CONFLICT OF INTEREST, PROTECTION OF PUBLIC OWNERSHIP, IN DRUG DEVELOPMENT DEALS BETWEEN TAX-EXEMPT, FEDERALLY SUPPORTED LABS AND THE PHARMACEUTICAL INDUSTRY PART 2

HEARING

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY

OF THE

COMMITTEE ON SMALL BUSINESS HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

WASHINGTON, DC, JUNE 17, 1993

Printed for the use of the Committee on Small Business

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CONFLICT OF INTEREST, PROTECTION OF PUBLIC OWNERSHIP, IN DRUG DEVELOPMENT DEALS BETWEEN TAX-EXEMPT, FEDERALLY SUPPORTED LABS AND THE PHARMACEUTICAL INDUSTRY—PART 2

THURSDAY, JUNE 17, 1993

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND TECHNOLOGY,
COMMITTEE ON SMALL BUSINESS,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:38 a.m., in room 2359–A, Rayburn House Office Building, Hon. Ron Wyden (chairman of the subcommittee) presiding.

Chairman WYDEN. The subcommittee will come to order.

Today, the Subcommittee on Regulation, Business Opportunities, and Technology continues its inquiry into bias, conflict of interest, and subversion of public ownership rights in collaborative agreements between tax-exempt, federally supported, research institutions and the pharmaceutical industry. As we have learned in previous hearings, these matters can have a devastating impact on small, technology-hungry companies.

We are pleased that our first witness this morning will be Dr. Bernadine Healy, Director of the National Institutes of Health. Dr. Healy, at the subcommittee's request, has been investigating a collaborative agreement between the Scripps Research Institute, a La Jolla, California-based laboratory which receives $70 million in NIH grants, and the Sandoz Corp. of Switzerland. Specifically, the agreement gives Sandoz exclusive access to almost all research and technology produced at this flagship medical research facility over the next 10 to 20 years. In the Chair's view, this deal amounts to a corporate takeover of one of our biomedical research crown jewels which very significantly is funded for the most part by the Federal taxpayer.

Our inquiry comes at a critical time. Federal research support is declining, and, as a result, drug companies, Federal research labs, private universities, and nonprofit organizations are moving to put together financial arrangements to fill this gap. Unfortunately, some of these deals may put the public interest in the back seat and private interests at the driver's wheel.

The subcommittee has learned that many of the economic interests seeking to put together these research partnerships consider

the Scripps-Sandoz contract an attractive model. We hope to disabuse them of the notion that this is the way to go, given that the National Institutes of Health has said that the proliferation of these contracts could destroy the NIH extramural grant program.

Finally, small businesses, which already face a crunch on credit and a crunch from foreign trade barriers, now confront the possibility of a technology-access crunch. These kinds of agreements can be anticompetitive and are especially harsh on our small entrepreneurs.

At our March 11 hearing, Dr. Healy termed the Scripps-Sandoz agreement possibly illegal and potentially destructive to the NIH relationship with many other research institutes that share almost $8 billion in Federal biomedical research funding. We expect the National Institutes of Health to define their objections to the Scripps-Sandoz agreement and to lay out the NIH plan for remedy.

Also today, Dr. Healy will set out the results of a 100-institution survey her agency has conducted at the subcommittee's request to explore the shape, character, and variety of 375 collaborative agreements within the NIH grantee community.

Scripps asserted at our last hearing that their collaborative arrangements were a little different from others that are common within the academic community. Given our concerns regarding the Sandoz agreement and an earlier exclusive rights contract between Scripps and Johnson & Johnson, this statement is troublesome. Therefore, the NIH survey is of vital interest and importance to the course of this debate.

The Chair believes that it is critical that the Federal Government move quickly to set out clear rules of the road to govern the growing activity in collaborative agreements between academia and industry. This is necessary because current rules articulated in the Bayh-Dole Act were written before many of the problems that have been uncovered by this subcommittee came to light.

I wish to make clear that it is not our intention to reinvent the Bayh-Dole Act, but the Chair believes that it is important to recognize that we face issues today that were not contemplated by the framers of the 1980 Federal law. Those problems need to be dealt with through reasonable adjustment and amendment. For example, it is vital that the Federal Government provide clarification as to the kind of business arrangements between academic administrators, scientists, and drug companies which the NIH and the Food and Drug Administration would consider to be a conflict.

The Chair notes that Scripps was invited to testify at today's hearing. They have declined, citing a preference to work out their differences with the NIH privately.

This subcommittee also is very interested in the matter of bias in clinical trials. Recently, the subcommittee alerted Dr. David Kessler, the FDA Administrator, to the potential for conflict of interest in the determination of proper dosage levels for the drug Ceredase. The subcommittee located a major gap in FDA disclosure rules for investigators conducting these important clinical trials. At present, little is required as to the disclosure of business relationships that investigators may enjoy with the manufacturers of the drugs that they test.

At the subcommittee's request, the FDA announced this week that they are writing new guidelines for this area, including a requirement that researchers declare whether they have a financial stake in the drugs that they test.

It is also our understanding that the FDA is asking the manufacturer of Ceredase to change its labeling with regard to lowering prescribed dosage levels, and this can be of great benefit to the consumer who now pays as much as $360,000 per year for this medication.

It is important to note that Ceredase, like so many other important new drugs, had its genesis in taxpayer-supported research. The Chair believes that Federal agencies like the National Institutes of Health and the Food and Drug Administration must assume new responsibilities as the guardian of those research dollars given the growth in the number of collaborative research agreements.

The taxpayer is a critical partner in this research and also deserves the very best price possible from the results of public/private collaboration. Protecting the public ownership in developing technologies, whether at Federal Labs or at taxpayer-subsidized universities, gives the Government one very important lever on the pricing determination. Government and this subcommittee will push hard to ensure that technology transfer takes place.

But the Government also has an obligation to guard against the Macy's bargain basement approach. The public does deserve more protection than just throwing open the door to private interests who want to grab valuable technologies dirt cheap. When a collaborative research and development deal is cut, Federal agencies must make sure that the taxpayer's throat isn't sliced with the same knife.

Following Dr. Healy, the subcommittee is going to hear statements from the representative of a small, high-technology firm that has been denied a useful technology because of one of these comprehensive exclusive agreements with another firm. We are also going to be hearing testimony from the American Association of Medical Colleges which represents many of the academic partners in collaborative agreements, and from a leading academic scholar who has done considerable research in this area.

[Chairman Wyden's statement may be found in the appendix.]

Chairman WYDEN. Before I welcome our witnesses, we want to have the opening statements of our colleagues. I particularly want to recognize my friend from Texas, Mr. Combest, who has been a very helpful member of this subcommittee. Obviously, these issues are in no way, shape, or form partisan, and it has been a pleasure to work with him. I want to recognize him for any statement that he cares to make.

Mr. COMBEST. Thank you, Mr. Chairman, for calling the hearing and for your opening remarks.

Today's hearing will focus on the National Institutes of Health's ongoing review of issues concerning commercialization of taxpayer-funded research. I would like to initially discuss the great success story of the Bayh-Dole Act. As you all know, this act is the vehicle that allows technology to transfer from Government-supported institutions to productive private agreements. This revolutionary act

has enabled life-saving drugs and technologies to reach needy consumers that, prior to the adoption of this act, may never have made it off the shelves of the NIH or a sponsored institution.

The success of Bayh-Dole can be seen in the number of patent applications filed. In the 10 years before the passage of Bayh-Dole, only 890 patent applications were filed on inventions developed with the NIH support. In the 10 years since, three times that many patent applications have been filed. I am also pleased to note that, besides Mr. Ralph Nader, everyone, including Dr. Healy, has testified in overwhelming support of this act, Bayh-Dole.

I believe like most pieces of legislation, however, there are segments of Bayh-Dole that must clearly be improved. Currently, it would appear that the multiple goals of the legislation can be contradictory. While small businesses should be given preference under Bayh-Dole, clearly the implementing regulations state large businesses should not be precluded. Furthermore, while collaborations are encouraged, it would appear that in many instances small business may not have the financial or technical capabilities to bring these technologies to market. Therefore, should such collaborations exist if not all the criteria of Bayh-Dole are met?

I plan on working with the NIH, Chairman Wyden, and industry to improve Bayh-Dole. I believe we must give clear guidance both in conflict-of-interest regulations and in implementing cooperative agreements. Having said this, any changes must be fully considered to ensure full accountability for U.S. taxpayers while not squelching the success stores under Bayh-Dole.

Mr. Chairman, I would be remiss if I did not touch on some of the concerns that were voiced at the previous hearing regarding the proposed Sandoz-Scripps agreement. I, too, have some concerns regarding the small business access to such research and to the allegations of conflict of interest. I believe that when questions are asked the parties involved have the responsibility to sit down and work out the differences between them. It is my understanding that both Scripps and Sandoz have related their willingness to change this proposed agreement to meet the concerns of the NIH and of this subcommittee.

In closing, Mr. Chairman, I have received copies of letters from both Scripps and Sandoz to this effect and would ask unanimous consent to enter them into the record at this time.

[Mr. Combest's statement may be found in the appendix.]

Chairman WYDEN. I thank my colleague for his excellent statement, and I certainly want to pursue these issues with him as we go forward with the NIH. Certainly, without objection, the documents the gentleman mentioned will be entered into the record at this point.

[The letters may be found in the appendix.]

Chairman WYDEN. Let me recognize now our colleague, Mr. Andrews from Maine, who has also done excellent work in these areas of health and drug pricing, and we welcome him to our subcommittee and today's hearing.

Mr. ANDREWS. Thank you, Mr. Chairman.

I have no formal statement except to congratulate you and to thank you for the work that you have done in this area. This is an extremely important subject, particularly with respect to my con-

stituents in my district who are very, very concerned about not only fiscal responsibility with their tax dollars but also the issue of the escalating price of prescription drugs.

So, I am very pleased to be here, Mr. Chairman. I thank you for your leadership, and I am very eager to hear today's testimony.

Chairman WYDEN. I thank my friend. Let me recognize our other colleague, Mr. Torkildsen, again, a colleague from a high-technology, entrepreneur-oriented district, and we welcome his involvement.

Mr. TORKILDSEN. Thank you, Mr. Chairman. I thank you for holding the hearing. I have no statement of my own this morning.

Chairman WYDEN. All right.

Our friend from Missouri, Ike Skelton, who has also been a member of this subcommittee and active consumer advocate for many years. We welcome Ike.

Mr. SKELTON. Mr. Chairman, I not only wish to say that you are doing pioneering work in this area but also congratulate you on that work, as well as this hearing. I look forward to the testimony.

Chairman WYDEN. I thank our friend.

It appears no one is going to have much to say before Dr. Healy, but we want them all to have the opportunity; our friend Mr. Dickey as well, a new Member.

Chairman WYDEN. All right. Dr. Healy, they all are anxious to hear from you. Let me say right at the outset that we have very much appreciated all the cooperation and assistance that you have shown this subcommittee. You have always been extremely helpful in working with us and have felt that this inquiry is important. We thank you for it.

I think you know it has been the practice of our subcommittee over the years to swear the witnesses. Do you have any objection to being sworn?

Dr. HEALY. No.

Chairman WYDEN. Also, I am told by the staff that your associates at the table are from the NIH, and because they may be involved in answering questions, it would be helpful to have them sworn at this time as well.

Dr. HEALY. Yes, Mr. Wyden. May I introduce them?

Chairman WYDEN. That would be very helpful.

Dr. HEALY. Mr. Dick Lambert, Ms. Sandy Chamblee, and Ms. Dacia Clayton. They are all lawyers.

Chairman WYDEN. Very good. We know how Shakespeare treated you all.

The only thing we will ask of all of you good legal minds is, when you do speak, if you could get close to one of our microphones. We have probably the most infernal microphones in the Capital.

We welcome all of you, and I gather none of you have any objection to being sworn then this morning. Please rise and raise your right hand.

[Witnesses sworn.]

Chairman WYDEN. We welcome all of you.

Dr. Healy, we will put your prepared statement into the record in its entirety. Why don't you proceed in whatever fashion that you consider appropriate.

TESTIMONY OF BERNADINE HEALY, DIRECTOR, THE NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DACIA CLAYTON, SANDY CHAMBLEE, AND RICHARD LAMBERT, COUNSELS

Dr. HEALY. Thank you, Mr. Chairman and subcommittee members. I am happy to put my prepared statement into the record, and I will have some brief remarks. I certainly welcome this opportunity to update you on the progress of the NIH's ongoing review of issues concerning the commercialization of the NIH-funded research. I will provide the subcommittee with the preliminary results of our analysis of research support agreements involving approximately 100 grantee institutions, including the pending agreement between the Scripps Research Institute and the Sandoz Pharmaceutical Corp.

Actually, it is 2 weeks from today, July 1, that marks the 12th anniversary of the Bayh-Dole Act. Around the time of the passage of the Bayh-Dole Act, there were predictions of potential problems and abuses. In the early 1980's, the chairman of the House Science and Technology Oversight Subcommittee convened several hearings on university-industry cooperation in response to this bill and focusing on biotechnology.

Specific concerns raised by the committee back then included whether research support agreements would stifle the free exchange of knowledge, promote secrecy, and distort academic research priorities to conform with commercial aims. There were speculations that companies might exploit taxpayer-funded research without providing an adequate return to the public. Of particular concern was the possibility that a foreign firm might skim the cream produced by decades of taxpayer-funded research.

The committee also expressed concern as to whether universities had effective mechanisms to buffer them from influences that might subvert their mission of education, research, and public service.

Fortunately, there is little evidence that these adverse effects have materialized. In fact, the risks have proved to be well worth taking. Highly productive university-industry relationships have blossomed since the passage of Bayh-Dole. We have seen a dramatic increase in the number of patents granted to American universities over this time. Total university revenues realized annually from licensing royalties has almost tripled since 1986. Moreover, in the 1980's industry's support for university research grew faster than other sources of funding.

Thus, the Bayh-Dole Act is not just working, it is working well. It may be necessary, however, to fine-tune the act's implementing regulations which are promulgated by the Department of Commerce but also may be necessary for granting agencies like the NIH to better clarify how certain principles of the act should be acknowledged and affected by the agencies and their grantees.

Let me cite briefly the key principles and objectives of the Bayh-Dole Act. The Bayh-Dole Act promotes the commercialization of taxpayer-funded inventions by U.S. industry and labor. It promotes free competition and enterprise. It promotes collaboration between U.S. businesses and universities as well as other nonprofit institutions. It encourages maximum participation of small businesses in

federally supported R&D, and it encourages job formation by requiring preference be given to companies that will manufacture licensed inventions in the United States.

At the request of this committee and you, Mr. Chairman, the NIH has embarked on a review of the research support agreements entered into by our grantee institutions in the context of these Bayh-Dole principles. Although preliminary at this point, I wish to share with you some of our findings.

We reviewed approximately 375 agreements involving some 100 institutions. We found that approximately 45 percent of the agreements are with small businesses. Roughly 80 percent of the agreements are with U.S. companies. Approximately 86 percent of the agreements are project specific, very focused, and very narrow. More than 90 percent of the agreements reviewed were for 5 years or less and for $5 million or less. Most institutions with agreements had been with multiple industrial partners, some with as many as 30 or 40 at a time.

Although in general most of the agreements appear to be in compliance with the Bayh-Dole Act and do not overly restrict scientific freedom, our survey does raise a few concerns. For example, only a small percentage of the agreements include a provision referring to U.S. manufacturing requirements of the Bayh-Dole Act. The breadth of some of the agreements, we also think, needs further reviews. Overly broad agreements, especially with large companies, may limit the access of small businesses and others to federally funded technology, and in at least one instance an institution agreed to assign to its industrial partner its ownership rights to inventions from federally funded research without first obtaining required Government approval, and this is a violation of the Bayh-Dole Act.

We plan to look more closely at all of these agreements. However, based on this initial review, we are convinced that the Scripps-Sandoz agreement is unlike any other agreement we have reviewed, and it is so in many key respects.

No other agreement requires an institution to help industrial partners seek a waiver from the Bayh-Dole requirement that it manufacture in the United States.

No other agreement allows industry to remove research projects from the hands of scientists at that academic institution's laboratories, and take that research to an industrial lab anywhere in the world, and then restrict the academic scientist from seeking funds from other sources or support to continue that work.

No other agreement provides for industrial representatives to be on the institution's board of directors.

No other agreement requires that the industrial partner review the institution's invention reports prior to their submission to the NIH with the ability to comment on them.

No other agreement requires the institution's president to encourage scientists to pursue projects of strategic interest to the industrial partner, thus influencing the overall research mission of the institution.

No other agreement gives the industrial partner the right to broadly restrict the institution's scientists from consulting with

third parties and provides a mechanism for financial payment to such scientists for not consulting.

Moreover, the agreement also gives Sandoz the right to review all existing commercialization agreements with other corporate sponsors and the right to restrict access to the Scripps Co. scientists from other institutions.

Only two other agreements allow the industrial partner to assume majority control over joint scientific councils which direct the course of research under these agreements. However, neither of the two other agreements give the industrial partner first option to exclusively license virtually all federally funded technology, including all inventions not supported directly by that agreement.

In short, the Scripps agreement with Sandoz is atypical in that it trades virtually all of Scripps' intellectual output derived from taxpayer-supported research in exchange for large amounts of funding from a single, private, foreign interest over a very long period of time. It is not at all surprising to me that a columnist from the San Diego Union Tribune called the Scripps-Sandoz agreement a leveraged buy-out of a taxpayer-supported laboratory.

Mr. Chairman, by virtually any measure, this agreement is an aberration and, in my view, a dangerous exception to an otherwise successful record of cooperation between industry and the NIH-funded institutions. Because it deviates from the principles of Bayh-Dole and also impinges on the freedom of inquiry that is central to scientific research, I fear that the Scripps-Sandoz agreement may tempt rash wholesale indictments of the many productive relationships that the Bayh-Dole Act has catalyzed between the NIH institutions and U.S. industry over the years.

The NIH has taken seriously its involvement in issues surrounding commercialization of its research. As I cite in my longer statement, the NIH is taking steps to ensure that our grantees uphold the Bayh-Dole Act in their agreements with private industry. We are currently engaged in a number of activities to further understand the range and the purpose of agreements between our grantees in industry. Our efforts should lead to policy recommendations in strong support of technology transfer.

These activities will be spearheaded by the Task Force on the Commercialization of Intellectual Property Rights from the NIH-supported extramural research, an internal NIH working group comprised of scientists, program officers, technology transfer specialists, and counsel. The NIH will continue its discussions with Scripps pertaining to their proposed agreement with Sandoz. We expect that the concerns we have raised will be addressed.

If, however, Mr. Chairman, the deficiencies underlying the agreement are not corrected, the NIH will, acting through the assistant secretary for health, place appropriate restrictions on all future grants the NIH makes to Scripps.

The NIH plans to hold an open forum involving grantees, research institutions, associations, industry, and members of the general public to address these issues as well. We hope to develop guidelines to better clarify issues related to the Bayh-Dole Act. We would expect such guidelines will enable the NIH to promote compliance and maintain involvement in these issues without unwarranted intrusion in the universities.

In closing, allow me to put my concern about the Scripps-Sandoz agreement in a broader context. Some have claimed that the NIH response reflects xenophobia, a fear of that which is different or even foreign. That is not my fear. Rather, I fear what has become all too familiar across this country in recent years—namely, the loss of American jobs in technology.

Over the past 12 years of the Bayh-Dole Act, we seem to have avoided such pitfalls for biotechnology. Nevertheless, the agreement between Scripps and Sandoz shows that those fears are not groundless. I fear that if we do not ensure proper compliance with Bayh-Dole, the burgeoning U.S. biotechnology industry could falter. I fear that small businesses, which are the prime producers of new jobs and innovative technology in this country, will be restricted in their access to taxpayer-funded research.

I am concerned that the spirit of free inquiry and discourse in science, so essential to science, will be compromised by exclusive industrial partners that wield excessive control and influence. I fear that so-called leveraged buy-outs of taxpayer-supported, academic centers of excellence by large corporate interests, foreign or domestic, could undermine the trust the public places in the NIH and its grantees.

Mr. Chairman, in my parting words as the NIH director, I ask this committee to assist the NIH in its efforts to safeguard American research and economic interest through greater clarification and enforcement of the Bayh-Dole Act.

Thank you.

[Dr. Healy's statement may be found in the appendix.]

Chairman WYDEN. Dr. Healy, thank you very much for a very helpful overview and an excellent way to begin this morning.

I am going to recognize first my colleague, and tell you, as we have talked before, that this committee isn't running a xenophobic operation. I am one of the few people in the House who will still call himself a free trader, as one of the Democrats who voted with George Bush for a capital gains incentive. So, much of what you have talked about in terms of American enterprise constitutes the views I share, and I am going to be touching on it here in a moment.

But let me recognize first my friend from Texas, Mr. Combest, to begin the questioning.

Mr. COMBEST. Mr. Chairman, thank you. That is unique. You are also very fair, let me say.

Dr. Healy, I agree with everything you said in your statement and in the direction that you want to see this go. The NIH is in a position of protecting the taxpayer dollar in that agreements between companies, a research company or laboratory, that may be receiving the NIH money and another company, private sector, don't have to be agreed to. They don't have to be written off by the NIH. You do hold a tremendous amount of leverage over them, and that is, of course, the fact that the NIH makes the determination of where the grant funds are going for research.

It would then obviously seem to me that it is in the best interests of a company or to companies that are entering into an agreement to have the approval and the blessing of the NIH, and I presume that we are in a little bit of a unique situation in this instance

since most proposed agreements, as we know this one has not been finalized, but proposed agreements are probably not aired in the public as much as this one has been. I would also presume—and please tell me if any of these presumptions are incorrect—that there may be difficulties in proposed agreements which, by sitting down and explaining the differences and the concerns, can be worked out.

It is also my understanding—and I submitted for the record transmitted letters—that, I think, the parties in this instance are very willing to do that. Many of the concerns, and I agree with you, are concerns that are very legitimate and very possibly can be worked out.

Those which, as you said, make this a very unique—it was not exactly the word you used, but this is somewhat different than most you have seen—those may be resolved, and I would hope that they can be, and I would certainly think that is the course that should take place.

It has only been within the last few days, I think, that the transmission of these letters has occurred, but I would hope that is the case, and it can be worked out, and that eventually something can come forward.

Under the Scripps-Sandoz agreement, it is my understanding that there are about 40 small companies that have licensing or collaborative agreements with Scripps. Is there any reason to think that under the Sandoz agreement that might change?

Dr. HEALY. As I and my lawyer colleagues, after reading the agreement, have determined, it does appear that Sandoz will have some controlling responsibilities or authorities over those existing contracts when they come up for renewal, if any of them come up for renewal, and they are with mainly small companies, and that Sandoz has the right to review the terms of those agreements and have some kind of a say as to whether those agreements should continue.

This contract does not terminate existing contracts with those 40. They come under a category of accepted research, but over time, as these contracts expire, most of which are short-term, then Sandoz has the right to participate in discussions as to whether or not they will be reinitiated.

Mr. COMBEST. In agreements which might be similar in that there is a major private firm that is investing money with a laboratory, would that be unique?

Dr. HEALY. From our review of the contracts, it is certainly unique for that kind of broad level of oversight of all other commercial relationships. Most of the contracts that universities have are fairly, what we would call, in the range of a million dollars or less. More than half of them—more than 80 percent of them—are $5 million or less, and most of them are focused on a specific discipline, a specific area, a specific project, and a specific intended outcome.

It is understandable that if you have such a relationship focusing on a particular growth factor that the company is interested in, that that company would not want that particular scientific group or laboratory to engage in other collaborative relationships with

other companies on the same or similar work in the same field. So, those kinds of restrictions are customary.

What is unusual is that all agreements, present and future, that Scripps engages in with outside commercial concerns comes under the scrutiny of Scripps. There is no defining area of science; it is just anything that has to do broadly with the biomedical research area.

I would just like to mention one other thing, and that is that we believe that the Bayh-Dole Act gave our grantee institutions a major privilege, a major responsibility, and a major authority, specifically to hold title to their patents and to oversee the licensing of those patents without the Government intruding itself in those negotiations or in the development of those contracts. We have never required prior approval of any of these arrangements, but we do have a requirement that they file licensing agreements with us so that we have an ability to monitor the activity that is going on among our grantees.

One concern that we have is that if contracts like the Scripps-Sandoz proliferate—and indeed when this first came to light there was some sense that might be the case back in December and January—I think that it will, in fact, force the Government to intrude itself in relationships that largely work very well, and I will additionally mention that the way this really came to our attention was not through some prior approval process but because of concerns registered by the public, by their own community, and by the newspaper in San Diego. They were the ones who said this is a problem and alerted us to it and, I think, alerted the subcommittee to it.

Mr. COMBEST. Again, I think that is good that discussion has taken place, and I am hopeful. I would be very interested in the end result of this in that we have been able to have some hearings on the proposed agreement up to this point that at some point, if it does reach some kind of a conciliatory rearrangement, that everybody is all happy in this, I would hope that we can also discuss that.

Coming from the business world as a background, and a small business—very, very small, I might add—is one of the reasons I sit on this committee. Small business is the backbone, really, of the work force in this country and the "mom and pop" operations, I am supposing, in everyone's district, and yet I realize also, there is a certain limitation, obviously, that I, as a small business person, would not be able to participate in a large monetary way in involving myself if I had been in this type of business. We have now some 40 small companies that are working—small businesses—that are working with Scripps.

What I would like to see us achieve is that we make for certain that under Bayh-Dole we do look at what has changed and what can we do to try to encourage the small business participation and yet realizing that the amount of capital that is required and the long-range investment that is necessary is not going to be possible by small business.

So, there are going to have to be no exclusions to large business operations such as agreement with Scripps, whoever the large company might be, and it is trying to find that balance that we are

certain that the taxpayer's interest, and that we are certain that the taxpayer's money, is protected and, at the same time, not being so strict and stringent that we are limiting the incentive that might be there to cause a business to enter into an agreement. It is that fine line that I am seeking and yet is many times very difficult to achieve because you may not know until afterward whether we have done good or done harm. It is a real dilemma. I find that in a lot of areas.

Certainly we have a responsibility, I think, and you do as Director of the NIH and your agency, to protect the taxpayer dollar and yet to do everything that is possible to try to get as much research and technology done in the field of pharmaceuticals and other areas in health.

As we go along, and from your experiences now or later in your career, whatever that may be, I would think we would be missing a valuable asset if we did not call upon your expertise in helping us to arrive as much as possible at what that balance is prior to the time that we put into regulation or into law a change in Bayh-Dole, again, with the understanding that we want to make it better. I think there is an overwhelming support for it, not always maybe something that we may solicit.

I would hope that you might feel free to, if you see us wandering off the path in sort of a crazy direction which is, I understand, not uncommon for us to do, weigh in on that with us. I would extend that invitation to you to do that, because those of you who have dealt with these on a day-to-day basis certainly have much more expertise in it than many of us do who have a goal in mind and make sure that we are not underly restrictive or overly restrictive. Again, we miss a tremendous information source out there if we don't have you call on it. As the chairman indicated, I appreciate your being very responsive.

Let me also just mention one other thing which I was not aware of and, again, just make sure that we do have it in the record. It is my understanding that Sandoz employs in this country about 10,000 people who are Americans, for their business operations in this country.

Dr. HEALY. Yes; if I could make two comments.

Mr. COMBEST. Please do.

Dr. HEALY. Yes; thank you.

First, we have lived extensively with Bayh-Dole, and I personally have read that bill many, many times with the help of my colleagues, and it is my impression that the Bayh-Dole Act—my personal view—is a brilliant document. It does give small business preference, but it does not exclude large businesses, and, in fact, when we look at it 12 years later, I think there was enormous wisdom in the way it was crafted. Roughly half of these agreements are with small businesses, but about half are with large businesses. So, we have not excluded large businesses, but we have mandated in the law—and you write the law—a preference for small businesses, which I think is appropriate.

Now, if you have an agreement like these very large agreements, $30 million a year, proliferating, particularly locking up all of the research output, all of the intellectual output, all of the NIH grant output, for an institution, regardless of what it might be, regardless

of its field, regardless of where it is going, and to lock it up for 10 or 20 years, and you have more than a few of those agreements, you are essentially freezing out small businesses.

There is no way a small business can come in with their typical pot of money, which is maybe $50,000 or $100,000, and say, "We have a special interest in this particular growth factor," or this particular drug, or this particular test, "that we want to develop." They will be frozen out. They will only be allowed in if it is a leftover, if it's a crumb that falls off the table, that the large company has decided that they don't want to invest in.

In addition, under this agreement, if the large company says they don't want something, and then a little company comes along with their $50,000 or $100,000 and want to participate with the crumb that has fallen off the table, Sandoz has the right to go back and pick up that crumb, look at it again, and see if maybe it is a pearl of great price that they ignored. So, I think that inherently subverts the intent and the principles of Bayh-Dole in a very substantial way.

I would also just like to say that I think when you create these enormous options you almost turn medical research into finance, not research. It becomes selling commodities or selling options. It isn't really focusing on a particular piece of discovery and try and take that invention, that piece of discovery and turn it into a product that will benefit the American public.

With regard to the foreign issue of Sandoz, Sandoz U.S.A. certainly employs a substantial number of people and is incorporated in this country. The disagreement is also an agreement with the parent company in Switzerland. What concerns us about this is not the fact that there is an agreement with the parent company in Switzerland, but two clauses in that agreement which make us raise concerns about the foreign ownership.

First, that research can be taken out of an American laboratory, the NIH-funded research, and can be moved to Switzerland, and the NIH American scientist is essentially frozen out of participating in that research, and can only do that research again if the foreign laboratory decides they are not going to pursue it anymore. So, you have the ability to take fairly early, exciting, important research, move it out of this country, and control it in a foreign laboratory.

Second, there is a specific statement in their contract, not acknowledging the fact that Bayh-Dole requires U.S. manufacturing, but to the contrary. A specific statement that says that Scripps up front agrees to help Sandoz get a waiver so it can go against the U.S. manufacturing requirement. I mean that certainly raises concerns about intent. If they have Sandoz U.S.A. why do they even need to put that clause in there. I would have hoped that they would have said, "Since we have a major U.S. facility we understand that any inventions that are developed under this agreement will be manufactured in the United States," not what it says to the contrary. It never mentions Sandoz U.S.A. as the site of manufacturing. What it says is, "You will help us get a waiver if we think we need it."

So, I think that the U.S.A. Sandoz may, in fact, even be a smokescreen for what is really going on in this contract.

Finally, let me just mention to correct the record, our lawyers met with the Sandoz lawyers on April 13th and explained to them in detail every one of our objections. So, to say that they just got a letter yesterday and this is the first time they heard what our concerns were is not correct.

Mr. COMBEST. Thank you very much, Dr. Healy.

Chairman WYDEN. I thank my colleague.

The gentleman from Maine.

Mr. ANDREWS. Thank you, Mr. Chairman and good morning.

First, let me just say that this testimony, what you are discovering, and what your task force is discovering is disturbing. I serve on the Armed Services Committee as well as this committee, and, obviously, the research that we invest in as taxpayers in defense technology and the possibility that this defense technology could end up in a foreign country which may in the future turn out to be other than an ally, in the hands of a private company serving that foreign country, raises disturbing implications. I am very interested in your research and your conclusions from that perspective as well.

Specifically at this issue, I'm thinking about my constituents at home who tell me they feel they are getting ripped off twice when they read about this particular situation. First, the price of drugs that they depend upon, prescription drugs, and second, the taxes that they are paying, which are going in this particular direction, is very disturbing.

Let me ask you, Dr. Healy, you said in your testimony—and I just want to clarify this in terms of this particular situation, the Scripps situation—if the deficiencies that we perceive underlying the agreement are not corrected, it is anticipated that the NIH, acting through the Assistant Secretary of Health, will place appropriate restrictions on all future grants the NIH makes to Scripps.

Now, what about the $70 million we are talking about right now and the contract that we are talking about starting in 1997 for 10 years? What about restrictions, changes, or corrections with respect to that?

Dr. HEALY. Well, we believe that since our grants are awarded annually, even though we will fund a grant for 3 years, there is an awards statement that is made every year that we could impose that restriction. Now, the restriction would be on whether or not Scripps could have unfettered title to any invention. We in no way want to interrupt the very good research that is going on there under our grants. But we could put a restriction on all of the grants at their anniversary, at the time that the awards statement goes out, which states if any of those inventions lead to a patent, the United States will maintain an interest in that title. It will not exclusively be the domain of Scripps and, therefore, Sandoz.

Mr. ANDREWS. So, we are not talking about a situation where after the $70 million is spent——

Dr. HEALY. No.

Mr. ANDREWS [continuing]. Then we can begin——

Dr. HEALY. Our understanding is that we could do it at the time of our awards statement, all of which go out annually.

Mr. ANDREWS. OK. You mentioned that in your view this particular situation, this deal between these two institutions is unique.

It is an aberration. Is part of the task force's work reviewing all of the contracts, all the institutions specifically, to see if this is being carried out in other instances?

Dr. HEALY. Yes; now, first, I said it is an aberration. Whether it is unique in every respect, certainly it is not. It is not unique in that it is large. It happens to be the largest that we are seeing, but there are other large agreements. We categorized about 44 of the agreements being large. The majority of them were small, under roughly $5 million, most in the range of hundreds of thousands of dollars.

The aberrant features I think I listed for you in detail. There are five or six highly aberrant features which do make this contract unique. There are some very large contracts, however, that we want to study further that do seem to give rather broad rights to research coming out, a substantial portfolio of research coming out of a particular grantee institution, and we want to take a closer look at those because theoretically there is an issue of size. The broader and the bigger the contract, the more you freeze out competition and free enterprise, the more you freeze out small businesses. So, we want to look at that a little more carefully, by the committee that we have assembled, the task force, which is being headed by Ms. Chamblee, and I hope we will be able to give you a better answer.

But we clearly saw nothing whatsoever to compare with this aberrant situation with Scripps and Sandoz.

Mr. ANDREWS. Thank you. Finally, this is a speculative question and it refers to a question that Mr. Combest referred to, and that is this fine line that he referred to. On the one hand, we want to encourage research. We want to encourage entrepreneurs and investment in this technology and the science. At the same time, we want to protect the interests of the taxpayers. We want to protect the interests of the consumers.

Do you think that we need to spend some time, both at the NIH and in Congress, looking into this fine line a little bit closer? Do you think that perhaps the consumer and the taxpayer should have some more specific guarantees that there should be some standards that we establish either in rule or in law that would assure a return on investment to the taxpayer, and that the consumer, who is also paying taxes, is going to, perhaps, see some relief, both in terms of the return on their tax dollars and in terms of the amount of money they are paying for prescription drugs? Should we be paying more attention to this side of that finally?

Dr. HEALY. I guess my own personal view is that the real promise, the major return, that we are going to see to taxpayers from this investment in the NIH research is going to be in jobs, in industry, and in companies forming to create jobs and develop technology, and in terms of better products which are going to be brought to the American public.

Obviously, the overall goal of the NIH is to make sure that we improve the health of the American public. The Bayh-Dole really focuses specifically on making sure that the fundamental discoveries locked in the laboratory, so to speak, get translated into products that will benefit the American public and also industry and jobs.

So, I think that is the real promise here. I mean you are looking now at about 70,000 jobs that are in the biotech field. In the next decade, we could be looking at hundreds of thousands, if not millions, of jobs that come from this industry based on the NIH-supported research, and 90 of that fundamental research is NIH-funded research. I think that is what we have to preserve.

I think the issue of price of prescription drugs is so complicated and so varied. There are some examples that people can bring out, but in the whole range of emerging pharmaceutical that are coming forward that have been developed in part through the NIH research, but in large part through industrial research that has been solely proprietary, I think that is not—my own personal view—that is not the place to go to start regulating prices. I mean I would much rather see competition, multiple drugs, and competing drugs. I am afraid that also deflects attention from the real benefit which is jobs, the overall industry, and the products that are life-saving.

I just find the drug pricing too much for the NIH to take on as well. I think it is outside the scope of our agency to become involved in setting prices for drugs. I mean that is in the domain of, perhaps, HCFA health care reform or some other body. But I think the NIH really should stay out of that. We don't have the expertise or the experience.

If I could just correct the record, I misspoke. Sometimes I get Scripps and Sandoz confused. On April 13th it was Scripps lawyers that we met with, and we have only communicated with them, not with Sandoz lawyers. I am under oath you know.

Mr. ANDREWS. Ms. Healy, I would like to thank you for your testimony and your work in this area. May I just say that I agree that we obviously need to be concerned about jobs and creating jobs, but I think we have to go a step further and ask the question, "Where are those jobs going to be?" When we have a situation like we are discussing right now, and you have foreign corporations making the decisions where a small business or a community in the United States may be just a blip on a computer screen, I think we have to be very concerned about where those jobs actually end up.

Finally, in terms of the promotion of health and creating drugs that promote health and confront disease, I agree we have the best health care system in the world in this country, if you can afford it. I think if the American taxpayer and middle-class working families are going to pay their hard-earned tax dollars to develop these drugs, then we have to go a step further to make sure that they can have access to those drugs and afford those drugs.

So, I just say yes; let's promote health and let's have jobs, but let's promote Americans' health at a cost that they can afford, and let's create some of these jobs here at home.

Dr. HEALY. I agree with that.

Mr. ANDREWS. Thank you.

Chairman WYDEN. I thank my colleague. The gentleman from Nevada.

Mr. BILBRAY. Thank you, Mr. Chairman. Welcome, Dr. Healy. I am sorry I was a little late, but I, as Mr. Andrews, am on another committee, and I had another committee meeting this morning.

I did read your statement, and the sections you are referring to on Scripps' agreement, that Sandoz would help to obtain a waiver from your department. I presume that waiver will not be granted. Is that an assurance we have?

Dr. HEALY. Well, we can't provide that assurance because the waiver has to be based on a specific invention that is going to be commercialized and then turned into a product, and since this is an agreement that is being signed before those inventions are made, we have no way of determining that.

My own personal view is that the language of that clause is not consistent with Bayh-Dole. In other words, it says that if Sandoz can't manufacture in the United States, Scripps will help them get a waiver, and the way Bayh-Dole puts it they essentially say that when a university is looking for an industrial partner to develop a discovery that it should look to industrial partners that will manufacture in the United States and that, if after they have looked at the whole range of potential partners, they can't find one that can manufacture in the United States, then a waiver can be granted.

But that is a decision that should be made by the university and then by the Government. It is not a decision that should be made by the commercial partner who says, "We cannot manufacture in the United States for the following reasons."

Mr. BILBRAY. OK. I understand what you are saying. So, clearly, at this point what Scripps should have done is gone out and solicited the American market, and if no American was willing to take on the project at that time, they would submit it to your department to say we can't get an American company to do it. Then they could deal with a foreign company. Is that correct? Is that the procedure?

Dr. HEALY. With regard to the specific agreement with a specific commercial partner, I think we believe that the contract should reflect the affirmative, the U.S. manufacturing requirement, rather than the opposite, which is we will help you get around the U.S. manufacturing requirements.

Mr. BILBRAY. Well, I understand that, but I can see what is happening. The highest bidder is coming in, and whoever the highest bidder is gets the contract. At that point, the institution, whether it is Scripps or any other institution—and I would like to point out that Scripps, has a fine reputation as my father was treated there 30 years ago, and my daughter even 2 months ago, as a student at the University of San Diego, went over there when she had a problem—they are going to be out to get the maximum return for the dollar they can for their institution. It concerns me that—and I think Representative Andrews brought it up—I really think the law needs to be modified to keep a proprietary interest in this technology with the Government, so that we have some interest. I think others who testified at the last hearing also brought that up.

But I really think that the chairman and the committee ought to look at going back into the law and keeping a proprietary interest, so we have some residual rights that belong to the Federal Government. Two things: First, it allows us to be part of the process; and second, it allows some return for the tremendous investment we are making out there.

You are right, it is creating jobs and it is helping our economy. But at the same time the taxpayers are paying hundreds of millions of dollars on research on this sort of thing. It is important, and I hope that the committee will look at trying to retain a proprietary interest.

The other thing was on cost because one of the things we find is a company will buy this technology from Scripps, and then when the cost of whatever the product is, whether it is a pharmaceutical product or some other product, they will say, "Well, we have to charge this huge price because it cost us $300 million for this product," when in reality the cost was much less than that and it was taxpayer dollars. So, then the product is now sold on the market and the poor patient ends up paying this huge price for a particular item that his taxpayer dollar has already paid for, and that is my concern, too.

If we allow an institution to take taxpayer dollars, develop the product, and then go off and sell it for 100 or 200 times what they have in it, or even the Federal Government has in it, we end up driving hospital and pharmaceutical product costs way up, and that is what concerns me.

If we keep a proprietary interest, I would think institutions like Scripps and others would be happy to get the tax dollars to develop the technology, and would be happy to be part of the research process, and to be able to turn this over. Maybe I am too idealistic, but I would like to think that people are out there doing this research with tax dollars in the hope of really coming up with the cure for all of these great diseases and getting things worked out. Not being out there to say, "Well, if we develop the pill that cures AIDS, we can make a billion dollars for our institution," even if all the money came from the Federal Government.

I would like to think that there are still some idealistic people out there and institutions that want to be part of the process because they want to develop this technology, not to make a profit.

Maybe I am too naive, I guess. But, that is what I am looking at, Dr. Healy, the fact if we spend our dollars to develop the technology—and in this particular product, how much money of Scripps was actually in it? I mean was it all Federal dollars or was it only 50 percent was our dollars and 50 percent was theirs? Or was it mostly ours?

Dr. HEALY. Well, I think that in this particular case, we are looking at an institution that gets about $70 million from the NIH, a little additional money from other Federal agencies, and roughly $30 million or less will be going in from Sandoz. I say less because some of that money will also go to pay salaries, bonuses, and consulting fees.

I would just like to make one additional point here though, and that is for drugs and devices that are coming to market, it is very, very rare, it is truly the exception for the taxpayer to be paying that full bill. In fact, for the development of drugs, most of the bill is paid for by the private sector. Even if you look at the total R&D cost in this country, or total R&D investment in the pharmaceuticals area, you will see that the pharmaceuticals industry puts more in R&D than the NIH does. If you narrow that down to very product-specific research you would see that the industry vastly invests

more than the NIH does in terms of actual products that come forward, if you were to say a product comes to market.

Mr. BILBRAY. I understand that.

Dr. HEALY. So, we are not the full underwriter. Now, occasionally, we are. In the area of certain AIDS drugs, we have done more than half probably, but, for the most part, industry has the balance in terms of investment.

Mr. BILBRAY. I agree. Where they put their money in and make that investment, they are entitled to a decent return on their investment. Not an obscene return but certainly a decent return.

On the other hand, where the taxpayer puts the money in and develops the product, then it becomes obscene to have it passed on from an institution, whatever that institution is, to some other body, whether it is an American company or a foreign company, and then turn around and have that product charged this obscene price to our patients and our people across the country. I think we have to look at the fact that as we put our dollars in that product, it should be able to go on the market at a much reduced cost. I mean you would realize what they are going to have to price. Sandoz is going to have to charge in the end for this product because the fact is they paid Scripps all this money for the product.

Dr. HEALY. Actually, I think one of the most obscene examples of a product coming to market at an excessive price was a foreign company that came out with an anti-AIDS drug for an eye complication. The drug was forscarnate. It was a Swedish company, and there U.S. money involved—the NIH money involved in doing the clinical trial—and that drug came out at an obscene price. I mean close to $20,000 a year for patients who are facing blindness, usually in the last year of their life, dying with AIDS.

So, I think that all of us were concerned about that. It is interesting, although it is an anecdote, that did happen to be a foreign company where we really don't have the standing to say, "Wait a minute, we think that there should be a return on the taxpayer investment because the NIH dollars did go in there and the NIH dollars were also important in terms of the last stage of the trial," giving it the credibility to say that this drug was superior to the other drugs on the market at the time.

Mr. BILBRAY. Thank you.

Chairman WYDEN. Dr. Healy, thank you very much. This has been very helpful. Let me start by saying that I think what has been most troubling to me is the prospect that the Scripps/Sandoz deal could be the wave of the future. My concern has always been that if left unchecked, this agreement, which you have cited has so many serious flaws, could be a model for other institutions, and that you might have almost every research institution tripping over itself to wear some pharmaceutical company's letter sweater and, in effect, have a pharmaceutical company as a sugar daddy.

What I find very encouraging are these comments you have made with respect to setting out new principles that would govern these agreements between research institutions, drug companies, and universities. When do you anticipate the NIH could have in the Federal Register some sense of these new guidelines, so that people would see that there were going to be some different rules of the road for the future?

Dr. HEALY. Well, of course, I couldn't predict that, considering my present situation. But I think that we do have a task force up and going that has already been at work for 2 months looking at the existing contracts. They have identified certain areas already that have to be considered for possible guidelines. Again, we don't want regs. What we would propose would be guidelines, agency-specific guidelines, which would alert the institutions to the areas that we have concern.

For example, I mentioned that only 20 percent of the existing contracts mention U.S. manufacturing requirements. Now you can argue they don't have to. What really matters is the U.S. manufacturing requirement that would come into play at the time the specific license is granted. But we would think it would be better if that were right up front when an industrial partner is identified. At the very moment that contract is developed, we think the U.S. manufacturing requirement should be in there as an understanding, as a term of the agreement up front.

There are other things that clearly suggest to us that some very distinguished institutions need to know the Bayh-Dole Act a little better. They need to know that they cannot swell their titles to research that has been partly funded by the Federal Government, their titles to patents to commercial concerns. That is a violation of the law. So, there needs to be, I think, some consciousness raising about what Bayh-Dole is, what the principles are, and we hope that our guidelines, which are based on very practical review of what is out there, will be not punitive, but helpful; not intrusive, but literally guides, as they struggle with these issues themselves.

I will say, Mr. Chairman, that the universities have been extremely cooperative and helpful. I think this kind of guidance would be welcomed by the community.

Chairman WYDEN. I do, too, and I am anxious to get it out there. Are any of your associates in a position to tell us more about the timing? I would like to see those guidelines, and I am pleased to see the Institute say there will be guidelines, and that they will be published in the Federal Register. I would like to see them out in the next year because, as I say, with dwindling Federal support for research, I think this pipeline is brimming with possible conflicts and problems along the lines you are talking about.

Is this something that the Institute can tell us more about with respect to timing?

Ms. CHAMBLEE. I think a year is reasonable. I mean clearly we have gone through these 300 and some agreements with a first cut, and we will be going to look at the 44 larger ones and having an open forum to bring in people to address various sides of the issue so that we fully understand all of the issues. It is something that we want to do in a very reasoned fashion. But I think a year is reasonable to look for some guidelines.

Chairman WYDEN. Let's go then to what some of these new principles might look at, particularly regarding the access to research data. You highlighted that in your testimony. What would you like to see in the principles with respect to that issue?

Dr. HEALY. Well, I think that we would want to have a rearticulation of the principles of Bayh-Dole which clearly say that there should be a promotion of free competition and enterprise, and I

think if you close off access, particularly to an entire institution or to an entire center of excellence, then de facto you are saying that you are not going to have access on the part of the community at large. In some cases, access is even restricted to other academic institutions and other academic relationships.

So, I think that we have to look at how much restriction of access is tolerable. Now you are going to have to have some. If you are dealing with a specific proprietary discovery with a product in mind and a relationship with a commercial partner, and patent rights are at issue, and you haven't yet filed the patents, there is going to have to be some restrictions. But there is a matter of degree. If it is one specific project, that is probably tolerable. If it is the entire output of a department, of a school, of a university, or of a research institute, then it becomes problematic. I think the task force is going to try and struggle with that and see if they can come up with some sense of what is reasonable and what is really in violation of the principle of competition and free enterprise.

Chairman WYDEN. My sense is that several of the other Federal agencies haven't been especially helpful in terms of our dealing with these issues, and that the Commerce Department in particular ought to be looked at as part of these new guidelines for a more constructive role. Do you share that view? If so, what might be done to get the Department of Commerce in a more helpful role here?

Dr. HEALY. Well, I certainly would like to see this issue a little higher on their priority list. I think that the Department of Commerce has a unique role with regard to Bayh-Dole. They are the agency that has responsibility for writing the regulations. The regulations may need fine tuning, and I think it would be helpful if Commerce saw this as an issue in which they would work in partnership with the NIH.

There is certainly a number of issues where Commerce would be especially valuable to us. For example, we talk about marching rights, and we talk about restrictions that can be placed on grants up front. The marching rights have to do with the Government basically saying that other entities can be licensed and the restrictions on the grant would have to do with the title. In both of these cases, the Government, as far as we understand and as far as we have been able to determine, really never exercised those rights in 12 years. We hear anecdotes that, "Gee, maybe once sometime ago someone threatened to use marching rights. Once many years ago the NIH may have threatened to use marching rights," but we really don't have experience from across Government with regard to specifically when those marching rights would be used, and also under what circumstances you would put restrictions on grants.

We also think that there are certain aspects of the regulations that are ambiguous. For example, the regulations clearly say that there is a preference for small businesses, and there is a sense that project specific or focused projects should be sanctioned under the Bayh-Dole, but then there is a somewhat ambiguous clause which says, "But of course this does not exclude the large scale, larger, long-term arrangements with big companies." So, that needs to be clarified. It is vague.

It is helpful in that it clearly says that you can have large companies, larger scale projects, and larger scale agreements. But what precisely do they mean in those regs and does that part of the regs need to be clarified? We think it does.

An ambiguity is never good in the law or in regulations, and it makes it much harder for an agency like ours to be able to negotiate these situations without having clearer regulations.

Chairman WYDEN. Is it fair to say that at this point, there just isn't sufficient monitoring and sufficient oversight with respect to how these inventions are utilized, and, as a result, taxpayers can't completely tell where their money is going?

Dr. HEALY. Well, I think we really can't say that yet. I mean from our preliminary review we have been largely pleased with what we have seen, and we would hate to introduce the large, intrusive oversight system because of some problems that we might be able to deal with in an incremental level through guidances and through regulation. So, I guess we are not prepared to make that statement yet.

Maybe after a year's time of studying this, we would be able to get a more informed response to that.

Chairman WYDEN. No; I think we want to stick to what has been a bipartisan thesis in this committee; that this act has been good.

Dr. HEALY. Right.

Chairman WYDEN. With respect to enforcement mechanisms, if you have the Commerce Department sitting on its hand, which they clearly have been doing, we are not getting the data with respect to how these inventions are utilized. Then people like Mr. Combest and I go home and try to explain this to our constituents, and we have taxpayers saying, "What is our money getting us?"

Dr. HEALY. This subcommittee could be very helpful by posing those questions directly to Commerce?

Chairman WYDEN. We will. Let's go to the enforcement mechanisms then as they relate to Scripps, because you clearly have in your hands, as you have said, the prospect of reducing grants. What will be the timetable for using the various tools in this case so that anybody who is thinking about Scripps/Sandoz as a model for the future is going to understand that there are going to be some rules out there?

Dr. HEALY. Well, we clearly have put Scripps on notice, and remember our relationship is only with Scripps. We have not dealt with Sandoz. I want to stress that. Our relationship and our authorities only extend to the grantee institution. We have no interest in intruding ourselves in the business life of Sandoz. We are only dealing specifically with Scripps, our grantee, because they are the ones who have a portfolio of $70 million of the NIH-supported research.

We have told them that we are prepared to exercise the exceptional circumstance exception under Bayh-Dole, which the agency has the authority to exercise, and that would involve putting a restriction on all of their present and future grants, and that we would do so if we felt we could not come to a reasonable understanding based on the existing contract.

The contract that we have seen has already been signed by Scripps and it had a July 1st deadline for Sandoz signing it. So,

Scripps has already agreed to this contract and this means that some things have to be done between now and July 1st, which is only a few weeks away, or Scripps and Sandoz will have to delay the actual signing and come to some other terms.

But we have notified them that if the contract goes forward as we have seen it, we are prepared to take swift action, and we have the support of the Department on that.

Chairman WYDEN. You certainly have my support because this will really be the case that is going to set out the new rules of the road. This will be the precedent until we get the new guidelines that we have been discussing here in a year, so this is a critical case.

I want to read you a case that we are looking at now, and I think the subcommittee staff gave you some brief information on it and asked you how the system ought to work in a case like this. The University of California at San Diego has been much in the news recently. It is an institution that in 1991 got $150 million in Federal research grants. A heart researcher developed a device to clear blocked arteries there. This researcher got involved with others to develop a company to commercialize the product. His stock in the company quickly became worth almost $15 million.

The University of California at San Diego, an institution with more than $100 million tax dollars, was never told that the device was being financed in part by the company. In fact, no reporting on possible conflicts ever was reported by this researcher to the university's standing conflicts committee because this researcher, and I was pretty amazed by this, thought that he had a minor financial interest when he had stock over $10 million.

The device had some problems. The university provided patients for experimentation. I gather that the doctor was paid as well for work in the experimental area. At UC San Diego nobody ever asked any questions. What ought to be done on the basis of those facts for a case that is in the news now, and I guess has never turned up on anybody's radar screen? That, too, is troubling, and I ask those questions about the Commerce Department monitoring because at this point, the way we find out about the frittering away of taxpayer dollars and these kinds of rip-offs is through whistle-blower and media people bringing them to us. It seems that we ought to have a better system when some whistle-blowers come forward.

Dr. HEALY. Of course, in this particular case, what we would need to know from the NIH's perspective is whether or not that research was funded by the NIH. If the NIH has funds in that particular project, which is either clinical research investigating the use of that particular catheter or developmental work with regard to the development of the device itself, then the NIH would have standing because we have conflict of interest guidelines.

I am sorry to report to you that these conflict of interest guidelines, which have been in development in my agency now for several years, are not finalized, have not been in the Federal Register, and have become like a tennis ball going back and forth between the NIH and the Department. I hope that within the next few months they will be issued.

But at the heart of our conflict of interest regulations, we specifically say that if the NIH dollars are there then we have very strict rules about this kind of situation and that it is the responsibility of the university to see that those conflict of interest rules are honored.

Chairman WYDEN. But isn't it inevitable that Government money is going to be involved, certainly in paying some of the overhead of this kind of research? I find that in virtually all of these instances the Federal Government is plowing the bulk of the research dollars into the operation. It seems to me that the Federal Government is certainly paying some of the indirect and overhead costs, and that alone ought to justify Federal involvement.

Dr. HEALY. Well, if that person developing the catheter is not getting the NIH money but he is getting the NIH indirect costs, that is a violation of circular 821 of OMB. So, I would hope that is not the case.

But I think you raise a broader issue, which is research that is outside the scope of the NIH funding, the conflict of interest is still of concern. I would say that university still has an obligation to be responsible for all research conducted within its laboratories whether or not it is NIH-funded. So, I would tend to shift the responsibility to the university.

I would also hope that the time that device gets presented to the FDA that conflict of interest relationships will also be explored at that time because that is at the heart of whether or not the research data and the results that were produced were biased or not. I don't think the inherent relationship, though, the fact that a scientist developed something and is participating in assuring in its development at the level of the patient is inherently problematic unless there is a financial conflict. Here you obviously seen to have a financial conflict, though I don't know the case.

Then the question is if there is a financial conflict is there a way to insulate? I mean, for example, industry is developing catheters all the time and they participate in generating research that is used to show the credibility or to prove the efficacy of a particular device. But you know it is industry and the data is very carefully monitored, audited, and must be impeccable. The regulatory agencies tend to deal with them, the FDA specifically.

Chairman WYDEN. Well, what we know in this case on the basis of their own admission, is you have a faculty member, a researcher, doing work on an experimental drug or device made by a company in which he has a financial interest, at a university that gets a massive amount of Federal funds. Even according to this article, the University of California at San Diego says that it has subsidizing the research, and if they admit it, I don't see how they could have done it without Federal dollars.

Dr. HEALY. Actually, if I could comment, you are making a very interesting point which is not in our current regulations, and we may look at it, is that the NIH has used its authorities in dealing with institutions that get the NIH money to make its requirements that govern research, such as clinical research, animal care, research involving animals, apply to all research in that institution. Routinely, that is done for EEO issues. It is a customary policy.

It is conceivable that we could explore whether or not such a clause should also be in our conflict of interest regulations. That if it is a grantee institution that all of its medical research should honor conflict of interest guidelines. It is not currently in there.

Chairman WYDEN. Let me ask then that the Institute look at applying that rule to clinical trials, because if we are going to bring about the disclosure of these kinds of financial interests, I think that may well be appropriate.

Let me ask you about one of the other kinds of structural problems I have with these new deals and that concerns the secrecy. It just seems contrary to good science and what science is all about. What I thought Bayh-Dole intended was trying to let 1,000 flowers bloom. The Federal Government was going to be involved in technology transfer, but these new deals, because they had these corporate sponsors, were all built around secrecy.

Are you troubled by that? Is that an area you want to see changed in the guidelines?

Dr. HEALY. Well, I am troubled if the secrecy is global and inappropriate.

Chairman WYDEN. That is the case in the Scripps/Sandoz deal.

Dr. HEALY. Unequivocally. In fact, I have been disturbed that there is an unwillingness to allow the community at large to see that 100-page contract. From our determination, there is really nothing proprietary in there, and there might be two or three sentences that might be redacted that have to do with royalties, but most of that agreement has nothing to do with proprietary scientific information or discloses the specific interest of the company with regard to lines of research or areas. There is really not a word about science in the whole contract.

There does not appear to be any proprietary research information in the contract, so it escapes me why that contract, which involves a substantial portfolio of taxpayer-funded research, should not be available to the public at large. I have been somewhat distressed because in our dealings with Scripps they have repeatedly said to us, both in writing and verbally, that this contract was unanimously endorsed by all of their scientists. Well, when we looked into it we found out that most of the scientists had not read the contract. If they wanted to, they could go to the lawyer's office and take a peek at it, but it is 100 pages, and I can tell you it takes a long, long time to read it.

Even the scientists who appeared before you at our last hearing, allegedly one of the scientists who made up that unanimous vote, had not read the contract. So, not only is there secrecy with regard to the public at large who have a stake in this contract, but there also seems to be lack of information on this contract even among the scientists who allegedly voted for it unanimously.

Chairman WYDEN. I think it is outrageous that Scripps will not make that contract publicly available. I think the reason they won't is because it can't pass the smell test. That contract is so objectionable in terms of its key features and is so clearly in violation of the spirit of Bayh-Dole that you couldn't explain it to a group of taxpayers anywhere in this country. You couldn't walk into a town meeting in my district and make a case for using taxpayer dollars that way. That is why they won't divulge it, and, again, I am hope-

ful that as we look to the new guidelines that we will have that examined as well.

The last question I wanted to ask on this round concerns the matter of how many other agreements there are that are like Scripps/Sandoz. Scripps says, for example, and they have been all over the map on this question, that they have written other agreements like the Scripps/Sandoz one. They point to J&J. They cite an Office of Technology Assessment report saying that there are 27 other similar agreements.

What do you make of these differing views of how many similar agreements there are at present?

Dr. HEALY. Well, I can only tell you that the ones that involve the NIH-funded research, based on our review of 375–380 contracts, that we would take issue with that statement. In fact, we did review the PPG and the J&J contract, and they do not bear much resemblance either in scope or in terms of restrictions and intrusiveness with the contract with Sandoz. They do not put people on the boards of directors. They do not have the ability to take research out of the Scripps laboratory, put it in the industry laboratory, and freeze out the scientists from doing that work. They do not have an agreement in which scientists are paid not to consult or paid for future consulting that they might get that they will not do. They do not have the ability to have a say over who the future CEO will be of Scripps. I mean this is a very, very different kind of agreement.

As I remember, one of those agreements did restrict access of other scientists to the campus, which we thought was a little peculiar. But, aside from that, it did not have the kind of scope or the aberrant characteristics that I outlined in my testimony.

Chairman WYDEN. One last question pertains to the way so many in this field are sort of living dual lives. They go back and forth between these research institutions and businesses. They take off one hat here where they are doing research, presumably of a nonprofit nature, and then put on their other hat and go off and make substantial sums.

Are you troubled by the growing amount of back and forth traffic along these lines? If so, what ought to be done about it?

Dr. HEALY. Well, I think that one can do that in a responsible and ethical way with integrity, but that one has to think about it and be careful about it in order to do so. The reality is that we must have those kinds of relationships with industry if we are ever going to bring our products to market. The NIH is not in the business of developing commercial products. It is in the business of doing fundamental investigation and precompetitive work.

So, partnerships and communication are essential in order to get products that will be life-saving to the American public. It is what we must do to achieve our mission.

Second, the sad reality is the Federal Government cannot afford to pay for the research that needs to be done in this county, and the NIH has faced extraordinary difficulty in terms of being able to sustain a budget, maintain a budget, and be given a budget that in any way meets the opportunities that are out there for doing research, particularly in this field of biomedical research.

So, I think that with the fiscal constraints on the agency, that grant funding is down around 20 percent or less, zero growth, and this year contraction of the NIH budget in most areas of science, there are greater and greater pressures on scientists who I think are first and foremost driven by the desire to pursue their craft, that they are looking for alternative sources of funding.

I think the pressure is on them to work with industry and that is good. But it can also be more challenging and more difficult. Most scientists, I believe, would like to sit in their laboratory, be left alone, have unlimited amounts of money, and never have to worry about commercialization, Bayh-Dole, university bureaucrats, or people like us in this room looking at what they are doing. I really do believe that what drives them is knowledge and what drives them is discovery, but the practical realities are that is not the way the world is.

Chairman WYDEN. We want to make it clear, for those who are using private sector dollars at a time research is declining, that we are not interested in having the Federal Government come forward in an intrusive manner. But it is quite another issue when the local senior citizens' center can't afford the money for a ramp to get into the center, and then they hear about a 10- to 20-year exclusive sweetheart deal involving vast sums that they don't even see. When you have, on top of it, people engaged in what some have described as this research two-step, where they go back and forth between the research operation and the drug company, and it is almost impossible to tell at any given point which one they are really working for because it is so commingled. I think it is of concern, and I hope that it will also be an area that the task force looks at.

The gentleman from Texas is on a tight time schedule, and I want to recognize him again.

Mr. COMBEST. I appreciate it, Mr. Chairman. Just a couple of followups.

First of all, Dr. Healy, there is a whole lot more people other than just scientists who would rather not have anything to do with us, so that is not limited to that field. Do employees of the NIH have to sign or make some kind of conflict of interest agreement?

Dr. HEALY. Well, the Federal employees have much stricter requirements with regard to conflict of interest. We have, of course, major restrictions on any kind of outside income. They can engage in consulting arrangements, but there are restrictions on the consulting relationships in terms of personal gain to that individual scientist if they are involved in a cooperative research and development agreement, a CRADA, which, of course, was made doable under the Federal Technology Transfer Act of 1986.

Mr. COMBEST. Would someone, let's say an employee of the NIH, would it be inappropriate or illegal or whatever for that individual to suggest to their spouse, who happens to have some other type of job, maybe some information regarding a grant or something in process that might be a good investment or maybe investment in a small company or something so that the spouse was the recipient of any benefits; would that be prevented?

Dr. HEALY. At certain levels. It depends on what level you are within the NIH leadership. Those of us in the senior executive

service, the Director of the NIH, the spouse cannot have any holdings in areas that would even give the perception of a conflict of interest, so that the spouse and the person involved are covered by those same rules. Also, there is a disclosure rule with the 278 form.

With regard to other levels, I mean there is really no way that we can even intrude on the relationship between a person and their spouse. Nor would we want to.

Mr. COMBEST. I understand. One other quick question in responding to Mr. Bilbray came to mind. You said one of the real obscenities that you recall happen to be a foreign country that——

Dr. HEALY. Company.

Mr. COMBEST. Right. Or a company that was involved with and came forward with a drug that was just terribly overpriced that the NIH had some participation in. How did they get that opportunity? Have you seen that agreement that allowed that company in that country to develop that drug?

Dr. HEALY. Actually, our participation was funding a clinical trial. It was not a specific development agreement, a CRADA-type of agreement with that company, as I recollect. I can check on that. But it was funding a clinical trial, really, just before the drug came to market and the data from the clinical trial was extremely important in getting the FDA approval and also putting that particular drug on the front burner as being the best——

Mr. COMBEST. But it wasn't a long involvement with a——

Dr. HEALY. No.

Mr. COMBEST. OK. Thank you.

Dr. HEALY. No; it was not a long term. We were not a developer of that drug as we were with AZT or DDI.

Mr. COMBEST. So, there would not have been an agreement that would have come to the NIH for review, or at least to look at, that this would have been a contract or an agreement between two companies in which basically the NIH would not have been involved?

Dr. HEALY. It is my understanding it was supporting a clinical trial, and we do not put any strings on any drugs that are studied in our clinical trials.

Mr. COMBEST. OK. Thank you.

Dr. HEALY. Nor do I think we should.

Chairman WYDEN. One other point. We read, very carefully, the letter that your counsel did, and it seems to me that Scripps is now in a situation where if they appoint a CEO who isn't acceptable to Sandoz, Sandoz can terminate the agreement.

Dr. HEALY. Yes; that is in the contract.

Chairman WYDEN. So, Sandoz can basically name the head of the operation and have veto power over him?.

Dr. HEALY. At least it gives them leverage to do so; yes.

Chairman WYDEN. Well, it is very hard to look at this contract and see what Scripps is really left to keep here after everything that Sandoz and the private sector get out of this. Whether you call it a corporate takeover, or whether you call it simply a matter of assigning the fruits of the biomedical research jewel to an international corporation, it is hard to see how the taxpayers will find this in the spirit of what was envisaged by the technology transfer law.

You have been very helpful to us. We certainly want to stay in touch with you in the days ahead. I note that, as you mentioned,

this may be your last appearance on Capitol Hill, and you have set out an agenda today that I think leaves much to follow up on. We are certainly going to be working closely with your associates to try to get those new guidelines set out in the Federal Register within that year timeframe. I think that is helpful.

I think the research community ought to make sure that it gets that message loud and clear—that we are going to stay after those guidelines. I think that unless we see new rules put in place quickly with this new private sector pipeline, we are going to see conflicts, we are going to see bias, and we are going to see problems that you and I don't wish to see and taxpayers don't wish to see, and that are contrary to the spirit of Bayh-Dole.

So, I am pleased that you have set out that kind of agenda. I know we are going to be talking to you and your associates often, and appreciate all of the help and cooperation you have given the subcommittee.

Dr. HEALY. Thank you, Mr. Chairman.

Chairman WYDEN. Thank you. The subcommittee has got a vote on the rule on the floor. We are going to, let us say, take a 10-minute break and then reconvene.

[Recess.]

Chairman WYDEN. The subcommittee will come to order.

Our next panel, Dr. Barbara Conta, patent administrator, Regeneron Pharmaceuticals, Tarrytown, New York; Dr. William Peck, M.D., dean of Washington University School of Medicine, and executive vice chancellor for medical affairs, Washington University, representing the Association of American Medical Colleges; and Dr. Sheldon Krimsky, Ph.D., Department of Urban and Environmental Policy, Tufts, in Medford, Massachusetts.

Let's see. I called three people, and we have four who have arrived at the table.

Dr. PECK. Mr. Chairman, I also wonder if I could introduce Dr. David Kipnis—make it five.

Chairman WYDEN. OK.

Dr. CONTA. Mr. Chairman, this is our general counsel of Regeneron. I would like to introduce him.

Chairman WYDEN. All right. Let us try to bring some order to this thing and see who we have. We have Dr. Krimsky.

Dr. KRIMSKY. I left my general counsel at Tufts.

[Laughter.]

Chairman WYDEN. Dr. Conta is here. Dr. Conta, you would like to have your counsel?

Dr. CONTA. Yes.

Chairman WYDEN. OK. That would be fine. What is his name?

Dr. CONTA. Paul Lubetkin.

Chairman WYDEN. Mr. Recorder, we are going to get you the spelling on that before too long. All right?

Dr. Peck is here. Dr. Peck, you would like to have your counsel as well?

Dr. PECK. No; Dr. Kipnis is a distinguished university professor of medicine, former head of the Department of Medicine, and the architect of the Washington University/Monsanto agreement. He is not a counsel.

Chairman WYDEN. We welcome him and all noncounsels. All right.

The practice of this subcommittee has been to swear all the witnesses. Since several of you have associates it would be appropriate to swear them at this time as well. Do any of you have any objection to being sworn as a witness?

[No objection.]

[Witnesses sworn.]

Chairman WYDEN. We are going to put your prepared remarks into the record. I am going to have to ask each of you to stick to 5 minutes this morning because we are really under the gun, and we will be having votes. I know it is almost a kind of biological compulsion to read one's statement, but if you would just talk to me and my colleagues for 5 minutes or so, I think that would be very helpful.

Dr. Conta, we welcome you, and appreciate your involvement in these issues for many years. Please proceed.

Let me also say, because of the infernal nature of these microphones, for people to hear what you have to say you are going to have to speak right into them.

Dr. CONTA. OK. Can you hear me now?

Chairman WYDEN. Good.

TESTIMONY OF BARBARA CONTA, PATENT ADMINISTRATOR, REGENERON PHARMACEUTICALS INC., ACCOMPANIED BY PAUL LUBETKIN, COUNSEL

Dr. CONTA. I am responsible for technology transfer matters at Regeneron. I would like, first, to thank you for your invitation to appear before the subcommittee, and I would also like to thank you, Chairman Wyden, for your support of the biotechnology industry, and also to commend you for your leadership in implementing an improved examination process for biotechnology patents in the U.S. Patent and Trademark Office. We have appreciated that.

We have been asked to provide the subcommittee with certain experiences and concerns of Regeneron in the area of technology transfer. To give you a brief picture of Regeneron, we are a small, biotechnology-based company, founded in 1988. Our mission is to treat neurological diseases and conditions for which no cures exist.

We are engaged primarily in the discovery and development of a specific class of growth factors called neurotrophic factors, and we believe that they have the potential to be used as drugs to treat a wide variety of neurological conditions such as amyotrophic lateral sclerosis—Lou Gehrig's disease—Parkinson's disease, or Alzheimer's disease.

We have our own research and development staff, and, in addition, we have entered into relationships with corporate partners, scientific advisers, and major medical and academic institutions which has allowed us to pursue the development of these potentially therapeutic drugs. We have two such drugs manufactured through recombinant DNA technology which have emerged as our leading product candidates, and of particular note is our current pivotal phase III clinical trail for human ciliary neurotrophic

factor for the treatment of ALS, which is an inevitably fatal disease of motor nerves.

We have also gained access, through our arrangements with academic, Government, and commercial institutions, to technology that has had a positive impact on the drug development process. We have a very limited number of sponsored research agreements with academic laboratories focused on these novel neurotrophic factors, and we have entered into licensing agreements for specific technologies for commercial development with a small number of academic institutions and corporations.

Regeneron has transferred technology and supplied proprietary material free of charge to over 200 researchers at academic, Government, and commercial institutions through collaboration agreements, and these collaborations provide scientists with research material and technology which is not commercially available and permits Regeneron to license potential technology which may result.

These agreements provide Regeneron with resources which are far beyond our current capabilities, and without these collaborations Regeneron would likely not have been founded and would not be as far along as we are in our development efforts. The ability of sophisticated, risk-oriented, biotechnology firms to identify potentially important basic or early stage technology and to obtain reasonable licenses is essential to the biotechnology industry. Therefore, we have two observations we would like to make to the subcommittee.

First, we have experienced and will describe here one concrete example of a comprehensive exclusive technology transfer agreement between an academic institution and a corporation that, at least for the moment, blankets a specific technology that Regeneron is ready, willing, and able to develop but cannot access. This experience supports your view, as we understand it, that such broad agreements can hinder the exploitation of scientific developments.

Second, we understand your interest, Chairman Wyden, and the interest of the subcommittee in problems faced by small, technology-driven companies. We believe that a bill under your sponsorship, H.R. 1334, would create further barriers to this. It will act as a Government supply blanket effectively shrouding technologies from exploitation by entrepreneurial-aggressive, biotechnology firms.

I will confine myself to just a few brief remarks about this proposed legislation at the end of my testimony. Your staff has requested that we provide you with the following information. Normally, Regeneron will conduct research and discovery on a product only after we have obtained a reasonably clear patent position or rights to such a position. In 1992, Regeneron learned that potentially important research about a novel neurotrophic factor had been conducted at a well-regarded, private, academic institution. When we attempted to negotiate a license to develop this technology, we learned that it was included under a comprehensive technology transfer agreement between the university and a major U.S. corporation.

Over a period of 6 months in 1992, we communicated regularly with the licensing director of this university in an attempt to secure a license. The university informed us that it was unable to obtain a release of the option rights it had granted under its comprehensive agreement. To our knowledge, this technology has not been developed by the option holder. It appeared to us that Regeneron was the most appropriate partner to develop this factor. Because of our extensive work in the area of neurotrophic factors, we also believe we could have assisted the university's researchers in this area by providing them with rare research materials and know-how.

While we were unable to obtain, in this instance, a license from this university, Regeneron has entered into a number of fruitful collaboration and consulting agreements with this institution and its faculty. We are not aware of the direct experience of other companies in this area.

Regeneron typically seeks licensing opportunities that are focused within our area of expertise, where technology and scientific exchange is a prime motivating factor. We do not have the resources to fund long-term, comprehensive, technology-transfer agreements with academic and research institutions which cover technology outside of our immediate business focus or capabilities.

To the extent that a comprehensive licensee retains rights to technologies that it is unable or unwilling to develop or exploit, certain technical opportunities are at least theoretically lost to other firms like us that are able and willing to develop. Because such comprehensive license agreements are only possible for large firms, they may disadvantage small, entrepreneurial companies in particular. They may also disadvantage the public interest if the licenser fails to exercise due diligence to ensure that the licensee undertakes commercially reasonable efforts to develop the technology.

We believe that the Federal Government should continue to support, at increasingly large levels, research in the biomedical area. Uninhibited academic scientific research able to take exceptional risks in order solely to move science forward is essential to American and scientific progress. If a university or researcher is forced to view basic research as a profit center, science and society will inevitably suffer. Therefore, we strongly urge increased R01-NIH funding. In our view, the Federal Government should refrain from taking any action which would further limit private or public funding options available to academic research institutions.

We believe that traditional license agreements, which contain due diligence standards, should in most cases protect the licensers and provide adequate incentives to the licensees to exploit the license. Universities and other institutions are experienced and capable in the protection and exploitation of their intellectual property. They have the legal basis to ensure its development and should demonstrate a willingness to enforce such rights.

The NIH should, in our opinion, continue to promote technology transfer of its funded research into the private sector in a fair and diligent manner and should exercise its march in rights to technology which remains undeveloped by a licensee. If our experience is not unusual, and if there is an occasional misuse of licenses to keep

technology out of the hands of a party that will develop it, any new legislative effort to correct such a relatively minor abuse will almost certainly be overkill and will have unexpected, and undoubtedly negative, consequences.

With regard to our second observation, we believe that you are a friend and supporter of biotechnology, Chairman Wyden, and that it is your intent to help us. We believe that the proposed H.R. 1334 would be counterproductive to that effort. It would retard the ability of companies like Regeneron to enter into technology agreements with any institution to which H.R. 1334 applies.

In my letter to the subcommittee dated June 14th, I outlined in more detail our views, and I understand that my letter is a part of the record of this hearing. But, in brief, first, Regeneron would not be able to find and obtain technology that other firms have not also identified. The fact of a proposed license would be publicized at a crucial moment and larger or better funded firms would simply outbid us for the license.

This effect strikes particularly at smaller companies which expend proportionately extremely large amounts of resources to identify potentially significant new developments closely linked to their business. Second, Regeneron's compliance with H.R. 1334 would be burdensome. A law that would require us to spend more on administration would directly undermine almost every small, technology-oriented firm. Third, although Regeneron is clearly identified as a leader in our area of technology, it appears likely that we, like other small firms, would probably have difficulty demonstrating appropriate commercial expertise as the proposed statute requires.

We in the biotechnology industry organization agree with the concept that commercial parties should pay royalties to the NIH under appropriate circumstances, and we also believe that competitive bidding under certain circumstances is in the best interest of the public. However, early stage research is not the time to establish a formula for a "reasonable price." This formulation is, in effect, an effort to jawbone or set prices without regard for risk, cost, competitions, or other factors that can only be known later in the process of developing a drug.

H.R. 1334, we believe, assumes that every technology transfer is tantamount to a sure thing. There is no such thing so far as a sure thing in biotechnology. Every new technology is an invitation to conduct time-consuming and expensive experiments to learn what the next time-consuming and expensive experiment should be.

We believe that H.R. 1334 is a constraint to science and to exploitation of technology that will particularly discriminate against small companies, and we oppose it.

Thank you once again for the opportunity to present our views.

[Dr. Conta's statement may be found in the appendix.]

Chairman WYDEN. Doctor, thank you. We will have some questions in a moment.

Dr. Krimsky. I really have to keep you all on this 5-minute clock. Let me say again, there is almost a kind of chromosomal urging to read one's statement. Everyone of those words, we are going to put into the record, and if you could just talk to us for 5 minutes or so it would sure be great.

TESTIMONY OF SHELDON KRIMSKY, PROFESSOR AND CHAIR, DEPARTMENT OF URBAN & ENVIRONMENTAL POLICY, TUFTS UNIVERSITY

Dr. KRIMSKY. All right, I will try to do that. I have been at a university now since the mid-1970's, and I have some familiarity with the culture of science and the culture of university faculty. I collaborate with many scientists, and I am here today to talk about some of the impacts of the technology-transfer legislation that has taken place over the past 2 decades.

One of the questions we have to ask is are we achieving some of the goals of these technology transfer acts and policies? I don't think anyone wants to see our short-term goals of technology transfer compromising the long-term integrity and quality of science. I don't think that is a wise thing.

Now, what I am going to be speaking to you about in the next 5 minutes is disclosure, because I think it is critical that we have a comprehensive disclosure policy in order to allow us to understand whether or not the objectives of technology transfer are, in fact, compromising other aspects of our American scientific institutions. I will have a little bit of data for you because I think it is important that we have effectual data to defend our positions in academia.

First of all, I think that the aggressive academic industry relations have had some effects. I disagree with Dr. Healy that there haven't been some significant and published results on some of these effects.

There have been trade secrets that have increased in universities and—we do have evidence of that—restricted flows of scientific information. We do have information that there are increases in real or perceived conflicts of interest. There certainly are hidden public subsidies to commercial activities that have emerged. That is when you have private firms developing some sweetheart deals with universities. Particularly, when their overhead rates are lower than the Federal overhead rates, then you are getting a subsidy that is not explicit but implicit.

There are no magic elixirs for solving these problems, but I believe that disclosure will enable competent researchers to be able to provide some information that would be useful to those who make public policy.

I believe that the disclosure has to be developed in three areas. First of all, there has to be a uniform disclosure policy for research contracts between private companies and federally supported, nonprofit universities and research centers. Second, I think there has to be disclosure of faculty research. This is probably one of the more controversial areas. Third, I think there has to be disclosure for peer reviewers in the Federal grant and contract system.

Regarding the Sandoz agreement, and a lot has been said about that, from where I stand at the university it sounds perilously close to making an institution's scientists indentured scholars to one corporation, and I think that has got to be taken very seriously because the view of science as a free-spirited, independent, and decentralized set of activities and culture is the thing that makes American science great, powerful, and strong.

When you begin to monopolize science in that way, I think you are going to be subjecting it to some very unfortunate consequences that I don't think anybody would care to have.

The problems of systematic bias of research is not well understood. We do have some limited studies that show that when you have single source funding for science there are real problems with systematic bias in the results. I am not going to go through this one study. It is in my prepared statement, but I can assure you that it is just the tip of the iceberg, and until we have disclosure, we will not have evidence of systematic bias in academic research when you have these very substantial agreements between pharmaceutical companies and faculty.

Now I am not saying that this is pervasive or not. I am just saying that we simply do not know how pervasive this is. We do know that there is evidence of systematic bias in the literature.

We need to have disclosure for individual faculty. I watch the presses very carefully, and I read, throughout the country, headlines in newspapers from research that is done by investigative reporters who, as we all know, are under the time constraints of trying to get information fast and furious. But there are things like "Agricultural Research is Beholden to Industry, Study Says," "Unproved Drug Enriches University Doctor," and this one, of course, in my hometown, the Boston Globe, "Flawed Study Helps Doctors Profit on Drugs." Now, these are increasingly found in the media, and it is unfortunate that we have to depend upon investigative reporters and not independent researchers to elaborate and investigate these kinds of situations.

A decade ago, we had no estimate of the magnitude of academic/industry relations. Today, we are beginning to understand just how pervasive it is. There have been studies which show that nearly 50 percent of biotechnology faculty have consulted with industry, and nearly 25 percent have grants and contracts with industry, with about 8 percent owning equity in firms. In one of the studies that I published, we found one-third of the faculty in one prestigious university, and all located in one department, had formal ties to various industries. In another university there were 43 different companies with which faculty had ties.

Now, you have to imagine, if you are in several departments in biomedical science, and you have a bunch of faculty, and they have formal relationships, equity relationships, they are on the boards of these companies, and there are 43 different companies, imagine the self-imposed constraints on communication that is going to take place at the universities with this kind of network of dual affiliations.

We have two agencies now that are considering conflict of interest regulations, the National Science Foundation and the NIH. The National Institutes of Health has not published anything yet. Dr. Healy is optimistic, and believes the NIH will release guidelines in a few months. We are not sure. NSF has published something. NSF has included in its proposed guidelines financial disclosure documents of academic researchers who seek Federal funds.

I think this is an important provision, and I have applied for many grants and received many grants, I know how much of a hassle it is to fill out financial disclosure or any forms. It is just

going to make the process more difficult. But in terms of trying to reconfigure the public interest in this area, I think it is a necessary thing that public policy has to do. The NIH, as far as I can tell, is against public disclosure forms for grant applications.

Two more aspects of disclosure, and then I am just about finished. One is that I believe there should be public access to conflict of interest information. That is, if these disclosure forms are submitted to the NIH or NSF, then I think the public should have access to these conflict of interest information forms.

Second, we have a problem with institutional conflict of interest that has not been addressed.

It is estimated that over a hundred universities have established for-profit companies. In one notable case, we have a university itself that has investments in a for-profit company. The individual board of trustees is invested in that company. The university president is invested in that company, and members of the faculty own equity in the company. How can we give this university the responsibility to manage its faculty conflict of interest and to set the moral climate for its faculty when it, itself, is very much a part of the process of developing for-profit enterprises.

I mention again the importance of disclosure and conflict of interest guidelines in the peer review process. I will conclude by saying we need a system of disclosure which will not undermine the incentives of scientists to pursue Federal grants, and we need a system of disclosure that will not be too ponderous or bureaucratic. We know how sensitive that can be because we recognize that the NIH had put out a proposed set of guidelines in 1989 and they had to withdraw it because the scientific community was so much against it.

While we need a comprehensive system of disclosure, we don't want to foster an ethos described in Michael Crichton's bestseller Jurassic Park: "If you want to get something done, stay out of the universities."

Thank you.

[Dr. Krimsky's statement may be found in the appendix.]

Chairman WYDEN. Very helpful, Doctor. We will have some questions in a moment.

Dr. Peck.

TESTIMONY OF WILLIAM A. PECK, EXECUTIVE VICE PRESIDENT FOR MEDICAL AFFAIRS AND DEAN OF THE SCHOOL OF MEDICINE, WASHINGTON UNIVERSITY, ST. LOUIS MO, ACCOMPANIED BY DAVID KIPNIS, UNIVERSITY PROFESSOR

Dr. PECK. Well, it is an undeniable reality that Government policy has contributed importantly to science, and has had an enormous impact on society, but that we have reservations about the unintended consequences of these prevailing policies. AAMC, as a matter of general principle, strongly supports research and technology agreements between academic health centers and industry, and we would emphasize four points:

First, these agreements seem to be having a positive impact on health and the economy; second, academic medical centers per se just don't have the resources or expertise to bring products to the

commercial marketplace; third, many scientists. if you talk to them, will tell you that they look forward to seeing the fruits of their endeavors accrue to public benefit; and fourth, industry support represents an increasingly important source of what we would call intellectual venture capital that initiates innovative research and thereby can have an enhancing effect on the NIH support.

The AAMC believes that Federal policy must, therefore, strike a balance between the public's interest by allowing unfettered access to the results of federally funded research, and meeting the public's expectations by encouraging commercial development of new diagnostic approaches and treatments. AAMC is concerned, as you are, about the chilling effect of these arrangements on free and open interactions and communication within academia, and we recognize the personal interest extant in some agreements can bias professional behavior. AAMC has traditionally recognized and emphasized the importance of disclosure as a mechanism for both identifying and managing potential conflicts, and, indeed, in 1990 the AAMC published its Guidelines to Deal With Faculty Conflicts of Commitment and Conflicts of Interest in Research, and those guidelines have been used by many universities, if not all universities, in crafting their own individual conflict of commitment and interest statements and policies. We believe that the central responsibility for identifying conflicts and managing these conflicts of interest resides within the institution. A fundamental characteristic of many agreements between academic institutions and industry is some form of exclusivity in licensing. We feel that limiting access to exclusive licensing agreements could impede the accumulation of public benefit.

Washington University, like many universities, believes its major mission is to teach and create new knowledge and enhance the propagation and amplification of that knowledge into a form that yields societal benefits. In 1982, we entered into a 5-year, $23.5-million agreement with the Monsanto Co. headquartered in St. Louis, and that agreement has been extended over and over again, and the total investment through 1994 will reach approximately $100 million.

It is a public activity and a public document. It was reviewed openly by the House of Representatives at a hearing on June 16, 1982, and what was concluded at that hearing is still true today. The agreement does protect academic freedom, is structured to avoid inappropriate influence on research direction within the university, does not restrict faculty interactions with academic colleagues or even with other companies, and provides an effective mechanism to create public access to technology as envisioned by Bayh-Dole. I can assure you that Monsanto does not involve itself in the selection of the dean or the executive vice chancellor or, for that matter, chancellor of the university.

It is important to stress that the Monsanto grant comprises a relatively small fraction of Washington University's total research funding. Washington University in fiscal year 1992 alone received $185 million in grant awards, of which $19.7 million came from corporations and only $10 million from Monsanto. The university's research base is broad and dominated by Federal funding. Corporate

support, while significant, does not drive our research enterprise, and won't in the future.

I would like to review some of the key features of the agreement that are of particular interest. First of all, it is institutional; that is, Monsanto allocates funds to Washington University, not directly to individual investigators.

Second, the program is investigator initiated and accessed by a broad representation of the faculty. Requests for application are distributed to all of the full-time faculty of Washington University, School of Medicine.

Third, the program is driven by internal and external peer review. Internally, a standing committee of Washington University and Monsanto scientists, equal in numbers, review each application for merit and make awards based on scientific merit. Every 3 years, an external committee, consisting of highly esteemed scientists nationally, reviews the program and assures its quality and compatibility with our academic goals. The external review committee meets not only with funded faculty, but also with graduate students, postdoctoral fellows, and unsuccessful applicants.

Fourth, the program is public, as I have mentioned. All publications acknowledge Monsanto's support, and it has been discussed publicly and widely, both in Congress and in the press, I might add.

Fifth, the program doesn't interfere with scientific freedom, and investigators are free to explore other funding relationships, as I mentioned. There is no scrutiny by Monsanto or by Washington University of other relationships a scientist wishes to pursue. Submission of manuscripts and abstracts is delayed no more than 30 days, during which time Monsanto must make a decision about whether to pursue a patent application or not. I would say that there has been no single case of violation of that 30-day limit in the 11-year history of the program.

Sixth, all royalties accrue to the institution and the investigator's department and laboratory, not to the investigator. There is no personal financial gain from this activity.

Seventh, the patenting and licensing components of the program are constrained to subject to the rule of law, and that is included in the agreement's provisions.

The results of the program have been significant. Since 1983, there have been 96 U.S. patent applications filed and 42 issued. Many of the patents cover technologies that are under active development in the pipeline at Monsanto. Two products are now in clinical trials through G.D. Searle, which is the pharmaceutical subsidiary of Monsanto. The patent portfolio is reviewed every year and adjusted.

Monsanto's option rights covering a dozen of the patents have been released so that the university could license them for development elsewhere, ensuring a return to society. Eight of the patents have been licensed elsewhere, and seven of those have been licensed to small businesses.

In conclusion, I would be remiss in not emphasizing the distinctive nature of this interaction, and also the fact that it is a model which is not necessarily exportable. That is to say, the proximity of the Monsanto Co. to Washington University has enabled interactions between our scientists and Monsanto scientists that I think

have been productive in terms of yielding benefits at the very basic science level, which we all want to support.

It has allowed us to understand something about the corporate culture, and I think it has allowed the corporate culture to understand something about how university scientists think and operate. One can't attach a dollar value to those kinds of interactions.

We appreciate the opportunity to appear before the subcommittee as you consider these very difficult concerns and issues, and would be pleased to answer any questions.

[Dr. Peck's statement may be found in the appendix.]

Chairman WYDEN. Very good.

All of you have been a very helpful panel. Let me recognize my colleagues first, beginning with Mr. Torkildsen.

Mr. TORKILDSEN. Thank you, Mr. Chairman. I also want to thank the members of the panel for your testimony. You shed, I think, quite a bit more light on the subject than perhaps we were able to have a few months ago when I think we originally brought up the focus of the subject. Again, Mr. Chairman, thank you for holding the hearing.

Dr. Krimsky, I appreciated your recommendations. You and I hail from the same part of the world. If I could ask you to explain a little bit further, Do you feel that the recommendations you make, if we could implement those, would adequately address the potential problem, pushing too far into the envelope, that can happen under current regulation? Do you think that would be adequate, or is that sort of like a step in the right direction? How do you view that?

Dr. KRIMSKY. I view my recommendations as necessary but not sufficient conditions for dealing with some of the problems of the technology transfer acts. In the short period of this presentation, I decided to focus in on disclosure. There are other aspects that were discussed today.

Mr. TORKILDSEN. With the greater disclosure, do you think there could be, if not a press review, at least with greater disclosure there would at least be better peer review? If individuals understood through that greater disclosure, would that be enough to try to encourage some self-policing in this area.

Dr. KRIMSKY. I think it could. I think I am reading the professional literature, and there is a lot of moral sentiment coming out of the professional literature about conflict of interest, and the fact is that many of the people who express this sentiment really don't have the information because they don't even know which of their colleagues are engaged in commercial activities.

Mr. TORKILDSEN. Thanks a lot.

Dr. KRIMSKY. I think it would help create that moral climate.

Mr. TORKILDSEN. Thank you. Dr. Conta, I just commend you for being willing to say that you disagree with a piece of legislation. I know that is not always easy for a witness to do, and sometimes the best answer we can get is when we know someone disagrees with a piece of legislation and alternatives to it. So, I want to thank you for that.

Thank you, Mr. Chairman.

Chairman WYDEN. I Thank my colleague. The gentleman from Nevada.

Mr. BILBRAY. Thank you, Mr. Chairman. First, I would like to ask Dr. Peck, when Washington University makes these agreements, goes into patent agreements, and production agreements with different companies, the profits that come back to Washington University, does that go back into basic research or does it go into other areas of the university?

Dr. PECK. Exactly. The royalties accrue to our research enterprise.

Mr. BILBRAY. That is where it has to stay; is that correct?

Dr. PECK. Yes; that is correct.

Mr. BILBRAY. OK. Dr. Krimsky, you brought up the idea of the disclosure which I strongly advocate myself. Would you envision within this disclosure that the disclosure would go on during the entire period of the grant? I could sign a disclosure statement now as part of my application for the grant, and 4 months down the road acquire an interest in that situation, or my wife could, or my children could, and I presume that it would have to go to a certain degree of consanguinity within the family relationship. Plus the disclosure you envision would go on during the entire time the grant was being granted.

As you know, there are unethical people in every profession. There are even unethical Congressman. That is hard to believe. It happens rarely but it happens. Would you envision these regulations also pertaining to, at the termination of the grants when the product is either gone out of the marketplace, even for a period of time after that, that any disclosure of any interest that is acquired in that particular technology would also be disclosed?

Dr. KRIMSKY. Well, I think that at the very first stage when a person applies for a grant there should be a financial disclosure statement. Now usually the grants are renewed every year, so that could be a continuous process—a yearly process at least.

I haven't thought about the prospect of some interim disclosure if there is a significant change in the relationship between that investigator and some company that is doing work related to the research. That is a very interesting idea and probably could be built into some set of guidelines.

As far as trying to monitor it after the grant is over, I am not sure how the benefits of that will be weighed against the problems of managing it. I haven't thought that out. It is a very intriguing question. I know that there are Government regulations that restrict activities of people after they leave Government. So, I think it is something worthwhile thinking about, but we have to be clear we understand what the liabilities are on both ends.

Mr. BILBRAY. Yes; because my fear is similar, I am sure, that President Clinton's is, that a person can be promised something during the time they are in Government. In this case, doing the research work and say, "Well, we can't give you anything now because of the disclosure problems, but when you get out a year or two from now, we will give you stock in the company or will hire you as a consultant. I think there should be a moratorium after these things go on, or a period of time when they are liable.

I am glad you are all coming with the same idea, and I think that is very, very important.

Do any of you favor the idea of the Government retaining a proprietary interest in the research where the grants go? I mean would you support this concept? It seems like to me with all the money, and that is why I asked Dr. Peck, if the money is going back into basic research, back into areas that the Government has an interest in or the public has an interest in, then I can say, that is fine. But if, on the other hand, it comes back and, as you mentioned, one university—and I know who you are talking about; I had to get the answer from staff, but I know who you are talking about, and I won't bring the university up—that formed their own corporation, and the president, the trustees, and everybody who had an interest in it, that concerns me.

If the Government had retained a proprietary interest, maybe they could have kept that kind of thing from happening. Would any of you advocate a proprietary interest on the Government? I have always envisioned building up this huge from proprietary interest that goes back into research, similar to what the Japanese do in private industry.

Dr. KRIMSKY. I have a fundamental belief that our system of capitalism operates best when private interests take risks and either gain or lose from those risks. It doesn't operate well when they use the risks of the public funds and then only gain. So, I think that when our Government funds research it should retain some proprietary interest.

It may be that the interest in a particular case will be to allow the company to patent and license exclusively, but that is something I think that policymakers can decide. There may be other situations where the Government wants to bring some of that funding back into research, and I think that would be quite appropriate.

Dr. PECK. Well, it is an interesting notion and a very complex and difficult issue to deal with, as you well know. I am concerned that our ultimate goal here is to accrue public benefit, and that these agreements are forged under laws and regulations in order to bring about that public benefit, and I am concerned that the return on investment is, in fact, that public benefit, and, of course, jobs and taxes that might emerge as a result of the sales of medicines and so forth.

The proprietary interest on the part of the Federal Government in an administrative sense is served in part through notification. I guess the question is what would be gained by a more substantive review and ratification mechanism.

Mr. BILBRAY. I was going beyond that. We pay $70 million to Scripps a year. They sign a contract worth $300 million or more to Scripps and the Federal Government gets nothing out of it. I mean the public policy would be certainly carried forward if Scripps, on the other hand, said the Federal money has been in. We are going to turn this over to be developed at a very low cost, and we are going to recover some for our research, but certainly not $300 million, because the cost of that particular technology or that particular pharmaceutical ends up going way up because the company rightfully says, and I have said it before, "We have to charge all this money because we paid $300 million to get the rights to produce this product."

"So, therefore, we have to charge $20 a pill or something to get our money back because we don't know if another technology is going to come on line 2 years from now that is going to wipe this pill out." But if they had paid $5 million or $10 million, they certainly would not have that problem.

So, if the Government retained an interest in it and not only had to approve the contracts but also had a proprietary interest to build up a fund, hopefully to create more research, because the biggest complaint I have out there right now, and I am sure you all know this problem, and every Member knows it, we have all these different groups coming in saying there is not enough money to do research in this or that area. It is all going to AIDS research. None of it is coming to our area, and people are dying from other things than AIDS. I am sure Mr. Wyden hears that all the time.

But, I hope the chairman will pursue this about providing proprietary interest and full disclosure, and we really move forward. I know he will. He is a pretty good guy.

Chairman WYDEN. I thank my colleague. This is obviously an area where we are going to have to focus in considerable detail on the remedies. This hearing, as I think our colleague would agree, has again excavated considerable evidence about the problem, and I think our friend from Texas, Mr. Combest, made a good point when he stated the American people don't want to see Congress march off in a crazy direction. So, we are going to work very closely with the gentleman from Nevada, who has good suggestions invariably on this and other subjects.

Mr. BILBRAY. When does Congress ever move off in a crazy direction?

Chairman WYDEN. I can't think of more than 300 or 400 current examples.

[Laughter.]

Chairman WYDEN. But we are going to work closely with the gentleman. Obviously, as we can dig deeper to address these problems, then we move on to the debate over remedies, and the gentleman always has constructive suggestions.

I want to ask a question going back to the matter of problems, and this might be one area where I have a little bit of a difference of opinion with Dr. Healy. My sense is there are a lot of problems out there, and that part of the reason we don't hear so much about them is that there really isn't much of a system to excavate information. You must have whistle-blowers bringing it up. Mr. Jenning and Mr. Forrer are two, very able characters by anybody's analysis, but they can't ferret all of this out. Unless you have whistle-blowers, newspaper reporters, people like this out there trying to raise these issues, I don't think they are going to come to the attention of the system in very many instances.

I think most of you were here when I cited this example of what is going on now at the University of California at San Diego. This is an institution that has an infusion of more than $150 million, at least in 1991, in terms of Federal investment—almost the textbook case in conflict. Clearly, the device seems to have potential, but the University of California at San Diego doesn't seem to know much of anything about what is going on.

I would like your assessment as to whether you think there are a growing number of these problems out there, and if part of the problem here is that these issues really don't come to light unless a whistle-blower or an adventuresome reporter gets a tip, and everybody is in a position to try to run it down.

Dr. Conta.

Dr. CONTA. I think that the university does have at hand the ability to monitor problems through setting, for example, milestones in any kind of license that it negotiates. I think one of the problems is that university technology transfer or technology licensing offices are usually very understaffed for the size of the faculty that they are responsible for and for the number of agreements that they are expected to monitor. I think it is probably impractical to expect that they could exert the kind of monitoring role that one might like to determine if due diligence is being used and to, perhaps, terminate any license where due diligence is not being used.

We think that there probably is a fallback in that the NIH does have march in rights, which we have heard this morning have not been frequently used. We were not completely aware of the extent of those march in rights. Now that we are, we would investigate whether we had access to utilize them. I think that those need to be made more available and used more frequently.

We think that most of the components necessary to monitor problems are in hand, if they would simply be utilized.

Chairman WYDEN. On the matter of the extent of these problems, do you share my view that there are more of them out there than meets the eye? Is one part of the reason we don't have a good handle on it is that unless you get adequately staffed university technology-transfer offices, an investigative reporter, or a whistleblower, we are not likely to hear about it?

Dr. CONTA. I can only answer from our own experience as a small company, and from our experience, we have negotiated over 200 collaboration agreements with academic institutions. In that process, we have only come up against a very, very small number of cases where we were unable to achieve our goal of a collaboration.

So, perhaps, we were fortunate in the institutions we approached, but that is our sense of it. From our personal experience, it has been a relatively small number.

Chairman WYDEN. Dr. Krimsky, what do you think? Are there more problems out there than——

Dr. KRIMSKY. Well, in the past 15 years, the whole academic arena has changed in biomedical science, and is still changing rather rapidly, so what we are seeing is many more individuals who now have direct commercial affiliations and formal links. Either they have set up their own companies or they are very involved in the management or advisory capacity of companies. So, with that context, you are going to find a potential for many more conflicts of interest, just because the nature of the culture has changed.

In the electronics industry, there was a different situation. The scientists who developed new electronic devices usually left the universities, and they set up their companies in Massachusetts,

around 128. But in the biotechnology field it is different. They decide to stay at the universities and also to have an active role in the firms, and that is when you get this conflicting missions and the urge to gain financially while at the same time maintain a university setting.

Chairman WYDEN. You have expressed some concern about the NIH conflict of interest guidelines, in that they focus more on persons, I gather, rather than institutions.

Dr. KRIMSKY. That's correct.

Chairman WYDEN. What would you do to remedy this? Would you just cross out persons and put persons and institutions?

Dr. KRIMSKY. I think there has to be some concern about an institution that has a for-profit company and the kind of award that institution can receive from the Federal Government if that institution has a for-profit company. Supposing the institution is in the process of trying to develop a drug, and then the question has to be raised should it be entitled to Federal funds to evaluate the research on that drug, forgetting about any individual investigator. I believe there needs to be a different level of disclosure and protection of the public funds for those universities that have decided to go directly into for-profit companies.

Chairman WYDEN. Well, we are not going to cause any riots here at the witness table, but I want to give Dr. Peck a chance to comment on that if he wishes.

Dr. PECK. Thank you, Mr. Wyden. First of all, our definition of what is a problem has changed, or is changing. It is an evolving issue since 1980 and even before then. So, I think the first thing we have to do is decide what is a problem, what is a conflict of interest, and what is a conflict of commitment?

My own view is that is a primary function of a university. The university must, in fact, define and apply standards as part of a review and management process to its faculty. A university that doesn't do that is not fulfilling its mission academically.

In terms of the administrative problem, I believe in disclosure. I share the notion that there should be disclosure, and perhaps even annual disclosure. Hopefully, this will be one of the matters that the NIH task group looks at very carefully.

Chairman WYDEN. Well, I certainly think disclosure is a useful antiseptic. I mean there has been so little oversight and so little scrutiny, in my view, in the past. We have heard a lot of the reasons. Dr. Conta gave us a good explanation in terms of the small staffs at some of these university programs. The Commerce Department, in my view, has been dragging its feet in gathering some of the data and holding it up to Bayh-Dole.

I just don't see how one can contest the proposition that these problems are increasing, because I hear industry talking about it, and I hear universities talking about it. Shoot! I think I remember reading a comment of Dr. Rubin at the University of Miami. Dr. Robert Rubin told the New York Times, and I quote: "As money becomes less and less available, more people are going to be compromising their principles and compromising their time. We can get to the point at some stage in the process where we're not research universities any longer, but fee-for-service corporations, hired guns."

I just hope we will have a system that offers more preventative medicine than what we have had in the past, which is essentially one where we basically play catch-up ball after somebody brings it out who is a whistle-blower or investigative reporter.

Dr. Conta, much of this is in the name of people like yourself having a fair shot in the marketplace and, at the same time, doing it in a way that balances the taxpayers' interests, because these are taxpayer dollars, and you do have to explain where they go at town hall meetings when people hear about these kinds of deals. So, you may have heard that the National Institutes of Health said that they were working on these guidelines—that they are going to try within a year to have them out—and I am going to push hard to get that, because I think that we need to have a clear understanding of what the rules of the road are.

Let's just say hypothetically that they call you up and say, "Dr. Conta, we have to make sure we do it. Ron Wyden and all kinds of other people on the Hill are going to be pushing us hard to get it done. What do you think ought to be in the new rules so as to make sure we can have the best of both worlds: The fruits of scientific research and sensitivity to the pricing of products and taxpayers' interests?"

Dr. CONTA. I think, from our point of view, what we would most like to see is the continuing ability to have access to the technology, and while we acknowledge the fact that there will be large corporations that support these kinds of agreements, we would like to see them be required or be asked by the universities to make a choice on their options within a given period of time. If they choose not to go forward and to develop something that has been invented or discovered at the university that they decline their option and that option then become available to other companies like us so that we can come forward and develop it if we choose to.

Chairman WYDEN. What would be a reasonable time period for these options? An interesting idea that clearly has not been looked at. Scripps, for all practical purposes, is a patent machine. They are really getting two very, very lucrative opportunities: One, the initial research work and the initial developmental effort; and two, the chance to go out the other door and send it to their patent arm and start cranking away on patents which, as we have learned, haven't even complied with Federal law. They haven't been willing to put down, as is required by statute, the nature of the Federal involvement.

So, I think it is an interesting idea. Do you have any sense of what period the Government ought to let the clock run for here?

Dr. CONTA. I am not sure that it ought to be the Government letting the clock run.

Chairman WYDEN. No; I am not saying that. There must be some rules.

Dr. CONTA. Yes; I think that the university licensing office needs to decide on the basis of each individual invention what an appropriate time point would be for a company to decide whether it could have the resources and desire to go forward and develop that, and I think that needs to be incorporated into each license on a case-by-case example.

Chairman WYDEN. That is an interesting idea. By the way, that is not unlike what we are trying to do in our legislation, which is to say, on a case-by-case basis, we would agree up front. That is the key to having some leverage in order to balance the competing interests here.

What has troubled me the most about this whole debate is that when you talk about the taxpayers' interest, when you talk about the interest of a variety of competing parties, these competing interests have no leverage when these new, exciting products are out the chute and people are suffering and dying in our country and everybody says, "Shoot! We've just got to get this in people's hands."

I think your suggestion has considerable promise, and I would point out that is not unlike the centerpiece of what I think needs to be done in some of these related areas like CRADAS, cooperative agreements, and the like.

Dr. Peck.

Dr. PECK. I just wanted to add that I agree, and in forging the Monsanto/Washington University agreement initially, we didn't have the benefit of hindsight in deciding how much specificity to apply to the option period, and so we wrote into the contract a 2-year period from initial patent filing to the exercising of a license, before the university had the opportunity to release the license, and, indeed, in most cases it has worked. It hasn't been a perfect process, again, because of the staffing problems and so forth. But we agree with that principle.

Chairman WYDEN. Well, we wish to work with you further. Again, let me say that I am of the view that it is not the job of the Federal Government to get out here and micromanage and try to set in place by Federal prescription various kinds of technical requirements on these contracts. But I think you must have some kind of process spelled out up front so you can weigh comparative risk, and so you can weigh, for example, the amount of dollars that the Federal Government is putting up and the amount of dollars that the private sector is putting up. I think the point Dr. Conta makes, that at some point there would be opportunities for others to share the fruits of the research, is a very good one.

I think you have given us an opportunity to end on a high point, and we should not pass that up. We are going to work closely with you.

Let me say that I would very much welcome from this panel your ideas and suggestions with respect to those NIH guidelines. We are going to work hard to oversee what the NIH is doing in that area. We are going to hold them to that 1-year timetable, and we would welcome your input after the hearing.

Thank you for your cooperation. The subcommittee is adjourned.

[Whereupon, at 12:36 p.m. the subcommittee was adjourned, to reconvene, subject to the call of the Chair.]

APPENDIX

OPENING STATEMENT
REP. RON WYDEN

DRÚG DEVELOPMENT DEALS BETWEEN TAX-SUPPORTED LABS AND PHARMACEUTICAL MANUFACTURERS:
WHO OWNS THE RESULTS? HOW SHOULD THEY BE PRICED?

PART II

BEFORE THE SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND TECHNOLOGY

June 17, 1993

Today, the Subcommittee on Regulation, Business Opportunities and Technology continues its inquiry into bias, conflict-of-interest and subversion of public ownership rights in collaborative agreements between tax-exempt, federally supported research institutions, and the pharmaceutical industry.

As we have learned in previous hearings, these matters often have a devastating impact on small, technology-hungry companies.

Our first witness this morning is Dr. Bernadine Healy, Director of the National Institutes of Health. Dr. Healy, at the subcommittee's request, has been investigating a collaborative agreement between the Scripps Research Institute -- a La Jolla, California-based laboratory which receives $70 million per year in NIH grants -- and the Sandoz Corporation of Basel, Switzerland. Specifically, the agreement gives Sandoz exclusive access to almost all research and technology produced at this flagship medical research facility over the next 10 to 20 years.

In the Chair's view, this deal amounts to a corporate takeover of one of our biomedical research crown jewels...which significantly is largely funded by the federal taxpayer.

Our inquiry comes at a critical time for three reasons:

* Federal research support is declining, and as a result drug companies, federal research labs and private universities and non-profits are putting together deals to fill the financial gap. Unfortunately, some of these deals may put the public interest in the back seat, and private interests at the driver's wheel.

* The subcommittee has learned that many of the economic interests seeking to put together these research partnerships consider the Scripps-Sandoz contract an attractive model. We hope to disabuse them of the notion that this is the way to go, given that the National Institutes of Health has said that the proliferation of these contracts could destroy the NIH extramural grant community.

* Finally, small business which already faces a crunch on credit and a crunch from foreign trade barriers, now confronts the possibility of a technology access crunch. These kinds of agreements are anti-competitive, and are particularly devastating to small companies.

At our March 11 hearing, Dr. Healy termed the Scripps-Sandoz agreement possibly illegal, and potentially destructive to the NIH relationship with many other research institutes who share almost the $8 billion per year in federal biomedical research funding.

We expect the National Institutes of Health to define their objections to the agreement, and to lay out the NIH plan for remedies.

Also, Dr. Healy will lay out the results of a 100-institution survey her agency has conducted, at our request, to explore shape, character and variety in 375 collaborative agreements within the NIH grantee community. Scripps asserted at our last hearing that their collaborative arrangements were little different from others which are common within the academic community.

Given our concerns regarding the Sandoz arrangement, and an earlier exclusive rights contract between Scripps and Johnson & Johnson, this statement bothers both Dr. Healy and the Chair. Therefore, the NIH survey is of vital interest and importance to the course of this debate.

The Chair believes that it is critical that the federal government move quickly to set out clear rules-of-the-road to govern the growing activity in collaborative agreements between academia and industry.

This is necessary because the current rules, articulated in the Bayh-Dole Act, were written before many of the problems this subcommittee has uncovered came to light. It is not our intention to re-invent the Act. But the Chair believes that it is important to recognize that we face issues, today, not contemplated by the framers of the 1980 federal law. Those problems need to be dealt with through reasonable amendment and adjustment.

It's vital, for example, that the federal government provide clarification as to the kind of business arrangements between academic administrators and scientists, and drug companies, which NIH and the Food and Drug Administration would consider conflicts.

The Chair notes that Scripps was invited to testify at today's hearing. They have declined, citing a preference to work-out their differences with the NIH privately. The Chair attaches no judgement on this decision.

This subcommittee also is very interested in the risk of bias in clinical trials.

Recently, the Chair alerted Dr. David Kessler, the FDA administrator, to the potential for conflict-of-interest in the determination of proper dosage levels for the drug Ceredase, a new and very expensive treatment for Gaucher's disease. The subcommittee located a major gap in FDA disclosure rules for investigators conducting critical clinical trials. At present, little is required on the disclosure of business relationships these investigators may enjoy with the manufacturers of drugs that they test.

At our request, the FDA announced this week that they are writing new guidelines for this area, including a requirement that researchers declare whether they have a financial stake in the drugs they test.

It is also my understanding that the FDA is asking the manufacturer of Ceredase to change its labeling with regard to lowering prescribe dosage levels...a real boon to consumers who are now paying as much as $360,000 per year for this medication.

It's important to note that Ceredase, like so many other important new drugs, had its genesis in taxpayer-supported research. The Chair believes that federal agencies like the NIH and the FDA must assume new responsibilities as the guardian of those research dollars given the growth in the number of these collaborative research agreements.

The taxpayer, as a critical partner in this research, also deserves the absolute best price on the results of public-private collaboration.

Protecting the public ownership in developing technologies, whether at federal labs or at taxpayer-subsidized universities, gives the government one very important lever on pricing determinations. Government must ensure that technology transfer take place. But it also has to guard against the Macy's bargain basement approach. The public deserves more protection than just throwing open the doors to private interests who want to grab valuable technologies dirt cheap.

When a collaborative research and development deal is cut, federal agencies must make sure that the taxpayer's throat isn't sliced with the same knife.

Following Dr. Healy, the subcommittee will hear statements from the representative of a small high-tech firm which has been denied a useful technology because of one of these comprehensive, exclusive agreements with another firm. We also will hear testimony from the American Association of Medical Colleges, which represents many of the academic partners in collaborative agreements, and from a leading academic scholar who has researched the history and implications of academic-industry partnerships.

We thank our witnesses and appreciate their cooperation.

LARRY COMBEST
19TH DISTRICT, TEXAS

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OPENING STATEMENT HONORABLE LARRY COMBEST
TEXAS 19
COMMITTEE ON SMALL BUSINESS
SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES AND TECHNOLOGY

JUNE 17, 1993

Mr. Chairman thank you for calling this hearing and for your opening remarks.

Today's hearing will focus on the National Institutes of Health's (NIH) on going review of issues concerning commercialization of taxpayer funded research. I would like to initially discuss the great success story of the Bayh-Dole Act. As you all know, this act is the vehicle that allows technology to transfer from government supported institutions into productive private agreements. This revolutionary act has enabled life saving drugs and technologies to reach needy consumers that prior to the adoption of this act may never have made it off the shelves of NIH or a sponsored institution.

The success of Bayh-Dole can be seen in the number of patent applications filed in the 10 years before the passage of Bayh-Dole, only 890 patent applications were filed on inventions developed with NIH support. In the 10 years since, 3 times that many patent applications have been filed. I am also pleased that besides Mr. Ralph Nader, everyone including Dr. Healy have testified in overwhelming support of this act.

I believe like most pieces of legislation, there are segments of Bayh-Dole that clearly must be improved. Currently, it would appear that the multiple goals of the legislation can be contradictory. While small business should be given preference under Bayh-Dole, clearly the implementing regulations state large businesses should not be precluded. Furthermore while collaborations are encouraged it, would appear that in many instances small business may not have the financial or technical capabilities to bring these technologies to market. Therefore, should such collaborations exist if not all the criteria of Bayh-Dole are met?

I plan on working with the NIH, Chairman Wyden and industry to improve Bayh-Dole. I believe we must give clear guidance both in conflict of interest regulations and in implementing cooperative agreements. Having said this, any changes must be fully considered to ensure full accountability for U.S. taxpayers while not squelching the success stories under Bayh-Dole.

I would be remiss if I did not touch on some of the concerns that were voiced at the previous hearing regarding the proposed Sandoz-Scripps agreement. I, too, had some concerns regarding the small business access to such research and to the allegations of conflicts of interest. I believe that when questions are asked, the parties involved have the responsibility to sit down and work out the differences between them. It is my understanding that both Scripps and Sandoz have relayed their willingness to change this proposed agreement to meet the concerns of the NIH and of the subcommittee.

In closing, Mr. Chairman, I have received letters from both Scripps and Sandoz to this effect and would like to enter them into the record at this time.

STATEMENT

OF

BERNADINE HEALY, M.D.

DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH

BEFORE

THE HOUSE SMALL BUSINESS SUBCOMMITTEE

ON REGULATION BUSINESS OPPORTUNITIES, AND TECHNOLOGY

JUNE 17, 1993

Mr. Chairman and subcommittee members, I welcome this opportunity to update you on the progress of NIH's ongoing review of issues concerning the commercialization of NIH-funded research. I will provide the subcommittee with preliminary results of our analysis of research-support agreements solicited from approximately 100 grantee institutions, including the pending agreement between the Scripps Research Institute and the Sandoz Pharmaceuticals Corporation.

Now is an appropriate time to revisit these matters. Almost two weeks from today--July 1st--marks the twelfth anniversary of when the Bayh-Dole Act (Public Law 96-517) first went into effect. And, according to the Scripps-signed contract, July 1st is also the date set for finalizing the agreement between Sandoz U.S.A., the U.S. subsidiary of the Switzerland-based company, and Scripps, a nonprofit research institution that, last year, received $61.2 million in NIH funding plus additional support from other Federal sources.

You may recall that, around the time of the passage of the Bayh-Dole Act, there were predictions of potential problems and abuses. In the early 1980s, the chairman of the House Science and Technology Committee's Subcommittee on Investigations and Oversight, convened several hearings on university-industry cooperation in biotechnology. The Committee noted its "continuing concern that our universities . . . may be permanently altered by the increasing number of commercial agreements. . ." Although not viewing such agreements as "bad, per se," the Committee did warn of the potential to "adversely affect one of America's greatest strengths"--the Nation's research universities.

Specific concerns of that committee back then included whether research-support agreements would stifle the free exchange of knowledge, promote secrecy, and distort academic research priorities to conform with commercial aims. A second set of concerns arose from speculation that companies might exploit taxpayer-funded research without providing an adequate return to the public. Of particular concern was the possibility that a foreign firm might, "skim the cream produced by decades of taxpayer-funded work." Also raised as an issue was the prospect that universities did not have effective mechanisms to safeguard the integrity of the institutions and to buffer them from influences that might subvert their missions of education, research, and public service.

Fortunately, there is little or no evidence that these adverse effects have materialized. In fact, the risks have proved to be well worth taking: Highly productive university-industry relationships have blossomed since the passage of the Bayh-Dole Act. These relationships have yielded new products, created high-technology jobs, and spawned a robust U.S. biotechnology industry.

Reports by the San Diego press last winter, however, focused attention on a pending agreement between Scripps and Sandoz, which revived many of the concerns raised a decade ago. Under the terms of this research-support agreement, which would go into full effect in 1997, and to which we have been given access, Sandoz would pay Scripps $30 million dollars annually over a ten-year span. Along with a four-year phase-in period from 1993-1997, the agreement could be extended an additional six years, making the total term of the agreement 20 years. Moreover, provisions of the pending contract may violate the Bayh-Dole Act by:

1) Giving Sandoz a first option to exclusively license virtually all Scripps inventions, including all those not yet made;

2) Allowing Sandoz to approve the renewal of all project-specific commercialization agreements that Scripps currently has with other corporate sponsors;

3) Pledging Scripps's assistance in helping Sandoz seek a waiver from the Bayh-Dole requirement that it manufacture in the United States, inventions licensed to Sandoz; and

4) Allowing Sandoz to remove Scripps research projects, funded wholly or in part by Sandoz, from Scripps laboratories to Sandoz laboratories anywhere in the world, for further research and development.

From my perspective, this draft agreement would give Sandoz excessive control over Scripps that facilitates potential Bayh-Dole violations. Furthermore, elements of the draft agreement raise concerns about infringement of academic freedoms by:

1) Prohibiting Scripps scientists from consulting with outside organizations without prior approval by Sandoz;

2) Restricting access to the Scripps campus of scientists from outside organizations other than Sandoz;

3) Placing two Sandoz representatives on the Scripps Board of Directors, and allowing Sandoz to terminate the agreement if dissatisfied with the choice of any future Scripps CEO;

4) Providing Sandoz with the chairmanship of, and ultimate control over a joint scientific review board to help determine the course of Scripps research;

5) Requiring Scripps' President to encourage Scripps scientists to pursue projects of strategic interest to Sandoz.

In light of these provisions, it is not surprising that a columnist for the San Diego Union-Tribune characterized the agreement--"a leveraged buyout"--of a taxpayer-supported laboratory.

Mr. Chairman, by virtually any measure, this agreement is an aberration, and in my view, a dangerous exception to an otherwise successful record of cooperation between industry and NIH-funded institutions. Yet, because it deviates from many of the principles of the Bayh-Dole Act and also impinges on the freedom of scientific inquiry, I fear that the Scripps-Sandoz agreement, may tempt rash, wholesale indictments of the productive relationships that the Bayh-Dole Act has catalyzed between NIH-funded institutions and U.S. industry. Those relationships are fostering the growth of a budding bioeconomy of small and large companies now germinating in many of the high-technology corridors across this country.

SUCCESSES OF THE BAYH-DOLE ACT

I believe that the Bayh-Dole Act is not just working--but working well. At most, it may be necessary to fine-tune the Act's implementing regulations which are promulgated by the Department of Commerce. It also may be necessary for granting agencies like NIH to clarify how certain principles of the Act should be effected by the agencies and their grantees.

I intend to discuss these issues later but, first, let me recount a few of the Act's primary objectives and highlight its success. The Bayh-Dole Act:

- Promotes the commercialization of taxpayer-funded inventions by U.S. industry and labor;

- Promotes free competition and enterprise;

- Promotes collaboration between U.S. businesses and universities as well as other non-profit institutions;

- Encourages maximum participation of small businesses in federally-supported R&D; and

- Encourages job formation by requiring preference to companies who will manufacture licensed inventions in the U.S.

Evidence of the Bayh-Dole Act's effectiveness is compelling. For example, the 1,155 patents granted to American universities in 1990 accounted for 2.4 percent of all U.S.-origin patents, as compared with 1 percent in 1980. According to the National Science Foundation, about one in every four university patents issued in the late 1980s was for a biomedical or health-related invention. In the early 1970s, the ratio was about one in eight. NIH-supported research figures prominently in this surge in academic inventions and patents. Between 1980 and 1990, the number of applications for patents on NIH-supported inventions increased by nearly 300 percent over the previous decade--from 890 to more than 2,600.

Total university revenues realized annually from licensing royalties now exceed $80 million, as compared with about $30 million in 1986. Again, the origins of much of this licensed technology can be traced to NIH-funded research. According to a 1992 General Accounting Office study, 35 major universities granted a total of 197 exclusive licenses during 1989 and 1990, generating $29.3 million in royalties. More than 175 of those licenses were for technologies developed with NIH funding. The GAO study also reported that of the 197 exclusive licenses granted for "technologies developed in whole or in part with NIH or NSF funding, 146--or 74 percent--were granted to small U.S. businesses. In contrast, 29--or 14 percent--were granted to foreign companies (18) or to U.S. subsidiaries of foreign companies (11).

Though impressive, such statistics should not obscure a more important dividend. These patents are not just sterile descriptions of inventions and discoveries. Embodied in products, those that have made it to the marketplace

are improving health and saving lives. These products are dissolving blood clots, combatting viral diseases, and reducing the incidence of infection in patients undergoing chemotherapy.

Also important to note is the trend of increasing industrial funding of academic research. Over the 1970s and 1980s, industry support for university research grew faster than did any other source of funding. NSF estimates that nearly 2 percent of U.S. industry's expenditures for R&D now goes to academic institutions, as compared with less than 1 percent in 1971. This welcome trend, which includes increasing industrial support for fundamental research at universities, can be attributed in part to the Bayh-Dole Act. However, the trend began at a relatively low dollar level so that, overall, industry funding still accounts for less than 10 percent of funding for academic research.

TRENDS IN THE COMMERCIALIZATION OF NIH RESEARCH

After twelve years of experience with the Bayh-Dole Act, NIH sought to assess, through a coordinated sampling, the types and scopes of research-support agreements entered into by our grantee institutions. Although preliminary at this point, I wish to share with you some of our findings and contrast them with our standing concerns about the proposed agreement between Scripps and Sandoz:

Trends in Agreements

- approximately 100 institutions surveyed
- approximately 375 agreements reviewed
- approximately 44 percent of agreements are with small businesses

- more than 90 percent of agreements reviewed were for five years or less
- more than 90 percent of all agreements reviewed were for $5 million or less
- approximately 22 percent of agreements contained provisions allowing an industry partner to delay publication by more than 60 days
- approximately 331 of the agreements, or 86 percent, are project specific
- no agreements contained provisions placing representatives of the industrial partner on the institution's Board of Directors
- no agreements had provisions that required the institution to assist in obtaining a waiver of the U. S. manufacturing requirement

I believe that it would serve the public interest for the parties--Scripps and Sandoz--to publicly disclose their agreement, with the proprietary information expunged as did Massachusetts General Hospital with their Hoechst AG agreement. This would allow the biomedical research community to adequately debate the issues surrounding research-support agreements.

While some institutions like Scripps may favor agreements that secure large sums of research funding extending for several years, the Bayh-Dole Act articulates fairly explicit policy objectives. In addition, the Act does not appear to contemplate that institutions with large federal grant portfolios would

strike their own individual policy balances that minimize small business involvement in favor of large amounts of sole-source corporate funding that only large companies could supply. In other words, maximizing competition through Bayh-Dole does not mean that every major pharmaceutical company should sponsor its own academic research institution. Therefore, these preliminary findings from NIH's review of hundreds of research-support agreements indicate that Scripps' agreement with Sandoz is an atypical example of arrangements between industry and academia in that it trades all-encompassing exclusive rights to government-supported inventions for large amounts of funding.

NIH'S CONTINUING EFFORTS TO EXPLORE COMMERCIALIZATION ISSUES

NIH has taken seriously its involvement in the issues attendant to the commercialization of its research. NIH expects in the near future, to complete a number of activities that will provide additional insight into the relationship between our grantees and industry, and contribute to sound and deliberative recommendations for policies that are in the best interest of the public. These activities will involve the "Task Force on the Commercialization of Intellectual Property Rights from NIH-Supported Extramural Research," an internal NIH working group comprised of a multidisciplinary group of scientists, program officers, technology transfer specialists, and counsel.

First, NIH will continue our discussions with Scripps pertaining to their proposed agreement with Sandoz. Hopefully, the concerns we have raised can be adequately addressed. If, however, the deficiencies we perceive underlying the agreement are not corrected, it is anticipated that NIH, acting through the

Assistant Secretary for Health, will place appropriate restrictions on all future grants NIH makes to Scripps. Such measures would ensure appropriate access to any NIH-supported technology by small businesses. We have already advised Scripps of the potential for this action.

Second, among its charges, the Task Force has been instrumental in analyzing information on research-support agreements of approximately 100 NIH-grantee institutions. It will complete its review of these agreements and provide a summary of the findings to the Director of NIH.

Third, NIH expects to hold an open forum involving grantees, research institutions, associations, industry, and members of the general public to address issues in this area and their implications for the conduct of research.

Fourth, public input, the data from the survey of grantee institutions, and other information amassed by the Task Force will be distilled into a statement of general NIH principles on research-support agreements. These NIH principles will be published in the Federal Register, not as rules, but as recommendations our grantees can consider when negotiating such agreements. Periodic audits of NIH's grantee institutions could aid in determining the ability of these institutions to comply with the general principles as well as learning of any developing trends in devising such agreements. This would afford NIH the opportunity to maintain involvement in this issue without unwarrented intrusion.

AGENDA FOR THE 90'S

In my view, the challenge for policy makers in the 1990s is to develop the necessary framework of guidelines to effect the objectives of the Bayh-Dole Act in the face of the practical issues that arise as a result of its success. Such issues include appropriate access to research data, standards of conduct, oversight of commercialization efforts, and appropriate return on the taxpayer's investment in university research. I am not suggesting that NIH or other agencies review every research-support agreement, but these issues warrant further exploration.

University research data has both scientific and commercial value. Companies with early access to such data have a competitive advantage in identifying and pursuing new products. The Government Accounting Office (GAO) raised concerns in a 1992 study about the extent to which inappropriate access to unpublished research data, generated under government-funded grants, was provided to large and foreign companies to the exclusion of U.S. small business. The GAO advised that:

> ...inappropriate access can occur if a business that has not sponsored a research project obtains inside information about it or gets favored treatment in obtaining license rights to the resulting technology. Such inappropriate access could result from a financial or personal relationship between the business and a member of the university or a financial relationship between the business and the university itself--such as through an industrial liaison program.

In light of the GAO's concerns and NIH's experience, appropriate access to publicly-financed scientific data is an issue that may require further attention.

The promulgation of standards of conduct is important in ensuring that financial or other interests do not compromise the objectivity, and the public's confidence in the objectivity, of academic research. As you know, Mr. Chairman, many academic institutions and professional societies have developed policies and procedures to help their researchers and technology transfer staff avoid conflicts of interest. A policy issuance by the NIH and the Department of Health and Human Services has been in preparation for several years and, I hope, is close to being released for public comment. Conflicts of commitment also must be addressed by institutions of higher learning to ensure that their primary mission -- education -- does not take a back seat to the pursuit of commercialization activities.

The Bayh-Dole Act authorizes funding agencies to require periodic reporting on the utilization or efforts at obtaining utilization of inventions. The Act appropriately and successfully removed these agencies as impediments to the overall technology transfer process. However, given this reporting authority and the last-resort authority of government agencies to "march-in" to ensure that patented inventions are not left to languish, NIH and other agencies must identify, gather, and monitor the data that they need to respond to these aspects of Bayh-Dole. Appropriate guidelines and utilization report formats must be developed with university and industry involvement. Greater attention is warranted to these aspects of Bayh-Dole. Clarification of agency

responsibilities would ease much of the tension associated by industry with the march-in provisions of the Act.

Lastly, an issue that your Subcommittee has grappled with in hearings over the past two years is the appropriate return to the public on its investment in academic research. The public does benefit from increased knowledge in numerous fields of endeavor as well as from the jobs created through development of technology transferred under Bayh-Dole. The extent to which the public's return on research investment should be in the form of royalty payments, price rebates, or other mechanisms is subject to further public discussion.

That these issues are on the table for discussion today also is a testament to the scientific and commercial importance of the Bayh-Dole Act and its tremendous success.

Mr. Chairman, I am encouraged by the increasing number of scientific opportunities that lie before us and by the benefits they promise for this and future generations. We have reached this time of opportunity largely because of strong, sustained Federal support for biomedical research. Universities and the entire biomedical research community are challenged to find alternative sources of funding. Although not substitutes for Federal support, the beneficial partnerships that are evolving between academia and industry should be viewed as welcome and needed developments. These partnerships must be crafted in ways that not only protect but advance the public interest. NIH is committed to providing the leadership needed to accomplish this lasting aim and to achieve the ultimate objective of biomedical research--that is, improving the health of all Americans.

ORAL TESTIMONY OF DR. BARBARA CONTA
BEFORE THE HOUSE SUBCOMMITTEE ON REGULATION,
BUSINESS OPPORTUNITIES, AND TECHNOLOGY
June 17, 1993

Good morning. My name is Dr. Barbara S. Conta. I am the Patent Administrator of Regeneron Pharmaceuticals, Inc. Thank you for your invitation to appear before this Subcommittee on Regulation, Business Opportunities, and Technology. Regeneron would like initially to thank you, Chairman Wyden, for your support of the biotechnology industry and especially commend you for your leadership in implementing an improved examination process for biotechnology patents in the U.S. Patent and Trademark Office.

We have been asked to provide this Subcommittee with certain experiences and concerns of Regeneron in the area of technology transfer. Regeneron, a New York corporation, was founded in 1988 to develop biotechnology-based products to treat neurological diseases and conditions for which no cures exist. Regeneron is engaged in the discovery and development of neurotrophic factors, which are naturally occurring proteins that promote the survival and function of cells of the nervous system. These neurotrophic factors may have the potential to be used as drugs to treat a wide variety of neurological conditions, including motor neuron diseases such as amyotrophic lateral sclerosis (ALS, commonly known as Lou Gehrig's disease), diseases of the peripheral nervous system (such as diabetic neuropathy), and diseases of the central nervous system (such as Parkinson's disease and Alzheimer's disease).

Regeneron has established its own research and development staff and facilities in addition to entering into relationships with corporate partners, scientific advisors, and major medical and academic institutions to pursue the development of these potential therapeutic drugs. Two such drugs, proteins manufactured through recombinant DNA technology, have emerged as the company's leading product candidates. Of particular note is our current pivotal Phase III clinical trial of human ciliary neurotrophic factor to treat ALS, an inevitably fatal disease of motor nerves.

Regeneron has also gained access, through cooperative arrangements with academic, government, and commercial institutions, to technology that has had a positive impact on the drug development process. Regeneron has a limited number of sponsored research agreements with academic laboratories focused on novel neurotrophic factors and their use, and has entered into licensing agreements for specific technology for commercial development from a small number of academic institutions and corporations. We have collaborative development agreements with larger corporations to conduct basic research and commercialize specific compounds. Regeneron has transferred technology and supplied proprietary material, free of charge, to over 200 academic, government, and commercial institutions through collaboration agreements. These collaborations provide scientists with research material and technology not available commercially, and permit Regeneron to license potential technology which may result. These agreements provide Regeneron with resources far beyond our current capabilities. Without these collaborations, the Company would likely not have been founded, would not be as far along as we are in our development efforts, and certainly would not have been able to obtain the financial backing from risk-oriented investors.

The ability of sophisticated, risk-oriented biotechnology firms to identify potentially important basic or early stage technology and to obtain reasonable licenses is essential to the biotechnology industry. Therefore, we have two observations to make to this Subcommittee. First, we have experienced, and will describe here, one concrete example of a comprehensive exclusive technology transfer agreement between an academic institution and a corporation that, at least for the moment, blankets a specific technology that Regeneron is ready, willing, and able to develop but can not access. This experience supports your view, as we understand it, that such broad agreements can hinder the exploitation of scientific developments. Second, we understand your interest, Chairman Wyden, and the interest of this subcommittee in problems faced by small, technology-driven companies. We believe that a bill under your sponsorship, H.R. 1334, would create further barriers. It will act as a government supplied blanket, effectively shrouding technologies from exploitation by entrepreneurial, aggressive biotechnology firms. I will confine myself to a few brief remarks about this proposed legislation at the end of my testimony this morning.

Your staff has requested that we provide you with the following information. Normally, Regeneron will conduct research and discovery on a product only after we obtain a reasonably clear patent position or rights to such a position. In 1992, Regeneron learned that potentially important research about a novel neurotrophic factor had been conducted at a well-regarded private academic institution. When we attempted to negotiate a license to develop this technology, we learned that it was included under a comprehensive technology transfer agreement between the university and a major U.S. corporation. Over a period of six months in 1992, we communicated regularly with the

licensing director of this university in an attempt to secure a license. The University informed us that it was unable to obtain a release of the option rights it had granted under its comprehensive agreement. To our knowledge, this technology has not been developed by the option holder. It appeared to us that Regeneron was the most appropriate partner to develop this factor. Because of our extensive work in the area of neurotrophic factors, we also believe that we could have assisted the university's researchers in this area by providing them with rare research materials and know-how. While we were unable in this instance to obtain a license from this university, Regeneron has entered into a number of fruitful collaboration and consulting arrangements with this institution and its faculty. We know of no direct experience of other companies in this area.

Regeneron typically seeks licensing opportunities that are focused within our area of expertise, in which technology and scientific exchange is a prime motivating factor. We do not have the resources to fund long-term comprehensive technology transfer agreements with academic and research institutions which cover technology outside of our immediate business focus or capabilities.

To the extent that a comprehensive licensee retains rights to technologies that it is unable or unwilling to develop or exploit, certain technology opportunities are at least theoretically lost to other firms who are able and willing to do so. Because such comprehensive license agreements are only possible for large firms, they may disadvantage small entrepreneurial companies in particular. They may also disadvantage the public interest if the licensor fails to exercise due diligence to ensure that the licensee undertakes commercially reasonable efforts to develop the technology.

We believe that the federal government should continue to support, at increasingly large levels, research in the biomedical area. Uninhibited academic scientific research, able to take exceptional risks in order solely to move science forward, is essential to American and scientific progress. If a university or researcher is forced to view basic research as a profit center, science and society will inevitably suffer. Therefore, we strongly urge increased RO1 NIH funding. In our view, the federal government should refrain from taking any action which would further limit private or public funding options available to academic research institutions.

We believe that traditional license agreements, which contain due diligence standards, should in most cases protect the licensors and provide adequate incentives to the licensees to exploit the license. Universities and other institutions are experienced and capable in the protection and exploitation of their intellectual property. They have the legal basis to insure its development and should demonstrate a willingness to enforce such rights. NIH should, in our opinion, continue to promote technology transfer of its funded research into the private sector in a fair and diligent manner and should exercise its march-in rights to technology which remains undeveloped by a licensee. If our experience is not unusual, and if there is an occasional misuse of licenses to keep technology out of the hands of a party that will develop it, any new legislative effort to correct such a relatively minor abuse will almost certainly be overkill, and will have unexpected (and undoubtedly negative) consequences.

With regard to our second observation, we respectfully believe that the proposed H.R. 1334 would retard the ability of companies like Regeneron to enter into technology

transfer agreements with any institution to which H.R. 1334 applies. In my letter dated June 14, 1993 to the Subcommittee, I outlined in more detail our views, and I understand that my letter is part of the record of this hearing. In brief: First, Regeneron would not be able to find and obtain technology that other firms have not also identified; the fact of a proposed license would be publicized at a crucial moment, and larger or better funded firms would simply outbid us for the license. This effect strikes particularly at smaller companies, which expend proportionally extremely large amounts of resources to identify potentially significant new developments closely linked to their business.

Second, Regeneron's compliance with H.R. 1334 would be burdensome. A law that would require a company to spend more on administration would directly undermine almost every small technology-oriented firm. Third, although Regeneron is clearly identified as a leader in our area of technology,it appears likely that we, like other small firms, would have difficulty demonstrating appropriate commercial expertise, as the proposed statute requires.

We and the Biotechnology Industry Organization agree with the concept that commercial parties should pay royalties to NIH under appropriate circumstances, and we also believe that competitive bidding, under certain circumstances, is in the best interests of the public. However, early stage research is not the time to establish a formula for a "reasonable price"; this formulation is, in effect, an effort to jawbone or set prices without regard for risk, costs, competition, or other factors that can only be known later in the process of developing a drug. H.R. 1334, we believe, assumes that every technology transfer is tantamount to a sure thing. There is no such thing, so far, as a sure thing in

biotechnology. Every new technology is an invitation to conduct time consuming and expensive experiments to learn what the next time consuming and expensive experiment should be. We believe that H.R. 1334 is a constraint to science and to exploitation of technology that will particularly discriminate against small companies, and we oppose it.

Thank you again for the opportunity to present our views.

Statement on University-Industry Relations, Conflict of Interest and Disclosure

Testimony before the

Subcommittee on Regulation, Business Opportunities, & Technology

Committee on Small Business

U.S. House of Representatives

June 17, 1993

Submitted by

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Executive Summary

Our government's efforts to stimulate technology transfer by creating incentives for close collaboration between universities and private companies inadvertently have resulted in threats to the integrity, quality, and independence of science. The liabilities associated with unmanaged university-industry partnerships include: 1) increased trade secrets and secrecy within academia; 2) foreign companies skimming the cream of American scientific innovations; 3) increased potential for research bias, conflicts of interest, and commingling of funds where federal research dollars are used to support commercial research; 4) hidden public subsidies to commercial activities.

Some contracts, like one negotiated between the Sandoz Corporation and the Scripps Research Institute, come perilously close to making a research institution's scientists indentured scholars to a single corporate entity. The intention of the technology transfer policies was to stimulate the growth of new business derived from the timely transfer of scientific knowledge. It was not meant to lock up our nation's research universities and independent centers who receive multiple sources of funding to one corporate patron. A comprehensive system of disclosure for faculty, institutions, peer reviewers, and scientific advisors to government should be adopted; it should be implemented by federal grantee institutions and monitored by a new independent Office of Scientific Integrity and Ethics.

Mr. Chairman, members of the subcommittee, ladies and gentlemen:

I appreciate the opportunity to appear before you today. I am a professor and chair of the Department of Urban and Environmental Policy at Tufts University. My research activities include studies on the societal impacts of science and the institutional context within which science is carried out. As former chair of the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science and as a current Board Member of the Council for Responsible Genetics, a public interest organization, I have had a special interest in conflict of interest pertaining to publicly supported science. Today, I am speaking on my own behalf to share with you my perspectives on current problems arising from university-industry relations.

The issues your subcommittee has selected for this hearing have evolved over a period of two decades when policies designed to achieve a set of laudable social goals inadvertently helped to create new problems. The goals pertain to technology transfer and to reinvigorating the American industrial economy. To achieve these objectives prior Congresses and Presidents have created incentives for corporations and our independent universities to collaborate more closely in pursuit of multiple and mutually reinforcing objectives. These objectives include the advancement of knowledge, the transfer of knowledge, and the marketing of knowledge. Moreover, the pursuit of these objectives may be carried out by a single scientist-entrepreneur or by a non-profit research or academic institution. In the United States it has been reported that over 100 universities have established for-profit companies (Porter and Malone, 1992, 27). Increasingly, the boundaries between academic institutions and corporate enterprises have become blurred. This has created an unusual set of problems since the missions and norms of academic institutions are quite distinct from those of corporations. As a result, a blending takes place, although some would argue that, in exchange for research dollars, the universities and non-profit research centers are making the most compromises.

The several acts and administrative rules that have been issued over the past decade to improve technology transfer have had several implicit or explicit goals. These policies were designed to stimulate the growth of science, to preserve its health, to achieve a high rate of return to society for federal support of science, and to help American industry, and particularly small businesses, reap the timely benefits of scientific and technological innovation.

The central question is: Are we achieving all or some of these goals and at what expense? The key to understanding the impact that these policies are having on the health of American science is through effective and comprehensive disclosure provisions. I do not think anyone wants to see some short-term gains in technology transfer at the expense of long-term damage to the integrity, quality, and independence of science.

Aggressive academic-industry relations incur a variety of liabilities, many of which have been widely reported in academic studies, congressional hearings, and in the media. They include:

- increases in trade secrets resulting in a restricted flow of scientific information;

- a skimming of the cream of American scientific innovations by foreign companies investing in university research;
- a potential of research bias where investigators have a financial interest in the outcome of the research;
- increases in real or perceived conflicts of interest;
- a potential for commingling of funds where federal research dollars support commercial research; and
- hidden public subsidies to commercial activities.

For example, a recent study of industry-funded research at the University of Wisconsin reported that over half of the industry research contracts studied paid less—— some significantly less——than the full overhead rate approved by federal auditors. In effect, one could view this outcome as a public subsidy for private research (Wisconsin Rural Development Center, 1993).

There is no magic elixir for solving these problems. But I believe that we will be moving in the right direction with a set of comprehensive disclosure provisions. The purpose of disclosure is often misunderstood. It is not, as some have contended, to insure that scientific research is done objectively. No amount of disclosure can insure good science. Nor will disclosure necessarily alter the norms of institutions or their scientists. But since these norms are influenced by public policies and are not solely internally generated, disclosure will allow us to understand whether our public policies are achieving the ends for which they were conceived. Disclosure will also make explicit any factors, which, if concealed, give the appearance of bias or conflict of interest. It is all too easy for the public to discredit good science because of the concealed financial interests of researchers. Therefore, disclosure is like "truth in advertising." If there are two published studies that give contradictory results on a drug's efficacy, it would be naive to think that, among all other factors considered, the researcher's equity interest in a drug company poised to manufacture the product is not a relevant piece of information.

Let me begin with a brief discussion of several types of problems.

1. Major corporations have negotiated special contracts with universities and private research institutes. The most recent of these is the agreement between the Scripps Research Institute and the Sandoz Corporation. According to published reports of this agreement, Sandoz will have rights to any discoveries by Scripps scientists, will be able to review the scientists' ties to other companies, and will be in a position to choose research topics scientists will pursue. It sounds perilously close to making an institution's scientists indentured scholars to a single corporate entity. This monopolistic view of science is inconsistent with the free-spirited, independent, and decentralized culture of science that has been central to its vitality. The Sandoz-Scripps agreement may represent such a conflict.

Since federal dollars support a significant part of Scripps research, there is a public interest in knowing how the discoveries derived from these dollars are used. This agreement may or may not be an efficient way to transfer scientific discoveries into commercial applications. But we will never be able to know this until we have full disclosure of the conditions of the agreement and the discoveries that come under the provisions of that agreement. How will we know whether some discoveries are held back from

commercialization by the company to protect its market share of a product? How will we know whether there is systematic bias on the part of Scripps' scientists in the evaluation of pharmaceutical products that would provide financial gains for Sandoz?

The problems of systematic bias in research resulting from single-source funding has not been adequately studied. As a result of limited disclosure it has been difficult to undertake a comprehensive study of research bias resulting from source of funding. However, one limited study, of the pharmaceutical industry, suggests there may be a serious concern. The study looked at how researchers assessed the efficacy of new drug therapies against traditional therapy. It reported that drug studies sponsored by pharmaceutical companies in comparison to other sources were more likely to favor the new products over traditional ones. In this particular case covering 107 clinical trials there was no instance in which an investigator found a new drug inferior to an alternative product, if the investigator's research was sponsored by the drug's manufacturers (Porter and Malone, 1992, 131). For investigators not supported by pharmaceutical companies there was greater diversity in the findings.

2. New rules for disclosure must also be developed in those cases where investigators apply for federal grants in areas where they have strong financial interests. Not too many years ago it was not considered a conflict of interest for investigators to be testing for safety and efficacy of products in which they had a financial interest. Recently, local newspapers in cities like Boston and Minneapolis have reported on the corruption of entrepreneur medical researchers who dispense ineffective drugs on patients in order to enhance the standing of a company in which they have equity. The *Boston Globe* headline read: **Flawed Study Helps Doctor Profit on Drug,** while the Minneapolis Star Tribune ran a lead which read: **Unproved Drug Enriches "U" Doctor.**

Today funding agencies have become more sensitive to such arrangements. But there are still unresolved issues regarding disclosure. Should it be voluntary? If it is mandatory, then who should administer it? Will the requirement that scientists disclose their financial associations or investments related to their grants poison the climate for science, creating an atmosphere of suspicion——or as one commentator put it "a new McCarthyism in science" (Rothman, 1993)?

As someone who has written and received many grants, I can say with confidence that grant applicants will not be pleased about filling out more forms, especially those that probe into the private financial affairs of scientists. But given the current climate and the public concerns about multi-vested science, some restoration of confidence is in order. One point should be underscored. Each case of fraud, misconduct, or conflict of interest that is connected, however tenuously, to the financial gain of scientists threatens public confidence.

A decade ago, we had no estimate of the order of magnitude of academic- industry relations. Today we are beginning to understand the extent of the linkages in the biomedical areas. In one study of approximately 800 biotechnology faculty, 47 percent consulted with industry, nearly 25 percent received industry-supported grants or contracts, and 8 percent owned equity in a company whose products were related to their research (Blumenthal, 1992). In another study colleagues and I published, we found one third of the faculty in one prestigious university had formal ties to various biotechnology companies. The biotechnology faculty of another university had close links to 43 different companies

(Krimsky et al., 1991). One can only imagine the self-imposed constraints on communication arising from faculty allegiance to 43 company policies designed to protect their own intellectual property rights.

Some federal agencies that sponsor research are considering disclosure guidelines for potential grantees. The National Science Foundation has proposed a program of "limited and targeted financial disclosure by faculty and staff" for funded research that may have a direct outcome on the financial interests of the investigator, their family, or business associates. Under the proposed program each institution would enforce its own conflict-of-interest policy, while grant applicants would be required to submit financial disclosure statements as part of their grant application. Investigator financial disclosure to university officials and the granting agency would not and should not affect the scientific evaluation of the proposed research. The Public Health Service and the National Institutes of Health are also in the final stages of reviewing a draft proposal. It is unlikely that this proposal will include financial disclosure submissions by grant applicants to PHS or NIH.

I believe the agencies are moving in the right direction in their efforts to establish institutional guidelines on conflict of interest. There are two limitations to this approach, however. First, under current proposals, there is no public access to the conflict-of-interest information. One reason for providing public access to this information is that it serves as a check against institutional deficiencies in the implementation of the program. Access to such information should not be capricious. Universities may insure confidentiality of disclosure statements unless preempted by state law. However, there ought to be public access through the Freedom of Information Act of the conflict-of-interest disclosure statements submitted to a granting agency by recipients of federal grants and contracts. It should be noted that a conflict of interest policy which did not require financial disclosure submissions to granting agencies would preclude public access to important information.

A second limitation to current proposals is that they do not address questions of institutional conflict of interest. Increasingly, universities have started for-profit companies. In one notable case, a university itself, individual members of the Board of Trustees, the university president, and members of its faculty own equity in a company (Blumenthal, 1992). How can the administration of this university be placed in charge of managing its faculty conflict-of-interest information and of setting the moral climate of its faculty? Institutions allied with for-profit companies should come under another set of guidelines pertaining to institutional grants related to their commercial activities.

Another reason for public access to investigator conflict-of-interest information is to enable researchers to gain more knowledge about the potential for bias between investigator affiliation and research outcomes. Much of what we know today is based on individual cases or surveys of scientists. By allowing social scientists access through FOIA to conflict-of-interest information more systematic research into affiliation and bias will be possible.

3. A third area where disclosure is needed is in the peer review process, which serves as the cornerstone of scientific accountability and integrity. The scope of university-industry relationships has caught the attention of international medical journal editors concerned about the objectivity of the peer review process that is essential to their review

procedures. Editors of medical journals are beginning to ask authors and reviewers to disclose financial and other conflicts of interest that may bias or create the appearance of bias in their work. Similar procedures should be in place for external reviewers of federal grant proposals. Here again I believe a registry of these conflict-of-interest disclosure statements should be available through FOIA requests. This has to be monitored very carefully to insure that the peer review process is not depleted of competent reviewers.

Policy Recommendations

1. A New Office of Scientific Integrity and Ethics

Congress should establish an independent Office of Scientific Integrity and Ethics. The function of this office would be to establish federal ethical standards and conflict-of-interest rules for all institutions that receive federal grant and contract support. The Office would evaluate the implementation of those rules and make periodic adjustments based on outcome measures such as compliance rate. The Office would also undertake research, intramural and extramural, on scientific integrity and on the nature and magnitude of the impacts of university-industry relations on science.

2. Conflict-of-interest guidelines for recipients of federal grants.

Federal grants and contracts to academic and research institutions should be contingent on an acceptable program of conflict-of-interest management including:

a) disclosure to an institutional office and funding agency of faculty consulting relationships and equity holdings in companies with commercial interests related to the subject of the research; and

b) disclosure of institutional investments in for-profit companies and institutional research contracts with private companies.

3. Scientific Advisors.

Scientists who serve on federal advisory boards and study panels of granting agencies should be required to disclose financial relationships in areas related to their expertise. These disclosures should be open to public review as through FOIA requests to the agency that oversees the advisory board.

4. Peer Reviewers

Agencies that sponsor research should maintain an updated registry of conflict-of- interest disclosure statements for peer reviewers. The anonymity of individual reviewers on a particular grant should be respected.

In conclusion, we need a system of disclosure that will not undermine the incentive of scientists to pursue federal grants, that will not make the grant process or the peer review process too ponderous or bureaucratic, and that can be effectively implemented by our universities and centers of research. The National Institutes of Health withdrew its 1989 proposed guidelines on conflict of interest because the vast majority of scientists found them unworkable. This retreat illustrates how delicate the issue of disclosure can be. While we need a comprehensive system of disclosure, we do not want to foster an ethos described in Michael Crighton's best seller *Jurassic Park*, "If you want to get something done, stay out of universities."

It is sometimes useful to look at similar periods in history when science was debating its ethical standards. A quarter century ago there were voices of protest from the scientific community that federal guidelines on the use of human subjects in research would strangle the independence of science. Instead, the guidelines on the use of human subjects have been an international model that has propelled science to a higher moral elevation. Carefully constructed, a disclosure policy for recipients of federal research dollars, in conjunction with guidelines prohibiting certain perniclous conflicts of interest, will go a long way toward reestablishing the public's confidence in the moral integrity of our academic and research institutions.

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Sheldon Krimsky

Sheldon Krimsky is professor and chair of Urban & Environmental Policy at Tufts University. He received his bachelors and masters degrees in physics from Brooklyn College, CUNY and Purdue University respectively, and a masters and doctorate in philosophy at Boston University.

Professor Krimsky served on the National Institutes of Health's Recombinant DNA Advisory Committee from 1978-1981. He was a consultant to the Presidential Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and to the Congressional Office of Technology Assessment. He also served on a special study panel for the American Civil Liberties Union that formulated a policy on civil liberties and scientific research. Professor Krimsky served as chairperson of the Committee on Scientific Freedom and Responsibility for the American Association for the Advancement of Science for 1988-1982. Currently he serves on the Board of Directors for the Council for Responsible Genetics.

Professor Krimsky's research has focused on the linkages between science/technology, ethics/values, and public policy. He is the author of *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* and *Biotechnics and Society: The Rise of Industrial Genetics*. He is co-author of *Environmental Hazards: Communicating Risks as a Social Process*. His latest book is a co-edited collection of papers titled *Social Theories of Risk*. Professor Krimsky has published over 80 essays that have appeared in many books and journals.

STATEMENT

OF THE

AAMC · ASSOCIATION OF AMERICAN MEDICAL COLLEGES

Robert G. Petersdorf, M.D., President

UNIVERSITY AND INDUSTRY COLLABORATION: TECHNOLOGY TRANSFER AGREEMENTS

Presented by
William A. Peck, M.D.
Executive Vice Chancellor for Medical Affairs
and Dean of the School of Medicine
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Saint Louis, Missouri

to the
Committee on Small Business
Subcommittee on Regulation, Business Opportunities
and Technology
U.S. House of Representatives

June 17, 1993

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My name is William A. Peck, M.D., and I am the Executive Vice Chancellor for Medical Affairs at Washington University and Dean of the Washington University School of Medicine. With me today are Dr. David Kipnis, Distinguished University Professor of Medicine and former Head of the Department of Medicine at Washington University, and Dr. Susan Cullen, Associate Vice Chancellor for Research at Washington University. This morning I am testifying on behalf of the Association of American Medical Colleges (AAMC), which represents all 126 accredited U.S. medical schools, 400 of the nation's major teaching hospitals and 90 academic and scientific professional societies. The member institutions and scientists represented by the AAMC play a major role in this nation's medical research efforts. Let me say at the outset that neither I nor members of the AAMC staff have had an opportunity to review the Scripps-Sandoz Agreement; my comments this morning concern technology transfer agreements in general and our experiences at Washington University.

The AAMC is gratified to note your position, as expressed in your opening statement to the March 11, 1993, hearing, that you recognize the importance of biomedical research collaboration and cooperation between publicly-supported labs and industry.

I would like to begin by briefly reviewing the evolution of federal policies related to technology transfer and university-industry relationships. The founding fathers recognized that conferring on an inventor the protection of an exclusive right to control the development and marketing of an invention was an appropriate incentive to stimulate technology development that contributed to the public interest. This policy seems, on balance, to have worked reasonably well for two centuries now, with debate and litigation focused principally on issues such as priority and infringement.

A quantitatively, if not qualitatively, new factor appeared on the scene during and after World War II, when the primary sponsorship of many types of research shifted from industry to government. The size and scope of the nation's research enterprise has since been expanding at a rapid rate. Over time, the basis for product development increasingly has become traceable to a kernel of intellectual property that came into being as a consequence of government-funded research, and intellectual property that was thus generally conceded to be government owned.

Throughout the 1950's and 1960's, the issues of intellectual property ownership, invention reporting, and patenting were almost unknown and rarely discussed in the research community of which the National Institutes of Health (NIH) was a part. Scientists sought to publish research results as quickly as possible in the open literature: the public domain. But by the mid-1960's, it began to be recognized that, because technical development, testing and evaluation of any potential product derived from new knowledge is expensive and fraught with risk, product development would be seriously inhibited unless candidate manufacturers could be offered a guarantee of investment protection through acquisition of a patent or an exclusive license.

The indispensable prerequisite for providing such protection was timely patenting of intellectual property generated by public funds and of promising commercial value. Licensing agreements, exclusive or otherwise, could be negotiated to encourage the development of marketable products. The ideological counterargument offered was that intellectual property arising from research funded with public money belongs to the public and any profit accruing from the exploitation of this knowledge for commercial gain should, in whole or part, benefit the public.

After lengthy debate within the NIH, the Public Health Service (PHS) and the

Department of Health, Education and Welfare, the judgement that finally prevailed was pragmatic, not ideological: the health of the public would not be advanced if the results of PHS-supported research projects that were potentially convertible into useful products were allowed to lie fallow for want of a developer.

Beginning in the 1960's, the NIH began to negotiate "institutional patent agreements" with major grantee institutions, with the objective of ensuring commercial development of potentially useful drugs, devices, diagnostics, processes, tests, etc., and expediting technology transfer. Under these agreements, grantee institutions were permitted to acquire patents on research discoveries, to award exclusive licenses to commercial developers and to receive and retain royalties from the latter.

Evolution of National Policy

The adequacy of prevailing patent policy to contemporary circumstances soon thereafter became a focus of general public policy debate because of several developments in the 1970's. One was the dawning recognition of the importance of technological advances and innovations for successful competition in global markets, and of the centrality of new knowledge derived from basic research as the fountainhead of ideas for new technology.

Another remarkable characteristic of the 1970's was the explosive growth, at the molecular level, of new knowledge in scientific disciplines such as cell biology, genetics, immunology and microbiology. These advances in fundamental understanding also presented obvious and evident opportunities for technology transfer into products of great value and utility in agriculture, ecology, environmental protection and medicine. The "new biology" opened up enticing prospects of producing on an almost unlimited scale highly

complex molecular entities that had long defied laboratory synthesis.

Federal efforts to ensure the United States' success in a global market included several important legislative enactments.

The Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480) was designed "to promote United States technological innovation for the achievement of national economic, environmental and social goals...." The legislative history of the Act clearly recognized the contributors to technological innovation -- academic institutions, government laboratories, big industry, small business and labor -- and the need to encourage interaction and cooperation among these under a comprehensive national policy.

The Bayh-Dole Patent and Trademark Laws Amendment of 1980 (P.L. 96-517) was designed to promote technology innovation, and it clarified uncertainties with respect to commercial exploitation of federally owned inventions. The statute explicitly invests in grantee institutions ownership of the intellectual property rights to research findings emerging from government-funded projects and allows these institutions to patent any derived inventions, to license, exclusively or otherwise, the technological development of products and to collect and retain royalties. Although the initial legislation limited licensees to small businesses, eligibility was extended to industry as a whole by an executive memorandum to the heads of Executive Branch departments and agencies on February 18, 1983, and by Executive Order Number 12591, issued by President Reagan on April 10, 1987.

The Federal Technology Transfer Act of 1986 (P.L. 99-502) extended authorization for science/industry collaboration to federal research laboratories such as the NIH.

Incentives were offered to create Cooperative Research and Development Agreements (CRADAs) between government scientists and commercial producers to expedite technology transfer of laboratory discoveries into the development and marketing of innovative products. Government patents were allowed to be exclusively licensed to the commercial collaborator and government scientists were permitted to accept royalty income as a supplement to their regular salaries.

New Relationships of Academe with Industry

Academic institutions and federal laboratories were both heavily engaged in research in molecular biology and, as opportunities for product development emerged, both took advantage of the options offered by the Bayh-Dole and Federal Technology Transfer Acts. As academic institutions entered into this arena, a variety of administrative and legal entities and arrangements for interacting with industry were devised. Some set up a discrete university-wide office to identify patentable advances and to carry out all of the necessary subsequent steps such as acquiring patents, negotiating with potential licensees, and receiving and allocating royalties. Others contracted with organizations that had been established for the sole purpose of offering patenting and licensing services to academic institutions.

A different form taken by the legislation encouraging cooperation between industry and academic basic research performers was the negotiation of agreements under which an industrial organization provided direct support for basic research in specific academic institutions in exchange for first refusal to patent rights on, or to exclusive licenses to exploit, discoveries felt to be potentially convertible to commercially useful and valuable products. The universities generally also received negotiated amounts of royalties from the profits from the commercial products. This general mechanism of cooperation has

evolved over time. The terms of the contractual relationship between the industry and academic partners have varied, especially with respect to ownership of patents when a discovery has been partially funded by government funds.

The federal legislation to encourage cooperation between government, academe, small and large manufacturing businesses and venture capitalists to foster technological innovation to improve the nation's competitive position in the global economy has had an unmistakable impact over the last decade or so. Invention reporting from federal and academic laboratories has increased sharply, as have patent applications and awards. The NIH testified before this subcommittee in March that in the 10 years before the passage of Bayh-Dole, 890 patent applications were filed based on inventions developed with NIH support. In the 10 years following Bayh-Dole, a total of 2,617 patent applications were filed. A new industry -- biotechnology -- of substantial size, dominated by U.S. companies and exerting a significantly positive effect on America's international trade balance has become established. In 1991, the President's Council on Competitiveness Report on National Biotechnology Policy stated that the biotechnology industry has the potential to surpass the computer industry in size and importance. This report went on to say that this $2 billion industry is expected to increase to $50 billion by the year 2000. NIH Director Bernadine Healy, M.D., testified before this subcommittee in December 1991, "The biotechnology industry has already contributed to a positive trade balance, and for pharmaceutical and medical devices we now lead the world." In the course of these events, the national research enterprise has now taken on characteristics, dimensions and values that were unimaginable 25 years ago.

Despite the undeniable reality that government policy has contributed very importantly to the creation of a U.S. biotechnology industry that has been a huge economic boon to the nation, some strong reservations about the unintended

consequences of this policy have been voiced. This morning, I shall address some of these concerns, as set forth by the questions posed by the chairman. However, I think I can be most helpful to the subcommittee by outlining our Washington University agreement with the Monsanto corporation and sharing our experience with you.

The AAMC supports technology agreements between academic medical centers and industry as a necessary, critical element to ensure the commercial development of products derived from the fruits of federally funded research. It is not the practice or purview of academic medical centers to bring products to the commercial marketplace; therefore, they do not possess the resources or expertise to do so. In fact, at a time when academic medical centers are being asked to expand their activities not only in their traditional teaching, research, and patient care missions but also to expand their community service activities, some might question the wisdom of asking them to undertake the commercial development of their scientific discoveries as well.

The nature of the partnerships that arise between academic medical centers and industry continues to evolve as our understanding of the biomedical sciences progresses and the demands of the marketplace change. In fact, one might view the current time as a period of experimentation, where different pilot projects for technology transfer are underway. It is difficult to predict *a priori* which of these experiments will be successful.

One element consistent to all of these models is that industry must have reasonable expectations of being able to recover its development costs, which may be considerable, or it will not participate. Exclusivity in licensing is one way to promote the financial recovery essential to industry and is consequently a fundamental and necessary characteristic of many university-industry arrangements. The AAMC is concerned that

modifications to the current statutory and regulatory framework to limit the availability of exclusive licensing agreements may discourage industry involvement, impeding the development of commercial products and denying both academic medical centers and their industry partners the synergistic benefits of their collaborations

The AAMC believes that to serve the public's interest, federal policy must recognize the danger that unfettered access to the results of federally-funded research would fail to meet the public's expectations of the commercial development of new diagnostic and therapeutic products arising from the investment of federal tax dollars in basic research.

Another concern that has been raised by the subcommittee is the possibly "chilling effect" of these agreements on the normal interactions and communications within the scientific community. Any technology transfer agreement between an academic medical center and industry should, in the opinion of the AAMC, have well-defined time limits within which the industrial partner must decide whether to commercialize the discovery. Such deadlines will preclude undue delay in publication of the research, which is the formal mechanism of communication within the scientific community.

Conflict of Interest

Much attention has been focused on the potential for conflicts of interest in the course of technology transfer agreements between academic medical centers and industry. Let me say that it is important to draw a careful distinction between federal policies for patenting and licensing and those for dealing with conflict of interest. Whether it is appropriate, for example, to permit exclusive licensing of federally-supported research to industry is a policy question ripe for discussion, but not one that should be couched in

terms of conflicts of interest. Conflicts of interest, on the other hand, relate to questions of bias that most often have nothing to do with licenses and patents.

As for conflicts of interest in research, the AAMC issued in 1990 guidelines to assist its membership in developing effective policies and procedures for the review of disclosure information and for the management of possible conflict of interest situations. The 1990 *Guidelines to Deal with Faculty Conflicts of Commitment and Conflicts of Interest in Research* emphasize the importance of disclosure and management of conflicts of interest. The primary focus of this document is on faculty research activities specifically rather than on administrative or institutional conflicts; however, the principles for appropriate disclosure and management are applicable to institutional situations.

The AAMC Guidelines state that conflicts of interest are inevitable and should not be equated with misconduct; rather, they must be acknowledged and managed responsibly and appropriately. In fact, any number of personal interests can have a biasing effect on professional activities ranging from the actual conduct and reporting of the research to the management of the institution, and these interests are certainly not limited to financial considerations. Complete eradication of the potential for conflicts of interest is not a reasonable or even a desirable policy objective. There are a number of potentially biasing rewards inherent in the academic environment that are completely unrelated to relationships with industry or private sponsorship. For example, investigators may wish to see their hypotheses validated through positive research results because these may contribute to opportunities for publication, promotion, tenure and grant renewals. The cognizance of these rewards can be as much a source of conflict in the search for truth as interest of a pecuniary nature. However, kept in perspective, such incentives are not inherently bad and are indeed the motivating forces for productive, diligent scientists.

The AAMC Guidelines stress that disclosure can be an effective means of dealing with conflicts of interest because:

> general awareness (institutional and public) of an investigator's relevant funding sources, financial interests and professional roles serve to direct appropriate scrutiny at elements of research commitment, design and reporting of data that might be biased or undermined by these factors. The investigator's cognizance of that scrutiny further encourages vigilance to avoid any biases or diversions that inadvertently may be introduced. Naturally, for this system to work, the disclosure process must assure that information regarding possible conflicts reaches all individuals with an appropriate interest in evaluating this question.

The Guidelines also note:

> The opportunity for investigators to receive financial or other personal rewards from their endeavors is not intrinsically unacceptable, as long as it does not adversely influence the objectivity, integrity, or professional commitment of an investigator .... [P]articipation in a situation with opportunity for personal gain does not constitute an unacceptable situation of itself; it is the potential stimulus for unacceptable behavior that must be addressed.

At present, there is much activity among the federal agencies to regulate the way institutions deal with possible conflicts of interest. The recently enacted National Institutes of Health Revitalization Act of 1993, Public Law 103-43, requires the Secretary of Health and Human Services to issue regulations within 180 days of enactment to

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"define the specific circumstances that constitute the existence of a financial interest ... that will, or may be reasonably expected to, create a bias...." The AAMC believes that the central responsibility for identifying, reviewing and managing potential conflicts of interest resides within the institution.

The provisions of P.L. 103-43 relate only to clinical research projects. It is our understanding that in addition to the NIH, the Food and Drug Administration (FDA) also is developing its own regulatory construct for dealing with conflicts of interest in clinical trials that it reviews. In addition, the National Science Foundation is developing a separate set of regulations on conflict of interest. It is unclear how the these approaches will mesh; however, the AAMC believes strongly that coordination among all agencies is essential if the system is to operate efficiently and effectively.

Small Business Preference

The question of giving preference to small businesses in licensing agreements is another topic that requires a balancing of competing federal objectives of encouraging small business and facilitating technology transfer. The position articulated in the regulations developed by the Department of Commerce [37 CFR 401.7] states that contractors are expected to use reasonable efforts to attract small business licensure. The AAMC does not have a formal position on this, but I find this approach to be appropriate. The regulation goes on to state:

> What constitutes reasonable efforts to attract small business licenses will vary with the circumstances and the nature, duration and expense of efforts to bring the invention to the market. Paragraph (k)(4) is not intended, for example, to prevent nonprofit

organizations from providing larger firms with a right of first refusal or other options in inventions that relate to research being supported under long-term or other arrangements with larger companies. Under such circumstances it would not be reasonable to seek and to give a preference to small business licensees.

The Washington University-Monsanto Agreement

Washington University, like many other major research institutions, believes that it is an important and participatory component of the complex fabric of society. It is our mission to teach as well as to create new knowledge and to enhance the propagation and amplification of that knowledge into a form that yields important societal benefits. In order to achieve this crucial transfer to the private sector, universities have formed ties with industry. Universities do not, for the most part, have the capacity to undertake the transformation of intellectual capital into a publicly useful form. Indeed, the provisions of the Bayh-Dole Act recognized that fact in giving universities both the opportunity and the obligation to bridge the gap between academia and the commercial arena.

In 1982, Washington University entered into a five-year $23.5 million Agreement with the Monsanto Corporation, headquartered in St. Louis, to conduct biomedical research. Since then, the Agreement has been renewed three times, most recently in 1989, extending it through 1994 and bringing Monsanto's total investment to approximately $100 million. The Agreement has been examined publicly and in great detail. It was one of the subjects considered at a House hearing on university/industry cooperation in biotechnology on June 16, 1982, shortly after the Agreement's inception. Then Congressman Albert Gore, Jr., commended Washington University and Monsanto "for the effort and thought ... put into this Agreement." What was concluded at that

hearing is still true today; the Agreement protects academic freedom, is structured to avoid inappropriate influence on research direction within the University, does not restrict faculty interactions within the University, does not restrict faculty interactions with academic colleagues or even with other companies and provides an effective mechanism to create public access to the technology, as envisaged by the Bayh-Dole Act.

It is important to stress that the Monsanto Grant and corporate sponsorship of research at Washington University *in toto* comprises a small fraction of Washington University's research funding. In FY 1992 alone, Washington University received new or continuing grant awards totalling over $185 million, of which only $19.7 million (10.3 percent) was derived from corporation sponsored-research; about $10 million was from Monsanto. The University's research base is broad and dominated by federal funding. Accordingly, corporate support, while significant, neither drives the research engine of Washington University nor selects its directions.

I should like to review briefly the key features of the Washington University-Monsanto Agreement.

First, it is institutional -- Monsanto allocates funds to Washington University, reflective of the overall mission to create and propagate new knowledge. The University is the sole owner of any and all patents that emerge.

Second, the program is investigator-initiated and accessed by a broad representation of the faculty; requests for application are distributed to all members of the full-time faculty of Washington University School of Medicine.

Third, the program is driven by internal and external peer review. Internally, a

standing committee consisting of five Washington University faculty members and five Monsanto scientist/administrators reviews all applications and approves proposals on the basis of merit. Every three years, an external review committee of Nobel Laureates and members of the National Academy of Sciences, among others, reviews the entire program, to ensure its quality, preservation of its mission and its compatibility with our academic goals. In seeking such assurances, the external review committee meets not only with funded investigators, but also with graduate students, post-doctoral fellows, and unsuccessful applicants.

Fourth, the program is in the public domain. All publications acknowledge Monsanto support; and all investigators understand the covenant -- your research will be supported and we will see to the return of its benefits to society.

Fifth, the program does not interfere with scientific freedom. Investigators are free to explore other funding relationships; there is no scrutiny by Monsanto or Washington University of other relationships the scientists wish to pursue. Importantly, submission of manuscripts and abstracts is delayed no more than 30 days, during which time Monsanto must make a decision about whether or not to patent the idea. There has been no single case of delay in submission beyond 30 days in the eleven year history of the program. This also protects the property of the discoverer. Furthermore, Monsanto pays domestic and international patenting fees.

Sixth, all royalties accrue to the institution and the investigator's department and laboratory, but not the investigator. There is no personal financial gain.

Seventh, patenting and licensing components of the program as well as other relevant components are subject to the rule of law. We included provisions in the contract

stating that the terms of our licenses with Monsanto will be consistent with the Bayh-Dole statute and its implementing regulations.

What are the results of the program to date? Since 1983, 96 U.S. patent applications have been filed and 42 patents issued. Many of the patents covered technologies that are under active development in the pipeline at Monsanto. Two products are now in clinical trails being carried out by the G.D. Searle arm of the Monsanto Corporation. Each year, the entire patent portfolio undergoes strategic review by Monsanto, and decisions about option release may be made either at this time or at other times as needed throughout the year. Monsanto's option rights covering a dozen of the patents have been released so that the University could license them for development elsewhere, ensuring a return to society, and the licenses ultimately issued have been largely to small companies. The University has established 8 such licenses that create public access to these inventions.

I would be remiss in not emphasizing the distinctive nature of the Washington University-Monsanto Agreement. The spirit of our interaction is as important to us as the words that formalize it. That spirit allows us to develop innovative technology while respecting the unique and different missions of each of the parties, and while doing what each of us does best to bring that technology to the public. One cannot attach a dollar value or convey in formal language the mutual respect, continuous intellectual debate and collegiality that has evolved over several decades. In this sense, the Washington University-Monsanto Agreement is truly more than the sum of its parts.

I should also stress that the Washington University-Monsanto model is not necessarily exportable or applicable to other situations. There is no doubt that it has been abetted by the close geographical proximity of the two institutions and their congruent and

complimentary scientific strengths. The strong corporate commitment of Monsanto to science "in house" has served to enhance the benefits of the relationship.

The AAMC appreciates this opportunity to appear before the subcommittee as it considers these diverse and critical issues. I will be pleased to answer questions you may have with regard to this statement.

SCRIPPS
Institutions of Medicine and Science

Charles C. Edwards, M.D.
President and Chief Executive Officer

[illegible] Lasuen Road, San D[illegible]
619.554.[illegible] Fax 619.457.[illegible]

April 5, 1993

Philip R. Lee, M.D.
Director
Institute for Health Policy
1388 Sutter Street, 11th I
San Francisco, CA 9410[illegible]

Dear Phil:

I trust that you are well and enjoying a smooth transition back to Washington. Since you've been hearing about the technology transfer arrangement between Sandoz Pharmaceuticals and The Scripps Research Institute (TSRI), and have no doubt been apprised of Bernadine Healy's position on the issue, I would like to update you and your staff from our perspective.

The agreement was negotiated with great care and stands up to stringent legal and ethical scrutiny. While it is of a greater order of magnitude than many, it is in no way different from other such arrangements executed for the last several years by universities throughout the country. Further, the many legal opinions we have sought in structuring the arrangement concur that we have rigorously adhered to the provisions of the Bayh-Dole Act of 1980. In turn, it has enabled TSRI to fulfill its mission in a number of important ways, at a time in which the increased number of investigator-initiated research proposals submitted to the NIH has escalated the already fierce competition for the shrinking pool of federal dollars for basic biomedical research.

A good example of the value of these arrangements is the recent FDA approval of a lifesaving treatment for hairy-cell leukemia discovered at Scripps more than ten years ago and developed and manufactured by Johnson & Johnson. It represents the first marketable therapeutic to emerge from the TSRI/Johnson & Johnson agreement and is a cure for a fatal disease.

The significant amount of non-governmental funding for basic research made available to Scripps as a result of the Bayh-Dole Act has been a critical element in our ability to maintain a leadership position in biomedical research in the international arena. That funding has been used to recruit and train many young, promising scientists; purchase state-of the-art research equipment; maintain facilities at the optimal level; and conduct other scientific inquiry that would not receive NIH funding in today's environment. In

some cases, corporate relationships fostered by the Act have provided Scripps' scientists access to essential biological materials that would not otherwise be available to academic researchers.

For reasons entirely unclear to us, Dr. Healy has called into question many aspects of the nature of the TSRI/Sandoz arrangement as well as its duration. It has been our overwhelming experience at Scripps, however, that the global, long-term licensing of rights to a large corporate sponsor is the most efficient and effective mechanism for developing practical applications of those inventions for the public benefit.

The terms of the Sandoz arrangement, which will not take effect until 1997, will grant an option to take a worldwide license to make, use or sell products based on technology discovered at Scripps. If Sandoz exercises its option, it must use reasonable efforts and due diligence to develop the technology and promptly market the resultant product. To the extent required by law, it must manufacture the product in the United States.

If Sandoz declines to exercise its option to any scientific discovery. Scripps can license its technology to another party. When one realizes that there were some 300-400 publications from TSRI scientists in this past year alone, it quickly becomes obvious that no pharmaceutical company has the ability or interest in licensing each Scripps discovery. In fact, some 100 licenses are excluded from the Sandoz arrangement.

While referred to by Dr. Healy as "an aberration," this agreement adheres to the same basic structure as those of the arrangements Scripps currently has in place with Johnson & Johnson as well as PPG Industries. We strongly believe that the agreements with sufficient duration and staying power will yield the greatest benefits to the two parties concerned as well as the public we wish to serve. The maturity of the relationship between the two entities on many levels is a critical component in the viability and ultimate success of these partnerships. In our case, the partnerships have allowed us to recruite outstanding scientists with international credentials, to establish the new Departments of Chemistry and Cell Biology, and to create two doctoral programs of superior quality. If the academic freedom of its scientific investigators had been impinged upon by the terms of these arrangements, as Dr. Healy alleges, the Institute could neither have attracted such eminent scientists nor enhanced its formidable record in research accomplishments. A unanimous endorsement of the Sandoz agreement on behalf of the entire research staff is testimony to that fact.

Another concern expressed by members of Congress and others in the Administration is the licensing of federally-funded technology to a foreign company. It is obvious, however, that the pharmaceutical industry is an international enterprise. The location of corporate headquarters is irrelevant and should not be a determining factor in the role an organization plays in science and technology. In fact, Merck, an "American" company, has a research agreement with Oxford University in England. Amgen Pharmaceuticals, based in Los Angeles, recently executed an agreement with a Canadian research institution.

Incidentally, Sandoz, which established its first U.S. subsidiary in 1919 and currently employs 12,000 Americans in its U.S. operations, conducts research and manufactures and sells many products in the U.S. Rather than fall victim to xenophobia, it may be wise for government officials and others to view the organization in the context of the benefits that will result from this cooperative effort in terms of enhanced health care and the creation of more jobs for more Americans.

In my opinion, it is very legitimate to ask the public policy questions about this issue. If this discussion is to take place, we would be pleased to become engaged in the public debate. As you know, we want to cooperate in any way possible with HHS and the Congress. We are concerned, however, that we are being singled out by politically motivated individuals who have a different understanding of the issues related to the prosperity of biomedical science in this country and their tremendous impact on the future of science.

I'd be pleased to discuss this with you further and I welcome your views.

Very sincerely,

Charles C. Edwards, M.D.

INSTITUTE FOR HEALTH POLICY STUDIES
School of Medicine
University of California, San Francisco
1388 Sutter Street, Eleventh Floor
San Francisco, California 94109

MAY 7 1993

Charles C. Edwards, M.D.
President and Chief Executive Officer
Scripps Institutions of Medicine and Science
4275 Campus Point Court
San Diego, California 92121

Dear Charlie:

I appreciated your letter regarding the propriety of the sponsored research agreement between The Scripps Research Institute and Sandoz Pharmaceutical Corporation. This agreement has been brought to my attention on a number of occasions within the last few weeks because I have been serving as a consultant to the Secretary pending my formal nomination and, hopefully, confirmation as Assistant Secretary for Health.

As you know, the agreement is a matter of considerable concern both to the research community as a whole and to the Public Health Service. I have been advised that, in consultation with the Department of Commerce, the NIH is carefully reviewing the agreement, along with sponsored research agreements from over one hundred other non-profit organizations to determine whether these agreements are consistent with the letter and spirit of the Bayh-Dole Act.

I have shared your letter with Bernadine Healy and asked her to respond with her own views. Your offer to cooperate in resolving this matter is greatly appreciated, and I encourage you to continue to discuss with the NIH its concerns. Once confirmed, I expect to review this matter in greater detail.

Best wishes.

Sincerely yours,

Philip R. Lee, M.D.

Hope to see you soon!

THE SCRIPPS RESEARCH INSTITUTE
10666 NORTH TORREY PINES ROAD
LA JOLLA CALIFORNIA 92037
619 455-9100

June 16, 1993

Congressman Ron Wyden
Chairman
Committee on Regulation, Business
Opportunities, and Technology
B363 Rayburn House Office Building
Washington,D.C. 20515

Dear Chairman Wyden:

Enclosed for your information is a copy of the letter Douglas A. Bingham, General Counsel of The Scripps Research Institute, sent to Robert Lanman, NIH Legal Advisor, earlier this week. Mr. Bingham's letter was in response to the letter Mr. Lanman sent to Scripps last Friday describing NIH's concerns about Scripps' proposed agreement with Sandoz Pharmaceuticals Corporation. (We understand you have a copy of that letter.) In view of the hearing your Subcommittee will be holding on June 17, 1993, we thought you would want to be aware of the current status of the discussions between Scripps and NIH.

As Mr. Bingham's letter suggests, Scripps does not agree with many of the views expressed by NIH in Mr. Lanman's letter. Notwithstanding these differences of opinion, however, Scripps understands that the questions being raised -- by both you and the NIH -- are important public policy issues that deserve serious consideration. We are ready to address those issues with NIH, and we feel confident that we will be able to resolve them.

All of us, we believe, share a common objective -- to do what is in the best interests of science, and the public. We hope that, in the end, the current public policy debate will help us, and others, achieve that result.

Sincerely,

William H. Beers
Senior Vice President

cc: The Honorable Larry Combest

SANDOZ PHARMACEUTICALS CORPORATION
59 ROUTE 10, EAST HANOVER, NEW JERSEY 07936-1080

SANDOZ

June 16, 1993

Mr. Robert B. Lanman, Esquire
NIH Legal Advisor
National Institutes of Health
Building 31, Room 2B-50
9000 Rockville Pike
Bethesda, MD 20892

Dear Mr. Lanman:

On Monday, June 14, 1993, officials of The Scripps Research Institute (TSRI) sent us a copy of your letter of June 11, 1993, which describes in some detail a number of issues relating to the proposed research funding agreement between TSRI and Sandoz Pharmaceuticals Corporation.

Over the past 48 hours, we have reviewed the points made in your letter and have given careful consideration to various ways in which the concerns of NIH officials can be addressed. We understand that these concerns may be shared by the House Subcommittee on Regulation, Business Opportunities and Technology. We appreciate your willingness to work with the parties to resolve these issues, and we pledge our full cooperation in that effort.

As you note in your letter, Sandoz Pharmaceuticals has not yet executed the agreement, although its right to do so expires on July 1, 1993. Thus, the parties currently have an opportunity to negotiate appropriate amendments before the agreement goes into effect. As previously communicated by our attorneys, Sandoz is prepared to meet with you at your earliest convenience to discuss these matters in depth. To the fullest extent possible, we will work with you in good faith to address all of NIH's concerns prior to July 1, 1993.

SANDOZ

Mr. Robert B. Lanman, Esquire
June 16, 1993
Page 2

We will contact your office before the end of the week to schedule a meeting. We look forward to bringing this matter to a satisfactory resolution in the very near future.

Sincerely yours,

Timothy G. Rothwell
President and
Chief Executive Officer

THE SCRIPPS RESEARCH INSTITUTE
10666 NORTH TORREY PINES ROAD
LA JOLLA CALIFORNIA 92037
619 455-9100

June 14, 1993

Robert B. Lanman, Esq.
Public Health Division
Room 2B-50, NIH Bldg. 31
9000 Rockville Pike
Bethesda, Maryland 20892

VIA FACSIMILE

Dear Bob:

I am writing to thank you for your letter of June 11, 1993 concerning the Scripps/Sandoz research agreement.

Your letter is helpful in clarifying NIH's position and sheds some light on the basis for the differences in our views. For example, we now see that there are some contractual provisions which we believe may have been misconstrued by NIH; we hope that we will be able to satisfy your concerns on these points. Other differences are more substantive: for instance, we appear to have a different understanding of the policy objectives of the Bayh-Dole legislation and the best ways of achieving them. But we also share many of the views expressed in your letter, especially those concerning the importance of scientists being free to conduct research. We value the independence that Scripps enjoys, and you should rest assured that we would do nothing to compromise it.

Now that we have all of your comments on our proposed agreement in writing, we will be better able to understand them, and, we believe, respond to them so as to resolve NIH's concerns. In the end, we are confident that we will arrive at a position that all of us agree is in the best interests of scientific research.

We look forward to a constructive dialogue, and we will be in touch in the near future to set up a meeting.

Sincerely,

By _____
Douglas A. Bingham

DAB:af

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Douglas A. Bingham, Esq
General Counsel
Direct Line: 619 554-2937 FAX Line 619 554-6312

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the General Cou

Public Health Division
Room 2B-50, NIH Bldg. 3
9000 Rockville Pike
Bethesda, Maryland 2089
(301) 496-4108
Fax (301) 402-1034

June 11, 1993

Douglas A. Bingham, Esquire
General Counsel
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037

Dear Mr. Bingham:

Thank you for your courtesy and cooperation in meeting at the National Institutes of Health (NIH) campus to discuss the proposed research support agreement between Scripps Research Institute of La Jolla California (Scripps) and Sandoz Pharmaceuticals Corporation of East Hanover, New Jersey (Sandoz). At our April 13 meeting, we agreed to provide you with specific written comments on the Scripps/Sandoz Research agreement. As we explained at that time, NIH is concerned that the agreement unduly restricts scientific research supported by the Government, appears to be contrary to the letter and spirit of the Bayh-Dole Act (35 U.S.C. §§ 200-211) and may impinge unreasonably upon scientific freedom because of its coverage of potentially all Government-funded inventions made by Scripps' employees, and because of the degree of control that Sandoz is given over the research and patenting activities of the Scripps Research Institute. The potential twenty year duration of the agreement exacerbates those concerns. This letter addresses those concerns principally as they relate to the Bayh-Dole Act. As you know, however, the proposed agreement has even broader policy implications. The Department will address these in the near future.

As stated in 35 U.S.C. § 200, the objectives of the Bayh-Dole Act are to (a) promote use of inventions arising from federally-funded research; (b) encourage maximum participation of small business firms in federally-supported research; (c) promote collaboration between commercial concerns and nonprofit organizations; (d) ensure that inventions made by nonprofit organizations and small business firms are used to promote free competition and enterprise; (e) promote the commercialization and public availability of inventions made in the United States by United States industry and labor; (f) ensure that the Government obtains sufficient rights in federally-supported inventions to meet the needs of the Government and protect the public against any nonuse or unreasonable use of inventions; and (g) minimize the costs of administering patent policies. Guidance on these objectives and other aspects of the Bayh-Dole Act is provided in

the Department of Commerce regulations at 37 CFR Part 401. Provisions of the Scripps/Sandoz agreement that appear to be inconsistent with these statutory and regulatory provisions are discussed below. Pertinent sections of the agreement are identified by number.

1. Broad Scope of Research Covered by the Agreement. Under the agreement, Sandoz will provide Scripps "General Funding" which can be used at the discretion of Scripps to support the direct and indirect cost of "General Funding Research." This would include all research, regardless of the funding source, undertaken by Scripps during Phase II, except "Excluded Research," i.e., specifically identified ongoing research projects with third parties, and "Specific Funding Research," i.e., research approved by the Joint Scientific Council regardless of funding source. Scripps, in return for the General Funding, grants Sandoz an option to acquire an exclusive worldwide license, with the right to sublicense, under all Scripps inventions related to "Medical Products" and "Manufacturing Products" developed during the term of the agreement except for those developed under Excluded Research, and an option to acquire a nonexclusive, worldwide license, without the right to sublicense, to make and use, but not to sell, "Research Products." "Research Products" includes any product, process or device developed from the Research Program and which is designed or utilized for discovering, improving, developing or testing a Therapeutic Product, Preventive Medicine Product or Diagnostic Product but which is not utilized as such a product. "Research Program" means all the research undertaken by Scripps in the performance of either General Funding Research or research supported by Specific Funding. Sandoz has the right to convert the nonexclusive license to an exclusive license in the event Scripps notifies Sandoz of Scripps' intent to license or sell the invention to a third party. During Phase I, the foregoing options only apply to "Specific Funding Products," i.e., those products developed through Specific Funding provided by Sandoz. (6.1, 7.2)

The broad scope of Sandoz's exclusive license rights appears to restrict competition, and exclude organizations other than Sandoz from reasonable access to Scripps' technology. The Scripps/Sandoz agreement does not appear to ensure that Government-funded inventions are used to promote competition and enterprise as required by Bayh-Dole. Rather the agreement severely limits access to Scripps technology by third parties. The agreement also may violate the "Preference for U.S. Industry" provision of Bayh-Dole, because the nominal research partner, Sandoz, is controlled by its affiliate, Sandoz of Europe. The agreement effectively gives a foreign firm control over large

amounts of technology developed with NIH funding. Participation by small businesses in research collaboration with Scripps is discouraged. Small businesses are not given preference in licensing Scripps inventions as required by 35 U.S.C. § 202(c)(7).

2. Controlling Access to Research and Inventions.

(a) The "Joint Scientific Council" created by the agreement has general responsibility for monitoring and fostering the relationship between Scripps and Sandoz and broad authority to control and influence the direction of research by Scripps' scientists. It consists of up to seven Scripps individuals and an equal number from Sandoz. The Council is chaired by a Sandoz representative. In the event of a tie vote, the decision of the majority of the Sandoz representatives is controlling. It appears that the following functions of the Council may have anticompetitive effects, and as noted, may interfere with reporting requirements under the Bayh-Dole Act: reviewing and being informed of all Scripps research projects, except excluded products; establishing procedures for disclosing inventions to Sandoz, for evaluating the desirability of patenting and providing prior Sandoz review of proposed invention disclosures to the Government; and, establishing procedures for Sandoz approval of consulting agreements between Scripps' researchers and commercial third parties. (4.1)

(b) Scripps must provide Sandoz copies of all Government funding agreements and grant applications relating to Scripps products for which Sandoz has option or license rights. Sandoz must be given an opportunity to review and comment on all invention disclosures and other reports to be filed by Scripps with the funding Government agency prior to their submission to the agency. Scripps must give due consideration to the recommendations of Sandoz concerning the disclosures and reports. (4.8)

This appears to be an unwarranted intrusion into the relationship between the Government and its grantee and could delay the commercialization of inventions funded by the Government. It provides Sandoz with an unusual degree of control and influence over the research direction of a not-for-profit research institution. It also appears to be anticompetitive in permitting Sandoz to hold up products that might compete with its products in the market place.

(c) Sandoz has the right to review and approve all consultancy agreements proposed to be entered into or renewed (other than through obligatory renewal) by Scripps employees during the term of the agreement. This review and approval right is not limited

to the subject matter of specific funding projects. Scripps employees that are prevented from obtaining or continuing consultancy arrangements may be provided financial compensation from General Funding. (4.1, 14.1)

(d) Scripps cannot extend or renew agreements for Excluded Research without consultation with Sandoz. Scripps cannot accept any third party Specific Funded Research where the third party obtains option or license rights (except for Government funding and excluded funding), unless Sandoz declines to fund it and is not otherwise conducting the research. At any time after undertaking to provide Specific Funding with respect to a particular research project, Sandoz has the right to transfer its further research and development directly to its own facilities or to the facilities of one or more of its affiliates. Apparently, Scripps cannot continue such research once it has been transferred, unless Sandoz decides to abandon it. In the event Sandoz decides to abandon the research, Sandoz must offer Scripps the first option to complete the Specific Research project. (4.9, 5.6, 5.7)

The provisions described in paragraphs (c) and (d) appear to give Sandoz the power to strictly limit any competition and any small business access to federally-supported research. The right of Sandoz to remove research from a researcher and prohibit him or her from continuing such work inhibits collaboration by Scripps with small businesses and others. Sandoz's right to expropriate research could result in its being sent overseas to the detriment of U.S. industry contrary to the Bayh-Dole objective of promoting commercialization and public availability of inventions made in the United States by United States industry and labor. In addition, the payments to scientists to forego consultancy arrangements limits the access of small businesses and others to Scripps' research expertise and creates a conflict of interest, because Sandoz by screening proposed agreements with other companies may have access to that company's proprietary information which should be protected by Scripps.

3. Preference for U.S. Industry -- Waiver of U.S. Manufacture Requirement. Upon notice by Scripps to Sandoz of the requirement of substantial U.S. manufacture, Sandoz agrees that licensed Scripps products will, to the extent commercially feasible, be substantially manufactured in the United States or its territories, subject to waivers from HHS or its designee. Scripps agrees to use its reasonable best efforts to obtain, at Sandoz expense, any waivers requested by Sandoz. (10.7)

This provision is inconsistent with 35 U.S.C. § 204. The statutory requirement is that an exclusive licensee "agree that any products embodying the subject invention or produced through the use of the subject invention will be manufactured substantially in the United States." The statute does not

contain the qualifying clause, "to the extent commercially feasible" that appears in section 10.7 of the Agreement. Commercial feasibility is one of the two grounds upon which a funding agency may, for a particular invention, waive the U.S. manufacture requirement; it is not a basis for Sandoz to refuse to agree to manufacture the product in the U.S. In addition, Scripps' agreement to use its best efforts to obtain a waiver of the requirement may show a lack of impartiality implicitly required of grantees under Bayh-Dole and vis-a-vis other potential licensees who would be willing to manufacture in the U.S. Finally, the limitation in section 10.7 that Scripps give Sandoz notice does not affect the requirements of 35 U.S.C. § 204 for U.S. manufacture. A failure of Scripps to give notice would not defeat the requirement for U.S. manufacture.

These concerns are heightened because, as noted earlier, the nominal research partner, Sandoz is controlled by its affiliate, Sandoz of Europe and because Sandoz appears to have the right under the agreement to remove research from a Scripps research and transfer it to its European affiliate. This appears to be contrary to the Bayh-Dole objective of promoting commercialization and public availability of inventions made in the United States by U.S. industry and labor.

4. Sandoz Control and Influence. In addition to Sandoz control and influence through the Council, Sandoz also has the right to request that Scripps include up to two persons designated by Sandoz to serve on the Scripps Board of Trustees. If Scripps appoints a new chief executive officer not acceptable to Sandoz, Sandoz may terminate the agreement. Further, Sandoz may assign up to 24 "Company Fellows" to work on projects on the Scripps campus and to keep Sandoz informed of scientific developments at Scripps. Scripps cannot permit employees of any pharmaceutical or biomedical companies (other than those companies such as Johnson & Johnson having pre-existing agreements) to be in residence at Scripps for an extended period of time without the approval of Sandoz. (4.2, 13.2, 4.3, 2.1)

In addition to Sandoz's influence on research directions through the Council, Scripps is obligated to use its reasonable efforts to encourage its Regular Professional Staff researchers to work with Sandoz in furtherance of areas of strategic importance to Sandoz. (4.4)

The influence of Sandoz effected through voting members on the Scripps Board of Trustees, the possibility that Sandoz will terminate its agreement with Scripps unless Scripps accedes to Sandoz choice for the Scripps CEO, and the presence of so many Company Fellows on campus insinuates Sandoz's control and influence throughout Scripps. This level of involvement would permit Sandoz to monitor and perhaps restrict competition in the commercialization of the products of Scripps research and will

provide Sandoz preferential access to research data and results. In addition, this will limit the freedom of scientists to collaborate with others both through explicit control processes and through the general influence conveyed by Sandoz's pervasive involvement in Scripps' activities. This restricts access by third parties, including small businesses, to federally-supported research at Scripps.

As you know, NIH strongly supported the Bayh-Dole Act and believes that the Act has been successfully utilized by our grantee institutions to enhance their funding base, as well as to transfer technology. The agreement between Scripps and Sandoz, however, is all encompassing, is for a long duration, and offers so much potential control over federally-funded technology to a large foreign firm that it appears to be qualitatively different from research support agreements that might otherwise be acceptable under the Act. This specific agreement between Scripps and Sandoz appears to raise significant issues of compliance with the letter and spirit of the Bayh-Dole Act which may compel us to make a determination under 35 U.S.C. § 202(a), that exceptional circumstances exist which require restriction or elimination of Scripps' right to retain title to subject inventions under future NIH funding agreements.

You have indicated that there is an opportunity to amend the Scripps/Sandoz agreement to address the concerns raised above, because it has not been signed by both parties and thus has not gone into effect. We look forward to your continuing cooperation in resolving NIH concerns. In the event that our discussions extend beyond July 1, you may wish to extend the deadline for Sandoz to exercise its options to ratify the research support agreement.

Sincerely,

Richard A. Lanman
for Robert B. Lanman
NIH Legal Advisor

AAMC

ASSOCIATION OF AMERICAN MEDICAL COLLEGES

2450 N STREET, NW
WASHINGTON, DC 20037-1
TELEPHONE (202) 828-040

June 14, 1993

The Honorable Ron Wyden
Chairman
Subcommittee on Regulations, Business Opportunities, and Technology
Committee on Small Business
U.S. House of Representatives
B-363 Rayburn House Office Building
Washington, D.C. 20515-6318

Dear Mr. Chairman:

I write to respond to your May 27 letter concerning the issue of dealing with possible conflicts of interest in FDA-reviewed clinical trials. Specifically, your letter recounts events that took place recently at a conference at Cold Spring Harbor and describes a controversy surrounding the results of a clinical trial of the drug Ceredase.

Your first question deals with the disputed claims over the results of that trial. The AAMC has no special knowledge of that incident or of the potential efficacy of the drug in question. However, on behalf of the AAMC, I can address your questions concerning conflicts of interest more broadly and am happy to do so. As you may be aware, the AAMC has a long history of outlining for its membership policy guidelines for assuring various facets of research integrity, including documents on dealing with conflicts of interest in both research and continuing medical education. I have enclosed these particular guidelines for your reference. In addition, a response to each of the questions posed in your letter is provided below.

1. Is your association aware of Dr. Beutler's claim, and does it share any of his concerns about bias in clinical trials conducted by member academicians who may have financial ties to the manufacturer of the drug, beyond any financial arrangement specific to the conduct of the trial?

The AAMC is not aware of the specific situation alluded to by Dr. Beutler. However, the AAMC does recognize that financial and other forms of personal interests can have, or may be perceived to have, a biasing effect on any range of professional activities. It is for that reason that the AAMC has traditionally emphasized the importance of disclosure, such that those who scrutinize the research findings can do so with an appropriate measure of skepticism. When such interests are known, it is also appropriate that FDA apply an added measure of scrutiny to the data arising from such clinical trials, such as might be accomplished through its Bioresearch Monitoring Program.

2. Do you believe that information regarding possible conflicts-of-interest involving clinical investigators should be made part of the FDA's record-keeping and evaluation system when processing data from IND or NDA investigations?

The AAMC supports disclosure of "relevant" financial interests when an investigator is undertaking a project of research. When research proposals are under development by faculty, the appropriate location for such disclosure is to the institution in which faculty are employed. If institutions believe that a clinical trial can be successfully and objectively conducted in spite of disclosed financial interests, then those interests and a plan for managing them should be forwarded first to the sponsor of research, and then may in turn to the FDA when the sponsor files an investigational new drug (IND) application. The FDA may

then assess whether the intense and rigorous review that it normally applies to clinical trial data is sufficient, or whether those data should be subject to more intense scrutiny through a mechanism such as its Bioresearch Monitoring Program. It is our understanding, based on contacts with that agency, that FDA is formulating a proposal for dealing with conflicts of interest that may employ this type of mechanism.

3. Please explain your association's current requirements, code of conduct, or conflict-of-interest guidelines, if any, with regard to disclosure of financial arrangements or other agreements which could pose conflicts-of-interest in the management and reporting of results from drug or device clinical trials.

In 1990, the AAMC issued guidelines to aid its membership in developing effective policies and procedures for the review of disclosure information and for the management of possible conflict of interest situations. Two year later, the AAMC issued Guidelines for Faculty Involvement in Commercially Supported Continuing Medical Education. As an association, the AAMC does not have the authority to mandate or prescribe activities of its membership, but it does play a forceful and constructive guiding role. The 1990 Guidelines to Deal with Faculty Conflicts of Commitment and Conflicts of Interest in Research, for example, emphasize the importance of disclosure and management of conflicts of interest. The document states:

> General awareness (institutional and public) of an investigator's relevant funding sources, financial interests, and professional roles serve to direct appropriate scrutiny at elements of research commitment, design, and reporting of data that might be biased or undermined by these factors. The investigator's cognizance of that scrutiny further encourages vigilance to avoid any biases or diversions that inadvertently may be introduced. Naturally, for this system to work, the disclosure process must assure that information regarding possible conflicts reaches all individuals with an appropriate interest in evaluating the research in question.

With regard to specific academic responsibilities, the document states:

> Academic institutions should...require disclosure of the investigator's relevant personal interests, including those of the immediate family. These may include, but are not limited to equity interests, outside professional positions, outside professional salary, gifts, honoraria, and loans. Such disclosure should accompany contractual research agreements and grant applications as they receive institutional review. Additional disclosure should be established on a regular basis by the institution based on local requirements and any relevant changes in faculty status. At a minimum such disclosure should occur annually.

4. Do you believe these current requirements are sufficient to avoid conflicts of interest which may jeopardize or call into question the integrity of this vital research to ensure the safety and efficacy of new drugs?

The standards that we have articulated should go a long way toward assuring an objective evaluation of clinical therapies, provided:

-- disclosure entails financial information with a direct and relevant bearing on the research being conducted,

-- all participants in the research process (investigators, their employing institutions, and research sponsors) uphold their responsibilities for providing and acting upon disclosed information, and

-- the findings of clinical trials and similar research projects are scrutinized to check for biases that may stem from the interests that have been brought to light.

5. Again, a little sunlight may be the best possible disinfectant in such conflict-of-interest matters. Therefore, would you support a requirement within the FDA drug approval system that applicants as a matter of course reveal all potential financial conflicts of extramural investigatnrs who research safety and effectiveness questions involving the drug or device in question?

The AAMC would support a system of disclosure that has the following characteristics:

-- When proposals for research are being prepared, initial disclosure must be from the investigator to the employing institution, which then evaluates whether conflicts of interest are present and determines how to manage them (which may range from mere disclosure of a financial interest to denying the investigator participation in the research study -- in the latter case disclosure to FDA would be a moot question).

-- If an institution chooses to accept funds to conduct a clinical trial, then it should report all relevant financial interests with a direct bearing on the research in question to the sponsor of the research project. The sponsor may then 1) evaluate whether that investigator is acceptable for the project, given a) his or her financial interests and b) the mechanisms the institution has proposed for guarding against inappropriate bias, or 2) ask the institution to identify another investigator with less potential for bias. In submitting the IND application, the sponsor would then make disclosure of those relevant interests to the FDA.

6. Do you believe that professional organizations such as yours should pose requirements of this kind for your members -- for example, mandatory disclosure in scientific papers regarding financial ties between reporting investigators and companies for whom they may be evaluating drugs or devices?

As an association, the AAMC is not in a position to police the activities of its members in this regard. However, the interest of its membership in addressing this issue has been keen and over the past three years we believe our members have made important strides in developing effective policies, or improving upon policies already in place. The AAMC Guidelines outline a model process of disclosure and conflict management that should place the Association's membership in a position to deal effectively with this matter. Apart from its procedural elements, the document outlines both institutional and individual responsibilities that, when adhered to, can preclude many problems ahead of time.

In closing, I would like to reemphasize the priority the AAMC has given to aiding its members in assuring the integrity of their diverse scientific and educational endeavors. Upholding the utmost standards of objectivity in all worthy professional endeavors is essential to the continued contributions of academic medicine and research.

Thank you for soliciting our views on this matter. If there is any way the AAMC may be of further service, please do not hesitate to contact me or my associate David Moore.

Sincerely,

Richard M. Knapp, Ph.D.
Senior Vice President for Governmental Relations

Enclosures

ASSOCIATION OF
AMERICAN
MEDICAL COLLEGES

GUIDELINES FOR DEALING WITH FACULTY CONFLICTS OF COMMITMENT AND CONFLICTS OF INTEREST IN RESEARCH

ONE DUPONT CIRCLE, N.W., WASHINGTON, D.C. 20036

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Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research

Adopted by the Executive Council of the
Association of American Medical Colleges
February 22, 1990

The Association of American Medical Colleges represents all 126 accredited U.S. medical colleges, the 16 Canadian medical schools, 92 academic and professional societies, 435 major teaching hospitals--including 74 VA medical centers--and the nation's medical students.

Additional copies may be obtained by writing to:

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PREFACE

As the revolution in biotechnology and other fields of science and medicine continues at an unprecedented pace, faculty at academic institutions are increasingly entering into collaborative arrangements with industry in fostering development of their research programs. Links with the industrial sector provide crucial research resources and channel scientific discoveries into the public domain. In addition, they stimulate innovation and creativity through transference of entrepreneurial spirit and enthusiasm.

However, the pursuit of these important opportunities must be carried out judiciously. Scientists have an overriding responsibility to maintain the highest standards of objectivity and freedom from bias. Incidents of scientists allowing personal or outside interests to cloud their professional judgment in conducting research are alarming and unacceptable. Such incidents are serious in and of themselves, but they are ever more troubling because, if true, such abuses of trust may pose risks to research subjects, institutional and individual reputations, the credibility of the scientific profession, and the well-being of society. In addition, they lead policy-makers to consider that academic institutions may be unable or unwilling to deal with situations in which personal interests may pose conflicts with professional duties.

The AAMC and its Ad Hoc Committee on Misconduct and Conflict of Interest in Research have addressed these issues, and find that the primary obligation for identifying and managing such conflicts lies with the research institutions themselves. In January 1989, the AAMC solicited policies from its membership to assess how medical schools and teaching hospitals were dealing with conflicts of interest and commitment in research. That solicitation and subsequent follow-up revealed that member institutions are attempting to deal with these issues effectively. The AAMC then extracted the fundamental elements from these policies, allowing the Ad Hoc Committee to develop this guidance document to further the efforts of our membership in these areas.

This document offers a conceptual framework; it defines institutional and individual responsibilities. In addition, it outlines a procedural approach that institutions may build upon and modify to fit their own unique circumstances. The document recognizes that the specifics of institutional policies and procedures are developed best by the institutions themselves. Each institution is best equipped to address its own needs in accordance with federal, state, and local requirements and with generally accepted academic values.

The AAMC and its Ad Hoc Committee continue to address this difficult problem. We appreciate any comment on this document and welcome suggestions for possible future action on the issue of conflict of interest.

Robert G. Petersdorf, M.D.
President
Association of American
Medical Colleges

INTRODUCTION

The spectacular research accomplishments of the past four decades not only have expanded the frontiers of science but also have created significant opportunities for translating basic research findings into commercially viable products. Previously, drug company-sponsored clinical trials and contract research projects represented the principal venues for interaction between medical schools and industry. However, the recent revolutions in biotechnology and other fields, the dramatic expansion of opportunity for advances in therapy, and the desire of many researchers to join industry in creating products, methods of treatment, and other techniques have further engaged biomedical scientists in this exciting arena of activity. In addition, certain initiatives in federal policy aimed at bolstering the national economy and promoting international competitiveness, such as the Patent and Trademark Amendments Act (1980) and the Stevenson-Wydler Technology Innovation Act (1980), have enhanced the process by which universities and colleges may share in the fruits of the commercialization of discoveries made on campus. The sum of these developments has created an environment in which academic institutions and their faculty are developing and expanding collaborative arrangements with industry at an unprecedented rate. These collaborations are generally mutually beneficial, with industry drawing from the collective intellectual and creative talents of university faculty, and academia benefitting from additional sources of research and other funds as competition for federal dollars becomes increasingly keen.

As the interface between research and commercial activities expands, faculty in our democratic society are confronted with often-conflicting realities. On the one hand, the freedom to pursue one's own economic interests is guaranteed by our system of government and, indeed, is the driving force of our national economy. At the same time, the requirement for objectivity and commitment in biomedical and behavioral research dictates extreme care as scientists pursue research activities while also pursuing their own economic goals. Without institutional controls, this objectivity may be threatened, the line between academic and industrial obligations may blur, and the temptation to use institutional resources for unauthorized personal endeavors may grow.

The opportunity for investigators to receive financial or other personal rewards from their endeavors is not intrinsically unacceptable, as long as it does not adversely influence the objectivity, integrity, or professional commitment of an investigator. Hence, participation in a situation with opportunity for personal gain does not constitute an unacceptable situation of itself; it is the potential stimulus for unacceptable behavior that must be addressed. Accordingly, the objective of the document is to provide guidelines for institutional policies and procedures that minimize the risk of unacceptable behavior in potential conflict situations, while

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facilitating and encouraging the full professional and personal development of faculty investigators through their research.

Institutions engaged in the conduct of biomedical research face a particularly difficult situation with respect to this issue. Publicly funded biomedical research is an enterprise in the public trust, which by its nature involves sensitive issues of human health and well-being. In addition, public awareness and scrutiny is more heavily focused on health-related research than other forms of research activities. Ruptures of public confidence that occur when biomedical researchers are involved in conflict situations, deliberate or otherwise, inflict long-term damage on societal trust and support.

Apart from considerations of public health and perception, it is a Public Health Service (PHS) requirement that grantee institutions have conflict of interest policies in place. The PHS Grants Policy Statement says,

> Recipient organizations must establish safeguards to prevent employees, consultants, or members of governing bodies from using their positions for purposes that are, or give the appearance of being motivated by a desire for private financial gain for themselves or others such as those with whom they have family business, or other ties. Therefore, each institution receiving financial support must have written policy guidelines on conflict of interest and the avoidance thereof. These guidelines should reflect State and local laws and must cover financial interest, gifts, gratuities and favors, nepotism, and other areas such as political participation and bribery.

The PHS statement adds that such policies must include provisions for implementation and sanctions for violations. Although the National Institutes of Health (NIH) and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) are in the process of developing additional requirements, PHS grantee institutions that now do not have conflict of interest policies in place are at risk of losing federal support for research.

Given the number of individual, institutional, and societal risks attendant to conflicts between personal and professional responsibilities in research, it is essential that institutions develop appropriate policies and procedures to deal with both the reality and appearance of such conflicts. As described in greater detail at the end of this document, other institutional policies will have relevance to conflict situations and must be carefully written to ensure that all facets of the issue are fully addressed. For example, if a situation involving a conflict calls into question the integrity of the investigator, the institutional policies and procedures

on scientific misconduct may apply. The process of policy development should also be coordinated with affiliated institutions. For medical schools, this is important to avoid subjecting faculty with off-campus clinical appointments to contradicting standards of conduct.

The rest of this document outlines means to deal with the two principal, yet not entirely exclusive, forms of conflicting situations that may affect the performance of academic personnel: conflicts of commitment and conflicts of interest.

CONFLICTS OF COMMITMENT

The term conflict of commitment relates to an individual faculty member's distribution of effort between obligations to one's academic appointment (normally "full-time" in teaching, research, and/or patient care) and one's commitment to "outside" activities. These latter may include professionally-related and generally encouraged activities such as consulting, textbook authorship, involvement with professional societies, and participation on review panels. Such activities are usually expected of faculty members to promote professional development and to enrich their contributions to the institution, to their profession, and to the community. Consulting relationships, for example, may serve to create conduits for the exchange of information and technologies that enhance the university environment and permit faculty to test the soundness of their ideas.

A conflict of commitment arises when these or professionally removed activities (e.g., outside teaching or business) come to interfere with the paramount obligations to students, colleagues, and the primary missions of the academic institution by which one is appointed and salaried. Conflicts of commitment primarily involve questions of obligation and effort, but are often tied to financial inducements. Such conflicts do not generally pose strictly legal violations, but they may constitute abridgements or compromises of institutional policy or the responsibilities attendant to retention of academic appointment.

In 1965, the American Council on Education/Association of American University Professors concluded in their statement, On Preventing Conflicts of Interest in Government Sponsored Research, that "a system of precise time accounting is incompatible with the inherent character of the work of a faculty member since the various functions he performs are closely interrelated and do not conform to any meaningful division of a standard workweek." The AAMC agrees with this assessment and finds that there is no universally applicable standard or formula for determining appropriate levels of faculty effort. A 1989 review of relevant policies of the AAMC constituency revealed that permissible levels of outside activity vary, though most institutions afford their faculty one day per work week for scholarly pursuits that relate to and advance professional growth and public service.

It is important to recognize that the standards of behavior maintained by an investigator in permitted extramural activities may negatively influence the reputation of the faculty member or the institution. Accordingly, investigators should be advised to ensure that their extramural activities are subject to the same rigorous ethical standards that are applied to the performance of institutional responsibilities.

Whatever locally appropriate standards the institution chooses to adopt, both faculty and the academic institution have responsibilities to prevent and to correct situations in which expectations of commitment are not met. Failure by faculty to attend to university or teaching hospital obligations serves to undermine the academic mission and potential accomplishments of the institution. Therefore, as an integral part of professional duties, faculty members should:

- Assure that research, teaching, and public service obligations to the academic institution are fully met,

- Abide by restrictions on the type and amount of outside activity as determined by the academic institution, or by subsequent agreements between faculty and the university or hospital administration, and

- Abide by commitments of effort as specified in contractual research agreements and grant applications.

Academic institutions, on the other hand, have a corresponding set of responsibilities. To encourage appropriate faculty behavior and to live up to institutional obligations, the university or teaching hospital should:

- Develop policies that explicitly state acceptable levels of outside activity and define the types of activities and corresponding levels of remuneration that are acceptable,

- Develop procedures to assure that proposals for research and outside activities are responsibly made and reasonably adhered to,

- Comply with federal requirements for reporting unmet commitments to government-sponsored activities, and

- Develop mechanisms whereby outside activities involving any potential conflicts of commitment are disclosed and evaluated on a regular basis, and resolved as necessary.

Policies and procedures that are related to conflict of commitment may be developed in parallel with conflict of interest policies as discussed below.

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CONFLICTS OF INTEREST

The term conflict of interest in science refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research. The bias such conflicts may conceivably impart not only affects collection, analysis and interpretation of data, but also the hiring of staff, procurement of materials, sharing of results, choice of protocol, and the use of statistical methods. Conflicts of interest can affect other scholarly duties as well, but are particularly important to consider in biomedical and behavioral research because of the impact such conflicts can have on human health.

It is not possible to completely eradicate the potential for conflict of interest because there are certain rewards that are inherent in the structure of our research enterprise. Such rewards may be completely unrelated to relationships with industry or private sponsorship. For example, positive research results per se may contribute to opportunities for publication, promotion, tenure, grant renewals, and so forth. In addition, positive results are often more gratifying and lead to greater personal satisfaction than negative outcomes. In a sense, these influences can be as much a source of conflict in the search for truth as interests of a pecuniary nature. But kept in perspective, such incentives are not inherently bad and are indeed the motivating forces for diligent scientists. Such conflicts become detrimental when the potential rewards, financial or otherwise, cause deviation from absolute objectivity in the design, interpretation, and publication of research activities, or in other academic and professional decisions.

The mere appearance of a conflict may be just as serious and potentially damaging as an actual distortion of objectivity. Reports of conflicts based on appearances can undermine public trust in ways that may not be adequately restored even when mitigating facts of a situation are brought to light. Apparent conflicts, therefore, should be evaluated and managed with the same vigor as known conflicts.

Conflicts of interest also have the potential to bias other aspects of academic life, particularly when faculty are in a position to set university or hospital policies, manage contracts, select equipment and supplies, involve students in sponsored projects, or have other administrative roles in which objectivity and integrity are paramount. In addition to these "administrative" conflicts that occur at the faculty, or individual level, there are also conflicts that may occur at the institutional level. The university or hospital may enter into a contractual relationship or other affiliation with a company that presents a conflict with its academic mission, its non-profit status, the activities of its board members, its need to be objective in its dealings with faculty, or with its obligations to other organizations. Decisions regarding institutional conflicts of interest must be made by the governing board.

Both administrative and institutional conflicts are important to manage and should be addressed in relevant policies, but will not be the primary focus of this document.

Individual conflicts of interest in research arise in large part because of the interplay between a faculty member's personal and financial interests and the opportunity to conduct externally-funded research. There is an inexhaustible matrix of situations in which faculty may find themselves, and it would be impossible for this document to provide a comprehensive list. Of the imaginable array of conflicting or potentially conflicting situations, it is up to the academic institution to decide which are acceptable in accordance with federal and state requirements and generally accepted academic values of honesty, objectivity, and integrity. This process is likely to be a difficult one and should involve joint participation of faculty and administration to avoid contention when cases arise.

The following examples of possible conflicts of interest are provided to alert institutions to situations that may be of concern. This list is suggestive and should be supplemented by each institution. The institution should consider not only situations that are unacceptable, but should also consider the "gray" areas that might involve the "appearance" of a conflict or in which monitoring or certain modifications of the situation might make it acceptable. A considerable degree of "brainstorming" should go into developing this list as for every situation contemplated, there will be some variant which adds a new set of considerations. Some possibly problematic situations include:

Situations That May Impart Bias in Research

- Undertaking basic or clinical research when the investigator or the investigator's immediate family has a financial, managerial, or ownership interest in the sponsoring company or in the company producing the drug/device under evaluation

- Accepting gratuities or special favors from research sponsors

- Entering into a consultantship arrangement with an organization or individual having an economic interest in related research

Situations That May Involve Inappropriate Use of Institutional Assets and Resources in Research

- Using students or employees of the institution to perform services for a company in which a faculty member has an ownership interest or from which he/she receives any type of remuneration

- Unreimbursed or unauthorized use of institutional resources, such as equipment, supplies, and facilities, for personal purposes or to support the activities of an independent entity in which an investigator holds a financial or other interest

- Associating one's name or one's work with the institution in such a way as to profit monetarily by trading on the reputation or good-will of the university or hospital, rather than on one's professional competence

Situations That May Involve Inappropriate Use of Information

- Unauthorized use of privileged information acquired in connection with one's professional responsibilities

- Accepting support for basic or clinical research under terms and conditions that results be held confidential, unpublished, or significantly delayed in publication

- Providing privileged access to information, developed with university resources or supported by independent sponsors, to an entity in which the faculty member has a financial interest

Situations That May Involve Self-Dealing

- Purchasing equipment, instruments, or supplies for research or teaching from a firm in which the faculty member has a financial or other interest

- Influencing the negotiation of contracts between the academic institution and outside organizations with which a faculty member has a financial interest or other relationship

- Requiring or recommending one's own textbook or other teaching aids

Special Considerations in Consulting to Federal Agencies

- Consulting to a federal agency when one is also conducting federally-sponsored research (the federal conflict of interest statutes 18 U.S.C. 202-209 should be consulted)

As with conflicts of commitment, the institution and faculty must work together to see that conflicts of interest are either avoided or properly managed when they arise. Faculty play a particularly pivotal role in identifying and managing potential conflict situations because it is ultimately up to the faculty to recognize potential problems and report them to appropriate institutional officials. Faculty can enhance their ability to avoid conflicts of interest if, in addition to abiding by proper deportment regarding conflict of commitment, they:

- Uphold as a primary responsibility the academic institution's scholarly mission of research, teaching, and public service,

- Read and adhere to institutional policies for review of all research proposals,

- Abide by institutional conflict of interest policies and standards,

- Conduct research and report results in an objective manner unbiased insofar as possible by the prospect of personal gain or recognition,

- Disclose fully those professional and relevant personal activities when required by the institution, or when there is potential for conflict of interest, and

- Remain cognizant of the potential for conflicts and take initiative to manage, disclose, or resolve conflicting situations as appropriate.

To assist faculty in reporting and dealing with conflicts, institutions should have appropriate mechanisms in place to enhance faculty awareness and to make effective use of disclosed information. Therefore institutions should:

- Develop and disseminate policies that clearly articulate the institution's position on 1) sponsored research, 2) acceptable types and levels of outside financial and professional interests, 3) the need to recognize and deal openly with real or apparent conflicts, and 4) the relationship of faculty and staff to outside institutions and third parties,

- Develop procedures for full disclosure to the institution, and to the interested public, of financial and professional interests that may influence, or may be perceived to influence, research activity or other scholarly responsibilities,

- Implement enforcement procedures, including appropriate sanctions and notification of university and other officials as required, when apparent violations of institutional rules or federal, state, or local laws occur,

- Develop procedures to assure that all research proposals are responsibly prepared and appropriately reviewed in accordance with institutional requirements,

- Implement accounting procedures which assure that research funds are expended for the purposes for which they have been provided and that all expected services have been performed,

- Assure appropriate and effective management and/or resolution of conflicts of interest through the institutional administrative officers and review committees,

- Respond expeditiously and with clarity to questions raised concerning potential conflict situations, and

- Serve as a model for faculty behavior and preclude inadvertently exposing faculty to conflicts and concomitant liabilities by avoiding conflicts at an institutional level.

PROCESS OF DISCLOSURE AND REVIEW

One of the keys to preventing and resolving conflicting situations is full disclosure followed by aggressive monitoring and conflict management. Full disclosure of relevant information is in the best interest of both the institution and the faculty member. It demonstrates good faith on the part of the investigator and protects his or her reputation and that of the university or hospital. Disclosure will not necessarily restrict or preclude an investigator's activities. In fact, activities that might be veiled in a cloud of suspicion and doubt may be found acceptable and permissible when all facts regarding the activity are brought to light a priori. The disclosure process probably will be carried out differently at each institution, and this is appropriate given the unique organizational and legal issues they face. However, a few guiding procedural principles are suggested.

First, all privately and federally sponsored research agreements in which a faculty member anticipates taking part should receive prior review and approval through appropriate institutional channels. Such approval should require the signatures of all relevant officials to document that appropriate review took place. In addition,

such signatures impart accountability upon the reviewers and help assure that these officials are aware of the nature and terms of the agreement. Academic institutions should also require disclosure of the investigator's relevant personal interests, including those of the immediate family. These may include, but are not limited to, equity interests, outside professional positions, outside professional salary, gifts, honoraria, and loans. Such disclosure should accompany contractual research agreements and grant applications as they receive institutional review. Additional disclosure should be established on a regular basis by the institution based on local requirements and any relevant changes in faculty status. At a minimum such disclosure should occur annually.

Initially, reporting mechanisms for disclosure should flow to chairpersons of departments, or equivalent supervisors, though simultaneous reporting could occur to the sponsored projects office. For some large departments, the chairperson may wish to develop a mechanism in which initial input is coordinated and evaluated at the level of section chiefs. Thus, the responsibility for initial collection and review of disclosure information rests with a supervisor closely familiar with the area or discipline that disclosure covers. This supervisory individual should advise the dean (or next level of review) of those cases which require further examination. The supervisor may also serve as an advisor to faculty uncertain regarding the appropriateness of a given activity or how to handle a given disclosure issue. It is, therefore, incumbent upon the supervisor to be familiar with institutional policy and federal, state, and local requirements so as to understand fully the implications of the situation in question. The supervisor may need to consult or engage the institutional offices of legal counsel, business, research administration, government relations, and technology-transfer, as appropriate. In addition, when presented with a questionable situation, the supervisor should reflect on issues raised by the "review questions" that follow this section, to evaluate the nature and acceptability of the situation. Such an evaluation should be supplemented with personal knowledge of institutional policy, local law, and federal requirements.

After appropriate evaluation, the supervisor may find that a proposed or ongoing research agreement and the faculty member's personal interests show no conflict or apparent conflict and are acceptable without further review. Conversely, the supervisor may determine that a given situation raises some questions of propriety and requires a higher level of review. The next level of review should be pursued whenever there is any doubt.

Subsequent review should occur at the level of the dean, chief executive officer, or other designated senior institutional official. The senior official should evaluate the situation in much the same way as the supervisor, employing key review questions and consultation. After appropriate consideration, the senior official may conclude that there is no conflict and should report such findings back to the

departmental level. If the senior official determines that there is any reasonable question of conflict or legitimacy regarding the situation, then all relevant information should be passed on to a designated institutional committee responsible for review of possible conflicts of interest.

The institutional committee for review of possible conflicts of interest should be, preferably, a standing committee. It should consist of institutional officials who represent or have access to the expertise of the university or hospital legal counsel, research administration, government relations, technology-transfer, and other pertinent offices. The committee's role should be tripartite.

The first role is evaluative. The committee should review all relevant information and make the final determination whether a conflict situation exists. Naturally, the review process should be designed to protect confidential information to the degree permitted by law. As part of its evaluation, the committee should make use of the review questions in the following section.

The second role of the committee is both adjudicative and arbitrative. The committee is ultimately responsible for determining how any conflicts might be managed or resolved. This begins with the committee reporting its findings to the administrative officials who have reviewed the case, the faculty member and, where appropriate per federal requirements, the funding agency. After appropriate evaluation, most situations will be found to be

- Unacceptable and thus prohibited, or
- Permitted with the implementation of one or more committee recommendations to preclude unreasonable levels of bias or inappropriate activities, or
- Permitted as is because the disclosed personal information does not represent a possible source of unreasonable bias or an inappropriate activity.

In a case where current faculty activity is permitted but requires implementation of certain recommendations, options for resolution and a mechanism for reporting back to the committee should be developed. The possible options are as numerous as the types of situations the committee may review. However, as the committee gains experience in the review of these cases, the appropriate action may become more obvious over time. Possible options include, but are not limited to:

- Public disclosure of all relevant information,

- Reformulation of the research workplan,
- Close monitoring of the research project,
- Divestiture of relevant personal interests,
- Termination or reduction of involvement in the relevant research project,
- Termination of inappropriate student involvement in projects, and
- Severance of outside relationships that pose conflicts.

The final role of the committee should relate to policy development. By virtue of the experience it will accumulate in handling this issue, the committee will be the most appropriate body for advising the dean, hospital CEO, and other administrative officials on policy issues. New policies or changes to existing policy should be formulated, or at least reviewed, by this committee.

Violations of institutional policies regarding the acceptance of honoraria, gifts, salary and so forth, must be handled expeditiously and conclusively through institutional mechanisms for dealing with inappropriate faculty behavior. Such mechanisms are often described in the faculty handbook under the rubric "standards of conduct." Violations that appear to have resulted in a misrepresentation of research results or other unprofessional conduct should be handled according to the institution's policies for dealing with allegations of misconduct in research. Violations of federal or state statutes and guidelines must be handled according to federal and state laws and requirements. All decisions must be documented. The nature and handling of such documents should be discussed by the committee or appropriate institutional officials.

REVIEW QUESTIONS

Individuals at all levels of review of disclosure information and research proposals need a framework for evaluating whether a situation presented before them is acceptable, and for assessing the degree to which it poses risk to the faculty member, the institution, and other entities that may be affected by the research in question. Presented below are sample review questions that should be utilized by anybody evaluating a potential case of conflict of interest. The list is not inclusive and other questions appropriate for special circumstances should be added.

When presented with the facts of a given situation, the reviewer must first determine if there is legitimate cause for concern over inappropriate behavior or the injection of undue bias into the professional activities of the faculty member. Therefore, initially one should ask, among other possible questions,

- Has all relevant information concerning the faculty member's activities been acquired (i.e., has there been full disclosure)?
- Do the faculty member's relevant financial interests exceed predetermined thresholds of acceptability, where specified?
- Do the faculty member's reported external commitments exceed permissible levels?
- Is there any indication that research results have not been faithfully and accurately reported?
- Is there any indication that the faculty member in his or her professional role has improperly favored any outside entity or appears to have incentive to do so?
- Has the faculty member inappropriately represented the institution to outside entities?
- Does the faculty member appear to be subject to incentives that might lead to inappropriate bias?
- Is there any indication that obligations to the university are not being met?
- Is the faculty member involved in a situation similar to any of those described earlier in the document that might raise questions of bias, self-dealing, inappropriate use of university assets, poor data management, or impropriety?
- Could the faculty member's circumstances represent any possible violation of federal, state, or local laws and requirements?
- Do the current engagements of the faculty member present any conflicts between outside interests (e.g., working on projects simultaneously for competing business entities)?

If it appears that there is genuine cause for concern, the reviewer must ascertain whether appropriate controls are in place to deal with possible conflicts. The reviewer should ask, as relevant,

- Will the negotiation of relevant research affiliations or other contracts be handled by truly disinterested representatives of the institution?
- Will the research workplan receive independent peer review prior to its initiation?
- Are there mechanisms in place to prevent the introduction of bias into research projects (i.e., Is the protocol double-blinded? Are research subjects randomly selected?)?
- Will the project be supervised by someone with authority and no conflicting interests?
- Are there means to verify research results (e.g., independent corroboration in another lab, FDA review)?
- Will data and materials be shared openly with independent researchers? If not, who determines accessibility to such resources?
- Will the product of the collaborative effort with an outside party be published in the peer-reviewed scientific literature?
- Will the sponsorship and relevant interests receive acknowledgment in public presentations of the research results?

The goal in applying these questions should be to determine the correct mode of dealing with any real or apparent conflicts as discussed earlier.

OTHER RELEVANT POLICIES

The issues of conflict of commitment and conflict of interest have far-reaching implications for a large number of institutional activities; it may not be possible to address fully all the important issues in a single policy. Instead, institutions may need to develop a matrix of policies, each with their special focus, that to some degree support the principal framework for avoiding conflicts. These may include, but are not limited to:

- Patent and licensing policies

- Publication policies
- Policies addressing student participation in research
- Policies concerning administrative conflicts of interest (procurement, board of trustees, etc.)
- Institutional affiliation policies
- Policies addressing the use of institutional assets
- Faculty standards of conduct

CONCLUSION

There is no simple approach to dealing with conflicts of interest among faculty. The strategies for managing conflicts are just as numerous as the types of conflicts that may occur. Therefore, this document can strive only to provide a useful level of guidance in assisting institutions in developing their own policies and procedures to fit their unique situations and local requirements.

It is important to be cognizant, however, that conflicts in research indeed will arise at some point in time. They are a natural product of the intersection of the vast matrix of faculty personal responsibilities and needs with the network of professional affiliations and activities that must be maintained. Conflicts are not necessarily unacceptable and many can be managed provided adequate mechanisms are in place for disclosure and oversight.

To be effective in dealing with conflicts of interests and commitment in research, academic institutions must have 1) standards of conduct that delineate the boundaries of conflict of interest and commitment, 2) requirements for timely disclosures of relevant information, 3) adequate review of disclosed information and potential conflicts of interest, 4) procedures for enforcing standards and providing sanctions for violations, and 5) policies and procedures consistent with governmental policies and rules. General awareness (institutional and public) of an investigator's relevant funding sources, financial interests, and professional roles, serve to direct appropriate scrutiny at elements of research commitment, design, and reporting of data that might be biased or undermined by these factors. The investigator's cognizance of that scrutiny further encourages vigilance to avoid any biases or diversions that inadvertently may be introduced. Naturally, for this system to work, the disclosure process must assure that information regarding possible conflicts reaches all individuals with an appropriate interest in evaluating the research in question.

The AAMC continues to work on various aspects of this issue and invites commentary on this document and other facets of the issue in which the Association may play an effective role.

REFERENCES

1. Conflict of Interest Statutes 18 U.S.C. 202-209 as amended

2. American Council on Eduction and the Association of American University Professors, On Preventing Conflicts of Interest in Government-Sponsored Research at Universities, Washington, D.C. 1965

3. Association of American Universities, University Policies on Conflict of Interest and Delay of Publication, Report of the Clearinghouse on University-Industry Relations, Washington, D.C. 1985

4. American Council on Eduction, Higher Education and Research Entrepreneurship: Conflicts Among Interest, Washington D.C. 1986

5. U.S. Public Health Service, PHS Grants Policy Statement, DHHS Publication No. 82-50,000 (Rev.), January 1, 1987

6. "Request for Comment on Proposed Guidelines for Policies on Conflict of Interest," National Institutes of Health and the Alcohol, Drug Abuse and Mental Health Administration, NIH Guide for Grants and Contracts, September 15, 1989

AAU Association of American Universities

President

July 19, 1993

The Honorable Ron Wyden
Chairman
Committee on Small Business
Subcommittee on Regulation, Business
Opportunities, and Technology
B363 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Chairman:

I am writing to let you know of the Association of American Universities' (AAU) interest in the issue of conflicts of interest in research. The AAU consists of research-intensive universities, all of which receive federal funding for scientific research. The AAU has a long-standing interest in and commitment to the development of institutional policies and procedures which protect the integrity of the institution and the research process, encourage the free flow of knowledge and ideas, and ensure that public and institutional resources are used appropriately.

Ms. Maureen Byrnes, of the AAU staff, has met with members of your staff, and I understand the record for the Subcommittee's June 17 hearing on "Drug Development Deals Between Tax-Supported Labs And Pharmaceutical Manufacturers: Who Owns The Results? How Should They Be Priced?" is held open for 45 days after the hearing. I am requesting that the enclosed brief statement and copy of the "AAU Framework Document on Managing Financial Conflicts of Interest" be included as part of the hearing record.

Thank you for your consideration of this request. I would, of course, be happy to answer any questions you may have and provide you with any further information that you may find useful.

Sincerely,

Cornelius J. Pings
President

CJP/MKB/ldw

Enclosure

Suite 730 • One Dupont Circle • Washington, DC 20036 • 202/466-5030 • FAX 202/296-4438

Testimony for the Record
by
Cornelius J. Pings, Ph.D.
President
Association of American Universities
before the
U.S. House of Representatives
Committee on Small Business
Subcommittee on Regulation, Business Opportunities, and Technology

June 17, 1993

Mr. Chairman and Subcommittee members, thank you for the opportunity to submit these brief remarks and the "AAU Framework Document on Managing Financial Conflicts of Interest" as part of the hearing record.

The Association of American Universities (AAU) consists of research-intensive universities, all of which receive federal funding for scientific research. The AAU has a long-standing interest in and commitment to the development of institutional policies and procedures which protect the integrity of the institution and the research process, encourage the free flow of knowledge and ideas, and ensure that public and institutional resources are used appropriately. The AAU believes strongly that the development and implementation of conflict-of-interest policies and procedures is the responsibility of each institution. The Framework Document we are submitting to the Subcommittee is designed to provide guidelines for institutions to use in developing their own conflict-of-interest policies. We thought you might also find it useful as you consider the adequacy of current laws and policies for protecting the public's interest in government-funded research.

I appreciate the opportunity to submit the AAU Framework Document for the record, and I look forward to working with you in the future.

Framework Document on Managing Financial Conflicts of Interest

May 1993

AAU
Association of American Universities

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Introduction

Universities have long recognized the importance of maintaining policies that address conflicts of interest. In 1964, the Council of the American Association of University Professors (AAUP) and the American Council on Education (ACE) issued a joint statement *On Preventing Conflicts of Interest in Government-Sponsored Research at Universities.* This statement, which continues to serve as the basis for many university policies today, underscores the importance of the transfer of knowledge and skill from the university to industry, as well as careful attention to institutional standards and procedures that protect the integrity of the institution and the research conducted there.

As support for government-sponsored research increased, and as policies and laws were developed to encourage relationships among universities, government, and industry, additional statements and reports were issued to assist universities in developing and refining their conflict-of-interest policies. In 1978, the Association of American Universities (AAU), the ACE, and the National Association of State Universities and Land-Grant Colleges (NASULGC) published *Principles to Govern College and University Compensation: Policies for Faculty Engaged in Sponsored Research.* In 1985, the AAU issued a report of the Clearinghouse of University-Industry Relations entitled *University Policies on Conflict of Interest and Delay of Publication.* Both the Association of American Medical Colleges (AAMC) and the Association of Academic Health Centers (AHC) have also recently published reports about conflicts of commitment and conflicts of interest.

The 1990s bring a renewed emphasis on technology transfer and economic competitiveness has emerged as a national priority. It is, therefore, particularly timely that universities review their conflict-of-interest policies to ensure that these policies continue to protect the integrity of the institution and the research process, encourage the free flow of knowledge and ideas, and ensure that public and institutional resources are used appropriately. This document is designed to provide a framework within which institutions can review their conflict-of-interest policies, with specific attention to managing financial conflicts. While there are clearly other aspects of an institutional policy that should be

carefully reviewed and considered (for example, conflicts involving the use of students in research sponsored by industry and other outside activities), this document focuses solely on managing financial conflicts of interest. The policies discussed are intended to cover all university employees, although particular attention is paid to faculty and their research activities. The document does not address the development of policies for institutional conflicts of interest, which develop out of links between institutional financial interests and the commercial application of faculty research results. However, universities are strongly encouraged to establish such policies, as well.

Managing Financial Conflicts of Interest

Faculty and staff owe a primary loyalty to their institution. Within this responsibility are several activities that often compete for attention. Faculty teach undergraduates, mentor graduate students, perform and report research, and participate in the management of the institution. While fulfilling these responsibilities to their institutions, faculty also advise and consult with private and public entities and provide service to professional societies. Balancing these external and internal responsibilities is difficult; conflicts over the allocation of time and resources are inevitable. Institutional policies governing conflicts of commitment (which most often involve the amount of time permitted in outside activities) have been developed to address, among other things, conflicts over the allocation of time. Conflicts involving the use of university resources for personal gain are addressed by conflict-of-interest policies. Virtually all universities have policies and procedures for managing conflicts of interest; however, demonstrating accountability requires that these policies and procedures be clearly expressed and implemented.

The transfer of knowledge and information from academia to industry gives rise to a range of activities and relationships outside the university that can be extremely beneficial to the public. Faculty involvement in private industry and national laboratories

can be a powerful mechanism of technology transfer, now a national priority. However, a degree of conflict may be inevitable whenever academic research addresses problems of the real world. What is important is that such conflicts be managed so that the purpose and mission of academic institutions are not compromised, so that the investment of the public and students is protected, and so that public confidence in the integrity of scholarly activities is maintained. Coherent conflict-of-interest policies can not only help guide relationships between industry and academia, but also help ensure the protection of the mission of the university.

Accordingly, the challenge to the university is to develop a mechanism for faculty and other employees to report outside activities so that the relationship between the faculty member's institutional responsibilities and his/her outside activities can be reviewed and managed appropriately by the institution. This is essential to ensure that research conducted at the institution is free from bias or perceived bias when a faculty member stands to benefit from a particular research outcome. In some cases, appropriate management of a disclosed conflict will mean eliminating the conflict (e.g., outside relationship or activity) altogether. In other cases, appropriate management may involve careful monitoring and reporting of research activities and data, allowing important research to go forward with assurances that the integrity of the science and the institution will be protected. These situations will require careful review, monitoring, and documentation throughout the life of the project. If government funds are involved, the institution is also accountable to the government and the public for ensuring that financial conflicts are disclosed and appropriately managed by the institution.

The development and implementation of conflict-of-interest policies and procedures is the responsibility of each institution. However, there are certain key elements that should be included in every university policy for managing financial conflicts of interest. These elements include the following: definitions, disclosure, review processes, recommendations and decisions, opportunity for appeal, and utilization of appropriate university procedure for noncompliance with the policy. The administrative

responsibility for each element must be clearly specified and a system of communication must be in place to assure that each individual affected by the policy is made aware of his or her responsibility under the policy. Each of these elements is discussed in this document, with suggestions for how these elements may be organized and implemented in a conflict-of-interest policy.

Institutional Policies and Responsibilities

The development and implementation of conflict-of-interest policies and procedures must remain the responsibility of the individual institution. The way in which institutions develop and implement their policies and procedures will vary since they will reflect the different culture and management styles of each university. Compliance with the laws and regulations of different states also necessitate that each institution develop its own conflict-of-interest policy. In addition, institutions also need to assure congruence of any new policy with the compendium of already existing institutional policies related to responsibility and conduct of faculty and university employees.

Institutions have codes of conduct that are derived from ethical principles related to faculty behavior toward students, colleagues, the institution, and the community. They address issues of unacceptable conduct related to instruction, scholarship, and public service. Among the types of unacceptable conduct are exploitation of students for private advantage, violations of the canons of intellectual honesty, and unauthorized use of university resources for personal purposes. Accompanying such codes are the policies and procedures applicable to enforcement and sanctions. Faculty are also bound to observe the codes of their professional societies regarding issues of integrity in exercising their professional responsibilities.

In addition, the procedures used by academic institutions for the advancement of faculty provide for peer evaluation of professional activities. These procedures are appropriate for the

management of conflicts other than financial conflicts of interest. The faculty promotion process reviews critically the creativity and excellence of teaching, research performance, and service to the institution. Faculty are rewarded for professional achievements as evaluated by peers through publications, teaching evaluations, service to the profession, service to agencies, and contributions to the advancement of knowledge. Honesty, openness, objectivity, and critical judgment in performing these duties, including the conduct of research, are significant elements in the academic reward structure.

Institutions also have other mechanisms for addressing conflicts of interest in research practices, usually through policies and procedures related to contract and grant terms. Such policies address issues about the openness of the research environment, the right to publish, the right to intellectual property, the use of the university name, and the appropriate use of university facilities.

Moreover, conflicts of interest are not limited to research performed by faculty. Academic institutions also manage conflicts of interest on the part of employees responsible for business decisions which occur in administering the institution. For example, employees involved in purchasing decisions are restrained from relationships with vendors that might impair the objective fulfillment of their duties.

Finally, the implementation of policies and procedures to review and manage financial conflicts of interest must recognize the existing codes, norms, policies, procedures, practices, and guidelines related to the issues and concerns raised. The development of new policies should be distinguished from better implementation of existing policies. Of greater importance will be the organizational structure adopted and the administrative responsibility exercised by the institution in implementing the policies and procedures. It is not enough simply to have good policies in place. They must be used, and it must be made clear who is responsible for what.

Elements of a Conflict-of-Interest Policy

Definition

Defining conflict of interest is a complex task. If not focused on the specific problem being addressed, the development of definitions will involve discussions of individual motivations, the nature of research, the nature of academic institutions, and other topics that, although very important, are not essential to defining conflict of interest. Rather, definitions need to focus on conflicts that may arise when an individual's activities inside the institution can be directed toward serving his or her outside activities.

A conflict-of-interest definition must be broad enough to include a spectrum of activities ranging from outside employment, consulting, ownership of stock, etc. The definition needs to focus disclosure categories on those activities needed to conduct a careful review and assessment of whether a particular activity or relationship is acceptable, unacceptable, or requires further review and careful monitoring.

Some university policies include specific disclosure categories, thresholds, and affected individuals as part of the definition. Others include a broader definition and identify thresholds and categories on the disclosure form. Most university policies cover certain family members, and it is important to indicate clearly who is included under the term "family."

The following are offered as examples of definitions that have been adopted by some institutions:

Institution A

A conflict of interest may take various forms, but arises when an academic staff member is or may be in a position to influence the university business, research, or other decisions in ways that could lead to any form of personal gain for the academic staff member or the staff member's family, or give improper advantage to others to the university's detriment.

Institution B

A potential or actual conflict of interest exists when commitments and obligations to the university or to widely recognized professional norms are likely to be compromised by a person's other interests or commitments, especially economic, particularly if those interests or commitments are not disclosed.

Institution C

A conflict of interest occurs when an employee has a financial interest in a university decision. A financial interest is described as:

- A direct or indirect investment in the sponsor worth more than $1,000;
- A position as director, officer, partner, trustee, employee of any or any other position of management in the sponsor;
- Income from the sponsor, including consulting income and gifts aggregating $250 or more in value, received by or promised to the principal investigator within 12 months prior to the time the award is made. (For the purposes of this policy, "income" is further defined as in Gov. Code, Section 82030).

A principal investigator has an "indirect investment" or "indirect financial interest" in a sponsor if:

- His or her spouse or dependent child has a financial interest in the sponsor;
- The principal investigator, his or her spouse, or dependent child own directly, indirectly, or beneficially a 10 percent interest or greater in any business entity or trust which has a financial interest in the sponsor of the research.

Disclosure

In addition to a definition, a conflict-of-interest policy must specify the information to be disclosed and to whom the disclosure is to be made. Disclosure forms should be limited in scope, yet sufficiently encompassing to allow an independent reviewer of the disclosure to determine if the outside activity interferes with the researcher's primary responsibility and duty of loyalty to the institution and the integrity of the research process. The assumption that drives the development of conflict-of-interest policies and procedures is that the financial potential of outside activity might bias the academic activity of the faculty.

Disclosure forms should be designed to capture as efficiently as possible only information pertinent to university conflict-of-interest concerns. The forms need to recognize that most faculty and staff will report no conflicts and their disclosed information will not require any review past the initial stage. Disclosure forms should capture the kind of information that is necessary to identify a financial conflict of interest and provide an opportunity for discussion, review, and appropriate management. Sample disclosure forms used at institutions across the country are included as Appendix A through C of this document.

Review Process

Initial Review

Disclosure forms should be submitted to and reviewed by an appropriate institutional officer, often an individual with first-line supervisory responsibility for the faculty member submitting the disclosure form. The institutional role of the officer will vary among institutions. In some cases it may be the dean, in others, the department chair. Each disclosure form should be reviewed according to criteria established to distinguish between negative disclosure (disclosures that reveal no financial conflict) and positive disclosures (disclosures that require additional review).

In most cases, the criteria will suggest the questions and categories to be included on the disclosure form. A recordkeeping system should be established and maintained for all disclosures, negative and positive.

The review process should be clearly stated and consistently practiced. The goal for all reviews of positive disclosures must be to gain a better understanding of the nature and extent of the conflict and explore options for managing it. In the vast majority of cases, a discussion between the reviewer and faculty member can result in steps taken by the investigator to eliminate or mitigate the conflict of interest. These steps should be carefully documented and filed with the initial disclosure form, unless the conflict has been eliminated.

In the AAMC's *Guidelines for Dealing with Faculty Conflicts of Commitment and Conflicts of Interest in Research,* a series of questions has been included that can assist the initial reviewer in evaluating positive disclosures. Some of these questions include:

- Has all relevant information concerning the faculty member's activities been acquired (i.e., has there been full disclosure)?
- Do the faculty member's relevant financial interests exceed predetermined thresholds of acceptability, where specified?
- Do the faculty member's reported external commitments exceed permissible levels?
- Is there any indication that research results have not been faithfully and accurately reported?
- Is there any indication that the faculty member in his or her professional role has improperly favored any outside entity or appears to have incentive to do so?
- Has the faculty member inappropriately represented the institution to outside entities?
- Does the faculty member appear to be subject to incentives that might lead to inappropriate bias?

- Is there any indication that obligations to the university are not being met?
- Could the faculty member's circumstances represent any possible violation of federal, state, or local laws and requirements?
- Do the current engagements of the faculty member present any conflicts between outside interests (e.g., working on projects simultaneously for competing business entities)?

Some universities may elect to institute an annual disclosure for all. Others may ask that disclosures be submitted (or renewed) whenever the institution contemplates the acceptance of an external research agreement or the execution of a technology transfer arrangement, or at the time a faculty member enters into such activities. In the latter case, the institution may wish to couple the initial conflict-of-interest review with the existing administrative review process.

Second Level of Review

In those instances where the financial conflict has not been resolved at the initial review stage, the disclosure should be referred to a second level of review. This review may involve other individual reviewers or a committee. At this point, consideration must be given to the organizational structure and responsibility for reviewing cases and making decisions about how conflicts will be managed. The degree to which the process is centralized must be established. Centralization will strengthen the possibility for gaining the experience required for consistency and continued policy development. Decentralization, on the other hand, can deal more effectively with issues that are specific to a given discipline at a given time. Whatever the organizational structure, the goals of second-level review should be an evaluation of the disclosure and a recommendation for how the financial conflict will be managed. The development of criteria for deciding what is unallowable and what can be conditionally allowed is crucial and should be undertaken in accordance with university policy and experience. Criteria should include, but should not be limited to, such elements as the extent and nature

of the involvement, the openness of the activity, the freedom of communication about the activity, the control of the intellectual property arising from the activity, and the use of university resources, including the involvement of students. Among those at the university who may be involved in a second-level review process are department academic administrators, faculty, contracts and grants officers, technology transfer personnel, and central academic administration personnel. Some institutions have found that by including faculty members in a fair and impartial review process, the credibility of the process and the recommended outcome are significantly enhanced.

In some cases, the nature of the outside relationship or activity will be such that it will not be possible to ensure the integrity of the science or the institution if the outside relationship or activity is maintained. In these cases, the conflicts should be deemed unacceptable and the outside relationship or activity should be eliminated before the research can proceed. In other cases, elimination of the outside relationship or activity may not be necessary or prudent. In these cases, careful monitoring and reporting are crucial to ensuring that the objectivity of the science and integrity of the institution are protected.

Again, the AAMC has outlined example questions that can be used at a second-level review to help decide which financial conflicts can be managed in a way that can ensure the protection of the integrity of the science and the institution and which cannot. These questions include:

- Will the negotiation of relevant research affiliations or other contracts be handled by truly disinterested representatives of the institution?
- Will the research workplan receive independent peer review prior to its initiation?
- Are there mechanisms in place to prevent the introduction of bias into research projects (i.e., Is the protocol double-blinded? Are research subjects randomly selected?)?

- Will the project be supervised by someone with authority and no conflicting interests?
- Are there means to verify research results (e.g., independent corroboration in another lab, FDA review)?
- Will data and materials be shared openly with independent researchers? If not, who determines accessibility to such resources?
- Will the product of the collaborative effort with an outside party be published in the peer-reviewed scientific literature?
- Will the sponsorship and relevant interests receive acknowledgment in public presentations of the research results?

Appeal Process

A process for appealing a formal decision about approval or disapproval of a disclosed financial conflict of interest should be included in a university conflict-of-interest policy. This appeal process should include a description of the circumstances under which a decision may be appealed and to whom.

Noncompliance

To the extent possible, existing institutional procedures for investigating and sanctioning violations of faculty codes of conduct should be used for any violations of the university conflict-of-interest policy. This may require institutions to include a specific designation that conflicts of interest will be addressed under university policies and codes.

INSTITUTE OF MEDICINE
NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE WASHINGTON, D. C. 20418

KENNETH I SHINE M D
PRESIDENT

June 15, 1993

Honorable Ron Wyden
Chairman
Subcommittee on Regulation,
Business Opportunities, and Technology
Committee on Small Business
U.S. House of Representatives
B-363 Rayburn House Office Building
Washington, D.C. 20515-6318

Dear Congressman Wyden:

I am in receipt of your letters of May 20 and May 27 concerning conflict-of-interest in university-industry collaborations and your scheduled hearings. This is an important topic and I regret that I am not available to testify at this time. As background to the questions posed in your May 27 letter, the Institute of Medicine (IOM) of the National Academy of Sciences (NAS) was established in 1970 under the 1863 Congressional charter that established the NAS. The IOM carries out studies at the request of government in areas related to health and health science policy. We participated with the NAS in the important study *Responsible Science: Ensuring the Integrity of the Research Process*. More recently we organized a workshop having to do with the patenting of gene sequences in which issues of conflict-of-interest were considered.

As a result of that workshop, a recommendation has been made that we undertake a major study on intellectual property rights and technology transfer in molecular biology for the public interest which would have, as a significant component, recommendations with regard to conflict-of-interest. Although the study will be particularly directed toward issues in molecular biology, we believe that a significant portion of the project will be generalizable to other areas of science.

The members of the IOM are elected on the basis of their contributions to health and health science. We conduct no direct research activities, although careful conflict-of-interest information is collected prior to each of our studies and in-depth bias discussions are held at the first meeting of any of our committees. Full financial disclosures are made in relation to participation in such studies.

We have not conducted any specific studies in the areas described in your letter, that is, Ceredase or specific issues of disclosure by scientists to the Food and Drug

Administration (FDA). In 1992, we did complete an important study for the FDA with regard to its advisory committees; the study did consider conflict-of-interest. A copy of that report is enclosed.

We believe that our anticipated study on intellectual property and technology transfer in molecular biology for the public interest, which is likely to take approximately 18 months, will be a thorough, well-balanced and comprehensive review of a number of the issues which you raise. We look forward to sharing the results of that study when the study has been completed.

Yours truly,

Kenneth I. Shine, M.D.

Enclosure

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