BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

July 20, 2010

Jerry Moore
NIH Regulations Officer
NIH, Office of Management Assessment
6011 Executive Boulevard, Suite 601, MSC 7669
Rockville, MD 20852-7669

Re: Docket No. NIH-2010-0001 RIN 0925-AA53, Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Funding Is Sought and Responsible Prospective Contractors

Dear Mr. Moore:

The Biotechnology Industry Organization (BIO) is pleased to submit comments on the notice of proposed rulemaking (NPRM) entitled "Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Funding Is Sought and Responsible Prospective Contractors" published in the Federal Register on May 21, 2010.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO long has argued that actual and potential conflicts of interest in research should be identified, disclosed, and appropriately managed. We support policies that emphasize disclosure of financial interests, rather than prohibiting certain relationships. Historically, relationships between industry and researchers have had an enormously beneficial impact on both research and patient care. Financial relationships between academia and industry help bring new products to the market for patients who need them and industry-academic relationships also fuel economic

development in states or regions and increase research budgets, supplementing funds obtained elsewhere.

As clinical trial sponsors, BIO member companies frequently collaborate with academic institutions and academically based researchers. Therefore, conflict of interest policies at academic health centers, medical schools, and teaching hospitals, if not carefully considered and implemented, could affect companies' ability to fund research and ensure commercialization of this research to bring new biotechnology products to patients.

Public-private partnerships and other collaborations among researchers, institutions, industry, and other stakeholders have become more common and increasingly complex. Therefore, BIO advocates conflict of interest policies that balance several objectives: ensuring patients receive high quality care, supporting necessary industry-academic collaboration, and maintaining research integrity.

BIO applauds the National Institutes of Health (NIH) for addressing this important issue and for its efforts to broaden disclosure requirements rather than prohibit beneficial collaborations. However, the justification for some of the proposed measures is unclear and, like the Advanced Notice of Proposed Rulemaking (ANPRM) on the same topic published by NIH last year, the proposed rule remains narrowly focused solely on financial conflicts of interest and fails to address other non-financial conflicts that could create bias.

Our specific comments are discussed more fully below.

I. Financial relationships between academia and industry have had a beneficial impact on research and patient care. New or revised policies should preserve this important benefit.

Some observers have argued that financial relationships between academia and industry inherently create a bias and private money in the health care research setting creates conflicts that may affect research results and/or the quality of care provided to research participants.

As NIH considers these issues, BIO urges recognition that the tremendous investment by the private sector over the past two decades has led to remarkable medical breakthroughs. Government policy to encourage private investment has been a major factor in the development of a biotechnology industry in the United States that is the envy of the world.

Biotechnology has created hundreds of new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS, autoimmune disorders, and many rare conditions. Equally significant, there are more than 600 biotech drug products and vaccines currently in clinical trials targeting more than 100 diseases. The vast majority of these projects involve collaborations with academic researchers.

The federal government recognized the potential benefits of such collaborations almost 30 years ago, with the enactment of the Bayh-Dole Act. The Act has encouraged close working

relationships between industry and academic researchers that take advantage of each stakeholder's expertise. It permitted universities and small businesses to own inventions made as a result of federal funding through patenting and authorized licensing to industry. The policy objective was to encourage the licensing of inventions developed in universities to industry, which would develop them further into products for patients. The Act has been enormously successful. The incentives it enabled have spurred research, led to the creation of new jobs, and facilitated the development and commercialization of important public health products, including a Hepatitis B vaccine, human growth hormones, and synthetic penicillin.

Thus, while there is a small risk that some relationships between industry and academia may be abused by bad actors, this must be balanced with the great benefits that continue to accrue to patients because of industry funding to augment public funding of academic research. Among these benefits are added opportunities for the full and appropriate testing of biotechnology products to secure approval for their marketing. Policies that prohibit such funding, rather than ensure that it is properly disclosed, may appear to address the small risk but, at the same time, ignore the great benefit. Such policies are not in the best interest of patients.

II. The proposed elimination of the exception for SBIR/STTR Phase I applications is unduly burdensome.

Current NIH rules exempt SBIR/STTR Phase I applications from conflict of interest disclosure requirements. By eliminating this exception, the NPRM treats small business applicants as "institutions" for the purposes of the rule. This could present significant difficulties for start-up and emerging companies because they would be forced to adhere to the rule's extensive requirements for reporting and managing conflicts of interest requirements - the same rules with which large research institutions with substantially more resources will be complying. Such small companies, which comprise a majority of BIO members, provide much of the pipeline of new discoveries that can translate to important medical products. Most of these companies have no revenues and must use their resources for research endeavors. Imposing the significant responsibilities under the rule on these companies would be overly and unnecessarily burdensome.

Although the regulatory analysis of the proposed rule acknowledges that approximately 2,000 small business concerns would be affected by this change, the proposal fails to identify an existing problem that would be remedied by eliminating the exemption. Instead, the NPRM justifies eliminating the exception by citing the increase in the amounts of grant awards and the likelihood that Phase I awardees eventually would be granted Phase II awards and subsequently be required to comply with the regulations.

In its 1994 NPRM addressing the same subject, the Public Health Service (PHS) determined that because of the nature of SBIR/STTR Phase I applications, it would be "burdensome and unproductive" to require reporting at that stage.[1] The 1995 final rule's regulatory impact statement indicated that the rule would not have a significant impact on small businesses in large

[1] 59 Fed. Reg. 33242, 33244 (Jun. 28, 1994).

part because of the exemption for Phase I applications.[2] It limited the exception to Phase I noting that Phase II grants are for larger amounts, which would allow companies to offset the cost of compliance with disclosure and reporting requirements.

The NPRM does not indicate whether costs of compliance would be offset sufficiently for Phase I applications. It also does not provide any evidence that there has been increased bias from Phase I applications that would justify the increased administrative burden. Moreover, it does not justify expanding the scope of current rules, since disclosure and reporting requirements can be imposed if and when Phase II awards are made.

BIO believes existing rules already strike the appropriate balance and urges NIH to retain the exemption for SBIR/STTR applications for Phase I funding.

III. The proposed rule does not take into consideration non-financial conflicts that could be harmful to patient care or research.

In its comments responding to the 2009 ANPRM, BIO urged NIH to include requirements for researchers to disclose non-financial conflicts, such as desire for faculty advancement, competing for research grants, and receiving prestige from publishing. Articles in the scientific literature have suggested these influence behavior.[3] We were disappointed the NPRM did not do so.

Once again, we urge NIH to include requirements for researchers to disclose non-financial conflicts. These can be disclosed using the same process as financial conflicts. The institution's conflict of interest committee – or the IRB if appropriate – should have the authority to manage the conflict or prohibit the researcher from participating in a particular project.

IV. More research is needed to determine whether financial or non-financial conflicts affect research quality or patient care.

Most conflict of interest policies focus exclusively on financial conflicts and potential conflicts. Yet, there are few empirical data about the impact of financial conflicts on research quality or patient care. In fact, as we pointed out in our response to last year's ANPRM, recent studies demonstrate that many assumptions about financial conflicts of interest are not true[4] ,). Some published analyses of university financial disclosure policies cast doubt not only on disclosure as a technique to manage conflicts but also on whether many financial relationships actually affect patient decisions regarding whether to participate in a research project[5].

[2] 60 Fed. Reg. 35810, 35814 (Jul. 11, 1995).
[3] For example, see Korn D. Conflicts of interest in biomedical research. *JAMA.* 2000; 284:2234.
[4] For example, see "Knowing Doctor's Financial Interests Doesn't Deter Clinical Trial Participants", *Science Daily*, April 2, 2008.
[5] For example, see Weinfurt, KP, Dinan, MA, et al, "Policies of Academic Medical Centers for Disclosing Financial Conflicts of Interest to Potential Research Participants", *Acad Med.* 2006 February; 81(2): 113–118)

Moreover, while agencies and institutions typically identify a conflict based on a defined financial relationship between the researcher and a commercial entity (such as the NPRM's use of a $5,000 threshold), there are few data to suggest that a specific dollar threshold would influence a researcher's behavior and if it did, what that amount would be. Perhaps reflecting this lack of consensus, the amount deemed to trigger a conflict varies by institution and by regulatory agency.

BIO urges NIH to sponsor research regarding the actual effects of financial conflicts on research quality before requiring compliance with the lower threshold of $5,000 that is suggested in the NPRM. In fact, neither the NPRM nor the comments submitted in response to the ANPRM provide evidence demonstrating that $5,000 is an appropriate threshold to reduce bias in research. The administrative burden of complying with the new threshold seems to outweigh any benefit, since there is little research to suggest what amount of money is likely to cause bias.

In addition, more research is needed to determine the influence of non-financial conflicts on patient care or research quality. We suggest that the NIH sponsor research in this area as well. Since NIH spends billions of dollars to support research and is developing a regulatory framework to govern the research – including management of conflicts of interest – it is essential for the agency to have sufficient data to make appropriate policy decisions.

V. The NIH should adopt the US Food and Drug Administration (FDA) standard for financial interests to be disclosed.

A "Significant Financial Interest" is defined by the current regulations as anything of monetary value, including but not limited to: salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include the following types of financial interests: salary, royalties, or other remuneration from the Institution; any ownership interests in the Institution, if the Institution is an applicant under the SBIR/STTR program; income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities; income from service on advisory committees or review panels for public or nonprofit entities; an equity interest that, when aggregated for the Investigator and the Investigator's spouse and dependent children, does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed $10,000.

BIO recommends that the NIH adopt the FDA standard. FDA rules apply to those potential conflicts that could affect the reliability of the data in a marketing application submitted to FDA. They focus on the bias that could arise from an investigator’s financial interest in the outcome of a study because of the way payment is arranged, because the investigator has a proprietary interest in the product, or because the researcher has an equity interest in the company sponsor of the study.

The FDA regulations require sponsors to disclose financial arrangements with clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor. Sponsors must disclose investigator equity interests of $50,000 or more or if they pay $25,000 or more to the investigator or institution exclusive of the cost of the trial or other clinical studies. Harmonization of FDA and NIH requirements would allow investigators to follow one set of rules for disclosure of relevant financial information. This will reduce confusion and improve consistency, compliance, and efficiency.

VI. The final rule should include further revisions to address institutional conflicts of interest.

BIO believes that institutional conflicts have the potential to affect research and patient care and should be identified and managed. As a result of the varied comments received by NIH in response to the ANPRM, the agency did not include a proposed section in the rule to address such conflicts. NIH states that it will consider the issue carefully and may address it at a later date. However, an attempt to address institutional conflicts of interest was dropped from the 1994 rulemaking for a similar reason and was to be addressed in a separate rulemaking.[6] Since the issue has yet to be addressed, BIO urges NIH to include at least a preliminary provision requiring the identification and management of institutional conflicts of interest.

Conclusion

Thank you for the opportunity to comment on the proposed rule. We look forward to working with NIH and other stakeholders to address these issues.

Respectfully submitted,

/S/

Andrew J. Emmett, M.P.H.
Director for Science and Regulatory Affairs
Biotechnology Industry Organization

/S/

E. Cartier Esham, Ph.D.
Director, Emerging Companies Health
and Regulatory Affairs
Biotechnology Industry Organization

[6] *Id*. at 35813.