives of "advanc[ing] medical science and personal benefits from publications and acquisition of grants ... reinforced by the interest of institutions in enhancing their reputations as research centers"), posted at http://content.nejm.org/cgi/content/full/347/10/759.

[8] *See* Paul Friedman, M.D., "*The Troublesome Semantics of Conflict of Interest,*" Ethics & Behavior, 2:4, 245-251 (Lawrence Erlbaum Associates, Inc. 1992) at 250: (stating that "[i]t would be a remarkably dull institution that managed to avoid conflicts altogether").

[9] *See* e.g., MME Johns, M Barnes & PS Florencio, "Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest," *JAMA*, 289:6 (Feb 12, 2003) at 741-6.

protection standpoint, it is significant that many of the more notorious lapses in human subject protection have had little to do with financial conflicts of interest. For example, inadequately educated researchers, poorly designed trials, and lax compliance seem to have been the primary causes of research misconduct in the U.S. Department of Energy's Radiation experiments, the Public Health Service's Tuskegee study, the death in the hexamethonium study at Johns Hopkins, and even the recent incidents involving human subjects research at the Veteran's Administration.[10] This is not to say that financial conflicts of interest are benign. But, the Department should recognize that focusing exclusively on financial relationships may have limited value in terms of protecting patients and ensuring research integrity.

Disclosure to Subjects Should Describe the Nature of Any Significant Conflicts, Not the Specific Details of Financial Holdings

In its Draft Guidance, the Department asks IRBs to 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 techniques applied." Pfizer staunchly supports the disclosure to conflict of interest committees or institutional officials of significant financial and non-financial incentives that may bias research. However, we are concerned that an IRB or conflict of interest committee could interpret that provision in the Draft Guidance to authorize or require the disclosure of detailed financial information to prospective research participants, down the last dime of related investments held by a researcher or host institution or detailed disclosures of what the sponsor is paying to support the study, etc.

In making recommendations about patient disclosures, Pfizer urges the Department to clarify that general information should be provided to patients, not detailed financial information.[11] Patients should be told about the existence of significant conflicts of interest, the nature of those interests, and any steps taken to manage any bias that could be introduced as a

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[10] *See* Nelda P. Wray, M.D., M.P.H., Chief Research & Development Officer for the Veteran's Administration, *Stand Down Memorandum* (March 6, 2003), posted at http://www.va.gov/resdev/fr/stand_down/memo.cfm.

[11] This approach is consistent with the position taken by the National Human Research Protections Advisory Committee in its comment on the Department's Draft Interim Guidance. *See* NHRPAC, Letter to Arthur J. Lawrence, Ph.D., Assistant Surgeon General, Acting Principal Deputy Assistant Secretary for Health, Office of Public Health and Science (August 23, 2001) at 11:

> A very real risk here is that if presented with confusing, chaotic, and detailed but undigested information about investments and compensation and money flows, patients could be utterly confused, and their ability to make reasoned choices impaired rather than assisted. Another very real risk is that patients may defer from participating in research if troubling financial relationships are exaggerated or ways of managing them are unclear. Efforts to inform patients about their own medical care often appear in long documents that patients sign but do not read, suggesting that both in medical care and in clinical research, physicians and other providers need to find ways to communicate risks and their management more clearly, accurately and effectively. For these reasons, among others, conflict of interest committees must be careful to identify when a possible conflict exists, and when it does not (in which case, no disclosure would be necessary).

result of those conflicts. Pfizer does not believe that an effective and appropriate informed consent process requires detailing numbers or values of shares of stock and other interests. In fact, if federal guidance or institutional practice requires such detailed disclosure, there would be no principled reason why every change in the value of those interests should not also be required to be disclosed to subjects, producing a massively complicated, continuing and time-consuming disclosure process. Overwhelming patients with precise descriptions of investigator and/or institutional financial and non-financial interests would greatly complicate the informed consent process and result in patient confusion and anxiety, thereby preempting the benefits of disclosure and unnecessarily distressing patients.

Principles of informed consent indicate that significant risks – not *all* risks and not *all* details – should be disclosed to subjects in order to allow them to make reasoned judgments.[12] Informed consent principles would require – and Pfizer would support – disclosure to subjects of the existence and nature of significant conflicting interests of researchers or institutions (with any relevant information as to how those conflicts are managed while the research is underway). If subjects have additional questions about those interests, those questions should, in Pfizer's estimation, be answered accurately and in greater detail, but the need for detail should only be triggered by express subject interest. Similarly, the fact that research is sponsored by an interested company is an important disclosure; however, the cost of the study or the revenue to the institution above its out-of-pocket cost (e.g., covering "overhead" and defraying the fixed costs of the research program), are not required for informed consent. We believe that, if researchers and institutions were required to make detailed financial disclosures to all subjects of all interests, no matter how small or attenuated, such required disclosures would create a significant disincentive for physicians to become investigators or for institutions to host research. For all these reasons, the Department and all institutions must be very careful about thresholds for determining conflicting interests and the detail required for disclosures to subjects.

Pfizer also recommends that, in the Final Guidance, the Department stress the need for confidentiality of conflict of interest disclosures. Failure to protect the confidentiality of investigators' and institutions' financial disclosures would only discourage full disclosures, thus

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[12] "Materiality" or "significance" as a threshold for disclosure was used in all three of the seminal cases which provided the first principled discussion of informed consent, namely *Wilkinson* v. *Vesey*, 110 R.I. 606, 295 A.2d 676 (1972); *Canterbury* v. *Spence*, 464 F.2d 772 (D.C. Cir.), *cert. denied*, 409 U.S. 1064, 93 S. Ct. 560, 34 L. Ed. 2d 518 (1972); *Cobbs* v. *Grant*, 8 Cal. 3d 229, 502 P.2d 1 (1972). For example, the *Wilkinson* court commented as follows: "[i]t is our belief that, in due deference to the patient's right to self-determination, a physician is bound to disclose all the known *material* risks peculiar to the proposed procedure" [emphasis mine]. *Id.* at 627. Disclosing to patients more risks than those which are "material" is not recommended because this can reduce patient comprehension of risks and benefits through information overload. *See* Ruth R. Faden & Tom L. Beauchamp. *A History and Theory of Informed Consent* (Oxford University Press: New York, NY; 1986) at 306-7:

> Professionals would have to make inordinately lengthy, and in large measure useless, disclosures in order to describe medical and research procedures in terms of all conceivably relevant characteristics, implications, risks, and consequences. Moreover, no matter how comprehensive the disclosure, there is no guarantee that everyone's interests and needs will be served. Finally, ... because of certain problems with information overload, overdisclosure is as likely under most circumstances to lead to inadequate understanding as is underdisclosure.

undermining the integrity of a conflict of interest process. Such a failure could also create disincentives for investigators to participate in research. Although, under our recommendations, disclosures to subjects of significant conflicting interests would be necessary, disclosure of other financial information should be prevented by strong institutional policies on confidentiality in the financial disclosure process.

The Potential for Discouraging and Hindering Medical Research

Reducing bias in research by requiring the identification and management of significant conflicts of interest is a laudable undertaking. The goal of the undertaking, however, is to safeguard the welfare of human research subjects and to protect research integrity, not to discourage or prevent research from being conducted, whenever there is any identifiable conflict of interest. While discouraging research is certainly not the goal of the Department's conflict of interest recommendations, such a chill could be an unintended consequence if these recommendations are implemented in an overly broad fashion. Although many institutions already have reasonable processes in place for evaluating conflicts of interest, we understand that some institutions that have, in response to conflict of interest recommendations, sought to disqualify researchers who have financial interests from conducting research (instead of requiring the management of those interests). For these institutions, elimination, rather than management, seems to be a less burdensome means of complying with conflict of interest requirements. Yet such extreme measures harm the national research enterprise by preventing involvement in research, or deter investigators from undertaking research in which they have financial interests.

In addition, in some cases, financial investments held by investigators in products they are testing may provide incentives for investigators to develop products, or to assist research sponsors in product development and refinement. Such incentives – far from endangering the research enterprise – may serve to advance research. This incentive was recognized by the National Human Research Protections Advisory Committee in its August 2001 report to the Department:

> Conflict of interest analysis should take account of, and contain "compelling and necessary" exceptions for, situations in which physicians who treat unusual conditions invent new devices or develop other interventions, and yet have significant financial interests in those techniques, interventions, or devices. In these cases, [conflict of interest] guidance should not discourage these physicians from acting as clinical investigators, particularly in the initial stages of investigation, since they may be in the best position to undertake critical research with a high assurance of safety for research subjects.[13]

Further, the "incentivizing" effect of institutional financial interests in research has been the policy underlying the *Bayh-Doyle Act*'s granting of intellectual property rights to institutions that produce new technologies (including medical technologies and products) under federal

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[13] *See* NHRPAC, *supra* note 12 at 6.

research grants. This congressional policy actually *produces* institutional financial conflicts of interest, and thus the Department should take care not to adopt conflict of interest rules so severe that they undermine or conflict with congressional intent and existing legislation.[14]

Indeed, overzealous policies that unnecessarily disqualify researchers (or even institutions themselves) chill new research projects, and undermine the purpose of conflict of interest policies. Pfizer urges the Department to investigate, consider and address the current state of institutional conflict of interest policies before putting new recommendations into place. Investigation could be accomplished by commissioning an independent survey of researchers, institutions, IRB officials, and research sponsors to determine carefully the procedures that are currently being used to address financial relationships, and to assess whether one or more of these procedures has had a negative impact on research. We believe that the result of such a survey would be very useful and perhaps surprising. We thus respectfully recommend that the Department consider commissioning a survey of the major academic and research centers.

Documentation and Staffing Requirements

Given the administrative burden that IRBs and institutions already face in reviewing research proposals, new recommendations should strive to limit the growth of additional paperwork obligations.[15] Pfizer recommends that the Department clarify whether IRBs and other research oversight committees are expected to deliberate most or all of the "points for consideration" and "specific issues for consideration" set forth by the Draft Guidance, and particularly whether the results of such deliberations should be documented in IRB or other committee minutes. Documentation of such deliberations for every research project would require a substantial increase in paperwork and staffing, with limited benefit to patient protection. Without further clarity on this issue, institutions may incorrectly assume that they may incur legal or regulatory risks by not documenting all of the recommended points for deliberation outlined in the Draft Guidance. In seeking to clarify this issue, the Department should consider the costs of additional paperwork, including overburdening the IRB process, IRB member defections, direct economic costs, and a slower research approval and oversight process.

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[14] *Bayh-Dole Act*, Pub. L. No. 96-517, 35 U.S.C. (1980).

[15] *See* e.g., D. Philips, "Institutional Review Boards Under Stress: Will They Explode or Change?," *JAMA*, 276:20 (Nov. 27, 1996) at 1623-1626; Snyderman & Holmes, *supra* note 5 (reporting the number of protocols reviewed annually by the Duke University IRB to be about 2200, as of January 2000, with a infrastructure cost for the IRB of about $1 million/year, not including the value of the volunteer time spent by faculty on the IRB).

Conflict of Interest Committees

Pfizer believes that the establishment of new oversight bodies, such as separate conflict of interest committees (COICs) to review investigator and institutional conflicts of interest, may be an unnecessary mechanism for managing research incentives, especially in light of the number of administrative bodies already in operation at most institutions. In addition to IRBs and the innumerable types of committees charged with overseeing every aspect of an institution's operations, institutions have been required to establish HIPAA privacy boards, and some research is also subject to review by data safety monitoring boards. Review of research proposals by one or more additional committees will simply add another level of complexity to the review process, whereby a single proposal may need to be reviewed by up to four or more separate committees: the IRB, one or more COICs, a privacy board and a data safety monitoring board.

A more efficient and effective model would be to designate responsibility for examining conflicts of interest to a single individual, either an existing member of the IRB or an appropriate official within the institution (such as legal counsel or an ethicist), to review any conflicts of interest. Additionally, if the Department is urging or mandating review of conflicts of interest by COICs, it is unclear how physician-investigators conducting research unaffiliated with an institution, such as research performed at private physician practices, would have access to these committees. This needs to be addressed by the Department before it endorses COICs as the appropriate mechanism for regulating conflicts of interest in research.

Pfizer recommends that the Department consult further with a full range of stakeholders, including institutions, IRBs, research sponsors and investigators, to determine the most efficient and effective mechanism for conflict of interest oversight before recommending the establishment of COICs or other new institutional committees.

Conclusion

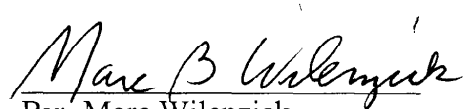
In summary, Pfizer recommends that the Department make its conflict of interest recommendations more specific with regard to how institutions should identify investigator, IRB and institutional conflicts of interest, what the reporting and review thresholds should be, and how institutions can manage those conflicts. When developing those guidelines, Pfizer recommends that the Department be conservative in its approach, so that vital medical research is not discouraged as a result of an excessively procedure-intensive and costly conflict of interest process. Process-oriented recommendations should be clear and simple, as to how they can or should be implemented, to avoid creating confusion among institutions, IRBs, investigators, and sponsors. Finally, we recommend that the Department examine more closely existing conflict of interest processes already in place at major institutions in order to ascertain how these are

currently being handled and what the most effective and efficient approaches are to identifying and managing conflicts of interest in research.

We thank you for the opportunity to comment on the Draft Guidance.

Respectfully,

Pfizer Inc.



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