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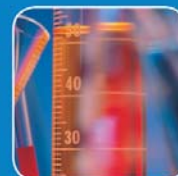


PROCEEDINGS OF A NATIONAL DIALOGUE ON BIOMEDICAL CONFLICTS OF INTEREST AND INNOVATION MANAGEMENT

SEPTEMBER 20, 2006, CLEVELAND CLINIC, CLEVELAND, OHIO

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Supplement 2 to Volume 74, March 2007

Supplement Editor

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Vice Chairman, Lerner Research Institute
Professor, Department of Cell Biology
Cleveland Clinic

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Articles in these proceedings were developed by the *Cleveland Clinic Journal of Medicine* staff from transcripts of audiotaped presentations at the “National Dialogue on Biomedical Conflicts of Interest and Innovation Management” and then reviewed and revised by the respective speakers.

GUY M. CHISOLM III, PhD

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The rapidly changing landscape of biomedical conflicts of interest

Academic medical centers (AMCs) have undergone major changes in the way they relate to the biopharmaceutical and medical device industries. This has led to changes in the public's view of AMCs with respect to these relationships—a view that is often refracted through the lenses of ambitious investigative reporters. The academic medical community must construct its relationships with industry in ways that merit the public's trust.

A shared desire to discuss and understand these changes prompted a gathering of some of the nation's most prominent thought leaders on biomedical conflicts of interest at Cleveland Clinic on September 20, 2006. The resulting event, "A National Dialogue on Biomedical Conflicts of Interest and Innovation Management," featured a number of perspectives on these issues from a slate of speakers hailing from AMC faculties, industry, government regulatory and prosecutorial offices, the bioethics community, and the media. This journal supplement is a collection of edited transcripts from that conference, with the essence of the messages from the presenters and audience members faithfully preserved.

■ FACTORS BEHIND THE CHANGES AT AMCS

The changes in AMC-industry ties have been precipitated by a number of factors:

- The Bayh-Dole Act and other federal and state initiatives encouraging commercialization of discoveries from academic laboratories
- A shift from performing science solely to advance the state of knowledge to keeping one eye on which discoveries emanating from AMC labs might become practical advances to improve patient care
- The deluge of discoveries resulting from the cracking of the genetic code
- Federal research funding levels that fall short of

feeding the nation's biomedical science appetite

- A growing biotechnology industry that is hungry for academic partnerships and has fine-tuned the art of forming new companies.

Whatever the principal driving forces, these changes at AMCs have manifested themselves in increased entrepreneurial activity and an expanded infrastructure for technology transfer.

■ NOVEL AND COMPLEX PREDICAMENTS

The growth and variety of academic-industry partnerships has resulted in novel and complex predicaments, in which financial gains appear as though they could compromise the validity of scientific data or the treatment of patients. Some of these predicaments stem from gifts or unrestricted grants from grateful industry partners, or from medical product marketers trying to influence buying or prescribing habits. Some arise from consulting relationships, and others from licensing arrangements. Still others stem from spin-off companies, in which employees of academic institutions, or the institutions themselves, stand to gain from the future success of commercialized discoveries or inventions.

Are all of these arrangements evil? Can they be allowed to go on in such a way that the inherent conflicts of interest are avoided? Can they proceed, sufficiently protected from bias, through artful and conscientious "management" of their inherent conflicts, when avoiding these conflicts would be tantamount to killing a beneficial project? These questions do not have easy answers, although some people believe there are certain "conflicted" arrangements that provide no room for management and should be forbidden outright.

Differing views of gifts and grants

Many believe that all gifts to physicians and on-campus marketing by industry should be banned, and steps related to this have recently been taken by a handful of AMCs, including those of Stanford

Dr. Chisolm reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

University, Yale University, and the University of Pennsylvania. Others will surely follow. The Pew Charitable Trusts is funding a \$6 million “Prescription Project” to document the effects of such gifts on prescribing practices and to advocate restrictions on physicians’ acceptance of gifts. However, the industry gifts in the form of grants that fund fellowships and educational conferences are likely to continue to be handled in varying ways by different AMCs.

Consulting for industry: To ban or to manage?

Consulting relationships are viewed differently. When industry wants a consultant to help it develop a new product or understand the medical implications of a product, it looks to academia. Specifically, it often looks to clinical scientists whose clinical insights are known to be superlative, who are thought leaders in their field, whose research is at the forefront, and who are respected by their peers. When AMCs recruit faculty, they look for people with these exact same attributes. Is it surprising, then, that the faculties of AMCs do a lot of consulting for industry?

For this reason, there is a strong tendency to try to manage the conflicts created by consulting for industry rather than ban the consulting itself. Few are suggesting that investigators outside of the National Institutes of Health (NIH) be subject to limitations on consulting as strict as those for intramural NIH researchers, which generally prohibit any consulting for companies that develop biomedical products (see pages S29–S31 for details).

When to hand off commercialized discoveries to disinterested parties?

What about the conflicts that directly arise from the commercialization of discoveries made at AMCs? In many cases there is arguably an early stage to the development of a discovery, during which the knowledge base, insights, laboratory resources, and “fire in the belly” of the discoverer/inventor are essential to bring the discovery to a level at which further development and validation can be turned over to an uninvolved party. Currently AMCs vary significantly in how they handle the conflicts that arise from keeping the “conflicted” discoverer/inventor involved in these early studies. Approaches range from banning the discoverer/inventor from performing research under certain circumstances to trying to manage all of the potential conflicts with adequate firewalls between the financial inducements on one side and the data and patient care on the other.

These approaches will continue to evolve. Only within the last few years have AMCs developed for-

malized and specific *institutional* conflict-of-interest policies to guide their faculty members and corporate leaders when the institution, or one of its officials, is a part owner or licensee of a discovery and related research on that discovery continues at the AMC.

■ **SHIFTING LANDSCAPE GIVES RISE TO A DIVERSITY OF VIEWPOINTS**

A confluence of competing interests

At a basic level, the challenge we face arises from a confluence of competing desires, needs, and duties:

- The desire of AMCs to bring forth new discoveries to benefit patients
- The need for AMCs to find new sources of income as their reimbursements dwindle and their research programs outpace the growth of federal funding
- The need for AMCs’ industry partners to make money for their shareholders
- The duty of government to protect patients and data from the effects of bias that would favor profit at the expense of best clinical practices or data integrity.

All of us need to reexamine what we do to accommodate the changing milieu brought about by these competing interests. This supplement serves as a good starting point by providing readers with a clear sense of the variability of stances on the above issues and a striking picture of the dramatically changing landscape.

A sampling of perspectives

Dr. Philip Pizzo, dean of Stanford’s School of Medicine, describes recent steps to ban industry marketing and industry gifts to physicians at all Stanford facilities (pages S10–S11). Dr. Edward Miller, dean of Johns Hopkins School of Medicine and CEO of Johns Hopkins Medicine, details ongoing efforts at his institution to formulate and implement an institutional conflict-of-interest policy (pages S70–S72).

The consequences of noncompliance with current standards are put into sobering perspective by Associate US Attorney James Sheehan (pages S63–S67).

The considerable efforts being made by industry to ensure ethical behavior in its partnerships with AMCs are touched on in numerous articles (see pages S12–S13, S26–S28, S38–S44, S45–S48).

Challenges to potentially overzealous limitations on these partnerships are offered by Dr. Thomas Stossel of Harvard Medical School, who views many such limitations as being based on shaky data and/or detrimental to medical progress (pages S14–S15).

The Association of American Medical Colleges (AAMC) has been one of the most influential forces driving AMCs toward more rigorous, transparent, and

uniform conflict-of-interest policies and procedures. Dr. Darrell Kirch, the new president of the AAMC, describes these past efforts as well as new AAMC initiatives to push institutions further (pages S23–S25).

This is but a sampling of the wealth of thought and information in this supplement; I remind readers that some of the supplement's most engaging reading is in the five interactive panel discussions.

In fact, the high degree of interchange of ideas was one of the clear successes of this "National Dialogue on Biomedical Conflicts of Interest and Innovation Management." Panel moderators made certain that the holders of disparate points of view had to face one another's ideas. Speakers and panelists were further probed by the conference's particularly interactive audience.

This audience of more than 300 was made up of representatives of the same diversity of communities as the speakers—biomedical research facilities, industry, government, the bioethics community, medical societies, the legal community, and the media. More than one third of attendees were front-line "practitioners" in these issues—faculty and administrators at AMCs who deal with biomedical conflicts of interest on a day-to-day basis. This latter group of attendees represented 40 of the nation's 125 medical schools and came from as far afield as Washington, Oregon, California, New Mexico, Texas, Louisiana, Alabama, and Florida, as well as from states closer by.

■ THANKS AND ACKNOWLEDGMENTS

Many from Cleveland Clinic generously provided resources, insights, and personal efforts to help make this ambitious conference a reality, including: Cleveland Clinic's Board of Trustees; Delos Cosgrove,

MD, CEO and President; Joseph Hahn, MD, Chief of Staff; Christopher Coburn, Executive Director, CCF Innovations; Robert Coulton, Executive Director, Staff Affairs; Ellen Rome, MD, Associate Chief of Staff; Michael Meehan, Esq., Senior Counsel; Eileen Sheil, Executive Director, Media and Public Relations; Marc Harrison, MD, Associate Chief of Staff; Cynthia Hundorfean, Executive Director, Clinical Affairs; and Susan O'Donnell, Corporate and Foundation Relations.

I am greatly indebted to three persons from outside Cleveland Clinic who made invaluable contributions: Blair Childs of Premier, Inc., for helping to conceptualize and organize the conference at every stage; Susan Ehringhaus, JD, from the Association of American Medical Colleges, for suggesting outstanding speakers; and Jamie Belkin of Jamie Belkin Events, for superbly planning, organizing, and running the conference from start to finish.

On behalf of all organizers and attendees, I gratefully acknowledge the support provided for the conference by Cleveland Clinic, the Ewing Marion Kauffman Foundation, the American College of Radiology, and the American Society of Colon and Rectal Surgeons. I am also grateful to Cleveland Clinic for supporting the production of this supplement. Finally, I would like to thank Glenn Campbell and Dr. Brian Mandell from the *Cleveland Clinic Journal of Medicine*, who were outstanding to work with in the preparation of this supplement.

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DELOS M. COSGROVE, MD

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The mandate of innovation management

It is important for major academic medical centers to play a leadership role in promoting constructive dialogue around innovation and its attendant conflicts of interest. Today's conference will explore how conflict of interest manifests itself and how it is managed within the health care arena. We appreciate the participation of experts from a variety of sectors, including government, the biomedical industry, academic medical centers, and the media.

■ THE INNOVATION IMPERATIVE

Conflict of interest arises most commonly around innovation and entrepreneurship. Although innovation has become synonymous with entrepreneurial activity, it is hardly a new concept. Abraham Lincoln captured its essence nearly 150 years ago when he looked out across a country on the verge of civil war and said:

The dogmas of the quiet past are inadequate to the stormy present. The occasion is piled high with difficulty and we must rise to the occasion. As our case is new, we must think anew and act anew.

For the past 25 years we have optimized our organizations for efficiency and quality. Over the next quarter of a century, we must optimize our entire society for innovation.

The Council on Competitiveness, in its 2005 call to action entitled "Innovate or Abdicate," argued that "America's challenge is to unleash its innovation capacity to drive productivity, standard of living, and leadership in global markets."

Similarly, Harvard Business School professor Michael Porter has recognized the "stormy present" of US health care and recently championed innovation at every opportunity, stating that "innovation is the only long-term opportunity for high-quality affordable health care."

Dr. Cosgrove reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

■ DRIVERS OF CONFLICT AND TOOLS TO MANAGE IT

The potential for conflict of interest is greatest at the crossroads of science, technology, and capital. These crossroads are characterized by several factors that have driven conflict-of-interest discussions into the boardrooms, operating rooms, news rooms, faculty clubs, and offices of some of our most prestigious public and private institutions.

One of these factors is an explosion in new knowledge. The total amount of new knowledge doubles every two and a half years. This expanding intellectual capital increases the potential for innovation, and this enhanced potential for development of new products and services in turn attracts increased corporate interest.

Health care's 16% share of the nation's gross domestic product and 25% share of all federal expenditures have likewise served to attract corporate interest.

The 1980 Bayh-Dole Act, passed to encourage universities to commercialize their intellectual capital, is also regarded as a conflict-of-interest accelerator. This legislation has contributed to breakthroughs in genomics, nanotechnology, and many other therapies, stimulating an increasingly entrepreneurial spirit within the academic medical community.

This entrepreneurial activity has prompted the formulation of increasingly sophisticated sets of rules governing conflict of interest. Increased scrutiny in this rapidly changing environment has led some to conclude that even the appearance of conflict of interest is detrimental and should be avoided at all costs, or that any economic incentive is corruptive of parties involved in innovation and entrepreneurial activities and may result in patient harm.

There is no question that the crossroads of innovation and commerce harbor forces that are complex, conflicting, competitive, and potentially corrupting. However, there are tools—simple, complementary, and constructive tools—that can be deployed to manage these forces. These include clearly documented and uniformly enforced standards for incentives, disclosures, transparency, and accountability, as well as standard operating procedures for the full, factual, and fair adjudication of noncompliance.

■ THE CHALLENGE: MANAGING INNOVATION

These are a few of the themes that will resonate throughout this conference. My hope is that this dialogue will accelerate the development of constructive policies that will continue to inspire, incentivize, and support the work of our most gifted physicians, scientists, entrepreneurs, business people, and government leaders while maintaining the highest standards of scientific integrity and patient care.

It is essential that we learn to manage innovation and its attendant forces—a challenge reflected in the

inclusion of “innovation management” in the title of this conference along with “conflicts of interest.” Managing innovation is an essential, fundamental, and comprehensive activity, and managing conflicts of interest is a necessary and important part of this larger innovation management process.

Innovation is imperative. We cannot become what we must become in patient care and scientific discovery if we fail to innovate.

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NINA TOTENBERG

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Prologue: A case study in biomedical conflicts

■ THE VERITAS CASE: FICTION THAT RINGS A BIT TOO TRUE?

The following is the transcript of
a fictitious radio news story.

This is Nina Totenberg for NPR News in Washington.

The death of a teenager at Rhode Island University Medical Center in Cranston last month is raising questions about conflicts of interest involving both the university and its faculty. The death is only the latest in a series of ethics problems that have plagued the prestigious medical center.

When the clinical trial for a new drug to treat cystic fibrosis began earlier this year, researchers had high hopes for its success. The drug had passed initial trial stages with flying colors, but something went terribly wrong, and within the first month of this first trial with cystic fibrosis patients, 13-year-old Brian Veritas was dead.

There was no doubt about the cause of death. According to hospital reports, it was complications from the drug. Moreover, young Brian's parents, Hazel and John Veritas, now contend that they were duped into allowing their son "to be a guinea pig" so that the university and its chief researcher, Dr. Howard Empathy, could become rich.

Dr. Empathy and university officials heatedly deny the charge, noting that the Veritas family was informed that the university and its principal investigator had a financial interest in the development of the drug.

The drug in question is patented under the name Fibergone. It has been in development for the last 5 years under a joint venture agreement between MiserTech Pharmaceuticals, Rhode Island University Medical Center, and Dr. Empathy, a renowned expert on cystic fibrosis. The joint venture followed basic research funded by the National Institutes of Health, which under long-standing policy will not fund commercial development of drugs.

Dr. Ron Honcho, dean of the medical school, said in an interview today that Dr. Empathy had followed the

university's policy in disclosing both his and the university's financial interests to Mr. and Mrs. Veritas at the time they agreed to have their son participate in the trial.

Mrs. Veritas acknowledged that she knew the university and Dr. Empathy were working with MiserTech and that the company had funded the research to the tune of \$17 million. But she said she had not understood that profits in the millions or even billions could accrue to both the university and Dr. Empathy if the drug were eventually approved for widespread use.

"I think they pushed the envelope so they could win the jackpot," said Douglas Torta, a lawyer retained by the Veritas family.

Dr. Empathy, reached at his vacation home in Hawaii last night, said his heart goes out to the Veritas family but that it was folly to suggest that any doctor would have anything to gain from risking a patient's life.

"It is the nature of the trial that things may not always go as one hopes," said Dr. Empathy. "This case is particularly tragic, but it proves that very point."

The death, he noted, sounds the death knell, for now, of a drug that he has worked on for years, and that the university and MiserTech have spent millions to develop. However, Dr. Empathy would not rule out a revised trial of the drug at a future date.

For years, critics of the medical school's conflict-of-interest rules have warned that mere disclosure is not enough to prevent research from being skewed by the profit motive.

In response to some of that criticism, the medical school last year adopted an internal policing policy under which an 11-member board of faculty members screens all arrangements with private industry for conflicts of interest. Unlike similar boards at some other medical schools, however, the board includes nobody outside the medical school, and critics note that eight of the board members have consulting arrangements with one or more of the nation's major drug companies.

The death of Brian Veritas comes at a time when the medical school and the hospital are under increasing scrutiny for other arrangements with private industry.

Earlier this year, an investigation conducted by NPR disclosed that all 53 of the fellowships at the medical center

Ms. Totenberg reported that she has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

are funded by MiserTech Pharmaceuticals, Orthonomics Device Company, or the SurgiTech Medical Device Company. The investigation also revealed that these three companies had reached agreements with the medical center to use their products on a preferred basis.

Rhode Island University Medical Center President John Uptight said that “the arrangements benefit both patients and industry by keeping prices down under negotiated price agreements while at the same time funding education for medical specialists.” In addition, he said that joint ventures with medical device and drug manufacturers provide needed funds to be plowed back into medical education while at the same time pioneering new devices and drugs to improve patient care.

Nina Totenberg, *NPR News, Washington.*

■ MANY QUESTIONS, THE SAME CENTRAL ISSUES

The preceding fictional piece (there is no such place as Rhode Island University Medical Center, by the way) is an example of what I call the “*Washington Post* rule,” namely, “Is your arrangement something you can live with when it is emblazoned across the front page of the *Washington Post* or *New York Times* and cast in a less-than-flattering light?”

Many questions will be discussed at this conference, apart from the ones raised in my fictional piece.

First, what are the repercussions of potential conflicts, not just for the academic institution but also for industry? On the more mundane front, do small gifts matter? Why does industry give gifts, be they free medication samples, free dinners, or free lunches? What, if any, educational gifts are appropriate for medical students, residents, or doctors, or for continuing medical education?

In a larger sense, though, every question boils down to the same core issues: How strict should ethics codes be? What kind of enforcement mechanisms should there be? Is mere disclosure enough? If not, how does an institution manage conflicts, since almost everyone in medicine has conflicts?

Indeed, in the world of academic medicine, every discipline is relatively small, with the best people most in demand to talk about and review the things they know best. These are the very people, of course, who have a conflict because they have done something important in their field.

Since almost no one in academic medicine is without conflicts, we should have plenty to discuss throughout today’s conference.

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Fostering innovation without compromising integrity

■ ABSTRACT

Industry's interaction with academia has created vast opportunity for innovation but also the potential for undue financial influence. Potential conflicts of interest can occur at the level of the individual researcher or the institution. Implementing guidelines and policies on conflicts of interest can help maintain appropriate separation between academic medicine and industry while permitting medical innovation to proceed. In an effort to retain public trust, Stanford University School of Medicine has enacted policies to identify and manage potential conflicts among its faculty, to divest of holdings in companies conducting studies involving Stanford investigators, and to ban all industry marketing and gifts from Stanford facilities.

The past 40 to 50 years have witnessed extraordinary improvements in our ability to diagnose, treat, and prevent a spectrum of diseases. This improvement has occurred, in part, because of parallel developments in academic medical centers and industry. Many of these developments have centered on innovation and discovery among and between these entities, which often is productive, but sometimes is not. I will share here some thoughts about how these processes are evolving and where we are today, as well as some relevant policies recently adopted by my institution, Stanford University.

■ THE CHANGING NATURE OF BIOMEDICAL FUNDING

Academic medical centers in the United States have tripartite missions in education, research, and patient care. These missions have grown over the past 30 to 40 years, largely for two reasons: (1) the funding that has emanated from the National Institutes of Health (NIH) and (2) the burgeoning of academic medical centers and clinical faculties in the wake of the Medi-

care program's creation in 1965.

At the same time, it is important to recognize the variations and undulations in these patterns of growth and the sources of its support. Witness the past 20 years, during which managed care has cut into the clinical profit margins of academic medical centers. These profit margins had been used to subsidize missions in education and research. Also consider that changes in NIH funding can alter the patterns of success within our academic enterprises, often turning the education and research missions into cost centers rather than profit centers. In the process, the support flowing into the clinical side of the equation has decreased. These developments have led many academic medical centers to look at alternatives to supplement their ability to carry out these missions.

Industry fills a vacuum

The pharmaceutical, biotechnology, and medical device industries have grown in parallel with the growth of academic medical centers, in some cases because of their underlying research and development aspects. Changes in these industries' interactions with academia have also occurred, some of which have been productive and positive and some of which have not. For instance, many of the interactions that broke down the traditional walls that separated academia from industry involved biotechnology and genetic engineering, which created vast opportunities. Significant degrees of intellectual property and patent royalties often resulted, leading to the process of technology transfer and establishment of offices for technology development at academic centers, thereby promoting innovation and discovery.

Unintended consequences

Over time, however, some of these interactions have become more challenged as some academic institutions, such as Harvard University, Washington University, and the University of California at Berkeley, have set up exclusive research arrangements with pharmaceutical or biotechnology companies. In

Dr. Pizzo reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

other cases, interactions with industry have led academic institutions to begin thinking of ways to direct their research to maximize the degree of intellectual property associated with it, which can in some ways abrogate the process of discovery and innovation.

■ A NEED FOR GUIDEPOSTS

The question that confronts us is this: How do we create an environment that fosters innovation and discovery yet maintains a degree of separateness that does not allow financial concerns to influence the success of our enterprise?

Conflict can be personal or institutional

In medicine, conflict of interest usually means that personal interest comes into conflict with an individual's role at a university or academic medical center. These conflicts can involve any of a number of aspects of personal interest, such as career development, academic development, or financial interests.

In addition to faculty or individual conflicts, there are also institutional conflicts of interest. For example, these may include situations in which an academic medical center has an equity holding in a product or device that is used in patients being treated at the center.

Understanding and managing both types of conflicts is important.

Apply guidelines to all, even if needed only by some

An idealist may argue that many physicians and academicians need no guidelines to manage conflicts because they are always going to do the right thing. For most of us, however, guideposts can serve as a boundary to help define what we cannot and perhaps should not do. Despite any regulation, there will always be a handful of individuals who will knowingly or unknowingly violate the rules and cause difficulty for themselves or their institutions.

■ WHAT STANFORD HAS DONE

At Stanford University School of Medicine, our policy with regard to conflicts starts with the recognition that we know they are going to occur. We want our faculty to be open with us, and we want to help them manage conflict so that they do not cause embarrassment or damage to themselves or to our institution. We also want the process of innovation and entrepreneurial activity to proceed successfully.

Faculty disclosure policy

We ask our faculty to do both an annual disclosure and a transactional disclosure for any activity that they have with industry. We insist upon disclosure of any financial component associated with the activity, of

any dollar amount. If a faculty member receives more than \$10,000 annually, more than 0.5% of equity in a publicly traded company, or any equity in a privately held company, a conflict-of-interest review is always triggered. We have a committee on hand that will help faculty to manage those conflicts to limit the potential for difficulty, either personally or to the institution.

Institutional divestiture policy

We also want to be clear with regard to our institutional responsibilities. We have decided that our institution will divest any equity that it holds in a company that is conducting a clinical trial in which Stanford is a participating center.

These simple formulations have helped us to accomplish our major goal, which is to manage these interactions with at least a reasonable degree of success, consistent with our overarching plan of allowing discoveries to move forward.

Ban on industry marketing and gifts

In addition, we have taken a firm stand against marketing and advertising by drug and device companies at Stanford facilities. Industry's practice of providing gifts and free meals at educational activities over the past few decades has created an uncomfortably close intermingling between industry and academia. This form of advertising has become almost a tradition at many academic medical centers, which I believe represents a violation that erodes public trust. As a result, we have instituted a policy effective October 1, 2006, that bans all of these interactions from taking place at Stanford and its medical centers and hospitals. The ban prohibits detailing by drug representatives, distribution of drug samples, provision of meals or refreshments, distribution of pens and other small gifts, the presence of industry booths and industry literature at educational talks, and all similar advertising and marketing activities.

Ultimate objectives

Stanford's goal moving forward is to accomplish two things simultaneously. The first is to foster an environment that promotes innovation and discovery by creating appropriate degrees of connectedness between academia and industry. The second is to end the marketing by industry that contaminates how faculty think about their relationships with industry, in order to ensure public confidence in Stanford as an academic medical center focused on innovation and discovery for the public interest.

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Innovation and industry-academia interactions: Where conflicts arise and measures to avoid them

■ ABSTRACT

Every phase of the development of biopharmaceuticals and medical devices has the potential for conflict of interest, but adherence to established rules and practices throughout product development can eliminate the possibility of conflicts. Adherence to good practices should continue through the postmarketing period, with swift reporting and vigorous investigation of any safety concerns. Although some academic medical centers are restricting interactions between their faculty and industry to prevent possible conflicts in physician education about new products, industry and academia should look for new ways to come together in mutually agreed forums that focus on educating clinicians about new products in an efficient, transparent way.

I have worked in academia and the pharmaceutical industry for more than 40 years. The potential for conflicts of interest between the two groups has always existed, but heightened recent concern has brought us to this meeting today.

Interactions between universities and the biopharmaceutical and medical device industries are important for two reasons:

- They are necessary to the discovery and development of new drugs, vaccines, and medical devices
- They are critical for providing scientific and educational information about new products to physicians for use in patient care.

I will review briefly the industry-academia interactions at each stage of the product development process in a key area of biomedical innovation—pharmaceutical development—with a focus on where conflicts can arise and how they can be averted.

■ DRUG DISCOVERY

Drug discovery generally takes place in industry but is

dependent on knowledge generated at universities. Certain basic research discoveries from universities are patented, as are all drug candidates discovered at universities. University patents can be licensed to an existing company or may be used to start a small company.

A number of financial interactions between industry and academia can occur at this stage, each of which benefits both sides and helps to build the biomedical enterprise in the United States. These financial interactions may include grants or contracts awarded to faculty who work on specific projects of interest to a given company, fees to faculty who are expert in a specific scientific area to consult with company scientists, or industry support of the training of graduate students involved in a specific project. Potential areas for conflict of interest exist since valuable confidential information is generated, but all universities and academic medical centers have rules in place for handling such information.

■ CLINICAL TESTING

Once a product candidate is identified by industry, it enters the development process. At this stage as well there is a need for university faculty—in this case clinical specialists at academic medical centers—to be involved in formulating a plan to take the drug candidate through all three phases of clinical trials. Faculty consult with industry physicians to design the clinical trials, act as lead investigators in clinical investigations, participate in data reviews, and help formulate a strategy for US Food and Drug Administration (FDA) review of the data.

These interactions—university experts acting as consultants to industry—are crucial to the innovation process. These faculty services are valuable to industry, and faculty are paid commensurate consulting fees for these services. At the same time, any inside information that is available to consultants must not be used in the trading of company stock.

The safety and welfare of human subjects can never be compromised by financial interests. Unless there are compelling circumstances to argue other-

Dr. Vagelos reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

wise, a financially interested person may not conduct research on human subjects.

■ MARKETING OF NEW PRODUCTS

Once a product is approved by the FDA, it is ready for introduction to physicians. This involves the transfer of important information about the drug to prescribing physicians and to members of the formulary committees that control the purchase of drugs.

Getting this information to doctors requires publication of the clinical studies, presentations at organized medical and scientific meetings, and advertisements in journals, and it is heavily dependent on company sales representatives. These sales reps are highly trained to teach doctors and formulary committee members about the positive and negative aspects of a drug. They must discuss only the indications that have been approved by the FDA and they are trained to deliver a balanced discussion, covering the positive and negative features of a drug so that it is used safely and effectively. The trick is to get enough time in the schedule of a busy physician to deliver this information well. Since physicians have limited time and many sales reps are competing for this time, physicians must prioritize such visits.

An exciting new drug gives an advantage to a sales rep in gaining access to physicians, but such drugs are not available on a regular basis. To gain physicians' attention, the pharmaceutical industry has offered inducements such as free meals, modest gifts (< \$100 in value), free drug samples, and financial support of educational activities, such as continuing medical education and medical conferences.

New policies to limit conflict in education— and an alternate model

Yale University, the University of Pennsylvania, and Stanford University have recently prohibited certain interactions between their medical school faculty and industry to prevent possible conflicts of interest surrounding physician education about biomedical products. (See previous article by Stanford's Philip A. Pizzo.)

An alternate approach would bring together the two sides to develop more efficient ways for industry to educate physicians and formulary committees about products, such as scheduled on-site meetings during which company products could be discussed. In return for such access to groups of physicians, a company could support continuing medical education, offer travel grants for stu-

dents, house staff, and faculty, or support academic conferences. Transparency would be crucial to such a model.

■ POSTMARKETING SURVEILLANCE AND DRUG SAFETY

When given at high enough doses, all drugs have side effects, some of them serious.

During the large clinical trials required for FDA approval, patients who do not have certain comorbidities that might confound study interpretation are selected for inclusion. The number of patients in the trials and the study durations are limited based on prior agreement with the FDA. Adverse events that are identified during these trials are included in the drug's package insert that is approved by the FDA.

Of course, after the drug has been on the market with broader patient exposure, new side effects, some potentially serious, may surface. These are required to be reported to the company that markets the drug and to the FDA.

Recent years have revealed several cases of serious drug side effects that did not surface until this postmarketing surveillance period. Among the most prominent cases:

- The fenfluramine/phentermine combination, used for the treatment of obesity, was found to cause heart problems
- Certain antidepressants were found to increase thoughts of suicide in some children
- Cyclo-oxygenase-2 inhibitors were found to increase cardiovascular risks.

When an early signal of a possible adverse event is reported, the right thing to do is to determine as soon as possible if the event is caused by the drug and, if so, report the event to the FDA and carry out a vigorous investigation to characterize the side effect. If it is not serious enough to cause withdrawal of the drug from the market, then manufacturers should work with the FDA to explain the adverse reaction in the package insert and carry out a broad communication to all prescribers and patients so that the drug can be used properly with a full understanding of the risks.

As the cases above illustrate, early action is imperative. The most important charge that a manufacturer of biomedical products has is to represent the benefits and risks of its products accurately. Any mistake can destroy a company in addition to destroying patient lives.

We need more efficient ways for industry to educate physicians, such as scheduled on-site meetings; in return, companies could support CME, travel grants, or conferences.

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Overregulation of conflicts hinders medical progress

■ ABSTRACT

The revolution in medicine and technology over the past few decades is largely the result of partnerships—or a “harmony of interests”—between private companies and entrepreneurial scientists and clinicians. Regulations to prevent conflicts of interest by restricting medical education, medical research, expert advisory functions, or researcher ownership of inventions may have the unintended consequence of slowing medical progress.

This conference was convened because of a prevalent perception that we are not doing the right thing when it comes to interactions between clinicians and researchers and the companies that develop biomedical products. The code words for this perceived wrongdoing are “financial conflicts of interest.” Only the imagination limits the extent to which financial conflicts allegedly compromise medical practice, medical education, and medical research, and this compromise is illustrated in the imagery of corruption and greed that accompanies the accusations.

■ DISCLOSURE RUN AMOK

This apocalyptic message has led to action. One action, euphemized as disclosure or transparency, has become an invasion of privacy. In the past, we named sponsors of our research and education efforts as a way to honor them. Now, we must itemize them so that others can discount our words and our work. Attempts to process this burden of information have given rise to bureaucracies charged with censorship. For example, the Accreditation Council for Continuing Medical Education (ACCME), which accredits CME providers for permission to confer CME credits on attendees (and charge them for it), imposes elaborate disclosure

Dr. Stossel reported that he has ownership interests in ZymeQuest, Inc., and in Critical Biologics Corp.; has intellectual property rights in Critical Biologics Corp.; has received consulting/advisory fees from Merck, Inc.; has received honoraria from Pfizer, Inc.; and has received royalties from Lippincott Williams & Wilkins.

demands on speakers, replete with “attestations” of independence from commercial influence. To maintain this accreditation, CME providers assign censors to sanitize presentations, in advance, of commercial content. We now live in an informant culture in which conflict-of-interest vigilantes, either activists or persons with grievances against us, scan for opportunities to embarrass us.

Nothing better illustrates the fact that what we disclose demeans us than the vigorous call to remove the best and brightest with commercial interests from useful advisory roles. Worse, the idea that commercial relationships drive us from objectivity to the moral low ground provides the media with license to abuse us.

■ ‘RED-LIGHT REGULATION’ STIFLES INNOVATION

The second major action is prophylactic law, or what I call “red-light regulation.” My university, for example, severely restricts researchers’ ownership of their inventions, and these rules have prevented companies from licensing Harvard Medical School technologies. Similarly, the National Institutes of Health forbids all corporate consulting by intramural investigators, and the result is that companies suffer from a shortage of expert advice. Red-light regulations are akin to preventing speeding by forbidding ownership of fast cars.

Some research institutions restrain themselves to “yellow-light regulations” by overseeing corporate interactions on a discretionary basis, as we heard about at Stanford University, but activists criticize them for their leniency.

■ MEDICAL ADVANCES SPEAK TO A HARMONY OF INTERESTS

None of these supposed solutions is solving problems.

Among my supervisors during my medical residency nearly 40 years ago were Mike Brown and Joe Goldstein, future Nobel laureates and contributors to the spectacular decline we have seen in mortality from heart disease. Moreover, many of my colleagues from residency are today in prominent positions in American medicine. Despite this intellectual fire-

power, we practiced terrible medicine by today's standards. Heart attack victims languished on our wards for a month; imagine what that would cost today.

While far from perfect, today's medicine is nearly miraculous when compared with medicine from even the recent past. Today's much more effective, innovative, and safe medicine resulted entirely from technologies developed by private companies abetted by entrepreneurial physicians and scientists, a partnership spectacularly epitomized by the biotechnology revolution. Having had the privilege to participate in that revolution, I see a harmony, not a conflict, of interests.

■ ATTITUDES ABOUT CONFLICT ARE UNFOUNDED

In a recent article in the *New England Journal of Medicine*,¹ I laid out how facts do not justify the attitudes or rules concerning conflicts. The accusations that such conflicts have compromised research are untrue and violate the very standards of scientific rigor they purport to protect. The allegations of harm arise from conjecture and very few anecdotes, certainly when compared with the full extent of academia-industry interaction. They provide no evidence that more adverse outcomes arise in the presence, as opposed to the absence, of commercial influence, or that institutions with more lenient (yellow-light) regulations have more research or education misconduct than those with stricter (red-light) rules.

■ WHERE DO THESE ATTITUDES COME FROM?

Why do we see such a glaring discrepancy between objective analysis and the prevailing mindset? One reason is that the immediacy of scandals and the inevitability of temporary failure overshadow the high risks, drudgery, and boredom underlying technological advances, which emerge inexorably but far too slowly to suit the attention span of the media and the public.

Another reason is that the scandals and mistakes that entrance the media and endanger academic administrators encourage protective overregulation.

I believe the most important reason, however, is ideological. As we have heard, authorities can see that we need interactions between companies, academic researchers, and clinicians, but they harbor a conceit that the scientific and promotional elements of private enterprise are separable. They demand that we wall ourselves off from the "commercial aspects" of companies. Curiously, they ignore the principal source of money exchange in medicine—clinical practice—even though promotion of clinical services is routine. For instance, is Cleveland Clinic's rating as one of the top three hospitals in America by *U.S. News & World Report* evidence-based?

A recent article in the *Journal of the American Medical Association* epitomizes this ideology,² and I will mention four notable points about it:

- Citation of relevant literature is generally considered good research practice, but although this paper appeared 4 months after my article in the *New England Journal of Medicine*,¹ it did not refer to it or address any of my arguments.
- It illustrates the definition creep that morphs conflict of interest from a conflict to any situation that certain persons do not approve of.
- It calls for the collectivization of corporate-sponsored research, a recommendation that, together with factual errors in the paper, undermines its credibility.
- Nevertheless, its call to separate science and business by banning pharmaceutical gifts and sales personnel from the academic medical center is being put into practice. Nowhere is the contempt for the market more apparent than the expressed disdain toward company sales forces, and I am disappointed that leading academic centers such as Stanford have accommodated such discriminatory recommendations.

■ FOCUS ON ACTIONS, NOT MOTIVES

Trust comes from a track record, not from who pays you or how much. The growing interaction between doctors and companies is an evolutionary adaptation to opportunity for all, not a diabolical commercial conspiracy. Let's celebrate the commercialism that has so improved medicine and shift our energies from bashing it to making it work better.

As for specific rules, academic institutions already require disclosures of faculty members' outside activities, which should be sufficient. Problems should be addressed when they arise, which is how we handle problems in most aspects of life. Give practitioners a little more credit for their ability to process information. For quality control, we should focus on what people say and do, not on their motives. In research, we operate with a narrow definition of misconduct, and we tolerate a lot of behavior that some people do not like because we progress best with freedom. That's a good model for medicine in general.

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Panel discussion

Research, innovation, and safety: Doing the right thing

■ WHY BOTHER MANAGING CONFLICTS?

Ms. Totenberg: Dr. Pizzo, are the arguments from Dr. Stossel's presentation not realistic for Stanford University or other institutions? He states that there is no evidence of malfeasance and, although I could point out a couple of examples, certainly I would agree that doctors aren't on the take all over the country. They are not skewing their research deliberately to kill patients, so why bother managing conflicts?

Dr. Pizzo: The debate in some ways focuses on how information is presented and how it impacts the way we think about it. First, at Stanford, we are very focused on trying to engage in the appropriate interactions with industry. Long before I was part of the Stanford community, it built its reputation on a highly entrepreneurial, proactive environment that has indeed helped to stimulate biotechnology development in Silicon Valley and beyond. We want this process to continue, so I think there is a very important distinction to be made between interactions guided by scientific collegiality and appropriate discourse, which promote the kind of discovery to which Dr. Stossel and I referred, and the marketing strategies that are also employed.

We recognize that the pharmaceutical industry today invests more than \$20 billion annually in marketing its products, much of it directed at physicians. This is not an accident: to the extent that physicians become marketing vehicles, pharmaceutical sales increase. While marketing may be appropriate in some cases, I don't think it's the right model for our students or for our clinical and related faculty to engage in. It's not what we are about. We want to educate our stu-

dents about the world they will be entering, which balances the traditions of academia with the important realm of commercial activities. But we do not want our students and faculty to form their opinions about medications or medical devices based on marketing. Their decisions should be objective and evidence-based.

■ THE INFLUENCE OF GIFTS: DOES SIZE MATTER?

Ms. Totenberg: Do gifts from industry matter, even if they are small?

Dr. Pizzo: To think that there is no suasion as a result of small gifts is somewhat naïve. For instance, I recently read in Doris Kearns Goodwin's biography of President Lyndon Johnson that he had a practice of giving small gifts to people all the time. In fact, he often gave toothbrushes because he wanted the recipients of his gifts to think about him morning and night when they brushed their teeth. That's part of the strategy. Similarly, if you believe that small gifts don't influence prescribing behavior in some subtle way, then you are running against the tide of reality. There's no reason why we cannot or should not be able to have strong interactions with industry and at the same time recognize that we don't need to be engaged in the commercialization.

Ms. Totenberg: Dr. Vagelos, let me ask you the question from another point of view. What do drug companies want when they give those gifts?

Dr. Vagelos: Companies have measured the impact of gifts or they wouldn't spend the money on them. The question is what to do going forward. I personally looked at this issue very hard when I was CEO of Merck—not gifts specifically, but the question of what is optimal for interactions between sales representatives and physicians. Companies want to transfer information about their drugs; that's the good side because they want physicians to understand the bene-

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fits and the risks. They are trying to get their sales reps time with physicians, so they have developed these gifts and other things that I am personally opposed to.

What is optimal? The two groups, academia and industry, should sit down and figure out the most effective way to transfer accurate information. I think that both groups would benefit from that type of meeting. The answer is not to unilaterally decide to prohibit interactions.

Ms. Totenberg: Dr. Stossel, the world of medicine has changed dramatically in the past 10 or 20 years, with academic medical centers' relationships with drug companies becoming institutionalized as a result of the 1980 Bayh-Dole Act. The news media are also entirely different now—they are not nearly as centralized, at least in broadcasting. And we live in a much more disclosure-oriented society. The somewhat sensational piece that I read at the start of this session was benign compared with what I could have written. It could have been much more destructive to Dr. Empathy and Rhode Island University Medical Center. The world of Jonas Salk does not exist anymore, and it seems as if you want to go back to a time that doesn't exist.

Dr. Stossel: I absolutely agree that it's different. I'm not proposing a free-for-all; I'm saying that we need to understand the world we live in. Rather than making medical students take organic chemistry, they should take a course in democratic capitalism. Friedrich Hayek's wonderful book, *The Fatal Conceit*, describes how the market arose, and gifts were front and center. Do I really need to learn from the *Journal of the American Medical Association* that advertising works? Anybody who hasn't been in a coma knows that drug reps come with a gift because they are trying to sell you something.

I would argue that academia is currently not in the real world. Medical students now think that all this technology comes from Santa Claus. What are they going to think when we permit less interaction with industry during their training and then, once they get out in the community, often the only way they will get information about new products is from drug reps? I think we're setting students up to be out of touch.

I'm not saying we shouldn't have oversight; let's just stop the sanctimony. Many of the people who agree with me have been so terrorized by authorities in the media that they don't want to speak out.

Ms. Totenberg: Members of Congress believe they

shouldn't have to disclose the names of their campaign contributors and that their votes aren't biased by lobbyist contributions, but their disclosure requirements aren't going to change.

Dr. Stossel: Doctors aren't government.

Ms. Totenberg: That's absolutely true, but we're talking about public perception.

Dr. Stossel: In government, politics and perception rule. In medicine and science, there is also plenty of politics, but if we allow perception to rule in this realm, the world becomes flat and medicine and science revert to a primitive state.

■ EDUCATION ABOUT NEW THERAPIES: IS THERE A BETTER WAY?

Dr. Pizzo: When it comes to educating physicians about new therapies and their side effects, I don't want to bifurcate information into that which comes from dispassionate sources versus that which might come from industry. Even under Stanford's new policy, we're not breaking off dialogue with industry. We're simply saying that it ought to be better governed by appointment, just as Dr. Vagelos has articulated. We have an entire program that educates students about how to receive and process information, both in medical school and once they go into practice, so that they'll understand how messages are being delivered and conveyed.

Given today's information technology, there is no reason why information about new drugs, side effects, or drugs in general needs to come from marketing reps. We live in a world where we can access information instantaneously in so many other venues and receive objective and insightful data. We ought to be using these venues rather than relying on marketing reps.

There was a story in the *New York Times* recently about how the marketing arms of pharmaceutical companies often hire individuals who are vibrant and exuberant—the cheerleader stereotype—as their sales reps.¹ They do so because it provides an entrée, a source of engagement. There's no doubt that it works, but I think drug companies can inform physicians about their products in ways that are much more objective and reasoned.

Dr. Vagelos: A better way to transfer information was something that I sought at Merck 15 to 20 years ago, at a time when I was, frankly, trying to eliminate the sales force. I set up experiments on information transfer minus

Academia is not operating in the real world. Medical students today think all this technology comes from Santa Claus.

—Dr. Stossel

the sales force in one region, comparing the sales generated there with sales in another region. We tried to introduce new technology. We tried to force innovation in information transfer by saying that we were going to cut back the sales force by 15% or 20% per year. As you can imagine, that really traumatized the sales force, and I got no positive results from my experiments because they all were carried out through the sales force.

The only place where a concept like this could work is at a small company that comes up with an important new product. The small company would have no sales force and would announce that information about its product would be available only in regional meetings to be held around the country or around the world. This would revolutionize marketing and sales in the pharmaceutical industry, but it would require an important product that physicians want to learn about and a company that does not have an existing sales force.

Ms. Totenberg: Has there been a moment like that in the past?

Dr. Vagelos: Perhaps with the introduction of the statins in the 1980s, which were developed at the Merck research organization under my leadership. Drugs like the statins could have been introduced essentially without a marketing group, although maybe not at a big company like Merck. Launching a drug class that exciting, with that big of an impact on health care, could be possible without a sales force today because of the information technology we now have.

Ms. Totenberg: Realistically, however, that doesn't happen. At one time, you couldn't turn on the television without seeing a Vioxx ad, not to mention whatever was spent on detail reps for the drug. The marketing budget for Vioxx was humongous. This is the world as we know it.

Dr. Stossel: In a perfect world, there might be some repository of perfect information that you could access online. It just doesn't exist in this world. As a physician actively engaged in research, I like to think I'm looking for objective information that is reproducible, but I know that in research there is as much promotion as there is in industry. The idea that there is some objective source of information—a direct connection to God—is a conceit. So we have to accept that we're going to have to navigate through competing sources of information. When given a choice of who decides which information sources are available—either the

market or wise authorities such as deans and department chairs—I'll take the market any day.

Dr. Pizzo: Some might say that the policies I've described are top-down positions, but those of us who work in academic medical centers know that there really is no top-down process because there are so many faculty with strong points of view. At Stanford, it took us a year of discourse to move to the policies that we're putting in place, and there is now uniform acceptance across our faculty that this is the right thing to do.

Ms. Totenberg: But there wouldn't be if you barred consultancy arrangements.

Dr. Pizzo: That's right, and so we're not barring consultancy arrangements.

■ **BIG-TICKET INTERACTIONS:
RESIDENCY FUNDING, TECHNOLOGY TRANSFER**

Ms. Totenberg: Let's open up the discussion to the audience.

Comment from the audience: I was involved in developing the first conflict-of-interest statement for the American Academy of Dermatology as well as in efforts to prevent industry from funding dermatology residencies. My question is to Dr. Pizzo, because the department of dermatology at his university has a single residency now being funded totally by a drug

company. Sixty-five percent of American Academy of Dermatology members think there is an insurmountable conflict of interest in such an arrangement, and I'd appreciate your comments.

Dr. Pizzo: This sponsorship of the residency by a pharmaceutical company started several years ago, at which time our faculty review group evaluated the idea to assess whether or not it was appropriate. The group felt it was a reasonable program to institute, so it went forth. We will continue to look at it, of course.* This case involved finding the right balance in the way we work with industry so as to promote the exchange of knowledge as well as Stanford's mission to bring forward discoveries that can be commercialized, which is a mission shared by other major academic medical centers. We will not succeed in our mission of translating discoveries if we try to do it in isolation.

Launching a drug class as significant as the statins could be possible today without a sales force, given the info technology we now have.

—Dr. Vagelos

* Editor's note: Dr. Pizzo has informed us that since the time of this conference, and in light of Stanford's new policies, Stanford has decided to discontinue this industry-sponsored residency.

We want to allow our residents and fellows to have appropriate kinds of interactions with industry so that they'll understand what's going on in the biotech and big pharma communities, which I think is an appropriate understanding to have. What I'm against is overcommercialization.

Ms. Totenberg: So the residency review committee at Stanford approved a residency that's fully funded by a company?

Dr. Pizzo: Yes. It is the only residency funded that way at Stanford.

Ms. Totenberg: Why that one, and why hasn't it been replicated? Usually something like that gets replicated.

Dr. Pizzo: This residency came about the way many things come about at Stanford, because a faculty member, in this case a department chair, made a proposal, and we looked at it objectively. I had my own personal concerns about it, but I asked others to review it as well. As to why it hasn't been replicated, I don't know—it just hasn't.

Ms. Totenberg: Regarding your point about commercializing discoveries, Stanford benefits financially when one of its scientists makes a discovery, does it not? Even though Stanford hands off the marketing, the university's legal department, which now has an intellectual property section, has patented their interest and the university stands to benefit, sometimes enormously.

Dr. Pizzo: That is correct, and this is an important issue. Stanford, the Massachusetts Institute of Technology, Columbia University, and a handful of other universities now have proactive offices of technology transfer and licensure and development, and it is now part of the culture that guides universities. We recognize that. There are two points I'd like to make. One is that the number of patents that have huge yields is very low. They're the ones that get all the attention, but there are hundreds if not thousands that fail or basically go nowhere. The second point is that we do technology transfer in a free and open way. There are some schools now that are aligning their academic promotions to faculty members' track record in getting patents. I think that is a misuse of scholarship because it skews things in a way that misses the opportunity for fundamental discovery.

■ THE PERSONAL VERSUS THE INSTITUTIONAL

Comment from audience: What I'm hearing today is

that we think promotion and marketing are unnecessary and hence we want to restrict them, but we think innovation is necessary and we want to foster it. So we allow institutions to have relationships that fund big-ticket items like residencies, fellowships, and research, but we are going to restrict pens and pizza. I see an inconsistency there. They are either both acceptable or both evil.

Dr. Vagelos: That's a very good point. My response is that one is personal and the other can be done through an institution. I would recommend that companies go to institutions and give money to the dean's office, for instance, to fund fellowships or scholarships. The dean's office and the faculty would then decide where to put that money. That makes the funding impersonal and does not suggest undue influence on prescription writing, whereas the pizza that is delivered by a sales rep does.

Dr. Pizzo: That is precisely the way the Stanford guidelines are set up. We leave open the opportunity for educational support to come from industry so long as it goes through a central source.

Dr. Vagelos: But there has to be a payback. No company is going to put money into a medical center and get nothing out of it. You'll have to provide an alternative, such as the scheduled meetings that I suggested.

Ms. Totenberg: Will people go to those meetings? I mean, detail reps show up at the office and sometimes doctors just see them to get rid of them. If there were that kind of informational meeting, and presumably it would be huge because there are tons of products, how would doctors know which booth to go to? It seems like a great idea, but how would it work?

Dr. Vagelos: That is why I suggest that industry get together with the academic medical centers and figure out how to make it work. The faculty, after all, want to be kept up to date. They want to learn about new methods of treatment, so if there are good, credible speakers on a regular basis, and if companies are scheduled to be present at certain times, I think it could be done. It just has to be worked out and the culture has to change.

■ CODEPENDENT NO MORE?

Ms. Totenberg: Dr. Pizzo, it's one thing for Stanford, Yale, or the University of Pennsylvania to ban gifts, as they all have fairly large endowments. But what about

The idea that there is some objective source of information—a direct connection with God—is a conceit.

—Dr. Stossel

other institutions that don't have huge endowments and rely on money from drug and device companies to fund fellowships? How can you get residents to go to informational lunches if you don't provide the lunches? Lunches cost money, and fellowships cost a lot more money.

Dr. Pizzo: One of the fundamental premises is that Stanford is well off because it is well endowed, but it costs us a lot to run these programs and it will cost us a lot not to have these additional funding sources. In fact, the cost is in the hundreds of thousands of dollars up to over a million dollars per year, so we too recognize the limitation.

Over the past year, as we were working out the details of our new policies, what I heard most often from faculty was, "This is the right thing to do and we really support it," coupled with a statement like, "But I don't know how I'm going to run my seminar series." This speaks to the fundamental problem: a codependency has developed. And that, I think, is the fundamental issue we are addressing.

■ **DRUG SAMPLES: BAD? GOOD? DEMEANING?**

Question from audience: I'd like the panel to talk about free drug samples. Should they be banned?

Dr. Pizzo: At Stanford, we have our free drug samples sent to our pharmacy and then distributed for use at the free clinics that we run. I think it's clear that drug companies use free samples as a strategy for marketing the most expensive drugs by getting physicians and patients hooked on them as opposed to generics. I'll be much happier when pharma is handing out free samples of generics.

Ms. Totenberg: Dream on.

Dr. Stossel: As there are more generics, it will happen. In the real world, doctors like samples. A lot of physicians and their office staff can only afford to take short lunches—20 or 30 minutes—so when the drug rep comes in with samples, the staff gets a quick and convenient lunch. This has a lot of appeal to harried docs who feel they couldn't run their offices without it.

Dr. Vagelos: I think that samples are demeaning to the sales reps. A better model would be to deliver samples to the central office of an academic center so that they get to poor people, which is something industry wants, of course. The idea of needing samples in order to get to see physicians suggests that physicians are not

anxious to simply get the good information that's available from reps. So both sides have been complicit in the way this has developed. We need to come up with a new paradigm.

■ **DOLLARS AND THE DRUG DEVELOPMENT PROCESS**

Question from audience: In its new recommendations on clinical and translational research, the Association of American Medical Colleges is going to recommend that medical schools and residencies incorporate research as a core competency. The idea is that our physicians, not to mention the general public, may not be entirely literate in the scientific process and may not be able to determine whether a claim is, in fact, a breakthrough. This was pointed out in a recent *New England Journal Medicine* article by Alastair Wood, who argued that breakthrough drugs are rare and that both the drug approval process and market incentives favor the development of "me-too" drugs.² In this context, we have all these claims of breakthroughs and the marketing that goes along with them. I would like Dr. Stossel to clarify whether he's arguing that there is no problem or that our solution to it is laughable.

Dr. Stossel: The latter. Life isn't perfect. There are saints and there are serial killers among us, with most of us in between. And anybody who hasn't been in a coma now realizes that there is concern about conflict of interest. Consciousness has been raised. Let's just keep things in balance and not slap on a lot of discriminatory and confining regulations that aren't helping.

Dr. Pizzo: There are some people who always do the right thing, regardless of the rules, but most of us need a sense of the rules of the road. We're just trying to provide guidance on appropriate behavior.

Question from audience: Dr. Vagelos described a series of events during drug development, with each stage of development posing potential conflicts of interest. We know that clinical drug development is an inefficient process—many compounds enter the process but few finally succeed, so that development is like a pyramid with a wide base of potential drugs and a few successes at the top. Separately, someone else mentioned the figure of \$20 billion spent on marketing. Is more money spent at the end of the development process, on marketing the drugs that are approved, than on grants to universities to support early-phase research?

Technology transfer and licensure is now part of the culture that guides universities.

—Dr. Pizzo

Dr. Vagelos: About equal amounts of money go into research and development versus marketing and sales. A relatively small amount goes into grants and contracts because the great majority of funding for basic research is within the industry, whereas the bulk of funding for clinical research goes to academia.

Question from audience: How does the money devoted to clinical trials compare with the money for postapproval marketing?

Dr. Vagelos: I don't know exactly, but certainly clinical trials are the biggest expense component of research and development. Of course, marketing and sales is another world unto itself, one that is also very big, and that's what has to be changed, frankly.

Dr. Stossel: An undercurrent that I'd like to address is the common perception that pharma doesn't innovate, that it produces only me-too drugs and from then on it's all marketing. Breakthrough drugs come along at unpredictable times. If you don't have the money from marketing the me-too drugs, you aren't going to develop those innovative drugs. If, as a public relations stunt, we tell pharma to stop marketing, the pharma companies will start downsizing and go into the dog food business, and we will end up with fewer drugs.

Dr. Vagelos: I will remind you that at Merck, between 1975 and the end of 1994, we introduced the first important drug for glaucoma, timolol (Timoptic); the first important drug for Parkinson disease, carbidopa-levodopa (Sinemet); the statins; the first drug for osteoporosis, alendronate (Fosamax); and the first recombinant vaccine in the world for hepatitis B. It goes on and on. It's a matter of having the research organization. Do you have the proper culture? It can be done without me-too drugs.

Dr. Pizzo: There have been challenges since that time. It's important to note that today it costs anywhere from \$800 million to \$1.2 billion to develop a drug. It's a huge investment, and many drugs do fail. If one critically looks at the pipeline of new agents, it's not as robust as one would like. The real action is not happening as much as one would like at big pharma; it's happening much more in the biotech arena, where more risks are being taken. Because industry has become so big and has such a great need to support itself, of course it's going to have to market its products aggressively, and of course there are going to be a lot of me-too agents.

It's a risk-averse environment as a result of these huge financial concerns.

■ COULD BETTER PEER REVIEW MAKE DISCLOSURE MOOT?

Question from audience: I wonder whether the excessive disclosure that Dr. Stossel referred to earlier is a reflection, in part, of the failure of the peer-review system. If we had a better ability to assess data and better access to the data that have been controlled by the pharmaceutical companies that sponsor some of the research, would it be less incumbent on researchers to make disclosures? Clinical trial data are closely guarded by companies; almost all clinical trial agreements have required surrender of data ownership to the pharmaceutical companies. That's one aspect of the issue. The other is that people assume that the peer-review system does, in fact, assess data to the point where the data can be deemed credible or not. Ultimately, isn't the purpose of conflict-of-interest management to assess and assure that the data coming out are, in fact, legitimate and not skewed because of someone's personal interest?

Dr. Stossel: Peer review is fine as far as it goes, although the people who worship it are the ones who live off of it. Its greatest value is that when you prepare to publish, you know that those nasty competitors are going to give you a hard time, and so you try to get your act together and do as well as you can.

As for disclosure, it has become a public relations tactic. I don't understand the policy of the *Journal of American Medical Association*, which says that *relevant* conflicts must be disclosed. But then it goes on to say that basically anything that in the future might make you money must be disclosed. Then there are the people who call out that you didn't disclose the slice of pizza you took from the drug rep.

Dr. Pizzo: Part of the challenge is whether disclosure always reflects reality, and this cuts back to the point made earlier, which is that we're dependent upon people telling the truth. People perceive the truth in different ways, which is a limitation of our system. At the end of the day, we rely on honesty and self-reporting to determine whether or not we're getting the information. Some have argued, even at our institution, that we ought to be looking at outside sources, including income tax returns. I'm against moving in that direction.

The disclosure system is limited by the reality that people perceive the truth in different ways.

—Dr. Pizzo

■ HOW TO HANDLE SPECIAL ON-SITE TRAINING NEEDS?

Comment from audience: One thing we haven't talked about today is that some forms of medical innovation, particularly novel devices, require that doctors receive special training to learn how to use them safely. For novel devices like this, the FDA requires that the manufacturer conduct physician training as a condition of market approval. This inevitably requires a nexus of interaction between the manufacturer and physicians and patients, not just in the classroom but at the bedside or in the operating suite. I'd like to know how Stanford's new policies address these types of situations.

Dr. Pizzo: At Stanford we do have device vendors come in and participate in education directly in the operating rooms, and we plan to continue allowing that to happen. It's selected by appointment, so that we know that someone from the vendor is going to come. Because they are there for educational purposes, we value this type of interaction and see it as not representing a conflict that gets in the way of our due process.

■ MISSING THE BIGGER PICTURE?

Comment from audience: With all due respect, I think this discussion is mostly about pulling weeds when the forest is rotten. When young people decide to essentially sacrifice their youth to go into medical training, they expect to receive a decent salary. Not necessarily an exorbitant salary, but a decent salary. When they enter practice, there is no compensation for teaching and education, there is no benefit to practicing ethically, and the overall reimbursement for services is down. I think that's the crux of the issue. In the old days, when the drug reps came to my office, they wanted me, as a physician, to buy something from them. It is now the other way around: we physicians want the drug reps to finance what we're doing. The day has come when I, as a colorectal surgeon, receive more money if my patient is in a clinical trial than I do for removing a rectal cancer. That's the corruption in the system, and until that's dealt with, the higher-echelon discussion isn't going to impact the doctor on the front line.

Dr. Pizzo: You are speaking to another important issue that's not the topic for today. The United States is the only developed nation in the world that doesn't

have a universal health care system, and that's part of what you're addressing. We're number one, best as I can tell, in only one thing, and that's administrative overhead.

Ms. Totenberg: It always strikes me as peculiar, as someone who lives in Washington and watches the body politic, that doctors are in a frenzy about tort reform but are not in a similar organized frenzy about reimbursements under Medicare, Medicaid, and similar programs.

■ REGULATE THYSELF, DOCTOR—OR BE REGULATED UPON

Ms. Totenberg: We need to proceed to the next session, but I'd like to make a closing observation. Part of the reason that the medical profession is having such a rough time in this area right now, I think, is exactly what the colorectal surgeon from the audience has just said. Salaries are going down and private medical practices are suffering more. Even at academic institutions, people increasingly are looked at in terms of the research they can bring in, the number of operations they perform, and whether or not they can essentially pay their own salary.

Yet medicine is the only profession that still is widely admired by the public and that is unregulated, in terms of ethics, from the outside. Even federal judges, by law, must disqualify themselves from any case in which they have even one share of stock. Yesterday, I filed a story about new rules that the Judicial Conference of the United States adopted for all federal judges. The rules bar judges from receiving reimbursements for expenses when they attend a seminar unless all the donors that have funded the seminar are fully disclosed publicly.

In contrast, the medical profession is still completely unregulated from the outside in terms of its conflict-of-interest rules. My suspicion is that if the profession fails to come to some sort of consensus about how to regulate itself from the inside, eventually it too will be regulated from the outside.

Medicine is the only profession that is still unregulated from the outside in terms of its conflict-of-interest rules.

—Ms. Totenberg

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Conflict-of-interest management: Efforts and insights from the Association of American Medical Colleges

■ ABSTRACT

The Association of American Medical Colleges has issued three major reports to help academic medical centers manage financial conflicts of interest in clinical research. One report addresses individual conflicts, another addresses institutional conflicts, and the third is a survey-based assessment of institutions' performance to date in conflict-of-interest management. While implementation of policies to manage individual conflicts has been significant and widespread, the extent to which institutional conflicts are being managed is unclear. Developing effective and accepted policies to manage potential conflicts involving the funding of education remains a major challenge.

The Association of American Medical Colleges (AAMC) is the representative organization of academic medicine. It comprises all 125 US and 17 Canadian accredited medical schools and nearly 400 major teaching hospitals and health systems. Through these institutional members, the AAMC represents 109,000 faculty members, 67,000 medical students, and 104,000 resident physicians.

With diverse interests at work, the AAMC's mission is to try to find consensus, especially on vexing issues such as conflict of interest. In fact, one of our newest affiliated entities, called the Forum on Conflict of Interest in Academe, is devoted exclusively to this topic. This article briefly reviews AAMC efforts to help its members manage potential conflicts of interest in clinical research, and concludes by assessing progress to date.

Dr. Kirch reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

■ A QUARTER CENTURY OF CHANGE HAS LED TO COMPLEXITY AND CONFLICTS

When I completed my residency training in the early 1980s, I remember firmly believing that the Hippocratic oath's guidance of "above all, do no harm" created a shield of self-regulation that would protect me in all situations. I had no idea just how complicated our world would become in terms of the ethical questions that have come to be intertwined with much of medical progress since then.

Megatrends at work

A number of megatrends have driven these complex interactions:

Complexity of science. The rapidly expanding complexity of biomedical science over the past quarter century is well established and does not require further discussion for this audience.

"Privatization" of higher education. Our great public universities—even those institutions forged 150 years ago in the land-grant tradition of access to higher education for all—have been forced to rely less on public funds and more on private sources of support.

Expectations for economic growth. A corollary to privatization, and one that applies to both public and private institutions, is the growing expectation that academic medical centers have to be the economic engines of our communities. In many major US cities, the largest employer today is the academic health center.

Pivotal role of Bayh-Dole

These trends, together with the Bayh-Dole Act of 1980, have largely brought us where we are today. The Bayh-Dole Act, which gave US universities intellectual property control of their inventions that arose from federal government-funded research, created a wave of entrepreneurship within academic medicine. Shortly thereafter, however, problems with potential conflicts of interest began to emerge.

TABLE 1

Association of American Medical Colleges reports on financial conflicts of interest in clinical research*

Title: *Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*

Issued: December 2001

At a glance: Provides guidance on *individual* financial interests in human subjects research

Title: *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*

Issued: October 2002

At a glance: Offers a conceptual framework for assessing *institutional* conflicts of interest and specific recommendations for oversight of certain financial interests in human subjects research

Title: *U.S. Medical School Policies on Individual Financial Conflicts of Interest: Results of an AAMC Survey*

Issued: September 2004

At a glance: Reports findings of an AAMC survey on conflict-of-interest management trends

* Full reports available at www.aamc.org/research/coi/

■ **AAMC EFFORTS TO GUIDE CONFLICT-OF-INTEREST MANAGEMENT**

As we have heard earlier today, there is a spectrum of philosophies on how to address conflicts of interest in medicine. At one end is the proposal to prohibit all relationships between academia and industry, which many fear would stifle innovation. At the other end is the admonition to allow relationships to grow unfettered, which others fear would undermine public trust and credibility. The middle ground consists of efforts to *manage* these complex relationships, which is where the AAMC's efforts have been focused.

As early as 1990, the AAMC began to publish guidelines to address faculty "conflicts of commitment" as well as conflicts of interest. In 1995, significant federal regulations were enacted regarding financial conflicts of interest in projects funded by the US Public Health Service, including grants from the National Institutes of Health. These federal regulations further heightened interest in conflict of interest as an issue, and in recent years the AAMC has issued three major reports on financial conflicts of interest in clinical research (Table 1) that have served as landmarks for the academic medical community.

First report: Guidance for individual conflicts

The first report was issued in December 2001 by an AAMC task force led by William Danforth, chancellor emeritus of Washington University of St. Louis. It was prompted by a speech by my predecessor as AAMC president, Jordan Cohen, at the AAMC's annual meeting in 2000. The speech, entitled "Trust Us to Make a Difference," was an eloquent plea to recapture the public's trust.

This first report, which is specific to individual conflicts of interest, exemplifies the shift that had taken place in the vocabulary surrounding these issues, as it contains several pages of definitions and serves as a road map for those of us struggling with these matters. It also describes how to construct monitoring efforts and, in my view, has become a useful document for many of our institutions. As confirmation of the controversy that surrounds conflict-of-interest policies, one member of the 28-member task force declined to endorse the report, primarily out of a concern that its recommendations would be an impediment to research innovation.

Second report: Guidance for institutional conflicts

The second report, issued in October 2002, is a continuation of the themes promulgated in the first report. It focuses, however, on institutional conflicts of interest, emphasizing the need for academic institutions to put a firewall between the management of their own financial interests, including those deriving from technology transfer, and the protection of human subjects. It also provides guidance on the process of evaluating institutional financial interests.

Third report: Survey of performance

The third report, issued in September 2004, presents results of a survey by the AAMC to assess US medical schools' performance in managing conflicts. Although this report found high levels of acceptance of AAMC recommendations regarding rigorous standards for conflict-of-interest management, some concerns were cited. These included a low rate of evaluation of significant financial interests by standing committees (prior to final review by the institutional review board) and a lack of public representatives in conflict-of-interest discussions.

Latest initiatives

A subsequent report, *Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials*, was based on the proceedings of an invitational conference convened by the AAMC in June 2005. It features standards to guide institutions and their investigators in

the analysis and reporting of clinical trials in which they participate.

Looking ahead, Roy Vagelos, the former CEO of Merck & Co. and a participant in today's conference, has graciously agreed to chair a new AAMC task force that will convene in the next few months in an effort to develop guiding principles for industry support of medical education.

AAMC conflict-of-interest efforts are highlighted at www.aamc.org/research/coi/, which is a popular Web page on our site. Access to all of the aforementioned documents is granted on this page.

■ HOW HAVE WE DONE SO FAR?

I will conclude with a brief personal perspective on how well the US academic medical community has addressed conflict-of-interest management to date in several different areas.

Individual conflicts

I am impressed by the progress we have made in handling individual conflicts of interest. I believe that

the rules have become clearer, and I see fewer and fewer failures to appropriately disclose and manage potential individual conflicts. I give the general community high marks in this regard.

Institutional conflicts

I am not certain where we stand in terms of institutional conflicts. An AAMC survey is currently in progress to gauge the types of systems that are (or should be) in place to manage institutional conflicts.

Conflicts involving support of education

The most difficult area to address, I believe, involves potential conflicts surrounding the support of medical education. As we heard earlier in this conference, this area involves many oblique issues, and speculation about motives, behavior, and influence abounds. The AAMC task force that will soon convene hopefully will add clarity regarding this most challenging topic.

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Medical devices and conflict of interest: Unique issues and an industry code to address them

■ ABSTRACT

Development of medical devices requires interaction between physicians and industry that is considerably more intimate than that in pharmaceutical development. Progress in procedure-based medicine would be stalled if this collaboration were eliminated. This degree of interaction, however, creates conflicts of interest that must be managed to avoid compromising trust, credibility, and patient care. AdvaMed, a trade association for the medical device industry, has developed a code of ethics to manage many of these conflicts and to guide its members' interactions with health care professionals. This article reviews the rationale for the AdvaMed code and provides a brief overview of the code itself.

In terms of conflict-of-interest considerations, the world of medical devices is significantly different from the world of pharmaceuticals because physicians are more intimately involved with devices than with drugs. This is inherent to the nature of devices, which often serve as extensions of the physician's hands and thus require more extensive training and a more central and essential role for clinicians in development and testing than is the case with pharmaceuticals.

In light of these differences, medical device manufacturers have come together to prospectively address conflict-of-interest issues in their industry under a defined code of ethics¹ developed by the voluntary

trade association AdvaMed (Advanced Medical Technology Association), which represents hundreds of device manufacturers. As chairman of AdvaMed's Special Committee on Codes of Ethics, I participated in the development of the code.

This article outlines conflict-of-interest considerations specific to the device industry and provides an overview of the AdvaMed code of ethics as well as conflict-of-interest issues that remain to be addressed by the industry.

■ A DEVICE BOOM

As medicine evolves toward less-invasive procedures, the device industry is developing and innovating at a pace that far exceeds that of the pharmaceutical industry. There is virtually no end to where devices are now deployed, be it the brain, the blood vessels, the bladder, or the skeletal system.

As a result, the device industry has become a financial magnet. It now includes six Fortune 500 companies with \$38 billion in cumulative revenues, and the overall industry has \$450 billion in market capitalization. Start-up companies in the device sector are too numerous to keep track of, and each year sees hundreds of new device approvals in the United States.

■ WHY ARE DEVICES DIFFERENT?

Devices are an extension of a physician's hands much as any tool is an extension of a highly trained professional. They differ profoundly from drugs as a result of the intimacy between the device and the physician who deploys it. Behind that intimacy lies the potential for enhanced patient outcomes as well as an enhanced potential for conflict between a physician's relationship with patients and his or her relationship with industry.

Physician-industry interactions are critical throughout the development process

In the world of devices, physicians are operators. They perform procedures and depend on devices to

Acknowledgment: The author is indebted to two individuals for their contributions to concepts discussed in this article: Donald S. Baim, MD, of Boston Scientific, and Christopher L. White of AdvaMed. Dr. Baim has coauthored a manuscript on this topic entitled "Medical Device Development: A Balanced Approach to Managing Conflicts of Interest Encountered by Physicians," resulting in part from the 3rd Dartmouth Device Development Symposium (3D3), October 27 and 28, 2005.

Mr. LaViolette reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article apart from his employment with Boston Scientific Corp., from which he receives a salary and in which he holds ownership interest.

do so, and those devices alter their success rates. Therefore, physician operators have to and want to be involved in the conceptualization and development of new device technology, starting with preclinical work. Often these physician operators are the inventors of the device or have been advisors to the company developing a device.

During clinical testing, physicians have roles as investigators, and again these roles are enhanced compared with pharmaceutical development because of the need to *deploy* devices, often with a specific technique, rather than merely prescribe them. This technique-specific nature of devices also makes physician involvement crucial to the training and education required after market approval, as specific techniques often need to be taught, and physician operators are best suited to provide this training to their fellow physicians.

Thus, physician-industry interactions are necessary at virtually every stage of device development if that development is to effectively meet the needs of the end users—physicians caring for patients.

A code born of competing needs

If we recognize that physician-industry interactions are unavoidable in device development, the question becomes how to address the potential conflicts of interest that these interactions can create.

There is no question that device development is replete with conflicts of interest. Most of the types of potential conflicts are the same as in the realm of pharmaceutical development—financial incentives for consulting or teaching, research grants, the potential for academic promotion as a result of a successful innovation, and so forth. In addition, because small start-up companies are so numerous in the device industry, the financial incentives may more frequently include stock options, which often are issued in lieu of cash by small device companies to physicians who contribute to the development of a product.

The only way to eliminate potential conflicts of interest in device development would be to remove physicians from the development process. This is not a sensible solution, as it would break the intimacy between physicians and devices, with the inevitable result that device innovation would suffer. The reality is that we have to *manage* conflicts, and we must do so with an awareness that conflicts can range in intensity from very basic involvement in device

development, such as with basic consulting, all the way through to the founding of a start-up device company by a physician.

From the device industry's perspective, management of conflicts is essential in order to preserve physicians' critical involvement in product development while maintaining adequate separation to enable physicians to freely exercise their primary role of serving patients' best interests. With recognition of this need to properly balance physicians' multiple roles, the device industry came together to develop and promote the AdvaMed code of ethics.

■ WHAT THE ADVAMED CODE ADDRESSES

The AdvaMed code of ethics¹ encourages voluntary, ethical interactions between its member companies and health care professionals, and draws a clear distinction between interactions that advance medical technology and those that influence decision-making inappropriately. The code specifically addresses arrangements with consultants, member-sponsored product training and education, support of third-party educational conferences, sales and promotional meetings, gifts, provision of reimbursement coding information, and grants and charitable donations.

The code states that compensation of physicians should not be linked to the commercial success of a technology or a company, that physicians be compensated according to clear principles and fair market values, and that, in general, there be clearly articulated rules up front about the work to be provided and the compensation to be paid. There is no justification for giving stock as compensation for a physician, in light of the potential to bias physician behavior. This same code of principles applies to training and education processes.

■ BEYOND THE CODE: IDEAS ON CONTINUOUS IMPROVEMENT

AdvaMed has not yet addressed some of the most difficult issues concerning conflict of interest. For example, we do not yet have full agreement on exactly what should be disclosed and how, so for now we are leaving policies on disclosure open to interpretation. To the extent that we do not tighten these sections of the code, AdvaMed members can and will differ in their practices in certain situations.

Industry and academic medicine must work together to develop principles in these areas that lack

An inventor should not be a principal investigator, and a major stockholder should never have a role in patient collection or in data collection or analysis.

consensus. Examples of a few such areas follow:

Clinical protocol development. We must ask basic questions about protocol development in clinical research so as to preserve trust in the credibility of research. For instance, an inventor should not be a principal investigator, and a major stockholder should never have a role in patient collection or in data collection or analysis. These are conflicts that are not necessarily addressed anywhere but for which policies need to be codified and implemented.

Disclosure of legacy relationships. When publishing in journals, should physician investigators disclose not only whether a given study has been funded by industry but also whether they have any legacy rela-

tionships with particular companies?

Activities that influence financial markets. We will need to address the role that physicians play in activities that can directly influence financial markets. I believe there is no justification for practicing physicians to serve as stock analysts or in similar capacities.

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The challenge for NIH ethics policies: Preserving public trust *and* biomedical progress

■ ABSTRACT

Recently updated ethics rules for employees of the National Institutes of Health (NIH) aim to prevent inappropriate influences on research decisions while preserving employees' professional and scientific interactions. Specific provisions require NIH employees to report their financial holdings in "substantially affected organizations" and require senior employees to divest all holdings greater than \$15,000 in any single such organization. Outside institutions that receive NIH grants are bound by separate disclosure requirements. Public-private partnerships have become more important to NIH efforts to advance biomedical research in light of flat NIH budgets in recent years. Such partnerships open the door, however, to financial conflicts that must be prevented or managed in order to maintain scientific integrity and public trust.

When it comes to conflicts of interest, the biomedical community in general and federal health agencies in particular are under a microscope from the public, the Congress, the media, and the Office of Inspector General of the US Department of Health and Human Services.

This article describes ethics and conflict-of-interest policies in place at the federal agency for which I work, the National Institutes of Health (NIH). I will focus on newly updated ethics rules for NIH employees, requirements for institutions conducting extramural NIH research, and the philosophy guiding NIH partnerships with the private sector. **Table 1** provides a framework of some general concepts that underlie my discussion here.

■ DUAL NATURE OF NIH

Conflict-of-interest policies at the NIH must be understood in the context of the agency's dual

nature. The NIH is a unique institution with a campus in Bethesda, Maryland, that houses some 17,000 NIH employees, about 6,000 of whom are scientists. At the same time, the NIH directs the funding of research at more than 3,000 institutions across the country and around the world, supporting an estimated 300,000-plus individual researchers. A full 83% of the \$28 billion allocated to the NIH in the federal budget goes to this "extramural" research at non-NIH institutions, and that is the research that I help to oversee.

■ RULES FOR NIH EMPLOYEES

Basic tenets

The NIH has a set of ethics rules for its own employees (including scientists), which boil down to three basic tenets, expressed here in my own layperson-friendly terms:

I may not serve two masters. An NIH employee cannot have another financial interest in the work that he or she performs for the NIH.

I may not double-dip. Since the taxpayers pay for the work of NIH employees, someone else may not pay an NIH employee again for that same work.

I may freely speak, write, and teach. Within the bounds of the first two rules, NIH employees are free to speak, write, and teach in their areas of expertise. This principle aims to protect employees' ability to have constructive interactions with other scientists and preserve the free marketplace of ideas.

Guiding principles

These ethics rules for NIH employees were recently updated in a formal final rule published in the *Federal Register* in August 2005.^{1,2} The following principles guided the development of the final rules:

- The public must be assured that research decisions made at the NIH are based on scientific evidence and not on inappropriate influences.
- Senior managers and others who play an important role in research decisions must meet a higher

Dr. Ruiz Bravo reported that she has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

TABLE 1
Central concepts in conflict-of-interest discussions

Types of conflicts

- Real
- Apparent
- Financial
- Personal

Who is subject to conflicts of interest?

- Individuals
- Groups or collections of individuals

How are conflicts managed?

- Regulation
- Policy
- Guidelines
- Societal and cultural norms

standard of disclosure than employees who are not decision makers.

- To advance science and remain on the cutting edge of research, NIH employees must be allowed interaction with professional associations, participation in public health activities, and genuine teaching opportunities.

Specifics from the final rules

The updated ethics rules for NIH employees contain a number of noteworthy specific provisions that I have again expressed in my own layperson’s terms:

- As in the past, no outside consulting by NIH staff with a “substantially affected organization” (generally, pharmaceutical, biotechnology, and device companies) is allowed.
- Holdings in substantially affected organizations in excess of \$15,000 per company are not permitted and must be divested; this rule applies to all senior NIH employees and their spouses and minor children, unless a waiver is given.
- Receipt of monetary awards is contingent on prior approval and is limited to awards determined to be bona fide through a prescreening process.
- Financial holdings in substantially affected organizations (including holdings of spouses and minor children) must be reported by high-level employees and those involved in clinical research.
- Contingent on prior approval and to the extent allowed under existing government-wide rules, the following outside activities are allowed:

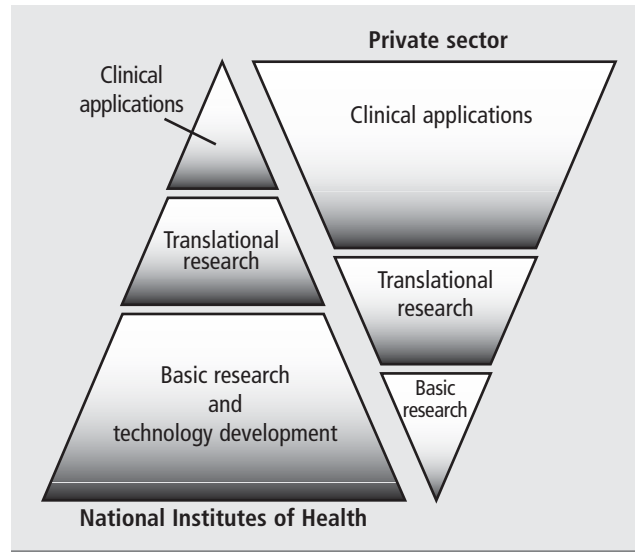


FIGURE 1. Relative contributions to US biomedical research spending by the public and private sectors.

- (1) Outside activities with professional or scientific organizations, and service on data and safety monitoring boards and scientific grant review committees
- (2) Compensated academic outside activities such as teaching courses, giving grand rounds lectures, writing textbooks, reviewing manuscripts and editing for journals, and the practice of medicine or other health professions.

REPORTING REQUIREMENTS FOR EXTRAMURAL INSTITUTIONS

Outside institutions that receive NIH grants are bound by reporting requirements as well. At the time of application for an NIH grant, outside investigators must report any significant financial interests to their institution. Before expenditure of funds, the institution must report any financial conflict of interest to the NIH and assure us that it has been managed, reduced, or eliminated. Any financial conflict identified after the initial report must be reported by the institution to the NIH within 60 days of its identification, and the institution must assure us that it has been managed, reduced, or eliminated.

RATIONALE FOR PUBLIC-PRIVATE PARTNERSHIPS

We are in an era of unprecedented biomedical advances, unprecedented scientific opportunities (in genomics, molecular libraries, etc.), and a transformation from curative to preemptive medicine. As a result, the NIH believes that medicine will become increas-

ingly predictive, personalized, and preemptive and that advances in these areas will require the participation of all players in the biomedical community. In addition, at the same time that scientific opportunities are unprecedented, budgets are constrained, prompting both the NIH and academic institutions to look to outside sources to help fund their research agendas.

Both of these factors have contributed to the NIH's increasing participation in public-private partnerships, which are critical for the translation of research from bench to bedside. The main contribution of the NIH in this equation is basic research and technology development, followed by translational research and more distantly by clinical applications. The private sector, which spends two to three times as much as the NIH does on biomedical research and development, does the bulk of the clinical applications portion of research (Figure 1).

Examples of NIH partnerships

The **Osteoarthritis Initiative** is one public-private partnership of the NIH whose purpose is to find biomarkers of osteoarthritis. Participants include several NIH institutes and centers, as well as outside universities and hospitals, industry, and the Foundation for the National Institutes of Health (FNIH). The FNIH is a congressionally mandated nonprofit organization that helps the NIH further its mission, often by brokering interactions between the NIH and industry.

The **Alzheimer's Disease Neuroimaging Initiative** is a public-private partnership whose purpose is to find neuroimaging and other noninvasive biomarkers for early Alzheimer's disease. As with the Osteoarthritis Initiative, participants include several NIH institutes and centers, industry, and the FNIH.

Partnerships raise issues

Despite the promise of public-private partnerships, they raise a number of issues and potential concerns that must always be addressed:

Conflict of interest. The NIH needs to be able to identify conflicts early and manage or eliminate them.

Technology transfer and sharing of intellectual property represent a large part of how the NIH now

functions, and agreements must be in place addressing how to govern these portions of a partnership with a private company.

Sharing of information is also necessary; NIH employees must be free to speak and write, but in some cases compromises must be made in this area consistent with the NIH ethics rules outlined above.

Human subject protections are paramount. We must ensure not only the safety of human research subjects but also the privacy and confidentiality of the information collected about them.

CONCLUSION

The NIH recognizes that maintaining scientific integrity and the public trust is critical, both in our public-private partnerships and in our policies for our employees and extramural institutions. Like the rest of the biomedical community, we need to prevent, eliminate, and manage conflicts of interest not because we are under a microscope but because it is the right thing to do.

I would like to close with a personal observation. People are capable of both enormous altruism and enormous greed—a fact that we ignore at our peril. Our discussions of conflict of interest in the biomedical community might benefit greatly from the expertise of behavioral social scientists and

others who could bring insights into the ways that groups of people interact. We should consider bringing these experts into our discussions moving forward.

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Medicine will become increasingly predictive, personalized, and preemptive, requiring the participation of all players in the biomedical community.

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Panel discussion

Guiding principles: Where are we headed?

■ NIH ETHICS RULES: UNINTENDED CONSEQUENCES?

Ms. Totenberg: Dr. Ruiz Bravo, the National Institutes of Health (NIH) was under considerable pressure from Congress because of alleged conflicts of interest. The head of NIH then handed down a new edict, followed by a hue and cry from NIH employees and a perceived threat of a massive exodus of scientists. The head of NIH then eased the rules. I am unclear about the changes from the first edict and how they differ from the situation as it now stands. What is permitted now that wasn't permitted under the initial edict?

Dr. Ruiz Bravo: Actually, the rules were both handed down and subsequently eased by the Office of Government Ethics and the Department of Health and Human Services. One rule that NIH staff disliked was the absolute prohibition against consulting for "substantially affected organizations" [generally, pharmaceutical, biotechnology, and device companies]. This prohibition is still in place, but there is an NIH ethics advisory committee that looks at specific instances in which these activities may be performed, to ensure that they are done in a transparent way and according to the law. An NIH intramural scientist who is available to one company or one specialty has to be available to everybody. Consulting per se is no longer allowed.

Ms. Totenberg: So if MiserTech Pharmaceuticals from the fictitious case study in my prologue wanted to hire an NIH expert on cystic fibrosis to review some of its materials, under the auspices of teaching and writing, could it do so under the NIH rules and pay him \$10,000?

Dr. Ruiz Bravo: No, it could not. However, an intra-

mural investigator may be able to collaborate in an official capacity (no compensation) with MiserTech. If it were in a public forum, on the other hand, then an NIH intramural investigator would be able to address specific issues that related to MiserTech.

Ms. Totenberg: What quelled the revolution among the NIH staff?

Dr. Ruiz Bravo: We have always had a prohibition against consulting with substantially affected organizations, but some NIH staff didn't know the rules. Having more exceptions and better education has helped, and over time staff have become more used to the rules.

Ms. Totenberg: The prohibition against stock holdings in those substantially affected organizations was new, wasn't it?

Dr. Ruiz Bravo: Yes, the divestiture rule is new.

Ms. Totenberg: How much divestiture had to take place, and how many scientists have you lost at NIH?

Dr. Ruiz Bravo: The overwhelming majority of NIH employees did not own stock in substantially affected organizations, and the divestiture rule was significantly changed from the interim final to the final rule: senior employees are the only ones subject to an absolute de minimis. So there has not been much divestiture. We have lost a few employees, although I don't have a number. Of those who have left, some may have left because of the ethics rules and some for other reasons. We have always had some turnover, but we have also been able to recruit some very good people. So I don't think it is necessarily the predicted end of NIH's ability to recruit good people.

Ms. Totenberg: One more impolitic question for you: What does the top scientist at NIH earn?

Dr. Ruiz Bravo: That information is publicly available. I think it's between \$200,000 and \$250,000 a year.

As federal employees,
NIH scientists should
be held to a higher
standard than
extramural scientists.

—Dr. Ruiz Bravo

Mr. LaViolette reported that he has no financial interests or relationships that pose a potential conflict of interest with this article apart from his employment with Boston Scientific Corp., from which he receives a salary and in which he holds ownership interest. All other participants reported that they have no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

Comment from audience: This is Philip Pizzo from Stanford University. The NIH is the engine that has driven this nation's entire biomedical research efforts. I was part of the NIH community for 23 years as an intramural scientist; during my tenure there were initially quite strict rules about what one could do in terms of consulting or interactions with industry, but consulting was allowed. Then, in 1995, the NIH director at the time, Harold Varmus, decided not to accept guidelines that had come down from the Office of Government Ethics, arguing that the ethics rules should be liberalized in order to attract the best scientists to NIH. While these actions were well-intentioned, at that point the NIH was able to "freewheel it" somewhat, and that's when equity ownership came in, that's when the ability to consult largely began. This did have a series of unintended consequences because there were a number of people who did not play by the rules.

That helps to explain the impetus for the new NIH ethics rules, especially for the controversial "first edict," as Ms. Totenberg put it. I was on the oversight committee that NIH director Elias Zerhouni put together to develop the current rules. We did not advise him to go to the extreme that he did, but Congress got involved and said, "This is out of hand; do something about it." It was that external pressure that likely tipped his hand.

Similarly, if Congress begins to look at conflict-of-interest issues more broadly and decides it wants to extend the intramural NIH rules to everyone who receives an NIH grant, we'll be in a whole new world. At Stanford, all of our faculty are on "soft" money: if they lose their grants or their clinical revenue goes down, so does their compensation. We may be endowed as a university, but as a medical school, we have our own financial bottom line. So we don't have a lot of resources to be able to provide for research activities. If the NIH were to adopt a policy that extended the rules for their intramural scientists to the extramural community, it would have tremendous implications. That's been one of my fears from the beginning, and one of the reasons why Stanford is trying to self-police its activities.

Dr. Ruiz Bravo: We have been asked why NIH's intramural rules don't apply to extramural scientists. As federal employees, we probably should be held to a higher standard. We had this discussion in many quarters. It's incumbent upon the biomedical research

community to come up with its own rules. The principles by which NIH has come up with its rules are good ones, and perhaps they ought to be considered seriously by the biomedical research community in developing its own rules.

Question from audience: Dr. Ruiz Bravo, there is a dramatic difference in the way NIH is treating its intramural versus extramural scientists. Extramurally, NIH is promoting translation, which in some cases means giving money to university laboratories to set up small-molecule and animal testing. These extramural investigators are trying to discover drugs; they want to become companies right inside the university. These are the people who will develop new products, and NIH is promoting that. Yet inside NIH you are saying that those kinds of people are not wanted. I wonder how the quality of the people who have left NIH compares with the quality of those who have remained. Have you peeled out some of your potential inventors?

Dr. Ruiz Bravo: I want to dispel that notion that NIH no longer wants to have innovation and interactions with industry. We've simply set grounds for how interactions with industry are going to happen. But we do have these interactions and we certainly encourage them. The intramural program would

take a dim view of the notion that our employees who have stayed with us are not innovative and not among the best in the country, let alone the world. As I said during my presentation, public-private partnerships are very much a part of our future at NIH. The question is how to do it in a way that maintains scientific integrity and maintains our credibility with the public while also furthering the biomedical research enterprise.

Question from audience: Dr. Ruiz Bravo just said that we have to maintain scientific integrity. The corollary is that we maintain scientific integrity by banning consulting. There's a lot of talk about trust, but don't we also want results? The ban on consulting is not promoting results. It may be that a different standard is needed for government agencies like the NIH, but I worry that it's going to spill over to universities and that research progress will suffer as a result.

Dr. Ruiz Bravo: What evidence do you have that NIH research has suffered as a result of stricter ethics rules?

Same questioner from audience: I know companies that had to shut down scientific advisory boards

A "modest" gift is something you get and then immediately give to your kids because you don't care about it.

—Mr. LaViolette

because they had NIH investigators who were trashed by the *Los Angeles Times*. I believe that's the real reason the NIH rules were put in place.

Dr. Ruiz Bravo: You have a point of view, and I respect that. But there are other points of view as well.

■ SHOULD INVENTORS EVER SERVE AS INVESTIGATORS?

Ms. Totenberg: I want to ask about the relationship between doctors and medical device companies. If a company has a new device, obviously the company has to train doctors how to use it, and a personal relationship develops that doesn't necessarily exist for pharmaceuticals. Mr. LaViolette, if I invent a new implant for back fusion surgery and I have a protocol to test it, does the AdvaMed code of ethics allow me to also serve as one of the investigators in the clinical trial?

Mr. LaViolette: The code doesn't address that yet, and it's a legitimate question. If we allowed an inventor—someone who is likely to receive royalties or who has some financial interest—to participate in a way that was not part of the exploratory research but rather part of the pivotal research (performing the procedures, looking at data, etc.), I think that would taint the research and would be a bad idea. I think that most in industry, certainly in big industry, would agree that that type of scenario should be fully prohibited. However, if I were in the venture capital world and thinking about starting a company, and if the physician who invented the technology were world-renowned and heavily influential, I would probably fight to have that person involved all along the way. That's the rub: there's some distance between doing things for the right principle and doing things for the marketplace, and we still have not fully bridged that gap.

Ms. Totenberg: By the way, in the AdvaMed code there is a good deal of talk about modest gifts. What's modest? At National Public Radio, we're not allowed to accept anything worth more than \$20.

Mr. LaViolette: Modest to me is something that you get and then immediately give to your kids because you don't care about it. I guess that's in the \$20-or-less range.

■ WHO'S SETTING ETHICS STANDARDS, AND WHO'S ENFORCING THEM?

Ms. Totenberg: Dr. Kirch, I want to ask you about the

emerging ethics at academic medical centers. We've now seen Stanford and Yale University ban all gifts, including drug samples and lunches for residents. Those institutions, as I noted earlier, have pretty big endowments, and I would imagine that the heat is now on Harvard Medical School. When Harvard goes, and a couple of other major institutions follow, will those institutions set the standard and change the culture? Or will we end up with a bifurcated system where the big fancy institutions have one set of ethics and everybody else has a different set?

Dr. Kirch: The program that Dr. Pizzo described at Stanford [in the previous session] and the others you mentioned have been very high-profile and have gotten a lot of attention. But it's a mistake to believe that they are the cutting edge of how to manage interactions between industry and the teaching and practice of medicine. For example, many teaching institutions long ago eliminated or severely restricted vendor interactions in the hospitals. What is significant about the Stanford position is that it has eliminated a very large number of small relationships but continues to allow a more limited number of large relationships. That's why I'm so enthusiastic about getting a broadly representative group of people to sit down and look at this issue of industry support for medical education—because the institutions you

mentioned have not established a consensus. They've taken some high-profile actions, and the profile derives mainly from their position in the community. But there are many other actions going on as well.

Ms. Totenberg: Are there penalties for not complying with the Association of American Medical Colleges (AAMC) code of ethics?

Dr. Kirch: The AAMC is the association that medical schools and teaching hospitals belong to. It is a parent of some of the regulatory entities—such as the Accreditation Council for Graduate Medical Education, which oversees residencies, and the Liaison Committee on Medical Education, which accredits medical schools—but it's only a parent of these bodies. At the same time, the AAMC does have policies that are established by its governing body, and I believe that these policies do set a bar. While AAMC policies may not have regulatory impact, I've been impressed that when the leaders from academic medicine who govern the AAMC agree on something, it is a hard-won consensus and it penetrates the field widely and effectively.

Will we end up with a system where the big fancy institutions have one set of ethics and everybody else has a different set?

—Ms. Totenberg

Mr. LaViolette: AdvaMed is in a similar position, being a voluntary association. We recognize the limits of our enforcement capabilities, but we have tried to create something to serve this purpose. So, in the process of disseminating the code of ethics, we opened it up to all members of the device industry, whether they are a part of AdvaMed or not. All members can have a license to the code, which requires meeting minimum certification and compliance standards and confers the right to promote adherence to the code through display of the AdvaMed logo. There are specific requirements to demonstrate compliance.

If a member, in good standing or not, were to violate the requirements, we would revoke its license. This would force the subject company to cease display of the AdvaMed logo, and it implies that basic compliance and certification standards are *not* in place. Increasingly, health care providers are asking vendors to certify code compliance. Failure to do so will have intensifying commercial implications in the future. So there is an effort to give the code some teeth, although it may not scare major corporations.

Ms. Totenberg: Does AdvaMed disclose license revocations publicly?

Mr. LaViolette: Yes, on the AdvaMed Web site.

Ms. Totenberg: Do you put out a press release?

Mr. LaViolette: We haven't reached that position yet, but it's something we might consider. I say that because the industry is very focused on credibility. To the extent that an individual member damages the credibility of the broader marketplace, that hurts everybody. So we certainly might look at taking on more aggressive disclosure of violations—or, if you will, incremental “enforcement” actions—over time.

Ms. Totenberg: Is there public disclosure at NIH when there is a violation of rules?

Dr. Ruiz Bravo: It depends on the violation and its nature. We have conflict-of-interest policies and rules, and while NIH itself is not a regulatory agency, it is in charge of implementing some of the regulations that have been passed down from Congress. When there are investigations, they are typically confidential until there is an actual finding of misconduct or something similar, at which time they are made public. But the finding of misconduct would be done by the Office of Research Integrity, not by NIH. There are very few such cases.

Question from audience: There have been a number of subpoenas from the US Attorney's offices in Philadelphia, New Jersey, Boston, and elsewhere in

recent years in response to questionable sales and marketing practices by drug and device companies. What impact have these subpoenas had on industry? I would like Mr. LaViolette to address this both from the general industry standpoint of the AdvaMed code and in terms of specific sales and marketing practices at Boston Scientific.

Mr. LaViolette: Any enforcement action sends a signal industry-wide of what the Office of Inspector General is interested in. At Boston Scientific we look at these actions and ask ourselves if our policies are clear, if we're acting in accordance with those policies, and if our policies need to change. Again, much of what we're talking about, at least as it relates to the AdvaMed code and ethical practice, is not legislated anywhere. We're therefore dealing with an area that transcends the law and is subject to interpretation. As a corporation, we're trying to have a degree of market equity that is above the norm. We're trying to act in a way that's respected and for the long term. Would we change our practices ahead of the industry? I would hope so. Would we then try to bring the industry along, for the greater benefit? The answer is yes.

Certainly, any set of subpoenas from the Department of Justice leaves a black mark. Do we work to prevent that? Yes. Do we work to prevent it just so that we don't get investigated? No. We work to improve so that we have a more productive system over time.

■ WHEN MEDICINE SOLICITS FUNDS FROM INDUSTRY

Comment from audience: I'm a leader of marketing in a privately held medical device company. I was pleased to hear Mr. LaViolette speak on behalf of the device industry because I was a bit troubled by this morning's discussion, which seemed to be moving toward a depiction of “big bad industry” that influences physicians. Many people in industry were thrilled with the development of the AdvaMed code of ethics because it provides an avenue for industry to walk away from some activities that we didn't necessarily want to do, such as providing free rounds of golf, sporting tickets, coffee cups, etc. Industry has an interest in diverting our marketing funds into education, but we find that physicians are getting more adept at marketing *to us*. They send a subtle message that our product might be pulled if we don't support an educational activity they're planning. It can amount to arm-twisting. AdvaMed and the industry are doing an effective job at trying to limit conflict of interest, in my opinion, but there needs to be

increased vigilance on the physicians' side to limit their marketing to industry for funding.

Ms. Totenberg: Your comment brings to mind the subject of foundations that are set up by academic institutions or private groups of doctors to fund their research or their fellowships. Let me ask the panel, how much of this type of activity is appropriate?

Dr. Kirch: The world of foundations was essentially invented by universities to accomplish purposes that the university itself believed it could not accomplish. I would argue that in most cases it has helped universities carry out their missions. Every university I've been involved with has very clear guidelines about how foundations can and should be established, and how the oversight occurs. So the real issue here exists outside the academic research world, in settings where there isn't oversight by a parent institution.

Mr. LaViolette: At Boston Scientific we certainly see foundations routinely. They're prominent, they're everywhere. They're generally legitimate, and you can tell when they're not. At our company we have a clear segregation of responsibilities for the purpose of evaluating research requests. It's entirely separate from anyone aligned with business success or failure. We make very clear our requirements from a foundation in terms of what the request is and how the funds will be used; if the request is legitimate, we're more than happy to deal with foundations.

Ms. Totenberg: But it's not a question of whether the foundations are phony fronts. Let's say that Dr. X sets up a foundation because he or she can't raise money directly from drug companies or medical device companies. It's a foundation to fund fellowships in ophthalmology, for example. Various companies say, "Yes, we'd be happy to give you \$5,000 for that." Suddenly, all the fellowships in this department are funded by three companies who now have a special relationship with that department. These companies, quite naturally, might now say, "We have some new, cutting-edge devices that we'd like the hospital to look at seriously. It would be great if you could use them first on an experimental basis." It's not that anybody has bribed anybody. It's just human nature.

Mr. LaViolette: There's a difference between legitimate investments and inducements, and we all have to look at those subtleties. We all have to look at

whether there is a connection between a grant made historically and a request for business made today. To the extent that the request for business today is made entirely on the basis of the technology or product in question, it's perfectly legitimate.

Dr. Ruiz Bravo: Let me say a few words about the Foundation for the National Institutes of Health (FNIH). As I said in my presentation, it was created by Congress and it is distinct from NIH. That's an important distinction. Also, we have found the FNIH to be extremely helpful in terms of furthering the NIH mission in biomedical research. It is able to partner with industry and others, and NIH forms one part of that partnership. So it brings us together with industry in a way that facilitates our interactions.

Ms. Totenberg: How does it actually work? Does the foundation give money for research to NIH scientists?

Dr. Ruiz Bravo: No, the FNIH funds programs through donations. It can accept contributions and gifts, and there is a link on the FNIH Web site for contributions. The foundation doesn't have its own scientists or any intellectual property of its own. The foundation is probably most helpful to the NIH through the partnerships that it brokers. For instance, for the Osteoarthritis Initiative that I mentioned in my presentation, FNIH brought all the parties to

the table to talk about how the initiative was going to work—which components industry would contribute, which components NIH would contribute, and so forth.

■ WHAT CONSTITUTES 'APPROPRIATE' INFLUENCE?

Question from audience: The panelists have talked about medical decision-making not being subject to inappropriate influences from industry. As a lawyer, my clients are always saying to me, "Don't tell me what I *can't* do; tell me what I *can* do." So I'd like to know what the panel considers to be appropriate influences that can arise from this relationship between industry and academe.

Dr. Kirch: I can't speak about the NIH policies, but I think that in academic medicine a wide range of interactions remain possible, accepted, and productive. Where the line needs to be very clear is when you get to the bedside, and whether influences are entering into the care of patients. Most of the regulations that I see being put in place aren't based on some abstract

If scientific discovery and educating the health care workforce are no longer seen as public goods, why are we surprised when everyone works to establish relationships with the private sector?

—Dr. Kirch

goal of stopping interactions. They're simply trying to prevent the contamination of patient care.

Mr. LaViolette: A lot of things are permissible, but you can either be heavily involved in investigations or be heavily involved in invention. You can't really be involved in both. If a physician comes to my company and wants to be a lead investigator, that's great. And he will be paid fair market value for his services. If another physician comes to us with intellectual property, wants to sell us an invention, and wants to participate in the marketing side, that may also be appropriate. But we can't let one spill over to the other. So there are a lot of things that you can do, but you can't mix and match roles. Drawing clear distinctions is key: the inventors cannot be the investigators.

Dr. Ruiz Bravo: Dr. Pizzo put it best when he said earlier that you want to distinguish between interactions that are scientific and interactions that are related to marketing. The first should be encouraged, whereas marketing is something we shouldn't do.

Ms. Totenberg: How many of these research decisions are affected by the type of drug or device being investigated? Some may help a relatively small number of people, whereas others can make a university a lot of money if they pan out, like the statins. When I was first at National Public Radio, before we were as large a news organization as we are today, I thought that our coverage was skewed by who was giving us money. We would get grants from a foundation to cover mosquitoes in Africa, for example, when that might not have been a top coverage priority. We don't do that anymore; we have rules against it and big firewalls. But I can't help but wonder whether research decisions aren't similarly skewed when intellectual property can benefit large institutions so greatly.

Dr. Kirch: That's why the focus has turned toward institutional conflicts of interest, and why they are more difficult than individual conflicts of interest.

One of the things that worries me is the underlying premise in discussions like this that we've allowed an unholy alliance to develop between the private sector and the academic sector and that we need to unravel that alliance. I view it differently. Some of the debate needs to go back to our priorities as a nation and what we are and are not willing to support. For instance, the issue of industry support for fellowships was raised. Part of the problem is that the support for residency and fellowship education has essentially been static. In terms of need, it's actually gone down. Residency directors are scrambling to "cross-subsidize" their educational

enterprise. If we continue in current trends and decide that scientific discovery and the education of the nation's health care workforce are no longer public goods, why are we surprised if everybody works so hard to establish relationships with the private sector?

I'm especially concerned about the core of medical education. We have pushed tuition for medical students to its absolute limit. Every medical school in the country is scrambling to figure out ways to fill the gap without burdening those students even more and undermining society and its need for doctors. This is really an issue of societal priorities.

Ms. Totenberg: Has anybody asked the AAMC to testify about this before Congress?

Dr. Kirch: Not yet, but the AAMC's governing body believes that this is *the* issue we have to put on the table. A convergence of developments has brought us to this conclusion: real distress at a number of our member institutions, growing evidence that we face major health care workforce shortages, and indications that physician scientists are becoming an endangered species. There is a compelling list of warning signs, and we need to get that list in front of the nation.

■ WISDOM BEYOND ONE'S OWN WALLS

Question from audience: From the standpoint of institutional conflict of interest, where can academic medical centers turn outside our own institutions to regulate collaborations with industry that are taking place within our own walls? Also, if patients are asked to participate in a clinical trial within a university, do they have the right to know whether the university stands to profit from its participation in the trial? If so, should we tell them a dollar amount or an equity amount, or is a general statement in the informed-consent form sufficient?

Dr. Kirch: In both instances, the solution lies in making better use of people outside our institutions. There is wisdom beyond our walls that we don't tap sufficiently. One finding in AAMC's initial survey on conflicts of interest was that there was less use of public representatives on research review committees than we had expected.

With regard to patients, I am a great believer in the effectiveness of representatives who are designated not to represent the institution but to represent patients, be it in the consenting procedure or in other matters. And there's a corollary benefit: the more the public is involved in these processes, the more we recapture its trust.

DICK THORNBURGH

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Building and retaining trust in the biomedical community

Trust is a very important element in our society. The integrity of our institutions, public and private, is essential to guaranteeing their credibility and effectiveness, their fidelity to the roles to which they are assigned, and the goals that they seek to fulfill. If important research, regulatory, and clinical institutions begin to lose the public's trust, we risk undermining our nation's capacity for experimentation, scientific innovation, and, ultimately, excellence in patient care. And the threat is a real one.

For example, this year marks the 100th anniversary of the passage of the Pure Food and Drug Act of 1906 and the creation of the US Food and Drug Administration (FDA). For decades the FDA was one of our most highly regarded public institutions, both nationally and internationally. In recent years, however, trust in that agency has eroded and the public has grown increasingly cynical about the FDA's performance.

A recent Wall Street Journal Online/Harris Interactive survey found that a whopping 82% of the public believes that FDA decisions are influenced to some extent or a great extent by politics and profit rather than by medical science.¹ In a startling short-term reversal, 58% of Americans now believe the FDA is doing merely a fair or poor job, whereas just 2 years ago 56% of Americans believed the FDA was doing an excellent or good job.¹

A similar trend appears in opinion polls on public confidence in health care institutions and industries.

Of course, trust is not something that can be produced on demand. It must be earned and it is, in large part, a product of a visceral belief in the good intentions of others. In the medical world, the Hippocratic oath reflects the bedrock principle for this trust: "Do no

harm." I do not pretend to hold the secret of how best to build and retain the public trust. I do hope, however, that my comments today will help remind, provoke, and motivate the individuals here and the important institutions they represent to be vigilant in making every effort to be good stewards of that trust.

In this spirit of trust and full disclosure, I preface my comments by disclosing that I am not a doctor, researcher, or bioethicist. Rather, my comments are based on my collective experience as a public official, a trustee of a major research university, a long-time advocate of joint public-private partnerships in research and development, a one-time director of a major biopharmaceutical company, and a private attorney involved in a number of significant and high-profile corporate governance and ethics investigations.

Because trust is fundamentally about relationships, I have organized my remarks around four key relationships:

- Government and industry
- Industry and the biomedical establishment
- The public and the biomedical establishment
- Product liability lawsuits and patient care.

I would argue that in each of these relationships there has been a breakdown in the management of potential conflicts, effective disclosure, or both. Rather than seek to eliminate conflicts, as some have proposed, I would suggest that we need to focus instead on how to facilitate effective disclosure of potential conflicts and how to ensure their transparent and consistent management.

■ GOVERNMENT AND INDUSTRY

According to one recent study, medical breakthroughs over the past 20 years have reduced deaths from heart attacks by about 50%, from stroke by more than 33%, and from breast cancer by more than 20%. Similarly, as a result of medical advances, there are an estimated 2.5 million fewer disabled seniors than originally projected in 1980. These figures serve as a magnificent tribute to the public-private effort in these fields. This

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progress would not have been possible without close collaboration between government and industry.

I recall the crucial role played by government-sponsored collaborations in technology transfer between universities and the entrepreneurial community in Pennsylvania during my two terms as governor through a vehicle called the Ben Franklin Partnership, named for that famous American who was a scientist, inventor, businessman, and educator—as well as a damn good politician. Similar initiatives have since been undertaken in all 50 states to foster both economic growth and scientific breakthroughs. And they have perforce brought the scientific community into much closer contact with its business counterparts.

Partnerships bring risks along with benefits

It must be recognized, however, that government-industry partnerships can pose risks, including opportunities for bias, uneven enforcement, and the appearance that business interests are taking priority over public welfare. The recent spate of high-profile drug and device recalls illustrates this point. People are asking: Has the FDA approved these products for marketing too quickly and without sufficient safety review? Have drug and device user fees for premarket submissions created relationships between the FDA and industry that are simply “too cozy”? Is lax enforcement allowing corporate “shortcuts” that sacrifice public safety in favor of corporate gains?

These questions are not new. The FDA, in particular, seems to go through constant cycles in public opinion. The agency is first accused of being too soft on industry and allowing unsafe products to be marketed; in response, there comes inevitably a tightening of enforcement and a slowdown in product approvals. The tide soon shifts, however, and the FDA is then accused of being antibusiness and overly cautious in product approvals, unwittingly allowing people to die while waiting for potentially lifesaving products. Criticism increases and again, almost inevitably, there appears to be an easing of enforcement and an acceleration of product approvals.

While it may not be entirely fair to subject the FDA to criticism from both ends of this spectrum, the underlying concern is valid. The FDA and its sister agencies are charged with protecting public health. How can we be sure that they are fulfilling their mission rather than inappropriately yielding to corporate interests or merely submitting to public pressures in disregard of science?

I suspect that in most cases, the FDA, the National Institutes of Health (NIH), and the other government health agencies try to strike an appropriate balance, prodded by a framework of federal and state laws, regulations, internal policies, and the potential deterrent effect of legislative hearings. Nevertheless, if rules are not enforced and internal oversight is not consistently and rigorously maintained, potential conflicts arise and the public trust wanes.

What the medical community can learn from corporate debacles

Corporate catharsis over issues of fraud, corruption, and conflicts of interest abounds today. The bankruptcy of WorldCom, the largest in the nation's history, gave me some specific insights into these issues during my service as the court-appointed examiner in those proceedings. Originally, our focus was on the

\$11 billion in accounting irregularities that had resulted from management's “cooking the books” to create a false illusion of steadily rising earnings within one of the world's leading telecommunications companies. On closer examination, however, we discovered a more serious problem—the near-complete breakdown of corporate governance. The normal checks and balances designed to prevent

improper activity simply did not work. The board of directors, dominated by an overbearing CEO, often offered mere token review of complex multibillion-dollar management proposals, at times granting approval based on brief conference calls and without proper documentation or justification. The board's audit committee failed to enlist the internal auditors and the outside accountants in a seamless effort to detect accounting irregularities. Meanwhile, the board's compensation committee was approving more than \$400 million in personal loans to the CEO, with little due diligence or attention to the sufficiency of the collateral offered. In short, the supposed “gatekeepers” left the barn door wide open.

As you know, the WorldCom debacle and others like it prompted a spate of criminal prosecutions, civil suits, and regulatory sanctions. Moreover, Congress responded with the Sarbanes-Oxley Act to force greater disclosure, transparency, and accountability for publicly held corporations in this country. The Securities and Exchange Commission and stock exchanges issued comparable rules.

Similar changes are occurring internationally as

Taxpayers have a right to know the extent and details of government health agencies' relations with industry.

well. Our Foreign Corrupt Practices Act has recently provided a model for actions by the United Nations, the World Bank, and other multinational organizations to combat fraud, corruption, and conflicts of interest in transactions that cross national boundaries.

How do these examples apply to the biomedical community? The integrity of our health care system—including product approvals, research funding, and patient care—depends on a fundamental trust that critical scientific decisions are rooted in science and not financial interests. Few people would question that the technology transfer activities of the NIH help speed research from the bench to the bedside or that industry's investments in discovering, developing, and distributing their products benefit countless patients. That being said, we as taxpayers and the intended beneficiaries of the public health system have a right to know the extent and details of these relationships. Only then can we debate in an informed manner how to strike the right balance between internal oversight and government regulation. But one thing is clear: potential conflicts must be fully disclosed and consistently and transparently policed if trust is to be restored and maintained.

■ INDUSTRY AND THE BIOMEDICAL ESTABLISHMENT

Distinct from the relationship between government and industry is the relationship between industry and the biomedical establishment, including researchers and practitioners.

No longer separate worlds

There was a time when research was primarily funded by the government. However, over the past two decades, hospitals, universities, and research institutions have increasingly entered into relationships with venture capitalists, investment firms, and for-profit companies. Industry-financed research and development has now reached a level in excess of \$2 billion a year. No one doubts that the primary goal is ultimately to improve patient care. Nevertheless, private funding from entities that have financial interests in the outcomes of scientific research and medical decisions has introduced a different type of potential conflict of interest—one that raises questions about whether business considerations may inappropriately influence medical care, purchasing decisions, and clinical research findings.

Nowadays, hospitals and research centers need to consider not only financial aspects of consulting and

research arrangements but also the apparent philanthropic funding of research chairs and other “good deeds” for the potential appearance of bias. Of particular concern are undisclosed relationships in published studies that describe clinical safety and effectiveness. Scientific publications are relied on by the medical profession in assessing various options for patient care. Unfortunately, there have been a number of recent cases, in prominent journals such as the *Journal of the American Medical Association* and the *New England Journal of Medicine*, in which authors either have willfully decided not to fully disclose their financial ties in conducting trials or promoting products or have made their own assessment as to what would be “relevant” disclosures. Even if the research results were not tarnished by financial relationships, it is often the *perception* of conflict that creates more lasting damage. The failure here is in establishing appropriately transparent procedures to assure effective disclosure and predictable consequences for less than complete disclosures.

Patient advocacy groups also affected

Nonprofit patient groups, such as the American Diabetes Association and the Arthritis Foundation, are not immune from these problems. The *Philadelphia Inquirer* recently explored the relationships of six nonprofit organizations, each a leading advocate for patients in a disease category, with drug companies. The newspaper found, based on tax returns and annual reports, that these groups collectively received at least \$29 million from drug companies in 2005 although little information was publicly disclosed about these relationships. This fiscal support is not widely discussed or attributed. Yet it has the clear potential to influence or bias the information conveyed to wide sections of the patient and prescribing populations.

Solution lies in managing, not ending, relationships

My own experience in both the public and private sectors instructs that the solution is not ending these relationships, which would be neither practical nor prudent. Rather, the most effective and beneficial response is to disclose and manage potential conflicts in a consistent and predictable way. Some of the best methods will likely be discussed over the course of this conference. These include restrictions on product endorsements, caps on donations, limitations on consulting arrangements and compensation, “firewalls” between funding/donations and use of the funds,

Not all potential conflicts of interest are equivalent in risk, but they *are* equally damaging in terms of public perception.

expansive disclosure rules, and recusals from decision-making involving the subject product.

These tools obviously do not apply equally to all situations. In some cases, upon investigation, the potential conflict may not present a real conflict; in other cases, there may be a real conflict, but it can be screened off. We must recognize that not all potential conflicts of interest are equivalent in terms of risk, but they *are* equally damaging in terms of public perception if not fully disclosed and considered. This brings me to the third relationship I want to discuss.

■ THE PUBLIC AND THE BIOMEDICAL ESTABLISHMENT

The public's perception of the biomedical establishment is critical to any dialogue regarding potential conflicts of interest. There was a time when a doctor's credentials and advice were accepted without question and industry was lauded as benefactors of public health. For good or ill, that time has passed. Today Medicare fraud settlements with health care companies are on the rise, health care providers are the subject of an increasing number of federal investigations, and commonly prescribed drugs and devices seem to be regularly pulled off the market following postmarketing revelations about safety.

Based on these phenomena, it is not surprising that there is growing distrust and cynicism toward doctors, industry, and their governing bodies. I believe there are at least three reasons for this erosion in the public trust:

- Insufficient transparency in the product approval process
- Inadequate recognition of the patient's right to make his or her own decision as to what is an acceptable amount of treatment risk
- Ineffective disclosure and management of the for-profit aspects of medicine.

The Tysabri case: Informed patient decision-making is key

Let me recount one of my personal experiences as a director of a publicly held pharmaceutical company, Élan Corporation, and the travails this company and its partner, Biogen Idec, encountered in securing FDA approval of the multiple sclerosis drug Tysabri.

Tysabri was approved by the FDA in 2004 and, by all accounts, was found to be highly effective. One patient, Lauren Roberts, described how Tysabri stopped her attacks and dramatically improved her condition. She wrote in a published article, "Within two weeks of my first infusion, I started to notice that

my balance and speech were improving. I was thrilled to be able to walk with just a cane, with no limp, and to be able to speak normally for the first time in over a year. I was delighted. Then came the bombshell: The manufacturer, under pressure from the FDA, took it off the market four months later."

Tysabri had been linked to a serious viral brain disease in three patients, two of whom died. And here the dilemma arose: How to balance these isolated tragic incidents with the ongoing tragedy of depriving some 8,000 patients of a medication that proved to be safe and effective in improving their quality of life?

After the FDA withdrew its approval, Biogen and Élan immediately petitioned the FDA for reapproval of the drug. The FDA disregarded the recommendation of its own advisory committee and granted itself additional time to consider the application. In June 2006, more than 16 months after Tysabri's withdrawal from the market, the FDA took the unusual step of approving its resumed marketing subject to a restricted distribution program. In the interim, thousands of patients had to suffer the symptoms of multiple sclerosis and bear the risk of possible debilitating decline that no drug could reverse.

What should we make of this approval process? One may certainly argue that the FDA was fulfilling its obligation of assuring that only safe and effective drugs are available in the US marketplace. However, one can also conclude that this is an example of excessive caution and aversion to adverse political reaction, particularly coming on the heels of the very public market withdrawals of Vioxx and Bextra and the mandatory black box warnings newly required for Celebrex and commonly purchased over-the-counter drugs like Advil and Aleve.

Clearly, no drug is without risk. I personally believe that those with multiple sclerosis and other degenerative or fatal diseases deserve a range of therapeutic options, a full disclosure of known potential risks, and the right to decide whether they are willing to accept those risks. Unfortunately, this decision was, at least temporarily, denied to many in the case of Tysabri, and to all too many in the case of other drugs and devices.

Transparency and proactive management are crucial
A transparent product approval process also requires full disclosure of potential conflicts and recognition of the growing for-profit nature of medicine. One need only look at the ever-increasing proportion of

Broad-brush legislative fixes to complex, nuanced issues often lead to unintended adverse consequences.

pharmaceutical and device company budgets spent on consulting fees, direct-to-consumer advertising, and physician outreach activities. The potential for biased decision-making is enormous.

Recent congressional investigations, federal prosecutions, and class action lawsuits have all highlighted the potential conflict between patient care and profit incentives. Again, this is by no means only a national concern. The age of personalized medicine is upon us, with worldwide advances in nanotechnology, stem cell research, and genetic mapping, to name a few. These developments place the inherent tension between medical care, scientific knowledge, politics, and profit at the center of the global stage. The answer is clearly not to put our heads in the sand but to be an active participant in the dialogue by proactively assessing and managing identified potential conflicts.

Laws, guidelines, and codes of conduct developed by the government and by industry and professional associations, such as the American Medical Association, the Association of American Medical Colleges, Pharmaceutical Research and Manufacturers of America (PhRMA), and AdvaMed, have helped define, control, and contain those interactions that have the greatest potential to create the appearance of bias. However, in the absence of effective public disclosure and transparent review, assessment, and management, it is difficult to counter the assumption that bias permeates research, product approvals, and medical decisions.

Targets for reform and investigation

In response to widespread media accounts of alleged bias and conflicts, as well as growing cynicism toward the biomedical establishment, it comes as no surprise that we are seeing a heightened level of congressional interest in Washington, DC. With this comes the specter of increased government oversight and regulation. We need to be reminded that broad-brush legislative fixes to highly complex, nuanced issues often lead to unintended adverse consequences. In a way, it is analogous to the old saw about watching both laws and sausage being made: it is not a pretty process—and in this case even the end result may be unappealing as well.

Cases in point, the following have become “topics du jour” in the media and, not surprisingly, favorite targets for legislative reform, federal investigation, or both:

FDA advisory committee membership and its objectivity in the face of industry funding or other

financial interests or relationships. The FDA announced in July 2006 that it intends to revise its conflict waiver system to make it more transparent, but multiple legislative initiatives have interceded, including a proposal that would bar the FDA from using outside experts with any personal or financial ties to companies with a stake in the advisory committee’s recommendation.

Outside activities of FDA and NIH employees, including consulting arrangements, awards, and other income-generating activities. All government employees are subject to conflict-of-interest rules. In 2005, as a result of congressional hearings, supplemental regulations were issued just for the FDA and NIH. In February 2006, the Department of Health and Human Services Inspector General issued a report concluding that the current disclosure and review process is inadequate to effectively assess requests to participate in outside activities. Congress is currently discussing additional legislative restrictions.

Industry-funded physician-sponsored foundations. The concern here is that the funding could bias treatment decisions and the reporting of research findings. A major device manufacturer is currently under federal investigation for its donations to several of these foundations, and more widespread investigation of other foundations, on a state and

federal level, is likely.

Interactions between sales representatives and health care professionals related to gifts, meals, consulting arrangements, and promotional activities. Increasingly, states are passing their own laws requiring reporting of gifts and other remuneration to hospitals and physicians. The sum effect of this is the possibility of 50 separate and distinct compliance reporting systems, each with its own paperwork requirements and potential fines. A recent corporate integrity agreement between Medtronic, Inc., and the US Department of Justice may signal the direction of things to come. According to the agreement, interactions between certain company personnel and any “actual or potential source of health care business or referrals” must be documented if they involve “directly or indirectly the offer, payment, solicitation, or receipt of anything of value.”

Appearance is everything

It is clear that in the absence of appropriate and transparent self-regulation, accounts of alleged conflicts and bias will continue to attract the attention

Increasingly, states are passing their own laws requiring reporting of gifts and other remuneration to hospitals and doctors.

of the news media and government investigators and take on a life of their own. Ironically, with all this attention on potential financial conflicts, a recent study found that excluding FDA advisory committee members and consultants with disclosed financial conflicts would not have altered the overall vote outcome at a single one of 221 drug advisory committee meetings held between 2001 and 2004.² Nevertheless, in 73% of the meetings, while one or more advisory committee members or voting consultants disclosed some type of conflict, only 1% of members were recused.

It all goes back to the old adage that appearance is everything. If the biomedical establishment and its governing bodies remain unable or unwilling to implement appropriate incentives and disincentives to assure effective disclosures and to manage them in an open and transparent way, we can expect increasing government involvement. This may or may not lead to better disclosure rules, more transparency, and better decisions. Exactly because difficult cases require differing analyses and measured steps, we need to be concerned about the figurative baby being thrown out with the bathwater—to the detriment of innovation, research and development, and patient care.

The absence of appropriate, transparent self-regulation will continue to attract attention.

■ PRODUCT LIABILITY LAWSUITS AND PATIENT CARE

Products killed by litigation costs

Sometimes it is the legal climate that affects corporate decision-making and ultimately patient care. In these situations, which are growing more common, the simple risk/benefit calculus focused on patient and health issues shifts. The critical part of the equation becomes the potential cost of defending or settling potential product liability lawsuits. When the cost becomes too high, products may be withdrawn from the market, to the detriment of both the company and the public.

Consider breast implant litigation. In 1982, a single plaintiff sued Dow Corning Corporation, claiming, without any clear medical proof, that silicone breast implants had caused a variety of ailments. A noted television journalist aired a story on breast implants that included inflammatory statements based on the opinions of two doctors with no medical research experience in the area of breast implantation. Members of Congress, and later the FDA, picked up the issue and a series of public hearings followed, raising public concern to a fever pitch. Years of litigation

ensued, millions of dollars were paid out in settlement costs, and the product's principal manufacturer went bankrupt. Virtually all silicone breast implants disappeared from the market. But now the evidence seems overwhelming that there is, in fact, no causal connection between implants and the injuries and ailments alleged by the claimants. In fact, the National Academy of Sciences soundly rejected the basis for these claims in 1999, and one company has recently obtained the FDA's approval to return these products to the market.

Litigation like this not only increases the costs to American businesses and ultimately the American consumer, but it also has a negative impact on the innovation that has been the distinguishing attribute of American research and development. Consider, for example, the drug Bendectin, a remedy for morning sickness. This drug was actually pulled from the market because annual sales could not support expenditures for litigation and insurance arising from claims that it caused birth defects, despite the fact that no claimant had ever prevailed against its manufacturer. Manufacturers of ephedra-containing dietary supplements now have made the same risk calculus, and virtually no ephedra-containing supplements remain on the market.

In the post-Vioxx era, we can expect the number of lawsuits to increase. According to recent estimates, Merck is facing some 11,500 product liability lawsuits over Vioxx, with estimates that the company may eventually have to pay between \$10 billion and \$50 billion to dispose of the litigation. The rest of the industry is wisely girding for challenges over other widely used drugs that plaintiffs' lawyers say have hidden and severe side effects or have been improperly marketed.

Potential solutions

The unfortunate consequence of the tremendous increase in product liability actions is that the public may well be denied therapeutic alternatives that may or may not be based on scientific considerations. Complete and effective public disclosure of known risks would help mitigate this, but tort reform may be the only real solution.

One area of notable concern is the continued proliferation of "junk science" purveyed by so-called medical experts battling one another in personal injury litigation. One answer, first proposed by Judge Learned Hand at the turn of the last cen-

ture and more recently endorsed by Justice Stephen Breyer, would be to substitute court-appointed expert medical witnesses for today's dueling partisan "experts," who often have a stake in the outcome and, more often than not, confuse rather than enlighten juries. Limits on punitive damages and a limited form of "loser pays" rules for legal fees could help as well. While progress is being made on these fronts, especially at the state level, much remains to be done.

■ NOW IS THE TIME TO ACT

Thomas Jefferson said, "Eternal vigilance is the price of liberty." In the biomedical context, vigilance requires an attention to appearances of conflict on a personal and institutional level. Our system of product approval, scientific research, medical care, and—not to be left out—the financial markets depends on a level of common trust.

We cannot hope to eliminate all potential conflicts of interest; indeed, it would probably not be prudent to

try to do so. But effective disclosure, together with open and transparent discussion, evaluation, and management, is one way to begin to reclaim the public trust. What is at stake is the personal and professional integrity of the biomedical establishment, the future of innovation, the state of public confidence, and the quality of patient care. These are pretty high stakes to be compromised through inaction. I wish you well in the deliberation and discussion of these important issues.

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Interactions of the public and private sectors in drug development: Boundaries to protect scientific values while preserving innovation

■ **ABSTRACT**

Industry, academia, and government have developed highly interwoven relationships in the pursuit of biomedical research. Establishing and maintaining boundaries among the public and private sectors at both the institutional level and the individual level is critical to protect core scientific values, preserve innovation, and allow product development to thrive. This article reviews principles that guide the interactions of these different sectors, sharing principles in place at Eli Lilly and Company as an example.

Biomedical research and pharmaceutical development are best conducted in a collaborative environment sustained by both publicly and privately funded research and by public policies that promote innovation. Since the passage of the Bayh-Dole Act of 1980, relationships between academia and industry have become closely intertwined. Because of the potential for conflicts of interest arising from these relationships, boundaries among the public and private sectors must be defined and maintained.

This article offers a “real-world” perspective on public-private relationships in pharmaceutical development. This perspective has evolved from my 9 years of experience in industry and 30 years, including a decade as a department chair, at the University of Alabama at Birmingham, as well as from my work on committees for the National Institutes of Health (NIH) and National Academy of Sciences. This paper

outlines basic principles for avoiding conflicts of interest and shares some boundaries established by Eli Lilly and Company as examples.

■ **DRIVERS OF INNOVATION:
AN INDUSTRY PERSPECTIVE**

What drives biomedical innovation? From the perspective of industry, the most important motivators are:

- Market-based pricing
- Intellectual property protection
- A predictable, expeditious regulatory climate based on sound science and innovative leadership
- Sustained public support for basic research
- A public policy environment that protects the current complementary and synergistic roles of publicly and privately funded research.

Although the first four factors are frequently cited, the fifth and final factor is rarely mentioned and is probably the least understood by the public and policymakers. Yet effective interaction between the public and private sectors is critical to the successful discovery and development of new medicines.

Traditionally, scientists in academic and government institutions have performed mostly basic (ie, fundamental) research, whereas those in industry have been more involved in applied and translational research. However, the gap between fundamental and applied research is rapidly narrowing and the boundaries are becoming blurred. Perhaps the two most significant factors contributing to this blurring of boundaries have been (1) the founding of the biotechnology (“biotech”) industry, with some of the first companies being based on technology licensed from universities (eg, Genentech in 1976), and (2) passage in 1980 of the Bayh-Dole Act, which facilitates technology transfer from the public sector to the private sector.

The influential business magazine *The Economist* has called the Bayh-Dole Act “possibly the most inspired piece of legislation to be enacted in America

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over the past half-century.”¹ Because of the impact of this legislation in the United States and the way it has been emulated by other countries, we are unlikely to return to the days when the commercialization process was stymied by slow technology transfer.

■ **A ‘TRIPLE HELIX’—
INDUSTRY, ACADEMIA, GOVERNMENT**

The two-stranded structure of DNA that codes the genome is popularly known as the double helix. Meanwhile, in the United States, the challenge of unlocking the secrets of human genetics—along with many other breakthroughs in biomedicine—depends on what some have called the “triple helix,” an interconnected complex of relationships between individuals and institutions in three sectors: (1) the vast research and development networks of private life-sciences companies, (2) universities, and (3) the research, grant-making, and regulatory agencies of government.²

Most people did not imagine that the Bayh-Dole Act would change the nature and scope of the economic partnership among industry, academia, and government so far beyond its original intent. A highly interwoven relationship between the private and public sectors has now developed, extending to all levels of academia and the research enterprise—and even to state and federal policymakers, who are encouraging universities to earn more of their income by licensing, royalty fees, and company start-ups.

A plethora of potential conflicts

The new relationships between the public and private sectors produce a plethora of opportunities for conflicts of interest of all types. They arise for several reasons:

- The number and diversity of players and stakeholders
- The enormous financial stakes for both the public and the private sectors
- A poor understanding of the nature of biomedical research (and of the drug development process specifically), leading to misperceptions and a lack of trust among all, including (most importantly) the public.

Few realize how interwoven this triple helix of industry, academia, and government has become.² A few striking examples from the University of California (UC) system highlight the interconnection³:

- One in three public biotech firms in the United

States is located within 35 miles of a UC campus.

- One in three California biotech firms was founded by UC scientists, including three of the world’s largest such firms (Amgen, Genentech, and Chiron).
- The University of California, San Diego, founded 113 biotech companies that were established in the San Diego area.
- The share of funding for clinical research in the UC system that is received from industry is about 10 times greater than the share received from the NIH.

High financial stakes

For academic institutions that take equity ownership in a start-up biotech company that has an initial public offering, academic equity has substantially outperformed licensing fees. In 2003 and 2004, 94% of academic equity value was captured by faculty members rather than by institutions, and half of these faculty members chose to remain in their academic positions rather than move to the private sector.⁴

With tens of millions of dollars at stake, it is not surprising that tensions are growing between faculty and university administrators, as well as between industry and academic institutions.

The financial stakes are also high from a societal perspective, as the development of new medicines continues to become more complex and more costly: public and private sector investment in biopharmaceutical research and development in 2005 consisted of \$39 billion from the pharmaceutical industry, \$28 billion from the NIH, and \$18 billion from the biotech industry. As we heard from Dr. Norka Ruiz Bravo of the NIH earlier in today’s conference, the funding mix increasingly includes public-private partnerships, a trend that is likely to intensify as the NIH continues to promote such partnerships.

■ **WHERE THE PUBLIC STANDS**

How have these developments affected public views toward biomedical research? In 2004, soon after the *Los Angeles Times* reported on conflicts of interest among scientists in the intramural NIH program, Research!America conducted a survey of the general public on views toward health-related research.⁵ The results showed a general lack of knowledge about how drug development takes place:

- Only 41% of those surveyed knew that most

Equity ownership in start-up biotech firms has substantially outperformed licensing fees in generating revenue for academic institutions.

drug development in the United States is conducted by pharmaceutical companies.

- Only 25% thought that institutions conducting medical research in this country, such as government, universities, and the pharmaceutical industry, work collaboratively rather than competitively.

At the same time, the results showed a good deal of openness to industry-academia-government collaboration in drug development:

- 91% thought that institutions *should* work together to develop new treatments and cures.
- 88% believed that it is a good idea for pharmaceutical companies to fund research in universities, hospitals, and other institutions.
- 69% believed that scientists should be allowed to profit financially from their discoveries.

■ ESTABLISHING BOUNDARIES

Given that industry-academia-government partnerships are not likely to diminish—and actually should be encouraged to enhance the synergy that leads to public benefit—our shared goal should be to identify and manage conflicts of interest so as to preserve core scientific values and the benefits of innovation for all of society.⁶

The following measures should be undertaken at individual and institutional levels to maintain public trust:

Encourage personal integrity of individual investigators through good laboratory practices, good clinical practices, and codes of ethics.

Encourage personal accountability for following guidelines that govern the individual components of the triple helix as well as those that govern interactions among its three component sectors.

Educate the scientific community, policymakers, and the public about the complexity of developing new medicines and the critical need for collaboration among the public and private sectors.

Provide appropriate oversight and enforce boundaries at all levels.

Punish appropriately those who break the rules.

Many boundaries between the public and private sectors have already been established by professional associations, institutions, and legislation, resulting in codes of conduct and guiding principles. Of the three components of the triple helix, the pharmaceutical industry is the most heavily regulated and monitored. In fact, the pharmaceutical industry is among the most heavily regulated industries in the world:

- The US Food and Drug Administration, the Office of the Inspector General, and the

Overview of 'boundaries' at Eli Lilly and Company

Principles of medical research

At Lilly, the conduct of research, payments to health care providers, and the communication of research results are governed by Lilly's "Principles of Medical Research." These principles, which were refined in 2004, were designed to minimize bias and conflicts of interest with academia and health care providers and to increase transparency, accuracy, objectivity, and balance in communicating the results of medical research.

Data access

Access to clinical data has been an important issue in the pharmaceutical industry. Any investigator conducting studies sponsored by Lilly is free to access and publish data generated at his or her site. For studies conducted at multiple clinical sites, the investigators who will serve as study authors have access to all study data relevant to the publication.

Publication

Lilly publicly discloses all medical research that is relevant to patients, health care providers, or payers, whether the results are favorable or not, in an accurate, objective, and balanced manner. Lilly complies with the authorship requirements of the International Committee of Medical Journal Editors, which were updated in October 2004.⁷ No payment is given for intellectual contribution or time spent authoring, and no ghostwriters or guest authors are allowed.

Lilly will not suppress research or veto any investigator's publication. Lilly reserves the right to review manuscripts, offer scientific comment, and delay publication for a short while only as necessary to take action to protect the company's intellectual property (eg, to submit a patent).

Funding of clinical research, continuing medical education

The medical division within Lilly is responsible for the design, conduct, analysis, and reporting of all clinical and outcomes research. Investigator-initiated grants are reviewed and evaluated by medical and scientific personnel, who also make the funding decisions.

The Lilly grants office reviews US requests for support from continuing medical education providers and makes funding decisions.

Funding of external research and continuing medical education is not contingent on the purchase or promotion of Lilly products.

Department of Justice all provide government oversight of the industry.

- The industry's trade associations (eg, Pharmaceutical Research and Manufacturers of America, International Federation of Pharmaceutical Manufacturers Associations) provide codes of ethics.
- Most scientists and physicians working in the industry are members of professional societies that have established guidelines and codes that govern interactions, including the Federation of American Societies for Experimental Biology and the American Medical Association.
- Individual pharmaceutical companies set codes of conduct, principles, and policies that must be followed by their scientists and physicians (see sidebar on previous page for an overview of some of Lilly's boundaries).

Failure to comply with these boundaries may result in a range of appropriate consequences, depending on the transgression.

■ CONCLUSION

Industry, academia, and government have developed highly interwoven relationships in the pursuit of biomedical research. While these relationships have been a powerful force for innovation, they give rise to a host of potential conflicts of interest. To manage these conflicts, all components of this triple helix need to have appropriate values-driven boundaries in place to preserve scientific integrity and the collaboration that advances patient care, and these boundaries must be well communicated and enforced.

Opinions vary on the details of how to avoid conflicts of interest, but three commonsense notions stand out:

- First, there needs to be a high level of *clarity* in internal conflict-of-interest rules to eliminate the gray areas in which accidental or willful abuses most frequently arise.

- Second, *accountability* must be relentless, which means that education and enforcement of conflict-of-interest rules are always job requirements within the triple helix.
- Finally, organizations need to promote *transparency*—the fullest possible disclosure of relationships, funding sources, and research findings—so that oversight can work.

Clear, rigorously enforced standards will assure the integrity of biomedical research while preserving the professional satisfaction of scientists and clinicians, the financial incentives for investors, and the breakthroughs for patients on which the triple helix depends.

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Beyond disclosure: The necessity of trust in biomedical research

■ ABSTRACT

Biomedical research is experiencing a crisis in public trust. Although the vast majority of clinical studies are conducted in an ethical fashion, public perceptions are fueled by well-publicized examples of unethical practices. Mistrust is further encouraged by the duality of the role of the clinical researcher, who is charged with both caring for patients and answering a research question. Disclosure is not adequate to fully address conflicts of interest in biomedical research; instead, efforts to protect patients' interests and enhance trust should combine disclosure with an attempt to reduce conflicts in the first place as much as possible.

Historical and recent breaches of ethics in the conduct of biomedical research have been well publicized, leading to a crisis in public trust. Moreover, the blurring of clinician researchers' dual roles as caretakers and scientists inevitably leads to confusion and distrust. This article discusses the historical context of breaches of trust, the inherent conflicts of interest in clinical research, issues surrounding disclosure, and the need to move toward better protection of research subjects' interests.

■ A CRISIS OF PUBLIC TRUST

Trust is an important issue surrounding biomedical conflicts of interest. As a bioethicist, I see just how central trust is to medical research from how frequently the media ask me some variation of the basic question, "Are all clinical trials rigged?"

As a faculty member in a medical school, I want to answer such loaded questions with, "No, of course not." Yet the fact that I am asked questions in such a provocative way provides a sense of public perception.

Dr. Kahn reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

Distrust is certainly compounded when the public reads reports that highlight real or potential research conflicts.

Overcoming a spotty history

Unfortunately, the biomedical research enterprise has a long history of trying to rebuild public trust, mostly to remedy breaches of trust. The Nuremberg war crimes trials following World War II, in which it was revealed that prisoners were misused for a variety of experiments, provide an early example. In the United States, the Tuskegee Syphilis Study, in which the US Public Health Service from 1932 to 1972 conducted deceptive research on African American men with syphilis in Alabama, is another important example. In more contemporary times, other cases can be cited.

As a result of these breaches of trust, the research community has had to work continually to convince the public that such cases are just a tiny portion of scientific research and that policies and practices are now in place to prevent serious breaches from recurring.

Track records can be read different ways

Earlier in today's conference, the notion that "trust comes from our track record" has been used in a positive sense: that biomedical research has accomplished great things. Yet this phrase can also connote the exact opposite sense: that the track record of biomedical research includes examples of misconduct. Although the good certainly outweighs the bad by a vast margin, the magnitude is uncertain. It does not take many bad cases to alter public perception and cause people to think that our track record is one of conflict of interest and the problematic use of human subjects.

■ CONFLICT IS INHERENT TO THE DUAL ROLES OF THE CLINICAL RESEARCHER

Notorious examples of ethical breaches are not the only factors that damage public trust. In addition, conflicts in biomedical research are inevitable when the researchers are also part of a team that provides clinical

care. If the same person is charged with both caring for a patient and answering an important biomedical research question, a problem of role responsibility arises. Blurring the roles of researcher and caregiver creates obvious conflicts on the part of the researcher and confusion on the part of research subjects.

Role responsibilities become even more complicated when financial stakes, equity interests, or consultancy arrangements are involved.

■ **DISCLOSURE ENHANCES TRUST BUT DOES NOT PROTECT**

Many people believe that one solution to conflicts of interest is to disclose everything—every potential conflict, financial or otherwise.

We already use disclosure extensively in the conduct of biomedical research in the United States and throughout most other developed countries. However, most people who are engaged in clinical research or other biomedical research involving human subjects can attest that disclosure does not always work to address the problems we are trying to solve.

Emerging research on subjects' views of disclosure

Recent studies have begun to evaluate issues surrounding disclosure. Weinfurt et al¹ examined what potential participants in biomedical research would want to know about financial conflicts of interest and how such information would affect their decisions. They found that people like to be informed of such conflicts, and that the importance of the disclosure to their decision to participate in the study depends on the level of risk that the research would entail. The authors concluded that disclosing financial interests enhances trust.

Disclosure does not equal protection

Yet disclosing risk is not the same as protecting people from risk. Experience with informed-consent procedures has shown that the process is inadequate and does not always work well to protect patients.

Blurring the roles of researcher and caregiver creates obvious conflicts.

Patients are already confused when their doctors invite them to participate in research. They wonder, “Am I their patient ... or something else? What is the doctor’s interest in relation to my interest?” We must recognize that adding even more information to the informed-consent process—ie, disclosure of financial interests—will only make the process more complicated and confusing.

Combine disclosure with serious conflict elimination

Rather than relying predominantly on disclosure, I believe it is more important for the research community to focus on the root of the problem and try to reduce conflicting relationships in the first place. Disclosure and reducing conflict are both important solutions, and not every conflict-associated relationship can be avoided, but I would argue that conflicts should first be eliminated to the extent possible.

■ **PROTECTING PATIENTS IS THE ULTIMATE GOAL**

Moving forward, we need to think about conflicts of interest and financial interests in research at three different levels:

- The individual researcher
- The institution
- The process (rules, regulations, and an oversight process).

We must not forget that our ultimate goal is to protect people—both by shielding subjects from risks that could arise from conflicting interests on the part of researchers and by ensuring that all patients have access to the benefits of continued research.

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Panel discussion

Applications in the real world: Case studies in defining boundaries and managing innovation

Dr. Adkison: Once upon a time, the rules and roles in medicine and medical product development were clear. Biomedical faculty worked full-time in universities, business was kept outside the academic ivory tower, and the two worlds didn't mix very much.

Those times have changed, and we now live in a far more complex world. The Bayh-Dole Act has turned over technology generated with federal funds to the universities that develop it, with instructions to partner with industry and move it to the marketplace. Faculty entrepreneurs have developed relationships with industry, and industry has entered the halls of academe. This complexity has ushered in a host of conflicts and conundrums, but in the process, much new technology has been moved to the marketplace to improve health care.

The conflicts of interest raised by this complex current landscape touch all aspects of the mission of academic medical centers—clinical care, research, education and training, and administration—as has been made abundantly clear by the earlier portions of this conference.

This panel discussion will attempt to bring today's discussion down to a practical level by exploring two case studies that spotlight specific challenges involved in managing potential conflicts that might arise from close interactions between industry and medical centers and their faculty.

Dr. Cassell reported that she receives a salary, grant/research support, and stock options through her employment with Eli Lilly and Company. Dr. Stossel reported that he has ownership interests in ZymeQuest, Inc., and in Critical Biologics Corp.; has intellectual property rights in Critical Biologics Corp.; has received consulting/advisory fees from Merck, Inc.; has received honoraria from Pfizer, Inc.; and has received royalties from Lippincott Williams & Wilkins. All other participants reported that they have no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

Case study 1: Dr. Tunnel and DeviceX

Submitted by Michael J. Meehan, Esq.
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Dr. Tunnel is an employed staff surgeon at Royalty Medical Center. He is also a consultant for DeviceX, Ltd., a company that manufactures medical devices. Dr. Tunnel receives \$25,000 a year from DeviceX for consulting on a variety of surgical devices. Royalty Medical Center purchases products from DeviceX, and Dr. Tunnel uses DeviceX products in his surgical practice. He currently conducts no research that is sponsored by DeviceX.

If Dr. Tunnel plans to implant Food and Drug Administration (FDA)-approved DeviceX products in his patients, should he disclose his consulting relationship to his patients?

Dr. Kahn: I believe that the need for disclosure depends on whether FDA-approved choices other than the DeviceX product exist. If there are no other approved devices, then he shouldn't necessarily have to disclose. But if there are, then the answer is yes, because he has a financial stake in the use of a particular product.

Dr. Pizzo: Let me put you on the spot and ask you to put yourself in the shoes of the patient. How would you then answer the question?

Dr. Kahn: If I were the patient, and Dr. Tunnel said that he wants to use the DeviceX product and that he has a financial relationship with DeviceX, I would ask him if there were other choices besides that device.

Dr. Pizzo: Dr. Tunnel may argue that he's not doing research on this device and that it's FDA-approved, so there is no reason to make a disclosure. And that may be appropriate. On the other hand, if you're the

patient, suppose that you have a complication or later discover that Dr. Tunnel did have financial stake in this. You might wonder why Dr. Tunnel did not disclose his stake. If your goal is to ensure trust, it seems that there ought to be disclosure.

Dr. Stossel: There is no harm in disclosing anyway; it seems like an easy thing. Ezekiel Emanuel at the National Institutes of Health (NIH) did a study of more than 250 patients in cancer trials in which the patients were asked if it mattered to them if their doctors had a financial stake.¹ The answer was overwhelmingly “no.” This question was asked numerous ways, involving stock, stock options, equity, cash, and others. To each, the patients said that it didn’t matter. They were also asked if they thought that a system for oversight existed. They did think that there was such a system. The question that wasn’t asked is if the patients would still not care even if there was no system for oversight.

Dr. Cassell: I side with Dr. Pizzo; in the interests of disclosure, transparency, and enhancing and building trust, I advocate informing the patient. To me, it wouldn’t make any difference if it were the only FDA-approved device. The question is whether it’s better to have that product or no device implanted at all. There is still opportunity for bias and conflict regardless of whether the product has regulatory approval.

Comment from audience: I’m a surgeon, and I can tell you that this practice is not limited to academic medical centers. There are many community hospitals in which an orthopedic surgeon will be asked to become a “consultant” to a device manufacturer, which may mainly consist of asking him to complete a compensation form with his Social Security number. He is paid a substantial amount of money—I doubt any of them would do it for as little as \$25,000—and it is linked to the use of certain prosthetic devices. As far as I know, in the real world those disclosures are not made to patients before the prosthesis is implanted.

Dr. Pizzo: Do you think they should be?

Same audience member: Yes, the relationship should be explained and the patient should be given credit for having the intelligence to sort it out. In cases in which the relationship with a company is legitimate, I think that will usually be quite clear to the patient. Some may even seek out a specific physician because he or she is recognized as an expert in the design of a particular device.

Comment from audience: The NIH survey of cancer patients that Dr. Stossel cited might be much less conclusive than it seems in that many of these patients face dying very soon. Do you think that the same overwhelming percentage that said that it’s all right would have said so 5 years before they got the cancer that is threatening their life?

Dr. Cassell: The same question occurred to me. It would be helpful to do a similar study in other patient populations and ask the follow-up question that Dr. Stossel mentioned. That could be quite valuable.

Dr. Stossel: When I was a medical student I was taught that there’s a conundrum. If you’re the type who likes to explain everything, some patients will appreciate being well informed, whereas others may think that you don’t have any confidence in what you’re doing or that you’re wasting their time. It’s not a one-size-fits-all proposition.

Dr. Pizzo: I agree; you have to adapt the information that you’re providing to the patient based on what he or she is willing to receive. At the same time, you do need to be transparent and at least offer the information, and then you can add the details based on the patient’s interest.

It would be fascinating to do the study that you proposed, but as a pediatric oncologist I find that patients, and particularly families, are very willing to accept experimental therapy when they think there is no other option. Even if you tell them that it’s a dose-finding study with no known benefit, the likelihood that they’ll sign up is still very high because of the fear and desperation that are part of their dilemma.

■ **NEXT LAYER OF THE CASE:
WHAT ABOUT OFF-LABEL USE?**

The FDA approves devices for certain specified uses. If Dr. Tunnel now wants to implant DeviceX products in his patients for off-label purposes, should he disclose his consulting relationship to his patients?

Comment from audience: In addition to giving information to the patient about the consulting relationship, it’s extremely important in this scenario that Dr. Tunnel make clear what off-label use means and what implications it has for the patient in terms of risk and benefit. I agree that it’s a discussion tailored to the patient’s level of understanding and willingness to hear the information, but it’s a crucial additional element.

Adapt the detail of the disclosure information that you provide to the patient based on what he or she is willing to receive.

—Dr. Pizzo

Dr. Adkison: What if the patient is counting on insurance payments? Does that make a difference?

Comment from audience: It does when the off-label uses are for diseases for which there are no research studies. There are many studies for common disorders such as osteoarthritis and lymphoma, but for very rare disorders you often have to resort to off-label use with the best available tools.

Comment from audience: I'm an orthopedic surgeon, and I've found that patients come in having already searched physicians' names on the Internet, where they can easily see a lot of our relationships with industry. For instance, information about many medical meetings is available online. Patients appreciate the dialogue. They often ask about these issues before we have a chance to raise them ourselves. If you have a frank discussion with your patients and tell them why you are doing exactly what you are doing—on-label, off-label, the issues that are raised, relationships—they appreciate it. They typically just move on to the next topic, which usually is how long they will be in the hospital.

■ NEXT LAYER: TECHNOLOGY LICENSING AND AN EXTENSIVE CONSULTING CONTRACT

Dr. Tunnel has conceived a special drug-eluting stent that could be deployed by a highly skilled surgeon to deal with challenging arterial anatomy or disease. Dr. Tunnel has worked with Royalty Medical Center's office of technology transfer, and the stent technology has been licensed by Royalty, as Dr. Tunnel's employer, to DeviceX. DeviceX would like Dr. Tunnel to oversee the early development of the research involving the stent that he conceived. DeviceX has sent him a consulting contract that proposes the following terms:

- *Dr. Tunnel will convene an expert panel to meet twice and help design the research, including both animal and human trials, at a compensation of \$20,000 per meeting.*
- *Dr. Tunnel will lecture at two national conferences to discuss currently marketed DeviceX products for a fee of \$10,000 per conference.*
- *Dr. Tunnel will generate a review article discussing any DeviceX product that is already FDA-approved, for a fee of \$10,000. If he does not have time to develop the article, DeviceX will assist in the writing.*
- *If Dr. Tunnel satisfies all of these elements in 12 months, he will get an all-expenses-paid trip to the Cayman Islands for two persons.*

Is the proposed consulting contract problematic? Should

Royalty review the consulting agreement before Dr. Tunnel is allowed to sign it?

Comment from audience: In this case, you could say that the inducements are excessive. Certainly the trip for two persons violates AdvaMed's code of ethics and all the other guidelines that we currently abide by. How do you manage the conflict? At my institution, we don't do research and consulting at the same time.

Dr. Pizzo: The issue of ghostwriting has come up at Stanford, and I was shocked by it because engaging in it violates every dimension of scholarship. At the most minimal level, my view is that if someone does it, that article should not be on his or her curriculum vitae. It seems to me that if you're a scholar working in an academic environment, you're going to want to do your own writing, not have someone do it for you, and you're going to want to examine the data and not have someone give it to you and then have you publish it. Otherwise, you're just behaving as a tool.

Dr. Stossel: I'm curious how widespread the use of ghostwriters and similar practices really is. Assuming that it goes on, how prominent and truly scholarly are the people who are doing it? You cease to be an opinion leader if

you're perceived as a shill for a company. I don't know who these people are.

Comment from audience: Being asked to lecture at national conferences to discuss a company's product is a very common experience for many faculty, especially because they are experts in the topic and it may be looked upon as expert information from an active clinician and researcher. The problem with a lot of these consulting agreements is that they don't discuss and carefully lay out who controls the content, the content itself, and the context in which the physician will be asked to deliver it, including all of the presentation materials that will surround the presentation and the introduction that will precede it. These factors will determine whether it is perceived as a genuine and legitimate scientific presentation or as a marketing presentation.

Dr. Kahn: This is getting awfully close to selling one's position; you have this supposed expertise and are taking money to speak as if you're independent when you're not. One would hope that the system would be self-regulating and that those people would cease to

You cease to be an opinion leader if you're perceived as a shill for a company.

—Dr. Stossel

be opinion leaders. The problem is that these kinds of relationships aren't disclosed, so there isn't a way for even their peers to know that this is what these people are engaged in.

Dr. Pizzo: Consider the good side for a moment. Someone is involved in carrying out a certain area of research and has tried to do it in a thoughtful way. Funding has come to them, in this case from industry. They want to share the information. I don't find that to be a negative as long as the disclosures take place.

Dr. Kahn: It depends on who controls the content; that is the crucial piece. Also, \$10,000 to give a lecture is a lot of money, and maybe that's a tip-off that it isn't quite as legitimate or defensible as it might be.

Dr. Stossel: It's very discipline-dependent. At the annual meeting of the American Society of Hematology, there are corporate-sponsored symposia that take place the weekend before the meeting. They're very popular because the practitioners are available to attend over the weekend. In my opinion, these symposia are of very high quality. For example, one symposium might be on anticoagulation in a broad sense, leaders in the field of anticoagulation will deliver the lectures, and the sponsor's product may or may not be mentioned. I think it's a win-win. If \$10,000 is the going rate, so be it.

Dr. Pizzo: I agree that the setting is really important. The American Society of Hematology does do outstanding educational programs, and anyone speaking there is going to be objective and stay focused on the primary topic. But if you translate that to a grand rounds or to a dinner event that residents have been invited to, that's when it gets confusing because the checks and balances are gone. The speakers are not before their peers, they're not particularly worried about their reputations, and if you look at the list of people who are lecturing at those sessions, they're not necessarily the thought leaders. They're often people who are simply willing to take the money to give those talks.

Comment from audience: Usually, the speaker discloses either in a consent form, in the conference, or in the paper that he or she has a conflict. But wouldn't it be much different if Dr. Tunnel disclosed that he was getting paid \$20,000 to give the two addresses? That information is never available. The landscape would change quite a bit if the amount had to be disclosed.

Dr. Adkison: That's a good point. A disclosure that

just says, "I have a financial relationship with the sponsor of this research," is perhaps not enough. A disclosure that says, "This company paid me X dollars to do such and such," is a better disclosure because whoever is reading the paper has more information on which to evaluate a bias or lack of bias in the paper.

Let's turn now to the other aspect of this latest layer of the case: the university has licensed Dr. Tunnel's technology to DeviceX, and now DeviceX wants him to oversee early development of the research and write protocols for the animal and human trials. Should Dr. Tunnel participate in designing the trials? What factors should be considered? Does it make a difference that he'll be paid to design the protocols?

Comment from audience: If one adheres to anything like the Association of American Medical Colleges (AAMC) recommendations for individual conflict of interest, Dr. Tunnel has already exceeded the level of income beyond which he should be presumptively prohibited, or have to demonstrate against a rebuttable presumption, from even participating in the design of the study. The argument by the AAMC is that even participating in the design is participating in human subject research. I'm curious how the panelists react to the AAMC standards that many of our institutions have adopted in one form or another.

A disclosure that says, 'This company paid me X dollars to do such and such,' is a better disclosure.

—Dr. Adkison

Dr. Stossel: I think there's a difference depending on whether it's a device or a drug being investigated. In this case, Dr. Tunnel is the guru in the use of a device that may not be ready for very widespread use at this point in its development; that may argue for his involvement in the study design. It's different with drugs, however, because it's not just a matter of ethics, it's a matter of common sense that a company would want to get as much replication and as much input into their technology as they can, so farming out the research and study design just seems like a commonsense approach.

Dr. Kahn: I was part of the AAMC task force that crafted the recommendations that were mentioned. The audience member is correct that there's a presumption that when a person has a level of financial interest over a certain dollar or equity amount, he or she has to make an affirmative case for being involved in clinical research, as opposed to someone else having to argue why that person should be excluded. We did point out that there are cases in which the individual has unique expertise, which is more likely to be the case in a device setting than in a drug setting.

Dr. Stossel: To be the devil's advocate, exactly what problem are we solving? Inventors don't design studies so that people die or to make their devices look as dangerous as possible; they want their devices to succeed. The assumption is that inventors are going to lie, cheat, and steal, but you could just as easily argue that they are going to bend over backwards to figure out how to make their product safe and effective.

Dr. Pizzo: This device-drug distinction is something we take into account at Stanford. We are much more willing, at least in the first phase of clinical trials, to recognize that the person who invented a device has the greatest capability, and therefore we may allow that person to be engaged in initial testing. By necessity, though, involvement has to be limited because the success of the device and the procedure will have to be extrapolated beyond that one surgeon.

Dr. Stossel: To show how crazy the rules at Harvard Medical School are, not only can I not participate in the design of a clinical study, I can't even be an author of a paper about my own technology.

Dr. Adkison: Any company whose long-term strategy is to market drugs and devices that are based on biased studies is seeking to cut its own throat because lawyers will eventually find out and come after the company.

■ NEXT LAYER: WITH EQUITY OWNERSHIP, HOW TO MANAGE INSTITUTIONAL CONFLICT?

As mentioned, the stent technology was licensed by Royalty Medical Center to DeviceX. In return, Royalty received 20% of DeviceX's outstanding common stock, a percentage of the stent's future worldwide sales, and two seats on DeviceX's five-person board of directors, one of which is held by Dr. Tunnel.

Should Royalty Medical Center adopt a conflict management plan that deals with Royalty's purchase of DeviceX products? Who should formulate and implement the plan—ie, who is sufficiently distanced to set up the institutional policy and deal with the individual and institutional conflicts of interest?

Dr. Adkison: I'll address the first question, since it's a straightforward one. Because Royalty now owns equity in DeviceX, it should definitely have a conflict management plan that provides some way of keeping its purchasing decisions at arm's length or that stipulates that Royalty will not purchase from DeviceX. How about the second question—who has the institutional responsibility for implementation and oversight?

Dr. Pizzo: I suspect that different institutions have

approached this in different ways. At Stanford, institutional review board (IRB) and conflict-of-interest oversight comes through the university, and so the dean of research or the vice provost of research is the person charged with that. That oversight is separate from the schools and provides an extra layer. The office of technology transfer is also not in the purview of the school of medicine but rather of the university. So there are firewalls that help in that regard.

Dr. Adkison: In this scenario, the equity is owned by the university, not by the school of medicine. In this case, who oversees the institutional conflict?

Dr. Cassell: Oversight by the board of trustees is not a bad idea, especially if you have a subcommittee that deals with these issues. Having served a year on the board of trustees at the University of Alabama, I believe that those boards have the expertise to deal with this type of oversight.

Dr. Adkison: The board of trustees is one suggestion. We also hear a lot from the AAMC about the importance of involving external people.

Comment from audience: I would like to digress for a moment. Although Dr. Tunnel is violating a lot of principles of ethics, what education did he have to fall back on? Often there is no curriculum in postdoctoral studies to teach research ethics. Nor was there necessarily an ethics curriculum during medical school or his surgical residency. The relationship he has with his patients is not a relationship of equals, but the ethical principle of coercion probably wasn't part of his boards. Even today, basic ethical principles are not a part of some medical curricula in the United States.

Dr. Adkison: Absolutely. We have a responsibility in our institutions to educate our students, our trainees, and our faculty in research ethics and medical ethics.

■ NEXT LAYER: DO THE INSTITUTION'S VARIOUS OVERSIGHT BODIES SHARE DISCLOSURE INFO?

The licensing agreement for Dr. Tunnel's stent also provides that Dr. Tunnel will personally receive \$10,000 upon achievement of certain milestones. One such milestone is surgical implantation of the stent in five dogs. Royalty Medical Center operates an animal facility where Dr. Tunnel could perform this, if approved, and Dr. Tunnel applies to Royalty's institutional animal care and use committee (IACUC) for approval to do this research.

How would Royalty's IACUC learn about the personal and institutional financial interests that lie behind this proposal? How would the conflict-of-interest committee know

that Dr. Tunnel has applied to do this animal research? What kind of mechanisms are in place?

Should Royalty permit Dr. Tunnel to conduct the dog surgeries in Royalty's own animal lab as opposed to using the lab and lab personnel of another facility?

Dr. Adkison: Many institutions have a practice or policy requiring review of all the consulting agreements that their faculty enter into and requiring shared files, databases, or some other mechanism for cross-checking. I believe that NIH regulations also require that the principal investigator certify potential conflicts or lack of conflict on the cover sheet for routing a proposal. If a potential conflict of interest is recognized, it goes to the conflict-of-interest committee.

Comment from audience: Our ideas of conflict of interest in the area of animal research or basic research are far less developed than those in human subject research. I'm the research compliance officer for a hospital, and the institutions that I've been involved with either don't have a transactional disclosure for animal or basic research, except if an NIH grant is involved, or are just beginning to have that kind of disclosure. Dealing with these issues in the area of animal research is a new endeavor at most institutions.

Dr. Adkison: Yes. The responsibility that federal regulations have placed on universities is not only to safeguard patients but also to protect against biased data, which presumably could arise from either animal or human research.

Question from audience: What if the question of licensing weren't involved in Dr. Tunnel's case? What if he was the inventor and was doing this research—so therefore the same skill set would be involved—but the financial conflict wasn't a key part of it? Does the financial conflict so affect our perception of what the results will be that it prevents us from allowing something that we would otherwise permit?

Dr. Stossel: You raise a good point. I have been doing research for 35 years, and I have never been subtly biased—I have always been totally biased. You have to be totally biased because on most days, things don't work and you need to overcome failure. It's a conceit to think that we're sanitizing research and that financial interests are worse than any other kinds of interests, such as promotions.

Comment from audience: My doctorate is in social psychology, and I think a key point has been omitted. There are many experiments showing that money and other inducements can change what people think,

what they believe, what they are willing to do, and even what information they pay attention to. At the same time, there's a ton of evidence that says that in most cases, we can't say what we are influenced by. In experiments time and time again, one group of people is influenced while another is not. You can ask the people who were influenced, "Did this influence change your opinion?" and they all say "no."

Dr. Stossel, many of your comments seem to ignore that the truth may be altered and patient care may be altered when these inducements get one to do things and think things that he or she wouldn't otherwise do or think.

Dr. Stossel: All I'm saying is that financial inducement is just one of many inducements. Why not get rid of them all? Of course, we can't do that. That's why I keep coming back to track record. I didn't mean it to be *aggregate* track record, which is a point Dr. Kahn raised in his presentation, but *individual* track record.

Dr. Pizzo: In my presentation, I mentioned career development and promotion as other conflicts, and I agree that they are very much a part of this process. That said, there is a weight to financial inducement, and you can see it influence behavior in so many different ways. Clinical faculty respond to incentives to do more relative value units, so there is a response to financial inducement.

You're saying, "Trust me—I'm Tom Stossel, highly recognized academician. I would never do anything wrong." I've known you for 35 years and I trust you, but that's not the issue because the public doesn't know you. Not everybody is necessarily going to follow the same pattern that you might. Not everybody is worthy of being trusted, regardless of what they may say.

Dr. Stossel: I'm not saying, "Trust me." I'm saying, "Don't trust me. Mistrust me. Be skeptical." Just because something is published in a prestigious journal doesn't mean it's true. All I can say is that, on balance, I try as best I can to be honorable but I'm going to make mistakes and, as I said, I am biased.

Dr. Pizzo: You say that being involved in research creates bias; I recognize that. But you are also saying that we don't need guideposts or regulations because at the end of the day, everything is based on personal trust. That's what I disagree with. I'm not for overregulation by any means, but I am for having certain standards so that people at least recognize the boundaries. In their absence, we would have organizational chaos.

Dr. Stossel: I couldn't agree more. We have speed limits, but we don't take people's cars away for speeding. We

catch them when they're speeding, we fine them, we imprison them for drunk driving. That's where I think we should be; I'm not advocating a free-for-all or chaos.

Comment from audience: As a prospective patient, every time the conversation leads to disclosing financial ties to patients, I get queasier and queasier. As a prospective patient—and an educated one at that—the sicker I get, the less capable I will be of evaluating disclosure information and the less interested I will be in doing so. I want to be able to trust. I am capable of doing the research but I don't want to do it; I want you to do it for me. It scares the hell out of me that you want to put the responsibility on me, when I'm at my sickest, to decide whether you are ethical and your concerns are compatible with my concerns.

■ NEXT LAYER: SHOULD THE INVENTOR BE INVOLVED IN HUMAN TRIALS?

Dr. Tunnel completes his animal research. In doing so, he has personally developed a new and unique surgical technique for using the stent under challenging anatomic conditions. He's eager to begin clinical trials with human subjects. DeviceX applies to the FDA for an investigational device exemption, and it is granted. Dr. Tunnel applies to Royalty's IRB for approval to conduct a single-site, phase I clinical trial involving five human subjects.

Should Royalty permit Dr. Tunnel to conduct this clinical trial in humans in Royalty's own hospital?

Dr. Adkison: I think the essence of this question is whether there are times when the unique skills required to test the device should override the rule that the conflicted investigator can't be the principal investigator in a clinical trial. Your thoughts?

Comment from audience: I think Dr. Tunnel should be allowed to do this because he has to work with his team. Surgery is not a one-man or one-woman deal. You have a team, you have equipment, and you need to see if the technique works; it's a high-risk technique. If I were on the IRB, I would have a great deal of difficulty with his financial conflict of interest, but I still think he should be permitted to do it. Yet it has to be transferable to other surgeons; otherwise it's pointless. He could do it on five patients and then train others to do it.

Dr. Stossel: A good historical example is hyperalimentation. In the early days, the physicians who developed this breakthrough technology had to live in

the hospital with the study patients, and the surgical team was up all night. You could never farm out a procedure like that until it became somewhat established.

Dr. Pizzo: Today at Stanford, we would do precisely that in a situation in which the technique was unique, still under development, and there was no expertise aside from the person who developed it. So at a very early phase, with oversight, we would let that happen.

Dr. Adkison: Dr. Pizzo, would you allow Dr. Tunnel to select the patients and obtain their consent?

Dr. Pizzo: No, we would not allow that.

Comment from audience: There may be some theoretical circumstances in which it would be okay for Dr. Tunnel to go ahead with this, but ultimately we're not

trying to develop a product, we're trying to find the truth to a question. Two things characterize good research. One is equipoise, which is an uncertainty about the answer to the question being asked. The other, which we have talked about, is not having a stake in the results of the research. I think this case violates both of these principles: there is a clear stake in the results here, and it is hard to imagine that Dr. Tunnel would have equipoise in finding out whether this device works or not. Simply disclosing these relationships to sick patients, as has been pointed

out, isn't enough. I would vote for not having this person do the research simply because there can't be equipoise and there is a clear stake in the results.

Dr. Adkison: And if Dr. Tunnel doesn't do it, it doesn't get done; you're comfortable with that?

Same audience member: There are some circumstances in which an IRB might determine that this must go forward because of some compelling reason why it cannot be done any other way, but I certainly would look for some other way, and then have others analyze the data, select the patients, obtain patient consent, and so on.

Comment from audience: I take exception to characterizing the outcome in this case as the research not being allowed to go forward if Dr. Tunnel is not allowed to participate. I'm affiliated with hospitals in the Boston area that are under the Harvard rule system, under which Dr. Tunnel's arrangement would not be allowed. Those rules wouldn't allow him to participate in this

As a prospective patient, the sicker I get, the less capable I'll be of evaluating disclosure information and the less interested I'll be in doing so. I want to be able to trust.

—Comment from audience

research *because he has chosen to have a financial interest*. The ideal solution would be to put the onus on the physician to make a choice between continuing the relationship or being involved in the research. He works in an academic medical center, so he can do the research, but he can't do so and at the same time be in a position to make a lot of money from it.

Comment from audience: A phase I study of a device is not intended to prove efficacy; it is undertaken in fully informed patients—and that includes conflict-of-interest disclosure—to rapidly understand the technique and to discover any changes in the device that might be necessary for progression to phase II.

This very complex problem of a physician inventor using his own device has been explored in a landmark paper by Dr. Richard Popp of Stanford.² That article discusses the oversight that is needed in this very special circumstance and also how to manage as early as possible the handoff from the expert investigator to a second set of nonconflicted investigators.

Dr. Adkison: Let's move on to another case study. Unfortunately, time won't allow us to get into all of its layers, but it's worth consideration because it raises a different kind of conflict of interest that institutions need to deal with.

The onus should be on the physician inventor to choose between continuing the relationship with industry or taking part in the research.

—Comment from audience

Case study 2: Dr. Parker, the junior colleague, and the start-up company

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Dr. Parker is chair of a clinical department in the school of medicine. She collaborates with a tenure-track assistant professor in her department, Dr. Adams, on an NIH-funded research project that results in an exciting novel compound with substantial promise as an important therapeutic drug. The university files a patent on the technology.

Is the collaboration between Drs. Parker and Adams a conflict of interest? If so, what kind? Should any safeguards be put in place?

Comment from audience: There clearly is a conflict of interest between the assistant professor and the chair because the assistant professor, being on a tenure track, has to do what the chair says.

Dr. Adkison: Yes, so this is an administrative conflict. As far as safeguards that might allow this collaboration

to go forward, something that has been tried, although with only moderate success, is to have all decisions concerning this tenure-track investigator—salary, allocation of space, promotion, and tenure—assigned to another chair in a similar department. This arrangement works at the initial level, but it can get dicey when the collaboration gets more complex, as we will see.

■ NEXT LAYER: THE START-UP COMPANY

The compound requires further research and development to make it attractive for licensing by a large pharmaceutical company, but funding for this additional research is not available from the NIH or the university.

Drs. Parker and Adams propose to form a start-up company, TheraRx, and ask the university to license the technology to their start-up company. The school of medicine has a policy that requires all such start-up activities to be approved by the dean's office and the office of technology transfer, and it also gives the university the right to take a reasonable amount of equity in the start-up company if it chooses. The school takes 20% equity in TheraRx. Drs. Parker and Adams fully disclose and seek approval, which is granted.

Should the school of medicine allow a chair to form an external company with one of its faculty members who reports to that chair? If so, should a management plan be put in place? What elements might suffice?

Dr. Cassell: Having been a former chairperson, and a research-intensive one at that, I think this arrangement should be allowed so long as appropriate oversight mechanisms and safeguards can be put in place and both investigators are fully informed of the consequences if they break them. In many cases, the chair can serve as the best role model for appropriate behavior. I realize that I'm biased, but I think it would be wrong to exclude the chair or the junior faculty member from this opportunity. Both could be protected by appropriate safeguards.

Dr. Adkison: Let me be the devil's advocate and point out that a department chair is an institutional official, and one could say that she should be held to a higher standard in terms of conflict of interest.

Dr. Cassell: I think that's true, but as long as the boundaries are defined, and as long as they act within those boundaries, they should be allowed to participate.

Dr. Stossel: I agree. University presidents, deans, and

department chairs are on boards of major corporations and receive stock or stock options from those corporations. Is a start-up company somehow unsanitary compared with those companies?

Dr. Adkison: Often the corporations on whose boards those university officials serve have no relationship with the university—they are not vendors to the university and do not sponsor research there.

Dr. Cassell: Dr. Pizzo, would Stanford allow this type of scenario?

Dr. Pizzo: Yes, under the right supervision, this type of partnership could be allowed.

Comment from audience: I'm sure that your hypothetical medical school has a mission of disseminating knowledge and caring for the sick. There is no NIH funding at this risk level and industry doesn't want to fund it either. If you're going to hold your leaders to a higher standard, what higher standard can there be than to tell your leadership to take this forward the only way it possibly can?

■ NEXT LAYER: SHOULD THE UNIVERSITY TAKE EQUITY?

The compound has great potential for use in treatment of disease. With this in mind, should the university take an equity position in TheraRx? What might be the downstream consequences?

Dr. Cassell: Yes, as long as the appropriate safeguards are in place.

Dr. Adkison: What are those appropriate safeguards?

Dr. Cassell: One would be total independence of any group responsible for the oversight. Another would be ensuring that you have the expertise in place to detect problems that might arise. These are two safeguards that initially come to mind.

The University of California system has made a conscious decision to take developments or discoveries much further before they license them to larger companies. Allowing the university to take equity in a company could be a tremendous teaching tool, in addition to providing a valuable source of income.

We've reached our limits in the amount of money that can be brought into universities through tuition and also possibly from state and federal funding. Universities have to look at other ways to generate income. We need to remain competitive in this area as a nation when you consider that the governments of all of the United States' technological competitors

are increasing their investments in basic research. Even Japan, as rigid and as cautious as it has been, has now set aside Ministry of Health money to promote interaction between academia and industry. The whole world is changing, and while we need to maintain a scholarship role for universities, we also have to make them a more integral part of economic development. Otherwise, I think we'll lose all around.

Dr. Pizzo: It is easiest to outsource development related to engineering or information technology, but it gets more complicated when there is a potential clinical trial involved, because that's ongoing research that involves patient care. Certainly, in the early phase, the university can be involved, as you've articulated, Dr. Cassell. But at Stanford, we divest our equity in a start-up company if a clinical trial of that company's product goes forward at Stanford. That is how we would draw the boundaries.

Dr. Stossel: In her presentation, Dr. Cassell mentioned the tension between institutional and individual ownership of start-up equity. One reason to keep ownership at the level of the faculty is that it can pay off even better in terms of future philanthropy to the university from faculty members with successful inventions.

Dr. Pizzo: That was Stanford's philosophy with regard to engineering. It didn't ask faculty for gifts; instead, philanthropy has been spawned from Silicon Valley, with faculty who have returned and contributed considerably to the university. This hasn't yet happened in the biomedical area, but perhaps it will over time.

Dr. Cassell: This brings up another point: industry-academia interactions have been much more common and much larger in scope in the physical sciences, including engineering, and even in business disciplines, in terms of consulting and the like. These fields have managed to either keep it from public attention in the media or else they have managed it very effectively. We need to look closely at how these fields have managed their interactions with industry.

Dr. Pizzo: I agree, but probably the key difference is that human subjects are not involved in those fields. When human subjects are involved, it gets muddy.

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Protecting subjects without hampering research progress: Guidance from the Office for Human Research Protections

■ ABSTRACT

The Office for Human Research Protections (OHRP) within the US Department of Health and Human Services aims to protect human research subjects without hampering scientific progress. Institutions can foster safe and efficient research by guarding against conflicts of interest, making research subject safety a priority, having a well-staffed institutional review board, and continually training new investigators. The OHRP provides education on its Web site (www.hhs.gov/ohrp/) and is available to make site visits to offer guidance on federal regulations.

Scientific and technological advances have created new challenges in the area of human subject protection. Protecting subjects who participate in the testing of new medical products is essential for maintaining public trust and is regulated by both the US Food and Drug Administration (FDA) and the US Department of Health and Human Services (DHHS). These two government entities have similar, but not identical, regulations governing human subject protection.

The Office for Human Research Protections (OHRP) within the DHHS is obliged to protect subjects and ensure that they understand their rights as research participants. Because medical innovation is also an important goal, the challenge for the federal government is to balance protecting research subjects with facilitating medical product development.

This article discusses issues that often impede medical products from moving smoothly through the development, testing, review, and approval processes, including conflicts of interest and delays involving either research institutions or the investigators them-

selves. Suggestions for enhancing efficiency while remaining compliant with human subject protections are covered, as are ways in which institutions can work with the OHRP to meet their goals.

■ CONFLICTS OF INTEREST IN HUMAN RESEARCH

The OHRP continually tries to identify and minimize issues that undermine the public trust. A known or potential conflict of interest on the part of investigators is often an important concern. Although financial conflicts are the first to come to mind, other conflicting interests can arise in research, including institutional, professional, and administrative types.

For example, an institutional review board (IRB) itself may be put in a conflict-of-interest situation: a member of the IRB may be urged to approve a research protocol by administrators or colleagues because a specific investigator who is needed by the institution may go elsewhere if approval is not granted. Both the FDA and the DHHS regulate conflicts of interest that arise from being a member of an IRB.

How OHRP handles complaints

When the OHRP receives a complaint about a potential conflict of interest in a research project, an initial investigation is performed to determine if enough evidence exists to pursue the matter. As for any complaint, we try to gather as much specific information as possible, preferably in writing, about the people and institutions involved and the exact nature of the problem.

The next step is to inform the research institution that a complaint has been made about a conflict of interest, and to ask if it is aware of the problem. If the institution is aware, we ask what actions have already been taken to resolve the problem. If it is not aware, we request that it investigate the matter and get back to the OHRP within a specific time period to discuss how it intends to handle the matter.

Dr. Schwetz reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

OHRP's purview

The OHRP has jurisdiction over studies that are conducted or supported by DHHS funds unless an institution has agreed, through the Federalwide Assurance agreement, to comply with the DHHS regulations for all research involving human subjects, regardless of the source of funding. If the OHRP does not have jurisdiction over a study in which a complaint arises, we can only inform the institution that a problem has arisen. If we have jurisdiction, we gather more information to determine whether we should pursue the matter further.

We also contact the FDA to determine if it has jurisdiction over the matter. We may transfer the case to the FDA, or, in some cases, both the FDA and the DHHS handle it, such as if the study is funded by the National Institutes of Health and involves a product controlled by the FDA.

■ IRBs CAN HINDER PROGRESS

The IRB sometimes hinders institutional research. A fine line exists between appropriate research oversight and actions that end up impeding research progress. Certain problems tend to arise that reduce efficiency:

Overinterpretation of regulations by institutions is a common problem. For example, some kinds of research are exempt from IRB oversight, but an institution may insist that it become involved regardless. This rightly upsets investigators and unnecessarily consumes the time and energy of the IRB. Often, extraneous burdens are added to avoid liability.

Treating guidance as regulation. Often the FDA or the OHRP issues a guidance that the IRB interprets as a regulation, resulting in the choice of a course that the investigator would not normally take. The purpose of guidance is to allow for flexibility in appropriate circumstances.

If an IRB spends too much of its time on tasks that are not mandated, it may not devote enough attention to its real work, which not only might contribute to research delays but may jeopardize the safety of research subjects.

■ INSTITUTIONS CAN FOSTER PROGRESS

Institutions can take a number of steps to promote good research practices and thereby create an environment that is conducive to safe and efficient product development:

Establish an institutional culture of concern for subject safety. Sometimes the OHRP team—after

meeting with an institution's administrators, IRB members, and investigators—senses a culture of indifference to protecting research subjects. Institutions of this type tend to get into trouble later with conflicts of interest and noncompliance with regulations.

Ensure a supply of well-trained investigators. Continuous training and mentoring of young investigators ensures that a continued pool of educated scientists is available, which is critical for good institutional research.

Achieve accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Voluntary participation in the accreditation program run by the nonprofit AAHRPP (www.aahrpp.org) helps ensure that procedures are in place to identify conflicts of interest before problems arise. An increasing number of institutions are becoming accredited, raising standards nationwide.

■ WHAT DELAYS RESEARCH PROJECTS?

IRB obstacles

The slow timing of IRB review is a major complaint on the part of investigators, delaying product development.

Lack of expertise among IRB members is often the primary problem. A common mistake committed by inexperienced IRB members is to send protocols back to investigators

for revision without providing specific directions to resolve the issues.

IRB overwork is another common problem. Understaffing the IRB leads to delays.

Antagonism may arise between the investigators and the IRB members, often because investigators believe that their protocols are returned for revision for trivial reasons. The antagonism may become an obstacle in itself, getting in the way of solving the problems and moving the protocol through.

Investigator obstacles

Investigators themselves often contribute to delays in the approval process.

Lack of knowledge on the part of investigators of federal regulations and guidelines, state and local laws, and institutional standard operating procedures often hinders protocol approval. Investigators may believe that they personally do not need expertise in regulatory matters so long as someone on their research team does. However, understanding how to minimize subject risk is critical for designing and writing an acceptable protocol. Most researchers have minimal training

Very few institutions have been shut down due to noncompliance with OHRP regulations; our goal is to prevent problems.

in medical ethics, which often leads to trouble when coupled with a lack of knowledge of regulations.

Lack of experience. Mentoring of young investigators by experienced investigators is critical. Inexperienced investigators not only need information, they need training to think through problems for themselves.

Rogue investigators. Occasionally an investigator unpredictably makes a poor decision, putting subjects—and the research sponsor—at risk.

■ OHRP FACILITATES RESEARCH

The OHRP continuously seeks input from the research community to learn about ways to improve the oversight process. Very few institutions have been shut down because of noncompliance with our regulations in the past several years; our goal is to prevent problems.

Site visits possible

We offer educational materials on our Web site (www.hhs.gov/ohrp/) and hold educational conferences and workshops. We also have a quality improvement program: an institution can invite us to spend a day and a half at their site so that we can examine

standard operating procedures and IRB meeting minutes and discuss questions from investigators.

We are happy to discuss issues with IRB members and investigators as well as with institutional officials, the public, funding sources, government agencies, and clinical research organizations.

Partners in clinical research

Investigators and the OHRP are partners in developing and testing new medical products and in protecting research subjects. Maintaining the trust of the public is critical to making the process run smoothly in the long run.

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Fraud, conflict of interest, and other enforcement issues in clinical research

■ ABSTRACT

Fraud in scientific research is a widespread problem. It can involve falsifying data or documents, or knowingly failing to comply with regulations protecting research participants. Fraud can be committed by individuals, institutions, or corporations; in the context of research, fraud often is motivated by considerations beyond financial gain. Institutional review boards (IRBs) are designed to ensure that researchers comply with human research subject protections, including conflict-of-interest controls, but IRBs may fail to do so if investigators avoid existing IRB processes or if IRB members do not take responsibility for addressing actual or potential conflicts of interest.

Most cases that I handle as an associate US attorney involve fraud or deception of some kind. The conflict of interest (or motivating factor for research misconduct) is sometimes financial. However, some research misconduct arises when a researcher hopes for professional recognition or simply believes intuitively in the “right” answer despite evidence to the contrary. Juries are most likely to hold an individual researcher responsible if they are convinced that he or she knowingly deceived others and had a plausible motivation to cheat.

This article discusses how fraud is defined in the courts and uses historical and recent cases to illustrate how fraud frequently manifests itself in scientific research. Guidance on the roles of institutional review boards (IRBs) in avoiding and detecting fraud is offered. This article expresses my personal opinions and is not official policy of the US Department of Justice.

■ THE FRAUD STANDARD

How is fraud defined and how does it apply to conflict-

of-interest questions in medical research? The concept of “fraud” has existed in the common law since its beginnings. However, with the passage of the first mail fraud statute in the 19th century, the federal courts have been called upon to provide a definition. The definition I rely on is “the knowing breach of the standard of good faith and fair dealing as understood in the community, involving deception or breach of trust, for money.”

Each part of this definition is worth analyzing:

“**The knowing breach...**” Knowledge of fraud, or whether the bad conduct was intentional, is the first concern when determining whether to prosecute a case.

“**...of the standard of good faith and fair dealing...**” Standards of fairness evolve over time and may differ depending on the point of view. Subjects participating in clinical trials may have different standards than investigators. If a case goes to trial, jurors think, “What if I signed up for a clinical trial? What would I expect? What would I rely upon? What is the standard of good faith and fair dealing with respect to me or my family?”

“**... as understood in the community...**” The community encompasses all of society, not just the research community. The jury, made up of people from all walks of life, determines whether community standards are met.

“**...involving deception or a breach of trust ...**” Deception typically involves a lie or a false document, or actions undertaken with the intention of creating a false impression (for example, “Photoshopping” a document or borrowing a photo from another study in violation of a protocol and without clearly labeling it as manipulated or borrowed). Breach of trust arises from specific relationships, and depends not only on specific undertakings but on the expectations of those within the relationship. This can be problematic in a research context. After all, what exactly is the responsibility to research participants of a principal investigator who is also a treating physician?

“**...for money.**” Many people cheat, lie, or steal for money. But in research, money may not be the prime motivator. Investigators may commit fraud for glory, for the desire to be first, or because they are certain that

Mr. Sheehan reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article apart from his salary from the US Department of Justice.

their conclusions are correct even if the data do not support them. Fraud cases require a victim. In recent years, some courts have expanded the concept of money to loss arising from fiduciary or agent relationships, including loss of benefit from economic relationships.

■ HISTORICAL CASES OF RESEARCH FRAUD ABOUND

Numerous examples of fraud occurred with prominent scientists in the past:

- Sigmund Freud fabricated cases studies.
- Isaac Newton altered records of lunar and solar sightings to fit his theories.
- Louis Pasteur made false statements about the first public trial of his anthrax vaccine.
- Gregor Mendel's plant breeding results were too good to be true.

What motivated these scientists to commit fraud? It is perhaps easiest to explain in Pasteur's case: he had a competitor with a vaccine that worked better. He publicized a study in which all his research subjects—sheep—survived anthrax exposure, but he had secretly used his competitor's vaccine.

■ RECENT FRAUD CASES

A few recent cases of scientific fraud demonstrate the varieties of scientific fraud, as well as the outcomes:

- Dr. Eric Poehlman of the University of Vermont was sentenced in June 2006 to 1 year in jail for falsifying and fabricating research data related to menopausal changes and metabolism.
- Professor Elizabeth Goodwin of the University of Wisconsin resigned in 2006 for making false statements in genetic research.
- Dr. Gary Kammer of Wake Forest University resigned in 2005 for fabricating two families in a National Institutes of Health (NIH) grant application.
- Professor Ali Sultan, a malaria expert at Harvard University, resigned in 2004 after falsifying a grant application.

The Office of Research Integrity in the US Department of Health and Human Services received one third more misconduct allegations in 2005 than in the previous year. The increase can be explained, in part, by a change in the regulatory process as well as by greater awareness of potential problems.

■ DEFINING AND PROVING RESEARCH FRAUD

Scientific or research fraud, defined as intentional misconduct, can take many forms, including fabricating or falsifying data, plagiarism, overstating or misreporting results, or misrepresenting credentials. But

key to proving criminal or civil fraud is determining the role of a conflict of interest: a jury must be convinced that a scientist would have a reason to cheat.

Related federal violations

Statutes other than those pertaining strictly to fraud are also relevant to cases concerning scientific research. One of the most important is section 1001 of title 18 of the US Code (18 USC §1001), which pertains to false records, statements, or documents (including billing records, statements to the US Food and Drug Administration [FDA] or the NIH related to approval of products or conduct of grants, written records of IRBs, and reports of results). The false documents need not have been submitted to the government to fall under this statute; they need only be part of the record created to obtain government approvals, or to be maintained at the institution to record and demonstrate work on a grant or an investigation covered by a New Drug Application to the FDA.

Fraud against the IRB

Defrauding an IRB is equivalent to defrauding a research grantor or sponsor, since virtually all grantors and sponsors make obtaining IRB approval a condition of the grant. Several problems that can lead to fraud occur commonly:

Knowing failure to request and obtain IRB approval. Sometimes institutions engage in research on patients but do not declare it as treatment. An article may result without an application ever having been submitted to the IRB or the IRB otherwise having been involved. Most major publications (at least in theory) now require compliance with human subject protections as a condition of publication.

Knowing failure to notify the IRB of protocol changes. Obtaining initial approval for research can be a long, difficult process. If changes are subsequently made to the protocol, some researchers forgo seeking the necessary approval again.

Knowing failure to comply with subject disclosures and protections, including conflict-of-interest protections. The IRB may require that certain disclosures be made, and investigators may not follow through. The IRB is not set up as an enforcement agency but rather relies on the good faith of investigators to assure compliance with study conditions.

Knowing failure to comply with third-party review entities or nongovernmental directives. Problems may arise if an investigator falsely represents that he or she complied with institutional guidelines or those of the Association of American Medical Colleges¹ that complement or implement government regulations or are

part of a condition precedent to grants (such as IRB approval). In such cases, the fact that a rule is not a government regulation is not the end of the discussion. If a grantor (including the NIH) testifies that a representation of compliance was relied upon or could be relied upon in connection with funding, then a knowing false statement of compliance may be considered fraud.

Violation of ‘good faith and fair dealing.’ A lawyer might ask the following questions when determining whether “good faith and fair dealing” was violated in a research project:

- Did the investigator ignore warning signs?
- Did the investigator decide not to consult guidance?
- Did the investigator seek advice and not follow it?

Knowing failure to comply with FDA guidance. FDA guidance is not, by itself, binding. An alternative approach may be used if it satisfies the requirements—and the spirit—of an applicable statute or regulation.² However, in determining whether a researcher’s and an institution’s conduct was consistent with the community standard of good faith and fair dealing, lawyers will ask why the decision was made to ignore or contradict the guidance.

Billing issues

A common financial conflict-of-interest scenario involves researchers who obtain grants and use the funds to meet other departmental goals. For example, services might be billed that are already paid by the study sponsor, services other than routine costs might be billed, or services might be billed that were meant to have been provided free as part of subject consent. These kinds of problems can be avoided by having adequate central billing controls and a system that can mediate such conflicts.

Failure to meet reporting requirements

Often we find resistance to compliance with reporting requirements that are mandated by law. Significant adverse events that occur during clinical trials must be reported to the FDA. Sometimes deaths of study participants are listed as the participant being “lost to follow-up,” which may be true technically but is intended to deceive. In other cases, we see study participants allegedly being followed up with contacts or telephone calls years after their deaths.

IRBs also require reporting of adverse events, and many states do as well. Within the past few years, more than 30 states have enacted legislation requiring the reporting of medical errors that occur inside medical facilities and result in death or injury.

Deaths must also be reported to the coroner. Reports from the US Inspector General comparing

death records with nursing home reports have found that up to one third of nursing home deaths were never reported. Dr. Adil Shamoo of the University of Maryland has suggested that a study comparing death records of research subjects with the reported death rates in clinical trials during the study period may reveal even more striking discrepancies.³

■ CASE STUDIES IN RESEARCH FRAUD

The following examples illustrate cases of research fraud committed by individuals, institutions, and corporations.

Data fabrication

As mentioned previously, Eric Poehlman, professor of medicine at the University of Vermont, fabricated research data in studies of menopause and aging, involving false grant applications and papers. After pleading guilty under 18 USC §1001, he was permanently excluded from all federal health programs.

In a similar case, BioCryst Pharmaceuticals, together with researchers from the University of Alabama at Birmingham, reported false results from a lymphoma study. The incident resulted in the conviction of a nurse and a scientist. Both the university and researchers involved in the study had financial interests in the outcome.

In cases like these, the IRB may receive warning signs suggestive of fraud or conflict of interest and should not hesitate to take a second look at the research results and other relevant documents.

Failure to disclose risks and report adverse events

In September 1999, 18-year-old Jesse Gelsinger died as a result of a participating in a gene therapy study at the University of Pennsylvania. The research team did not stop the study after learning of serious toxicities and failed to disclose risks to participants. James Wilson, lead investigator of the study at Penn, was barred from performing research on humans until 2010.

The conflict of interest in this case allegedly included significant financial interests in the outcome of the study by some of those involved in it. However, a contributing factor to the research team’s failure to halt the study was eagerness to be the first to achieve success in genetic therapy of a particular rare disease.

Modern-day Martin Arrowsmiths

Another common motivator is the desire for simple professional advancement: graduate students covet their PhD and job placement in a hot field, postdoctoral fellows hope to be hired at a better institution, and principal investigators want to conclude a study successfully and move on to the next one. Sinclair Lewis’ novel *Arrowsmith* describes medical research 80

years ago, but the personalities are similar today; the character of Martin Arrowsmith wanted to save the world and felt intuitively that he was on the right track even when the evidence was inconclusive or contradictory. The same qualities of intuition and persistence that characterize good scientists have on occasion led some to suppress or ignore contradictory evidence, or to ignore warning signs of risks to subjects.

In the Gelsinger case, the Department of Justice attempted to create a corporate integrity agreement model with the NIH to ensure that what happened at the University of Pennsylvania does not occur again. Documents relating to this case illustrate how the Department of Justice and the NIH approach these issues.⁴

Technology-fueled fraud through data manipulation

In the 1970s, William Summerlin used black felt-tipped pens to make it appear he had successfully grafted tissue from black mice to white mice. Today, powerful image-processing software has made fabrication of research data easier and more convincing.

Recent cases of data manipulation involve Charles Rudick, a Northwestern University graduate student who falsified illustrations of electrophysiologic recordings using imaging software; T.S. Ramalingam of the California Institute of Technology, who plagiarized and electronically manipulated images; Dr. Regina Horvat, a Northwestern University postdoctoral fellow who falsely labeled a Western blot result to support her results in an NIH grant; and Dr. Hans Geisler, a physician at an Indianapolis hospital who solicited a false report from a pathologist and submitted it to justify enrollment in an NIH protocol.

Mike Rossner, editor of *The Journal of Cell Biology*, found 8 cases of major improper digital image manipulation in a survey of 800 manuscripts.⁵

FRAUD APPEARS TO BE WIDESPREAD

How extensive is the problem of fraud in medical research? Several studies have found that more than 40% of surveyed researchers were aware of misconduct but did not report it.^{6,7} Gardner et al reported in 2005 that 17% of surveyed authors of clinical drug trials reported that they personally knew of fabrication in research occurring over the previous 10 years.⁸ These kinds of sociological survey results may not be totally reliable, but the findings suggest that a substantial problem exists.

The Office of Research Integrity, which oversees research funded by the US Department of Health and Human Services, receives 265 reports of research fraud each year. The National Science Foundation receives 100 complaints of misconduct each year.

GOVERNMENT ENFORCEMENT OF RESEARCH STANDARDS

Researchers who are caught cheating are devastated, and often their lives are ruined. Pursuing these cases through legal and/or disciplinary means is still important, however, because crucial values are at stake: honesty and accuracy in research, as well as the public trust.

In identifying cases appropriate for investigation or prosecution as criminal or civil violations, as well as other cases appropriate for deference to an internal review, the Department of Justice strives to make institutions responsible for the conduct of their employees and researchers, to create a climate of high ethical standards, and to support robust internal efforts to achieve these goals. Researchers must also be held accountable for intentional misconduct and for undisclosed conflicts of interest that threaten their objectivity as researchers and protections for research subjects.

We also aim to empower patients and research subjects. Much of the research in the United States involves participants who have much less power than the researchers and institutions have. Because subjects often are not in a position to protect themselves, the IRB has the responsibility to do so. If the IRB repeatedly fails in providing needed protections, or if the researcher evades the protections in place, the government must on occasion intervene to assure that these protections are enforced.

TAKING RESPONSIBILITY IS KEY

Well-drafted language in contracts relating to research often tries to shift specific risky or costly responsibilities, including conflict-of-interest and patient protection obligations, onto another party. This is what good lawyers are trained to do, but in research it can mean that no one takes responsibility. A study sponsor may hire a contract research organization. The contract research organization might hire a site management organization and shift responsibility to it. In turn, the site management organization may claim that the principal investigator, university, or medical center is responsible, and that it was relying on the undertakings of those subcontractors. At the end of the process, however, the sponsor, the institution, the investigator, and the IRB all have compliance and oversight responsibilities that remain their obligations by law, whatever the language of their contracts.

Another way that some academic and research institutions have tended to manage conflict is by establishing committees. In fraud cases, I have often seen numerous committees set up in addition to the IRB, including compliance committees, institutional

conflict-of-interest committees, ad hoc committees to review allegations of research misconduct, and committees on privilege and tenure.

It is important that each party's responsibilities are understood so that when potential conflicts arise, someone will identify the problems, pay attention to them, and resolve them before they become real issues. We do not suggest that one individual do all the work but instead that someone be responsible for ensuring that problems are identified and addressed. Someone must guarantee that federal guidelines and institutional policies are adhered to, and someone must have the authority to inquire about the activities of researchers and their departments.

■ THE ROLE OF THE IRB— INTELLIGENT, INDEPENDENT OVERSIGHT

Most types of law (eg, tax law, immigration law) use a unitary body of statutes, regulations, and series of opinions upon which cases are based. Most questions that arise in these fields can be answered by searching the relevant body of law.

This is not the model used in setting up IRBs. Because of the belief that doctors and professional researchers know more than the government does about how best to protect research participants and patients, the IRB processes were designed so that overseers understood and assimilated the issues and applied their knowledge to protect the participants as well as the research system.

In some cases, IRBs are completely independent of an institution. Regardless of affiliation, an IRB is expected not merely to follow regulations blindly but to exercise independent professional judgment about how to protect the interests of research subjects. In many situations, there is no definitive right answer to an issue that arises.

■ THE ROLE OF REGULATORY AGENCIES

Regulatory bodies have expanded to include private and nonprofit agencies and the traditional government watchdogs, a trend that reflects society's expectations of high community standards (Table 1). These organizations provide guidance on the community's expectations of the IRB and what potential jurors might expect in terms of conduct on the part of a researcher.

'Bad acts' draw attention

Lawyers are taught the maxim, "The guilty fleeth where no man pursueth," and are trained to look for cover-ups, obstruction, and alteration or destruction of records. We also investigate whether anyone has been told to lie or has been threatened, something that is more likely to occur if there is something important to hide.

TABLE 1
Agencies relevant to research fraud

Office for Human Research Protections* (www.hhs.gov/ohrp/)
Office of Research Integrity* (http://ori.dhhs.gov)
US Food and Drug Administration (www.fda.gov)
Office of Human Subjects Research, National Institutes of Health (see http://ohsr.od.nih.gov/guidelines for regulations and ethics guidelines)
Association for the Accreditation of Human Research Protection Programs, Inc. (private accrediting agency) (www.aahrpp.org)
Association of American Universities† (www.aau.edu)
Association of American Medical Colleges† (www.aamc.org)

* Part of the US Department of Health and Human Services

† Provides guidelines for researcher conduct

Other red flags for regulators include misleading or cheating sponsors, including the US government; fraud related to approval of a drug or medical device; the use of fake science; and undisclosed conflicts of interest.

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Panel discussion

Conflicts, compliance, and enforcement: Government priorities and initiatives

■ **WHO IS RESPONSIBLE FOR ENSURING ETHICAL BEHAVIOR?**

Dr. Kahn: Much has been said today about where responsibility lies for ethical problems that may arise in research. We know that institutional review boards (IRBs) are overburdened and already take a long time to do their work. Where else do we turn?

Dr. Schwetz: There isn't one entity that can adequately be responsible for every issue that may arise in research. While the Office for Human Research Protections (OHRP) deals most directly with the IRBs, institutions are also held responsible. A signatory official must provide assurance that the institution will comply with regulations in order to receive Department of Health and Human Services (DHHS) funds, such as from the National Institutes of Health or the Centers for Disease Control and Prevention. This official is sometimes referred to as the designated "go-to-jail person." Joking aside, responsibility is definitely shared between the institutional official, the IRB, and the investigators.

The government must also be accountable for its actions. For example, if we hear from the research community that our guidance is widely misinterpreted, we must step in to correct it, especially if subjects may be put at risk as a result.

Finally, we must also consider the degree to which subjects must be responsible when participating in research. Who is to blame if they are injured for not following study directions clearly provided to them?

■ **THE IRB AS A LAWSUIT TARGET**

Mr. Sheehan: It's important to look at where the IRB enterprise is going from a legal perspective. As Marshall McLuhan said, lawyers drive into the future by looking in the rearview mirror. So whenever we

see a good idea behind us, we try to apply it going forward. Over the past 10 years, corporate governance has become a popular model—the Sarbanes-Oxley Act, signing certifications, etc. So now IRBs are being discussed in the legal literature the way that corporate boards are. This is despite key differences between the two: unlike IRBs, corporate boards have legions of advisors, are allotted substantial funds to manage, and are often are paid very well for very little work.

Alan Milstein is an active lawyer in the area of liability of researchers, IRBs, and research institutions. He has some very aggressive theories and strategies, some of which have been successful in obtaining significant settlements. In the case of Jesse Gelsinger, who died from taking part in a gene therapy study at the University of Pennsylvania, Milstein brought a private action and sued every member of the IRB. I disagree with this as a governmental strategy, as it dissuades people from serving on IRBs, but this may be the direction in which private law is heading.

Question from audience: As far as I know, Alan Milstein and his aggressive tactics of suing IRB members have not been successful so far in court. Is that true?

Mr. Sheehan: Milstein has brought a number of cases and has succeeded in blocking some motions to dismiss and in bringing about some settlements. He pursues cases in which patient outcomes are poor and he alleges bad conduct on the part of the IRB, the principal investigator, or the institution. The institutions are not prepared to defend themselves because the underlying facts can be complex. Experience shows that, to some extent, the law evolves out of an approach like this, and only several years later is there real analysis of the opinions by the court about whether the law is reasonable. This issue is much discussed in the legal literature, but so far I haven't seen opinions that support the full implications of Milstein's approach. However, some very large settlements have been granted, which suggests that IRBs may be held liable in the future.

Drs. Kahn and Schwetz reported that they have no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article; Mr. Sheehan reported no such interests, relationships, or affiliations apart from his salary from the US Department of Justice.

■ IDENTIFYING PROBLEM INVESTIGATORS

Question from audience: The California Medical Association did a study about 30 years ago to try to define the kind of doctor who is most likely to be sued for malpractice. They came up with a profile of an arrogant, uncaring, uncommunicative person. Has anyone done a similar study to predict who is likely to commit fraud, to help identify them before they cause trouble?

Mr. Sheehan: I am not aware of any such study of fraud perpetrators. The malpractice suit study that you mention tried to determine if the doctors who got into trouble did so because they made a mistake or because they had personality disorders. The researchers found that problem personalities were more often to blame. However, if we assumed that the findings of this malpractice study extend to researchers as well, how would we know that some of these traits don't reflect traits of researchers? I've noticed that many of the people I've investigated are incredibly confident of their ability to get the right answers. This is probably the same type of person who is successful in research.

Comment from audience: One study I've seen showed that people who are more likely to get in trouble with state medical boards for various violations are also more likely to have been cited for dishonesty or to have been in trouble in some other way when they were medical students. Perhaps we should focus on enhancing professionalism during medical school and start to identify students who are likely to get in trouble later.

Dr. Kahn: A recent national study that looked at questionable research practices among scientists deliberately included a large subsample of early-career scientists,¹ so there is definitely an interest in how early in one's professional life this behavior might start.

Dr. Schwetz: I have asked IRB chairs if, among the investigators who submit protocols for review, there are perhaps two or three people who make them nervous because of their interaction with the IRB. Perhaps they are intractable or unwilling to listen to advice about how to get their protocol approved. The IRB chairs invariably can immediately think of some, but when asked what they can do about it, they answer, "Nothing; we have to wait for something to happen."

Mr. Sheehan: Researchers in the compliance field have developed theories for how poor behavior arises. The "personal failure" explanation says that bad people are the ones who do bad things. The "sociological" explanation says that most people inherently have about an average proclivity to do something wrong

and that their conduct is guided by what they see around them in their organizations. If one accepts the sociological explanation, it is incumbent upon the institution to create a culture of compliance in which poor behavior is not supported or encouraged.

■ NOVEL SURGICAL TECHNIQUES: BEYOND THE REACH OF OVERSIGHT?

Comment from audience: I am a colorectal surgeon and I remember watching a procedure with a group of observers in the operating room at Cleveland Clinic many years ago, in which a prominent surgeon performed something that none of us had ever seen before. Someone asked the surgeon if he had always done the procedure that way, and he said he had. Here he was doing something very different from normal operating procedure, and I'm sure the thought of running it through the IRB never crossed his mind.

While the use of new devices and drugs must go through rigorous IRB review, in the operating room surgeons are quite free to invent new procedures and promote them to others. Yet the potential of severe harm to patients from this kind of experimentation is very high.

Mr. Sheehan: This subject really merits an entire conference by itself. The practice of medicine is not regulated by the federal government but by the states, and generally they give physicians a wide berth to practice in a manner they feel is appropriate.

In such situations the line between treatment and research can be blurred. Surgeons try new techniques all the time, and that is desirable, to some extent. These new methods are unlikely to be submitted to the IRBs or to involve the federal government.

Three questions can help determine whether a new technique is justified for use: (1) Is use of the technique a knowing breach of the standard of good faith and fair dealing, as understood in the community? (2) Has the patient been advised of the risks and benefits? (3) Does the surgeon believe that the technique is most likely to get the best result?

Dr. Schwetz: I am occasionally alerted to such situations, and some do fall under the jurisdiction of the OHRP, although this example would not unless funding came from DHHS. I have discussed this question of whether and how to oversee novel surgical techniques with David Korn of the Association of American Medical Colleges, and I know that organization is looking into it.

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Creating an institutional conflict-of-interest policy at Johns Hopkins: Progress and lessons learned

■ ABSTRACT

Unlike policies that address biomedical conflict of interest for individuals, conflict-of-interest policies for academic medical institutions are rare and lack consensus principles. Johns Hopkins Medicine is currently developing an institutional conflict-of-interest policy that emphasizes case-by-case review and disclosure of conflicts to research subjects and the public. Implementation of the policy will focus on transparency, consistent enforcement throughout the institution, thorough employee education about the policy, and ongoing policy review.

While biomedical conflict-of-interest policies for individuals abound, policies on institutional conflict of interest are few. Johns Hopkins Medicine (which includes the Johns Hopkins Hospital and Health System as well as the Johns Hopkins School of Medicine) is completing development of a policy on institutional conflict of interest. This article discusses the impetus and rationale for the new policy, its key provisions, and broader issues for academic medical centers looking to effectively manage institutional conflict of interest.

■ CONFLICTS ARE INEVITABLE; MANAGING RISKS IS KEY

Conflicts of interest are inevitable byproducts of translational research and institutional interaction with industry. The Bayh-Dole Act of 1980 mandated such interaction by giving US universities, small businesses, and nonprofit organizations intellectual property control of their inventions that result from federal government-funded research.

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Dr. Miller reported that he has no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

Institutional relationships with industry generate financial interests. Conflicts of interest are driven by economics, such as the needs of institutional budgets and local economies. The inherent risk is that financial interests will compromise or endanger primary objectives, such as patient safety, research integrity, independence in clinical decision-making, and, most fundamentally, the public trust and institutional credibility.

Academic medical centers should focus not on eliminating conflicts of interest altogether but on managing the risks associated with them.

■ THE STATE OF CONFLICT-OF-INTEREST POLICY

Individual conflicts: An emerging consensus

A relative consensus on policies concerning *individual* conflict of interest has taken shape in recent years. Leading academic medical centers have robust policies concerning individual conflicts as a result of direction from the Association of American Medical Colleges (AAMC), the Association of American Universities (AAU), the AAMC's Forum on Conflict of Interest in Academe, and similar bodies. Disclosure of individual conflicts is now required in publications and presentations, and individual conflicts of interest are limited in clinical research.

There remain some inconsistencies among institutions in their policies on individual conflicts, particularly on points such as disclosures to research participants and the scope of clinical research activity allowed, but policies on individual conflicts are now widespread and characterized by an emerging consensus.

Institutional conflicts: Little progress, growing pressure

In contrast, *institutional* conflict of interest remains unregulated and largely unaddressed in a formal way. Few institutions have policies on institutional conflicts, and little consensus exists on principles, despite some guidance from the AAMC, the AAU, and the US Department of Health and Human Services. Meanwhile, highly publicized cases of institutional conflict of interest have arisen recently at prominent

institutions such as the University of Pennsylvania, University of Toronto, Cleveland Clinic, and Johns Hopkins Medicine. These cases have driven concern about institutional conflict of interest in Congress, at the National Institutes of Health, and at academic medical centers themselves.

■ WHAT CAN HAPPEN WITHOUT A POLICY ON INSTITUTIONAL CONFLICT

Johns Hopkins Medicine recently had a formative experience in the context of having no institutional conflict-of-interest policy in place. We entered into a business arrangement with Klinger Advanced Aesthetics (KAA), which markets skin care products under the name Cosmedicine. The company's objective was to add scientific rigor to its skin care products; Johns Hopkins' objective was to generate income for the institution. Johns Hopkins agreed to help design clinical trials of KAA products and analyze the data but not to endorse the products in any way. In the original agreement, Johns Hopkins was to receive payments, have stock in KAA, have a seat on the KAA board, consult on research, and define the use of our name.

In April 2006, the *Wall Street Journal* ran a front-page story about this arrangement, claiming that Johns Hopkins endorsed the products. Following this, there was a substantial renegotiation of our contract with KAA.

Lessons learned

What lessons did Johns Hopkins learn from this experience?

- If it "smells" like research, the public will probably consider it research despite disclaimers.
- Owning stock must be justified while engaging in research.
- Clear, consistent policies on institutional conflict of interest are needed, both internally and across all academic medical centers. These policies should cover more than just clinical research.
- Institutions must educate their employees about their policies.
- Institutions must enforce their policies.

■ CREATING A POLICY AND A CULTURE OF ETHICS

Johns Hopkins University is in the final stages of drafting a policy regarding institutional conflicts of interest that will include both the university and the health system. The policy is guided by a pair of principles: (1)

institutional conflicts of interest are not inherently problematic and risks need to be assessed on a case-by-case basis; and (2) risks cannot be assessed without disclosure and clear procedures.

Key provisions of the draft policy are as follows:

- Disclosure will be required from institutional officials and from institutional actors responsible for technology transfer.

- Disclosures will be cross-checked against research and other activities.

- A process of case-by-case review will be used to identify and evaluate risks.

- Institutional conflicts of interest will be managed, reduced, or eliminated, based on the case-by-case details.

- The default position will always be to disclose potential conflicts to research subjects, the scientific community, and the public.

More broadly, we are working to create a culture of ethics by attempting to evaluate risk, anticipating how the public will view it, and having clear, accessible, and manageable policies and guidelines in place. We are working to get the message out as widely as possible (there are about 30,000 employees in the system) and to educate employees not just about what the rules are but about why they are important—that institutional credibility and scientific integrity are at stake.

Educate employees about why the policy is important—that institutional credibility and scientific integrity are at stake.

tional credibility and scientific integrity are at stake.

Implementation strategies

Although we begin from the assumption that our faculty and administration consist of honest people, we intend to enforce our policies consistently. Our process will be transparent with regard to review criteria, possible outcomes, and management techniques. We are moving toward implementation of an electronic disclosure process linked to other databases (those of the institutional review board, the institutional animal care and use committee, etc.) so that all employees have access to the same information.

We already have trained more than 12,950 employees on the conflict-of-interest policy using Web-based didactic, small-group training. We stress leading by example: institutional officials should set a good example, as should principal investigators and the institution as a whole.

The policy will be reviewed over time to ensure that it is effective and that we are monitoring compliance, practicing consistent enforcement, and addressing breaches. Currently, cases drive our poli-

cies, and we advocate evaluating cases individually rather than devising a blanket policy.

■ MOVING FORWARD AT HOPKINS AND BEYOND

Changing institutional culture is not easy and can be slow and labor-intensive. Change takes resources and commitment from the entire leadership, including institutional officials, department heads, and faculty.

On a national level, research needs to be done to better understand the positive and negative impacts of conflicts of interest on research integrity, the translation of research to the bedside, and health care costs. We at

Johns Hopkins are trying to add data to the debate.

Another of our goals is to educate the public, both locally and nationally, about the issues and considerations involved in institutional conflicts of interest. Indeed, the challenge for all academic medical centers is to educate Congress, the press, and the public about these issues and to demonstrate that we are managing these conflicts appropriately.

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Managing ethical performance in organizations: Insights from the corporate world

■ ABSTRACT

Medical organizations can learn at least three lessons from the recent spate of corporate scandals and the regulatory response they triggered. One is the importance of identifying and eliminating those conflicts of interest that pose unacceptable risks to an organization's reputation or to an industry's public profile. Second, although disclosing a risk attendant to a conflict of interest is of crucial importance, disclosures are not automatic absolutions, regardless of how full and complete they may be. Third, an organization's ethical performance is first and foremost a function of its culture. If there were any doubt, the likes of Enron Corporation and WorldCom confirmed that formal controls and legal sanctions are no substitute for the importance that members of an organization accord to playing by the rules and working with integrity.

I approach this subject from a corporate perspective; although a business school professor at present, my career began in public accounting and included service as a chief financial officer in the securities industry. And although my experience with medical research institutions is quite limited, I have observed that struggles to manage conflicts of interest in the corporate realm bear more similarities than differences with those that confront managers of not-for-profit organizations.

Using recent corporate scandals as examples, I will address a few issues that might be pertinent to medical organizations:

- How to determine which conflicts of interest cannot be managed and must be eliminated
- The limitations of risk disclosures
- The importance of fostering a positive ethical culture, and some ideas on how to do so.

For a more complete discussion of these issues,

readers are referred to the report entitled *Embedding Ethics in Business and Higher Education: From Leadership to Management Imperative*.¹

■ WHICH CONFLICTS TO ELIMINATE?

Conflicts of interest are ubiquitous facts of organizational life. Fortunately, most of them can be managed without any untoward consequences. In other words, the possibility that the conflict will give rise to unethical conduct can be reduced through a combination of oversight, sanctions, and incentives. However, some conflicts present temptations too seductive to resist, regardless of how assiduously they are managed. In other cases, a practice appears to represent a conflict in opposition to an organization's professed duty to its customers or patients, regardless of whether the practice is genuinely hazardous or not.

The corporate world has produced some vivid examples of how important it is to identify and eliminate unmanageable conflicts of interest before they damage the reputation of an organization or the standing of an entire industry. A method for distinguishing manageable from unmanageable conflicts is to ask questions such as the following:

- Would our reputation survive a *candid* disclosure of this practice, one that included its true nature and our genuine motivations for seeing it persist?
- What are the chances that we could convince the public that what appears to be a pernicious conflict of interest is actually innocuous?

Conflicts that cannot be candidly disclosed

The insurance brokerage division of Marsh & McLennan Companies was mired in scandal when the attorneys general of several states filed complaints of bid rigging and deceptive uses of contingent commission agreements (ie, arrangements whereby an insurance company rebates a portion of the premium to the broker). In his public statement, the Massachusetts attorney general observed that although Marsh had disclosed the existence of contingent commission agreements, the company had consistently concealed their "true

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nature.” Such obfuscation was not surprising, since to lay out the “true nature” of these practices and Marsh’s motivation for them would have been an exercise in self-indictment. In effect, they would have had to say something along the lines of, “Notwithstanding the trust we elicit and the values we profess, we engage in sneaky practices for selfish reasons.”

Clearly, if candidly disclosing the true nature of a conflict would impair an organization’s reputation, then the practice giving rise to the conflict is a good candidate for elimination.

Conflicts that cannot be defended

As Dr. Thomas Stossel argued earlier in this conference, conflicts of interest in medical research are often quite innocuous and have little or no influence on many patients’ willingness to undergo treatment. Nevertheless, the absence of bad intent may not protect against institutional embarrassment and reputational harm. Depending on the severity of public attitudes, eliminating the conflict might represent the best option. The accounting industry provides a case study of the perils of acting otherwise—ie, that persisting in the face of public concern, whether such concern is justified or not, invites a potentially intrusive regulatory response.

Accounting firms’ practice of consulting for their audit clients was controversial before the series of corporate scandals involving Enron Corporation, WorldCom, and Arthur Andersen LLP. Some observers supported the practice because it provides greater insight. Others opposed it on grounds that the quest for consulting fees would impair an auditor’s independence. Years ago an effort was made to diffuse the controversy by striking a compromise: footnote disclosure of the consulting fees paid to the auditor. That requirement was lifted several years later after a showing that the disclosure had no influence on investor behavior.

Fast forward to December 21, 2001, when Enron declared bankruptcy. Shortly thereafter, the notion that gargantuan consulting fees had compromised Andersen’s audits of Enron went from a working hypothesis to received wisdom. Seven months later, Congress passed and the president signed into law the Sarbanes-Oxley Act, portions of which severely impacted the accounting profession. The act went far beyond the typical device for regulating capital market activity (ie, disclosure) by barring the provision of consulting services to audit clients.

Time will tell whether this constraint is positive or not. I mention it here because the experience of the accounting profession bears the attention of the biomedical community. The accounting industry’s failure to manage its conflicts of interest—perceived or real—triggered a ferocious regulatory response. The stakes of managing such conflicts could not be higher—a fact that is hard to appreciate until one’s own profession is on the receiving end of hastily drafted legislation.

To draw one more insight from this episode, most conflicts of interest emanate from practices that have a beneficial side. For this reason, elimination of conflicts often can be expected to engender some costs, both predictable and unintended. One possible consequence—certainly relevant to biomedical research—is that the profession’s long-term attractiveness and its ability to lure top talent may be compromised.

■ DISCLOSURE IS NO PANACEA

Throughout this conference there have been numerous mentions of disclosures and what counts as adequate and complete. Although this is a crucial consideration, I would caution against loading too much ethical weight on the fact that a risk was revealed.

Necessary but not sufficient

The motivation for disclosure is something along the lines of “forewarned is forearmed.” In reality, some warnings

do not arm. If the warning concerns a complex practice whose attendant disclosure is equally complicated, then the patient (or customer, investor, etc.) should not be expected to accurately assess his or her risk. This is especially true in medicine, where trust in their physician will incline most patients to discount the risks and exaggerate the benefits of a proposed therapy. Simply put, physicians are ethically bound to care for the health of their patients, a duty that is not discharged by enumerating risks alone.

Do disclosures change behavior?

To return briefly to the example from the accounting industry, consulting fee disclosures were discontinued because they were being ignored. They produced no measurable impact on financial statement users. This was not an altogether surprising finding since investor trust in the representations of public accountants has been rewarded over time. One would not expect it to erode over the disclosure of an arrangement that had existed for decades.

This raises a similar issue in the biomedical con-

The accounting industry’s experience bears attention: Failure to manage conflicts of interest can trigger a ferocious regulatory response.

text: Do clinical research participants care about investigators' financial arrangements? Even assuming that the participants may want to know, would they act differently with that knowledge? These are questions that deserve formal research. I conducted some research of this type on a crudely informal basis by describing a financial arrangement between a research physician and a medical device manufacturer and asking a few people whether such an arrangement would affect their decision to proceed with treatment from that physician. Most people I queried said that it would not because their reasons for seeking the treatment would be more important. Some said that the knowledge of a conflict of interest might prompt them to seek a second opinion; for obvious reasons, this may or may not be a wise reaction.

My point is that the quest to "cover the bases" with increasingly complex disclosures of financial arrangements may or may not have the desired result. If patient welfare is the ultimate goal of risk disclosures, then the way patients typically respond to these documents deserves greater study. We should not assume that disclosures are performing a function without empirical evidence to back it up.

■ FOSTERING ETHICAL PERFORMANCE: LESSONS FROM CORPORATE SCANDALS

Recent corporate scandals have been carefully documented by a variety of outside experts. These "organizational autopsies" contain several lessons applicable to the academic medical center that is intent on improving its ethical performance, by which I mean the extent to which it satisfies the ethical expectations of its stakeholders and society writ large.

Leadership is necessary but insufficient

The ethical tone of an organization is set at the top. But although a highly ethical leadership is vital, it does not guarantee ethical performance. This is particularly true in complex organizations with multiple leaders, in organizations that sprawl geographically, and during times of organizational instability. In short, without systematic management of ethical performance, calls for ethical conduct are little more than cheerleading.

Culture trumps compliance

Failures along the lines of Enron and WorldCom are case studies in the limits of compliance efforts, be they internal controls, outside gatekeepers, or the vast

array of oversight systems (eg, whistleblower hotlines). Among the reasons for these catastrophic breakdowns is one that cannot be eliminated: compliance mechanisms are only as good as the culture in which they operate. Said another way, culture trumps compliance.

As long as organizations are comprised of people, unethical conduct will be a fact of organizational life. However, those organizations with positive ethical cultures self-correct from such conduct and grow stronger as a result. In contrast, the same conduct can destroy an organization with a degenerate culture because instead of repelling and correcting the behavior, the culture reinforces it.

The notion that ethical culture is of overarching importance is the one finding that cuts across all of the scandalous failures of recent years. But it can also be gleaned from the reaction of the US Sentencing Commission to these same episodes. An advisory group to the Commission dealt with the uncomfortable finding that Enron and WorldCom would have received favorable culpability scores. That is, both organizations had in place the sort of controls that would have ameliorated any fines for criminal fraud. Boldly, the Commission asked, "What did we miss?" The answer—"the culture"—is contained in the report of

the Ad Hoc Advisory Group on the Organizational Sentencing Guidelines (October 2003).² Thus, whether or not one accepts this conclusion, the ethical culture of an organization will be considered in future culpability score calculations.³

■ COMPONENTS OF MANAGING ETHICAL CULTURE

Creating and maintaining a positive ethical culture requires proactive management efforts. As with any important objective, managers carrying out these efforts need detailed goals, proper incentives, and the resources to succeed. I have discussed what this entails in a previous publication;¹ the key elements are as follows:

- The organization's baseline ethical culture must be assessed.
- Those with operating responsibility should be assigned the task of managing the assessment. If the culture is acceptable, then they should maintain it in that condition; if the culture could stand improvement, then they should have clear targets.
- Through successive assessments, a manager assigned this responsibility should be held accountable for the results—ie, his or her compensation

Without systematic management of ethical performance, calls for ethical conduct are little more than cheerleading.

should reflect whether goals are achieved.

- In addition to systematic management of the culture, it is often necessary to harmonize an organization's strategy and tactics with the ethical expectations of key stakeholders and society generally. More times than not, this will require elimination of pernicious conflicts of interest and similarly corrosive practices.

- Ideally, efforts should be made to cause the ethical condition of the organization to become as transparent as possible. Insofar as this factor is the one piece of information that is predictive of ethical performance, board members and other interested parties would be well advised to demand it.

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Moderator**SUSAN H. EHRINGHAUS, JD**Associate General Counsel for Regulatory Affairs,
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Washington, DC**Panelists****EDWARD D. MILLER, MD**Dean of the Medical Faculty, Johns Hopkins School of Medicine,
and CEO, Johns Hopkins Medicine, Baltimore, MD**EDWARD SOULE, CPA, PhD**Associate Professor, McDonough School of Business,
Georgetown University, Washington, DC**Panel discussion****Guidelines and performance:
Creating a culture of ethics****■ WHAT CHANGES INSTITUTIONAL CULTURE?**

Ms. Ehringhaus: I'd like to lead off this discussion with a couple of very fundamental questions: How do we define ethics, and what are the markers of a culture of ethics? Dr. Soule, since you've written a good bit in this area, I'll let you tackle this one.

Dr. Soule: I think I would say that ethics involves an informal system of behavioral norms whose purpose is to reduce harm to others. In the medical context, the key areas where ethics matter seem to center around the patient's interaction with the doctor and the hospital. So a positive ethical culture would be one in which people put patient welfare ahead of everything else—not because “it says so” in the code of conduct, but intuitively. When novel situations arise or when the best course isn't completely clear, that interaction with the patient will be the default priority if the organization has a positive ethical culture.

Ms. Ehringhaus: Can you give us an example of an organization that turned itself around by creating a culture of ethics?

Dr. Soule: As Dr. Miller said in his presentation, changing culture is very difficult, but it does happen. It tends to work most effectively after a scandal: new people are usually brought in, everyone is held accountable, and creating a culture of ethics becomes a high priority. My biggest worry in such situations is that the gains will be followed by backsliding: culture can be incredibly unstable. The only way to prevent backsliding is through systematic assessment and making the assessments transparent. I don't subscribe to

As we developed our policy at Johns Hopkins, the comment we heard over and over from employees was, “First tell us the rules.”

—Dr. Miller

the theory that “we manage what we measure”; we measure all kinds of things that never get managed. On the other hand, if something is not measured, it is not likely to be attended to.

Ms. Ehringhaus: Dr. Miller, what's your take on this from the academic medical center perspective? Just how capable are medical institutions of either turning themselves around or enhancing their existing culture? Does your experience at Johns Hopkins speak to this?

Dr. Miller: I think the death of Ellen Roche [a previously healthy 24-year-old who died from volunteering in a 2001 medical research study at Johns Hopkins University] had a dramatic effect on the whole issue of human subject protection at Hopkins. In some ways, we as researchers were somewhat arrogant, believing that we knew the best ways to do things, and then this happened. Since then, incredible safeguards have been put in place, and employees have been trained to know the rules. When employees comply with those rules, the work of the institutional review board is more effective. I think we have a very good program, but it took this event to bring Hopkins to its knees, and we all felt it. Another important event was the death of Josie King [an 18-month-old child who died due to medical error at Johns Hopkins Hospital in 2001]. Such events can galvanize an institution to really change.

Ms. Ehringhaus: Does it take a sentinel event to prompt real change?

Dr. Soule: It doesn't hurt. New leadership can also bring about change in an institution's culture. One example is when Paul O'Neill, who since served as US treasury secretary, became CEO of Alcoa. When he arrived, Alcoa already had a good worker safety

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record, but he made worker safety a key priority and drove the accident rate down to virtually zero. How he did it is a great case study in how to alter a culture. First of all, he made safety his personal priority. Second, he terminated a highly ranked superstar—an employee manager in Brazil—for failing to report an injury within 24 hours of its occurrence. Interestingly, since O’Neill left Alcoa, safety measures have continued to improve—an indication that a real cultural shift occurred.

Dr. Miller: I understand that O’Neill also had his computer set up so that every morning the first thing he saw on his monitor was a report of injuries and accidents at Alcoa worldwide so that he could identify trends early.

■ BUSINESS AND ACADEME: IS THE ANALOGY VALID?

Question from audience: Are businesses really a good model for academe? Businesses come and go, make mistakes, fail, and declare bankruptcy. They are sometimes dissolved, and their leaders are sent to jail. Academic institutions, with few exceptions, seem to never go away. We’ve had some of the same academic institutions for the past 300 years even though some have had their share of missteps along the way. Are they just better than businesses? Or is there a kind of institutional resilience in academe that’s just different in character?

Dr. Miller: Academic institutions have a resilience that no other institutions have. Those of us in leadership positions at an academic institution know that we hold our positions for only a short time. We try to protect the institution and make it move forward. We’re going to make mistakes, but a place like Johns Hopkins that has so much tradition can withstand much because of its culture and heritage. I don’t think the situation is comparable in many companies.

Dr. Soule: Although there are big differences between the two models, they also have a tremendous amount of overlap. I think that both, frankly, can learn from one another. One of the big differences between the two models is that education has been a growth industry for the last 300 years, and that doesn’t happen with many products or services.

Another difference, and an interesting one, is that bribery has found its way into virtually every nook and cranny of corporate America, but if you look at a university, about the only place you might expect to

find bribery is on the admissions committee, since admission is probably the most precious resource the university has, which relates to education being a perennial growth industry. Of course, money is not the only corrupting force: status and prestige are very important in academe, but they generally are not qualities that are enhanced by rigging the system.

■ MEDIA INFLUENCE ON INSTITUTIONAL CULTURE

Question from audience: I’d like to revisit the Johns Hopkins case with the cosmetics company that Dr. Miller mentioned in his talk. He said that Johns Hopkins’ relationship with the company “didn’t fly” with the public, but how do we know that it merely didn’t fly with a few reporters from a couple of newspapers? To what extent do the media accurately reflect the culture in medicine, and to what extent does media attention guide what we do as institutions?

Dr. Miller: That’s a good point, because about 5 weeks after the *Wall Street Journal* broke the story, the *New York Times Magazine* ran an article that was actually quite positive. It said that this was an area where research was needed and that Hopkins conducted itself very well: we disclosed all interests and did not perform the actual research. So, two totally different sides were taken by two newspapers: the *Wall Street Journal* looked at the darker side of the picture, while the *New York Times* was very positive. How things are presented can be very important to public opinion.

Question from audience: I was interested in the comments in your presentation, Dr. Miller, about creating a culture of ethics not just at Johns Hopkins but on a broader stage. You mentioned efforts to educate the public—can you expand on that? The public’s ability to weigh and evaluate differing media accounts such as the ones you just mentioned depends on how well we educate the public about how we do things, especially if we are proud of our activities.

Dr. Miller: I don’t have all the answers on this, but after the death of Ellen Roche, Johns Hopkins invited the *Baltimore Sun* newspaper to do a retrospective piece on what occurred and the changes we have made since. There’s also an upcoming public television story that will deal with the Josie King death, and it too will highlight changes that have been implemented at Hopkins and at other institutions to improve the culture of safety. We’ve tried to use the media when we can, as well as to

Embedding compliance into everyday activities is preferable to making it an add-on activity.

—Dr. Miller

take other opportunities to get our programs in front of the public, such as by meeting with top government agency officials, testifying before Congress, and the like.

■ DOES MANDATORY ETHICS TRAINING WORK?

Question from audience: Our academic institution is planning to implement mandatory ethics training for all employees, with separate modules for investigators and institutional officials. Are such programs effective in developing a culture of compliance?

Dr. Miller: As we were developing our policy at Johns Hopkins, the comment we heard over and over again from employees was, “First tell us the rules.” People wanted to know the parameters and what they should be thinking about. We’ve found that employees are now more apt to disclose than before: if they believe they are even close to the threshold for disclosure, now they would rather disclose than not. I don’t know whether that really fixes the culture, but at least we’re past the time when not everyone knew what the rules were.

Dr. Soule: It’s hard to generalize about this question. The answer depends on the training and the circumstances under which it is delivered. For example, after WorldCom entered bankruptcy, every person in the company had to go through ethics training, which was just a prescription for cynicism. Employees felt, “We didn’t do anything wrong, yet here we are sitting in this training.” On the other hand, if the senior people are really a part of the process, the organization is telegraphing the message that this really matters.

■ LEADERSHIP, COMPLIANCE, AND CULTURE

Question from audience: I’m a little perplexed by some apparent contradictions in your advice, Dr. Soule. You stress the importance of leadership, but on the other hand you say that leadership is overrated as a key component. Also, while you say that compliance systems are essentially fragile and that efforts to improve compliance yield diminishing returns, you emphasize that enhancing a culture of compliance is central to creating an ethical culture.

Dr. Soule: I’m afraid I didn’t have enough time to do the subject justice. The basics of what I was trying to recommend are assessment, responsibility, and accountability. Assessment is critical because you can’t really manage something unless you have good assess-

ment to determine what is actually occurring at the institution. Next, someone must be held responsible in each operational area—such as a business unit or a clinic—for either maintaining a healthy culture or improving a culture that is inadequate. When assigning that responsibility, the institution must provide resources to assist managers in moving in the right direction. Then these managers must be held accountable. This is directly analogous to quality improvement, which can also pose difficult, idiosyncratic, and intangible management issues. In short, reduce the job to accountable responsibilities and make it part of a manager’s job description and rewards.

Question from audience: I’d like to go back to the question of whether training and education are effective in changing a culture. As an administrator of an academic health center, I look to the example of when we were fined enormous sums of money after the Physicians at Teaching Hospitals (PATH) audits because of compliance problems with billing and coding systems. Across the country health institutions implemented comprehensive training programs to teach physicians how to properly code and bill to be compliant. Did that change the culture? I don’t know, but it certainly changed what our academic physicians do, and for the most part it has made a big difference. These programs must be offered on an ongoing basis because new people arrive and new rules are developed.

Dr. Miller: Having lived through the PATH audits with everyone else, I think it improved things at our institution. Other areas where we have spent a lot of time on compliance have also undergone positive changes, such as billing operations, animal care, and human subject protection. I think that embedding compliance into everyday activities is preferable to making it an add-on activity: everywhere that we’ve been able to build compliance into our activities we have improved our operations.

Dr. Soule: We need to calibrate our expectations. The goal is not perfection, and it can’t be as long as human beings are involved. No one can take responsibility for the ethical conduct of another person, but we can and should take responsibility for the environment in which people work, because that can be controlled. I have noticed that when an ethical fail-

No one can take responsibility for the ethical conduct of another person, but we can and should take responsibility for the environment in which people work.

—Dr. Soule

ure occurs, organizations with a strong ethical bearing actually get stronger. For others, such a failure simply reinforces what is already wrong with them.

■ WHAT DOES DISCLOSURE REALLY ACCOMPLISH?

Question from audience: Can you expand on the issue of disclosures? Dr. Soule mentioned that disclosures aren't a full antidote. I know that sometimes they can become a "solution" that simply maintains the status quo. Some studies have shown that disclosures can actually have the opposite effect of what they should accomplish: they may allow institutions to "strategically exaggerate" to make it seem that they are towing the ethical line. It would be interesting to apply social psychology research to evaluate how conflict-of-interest disclosure affects people's interpretation of medical research. We all want evidence-based information regarding conflicts of interest, but I think our discussions here suffer from a lack of such evidence.

Dr. Soule: Don't misunderstand me that we shouldn't put too much on disclosures: there is no excuse for not disclosing risk to the people you have a duty to, especially if they trust you. Studies show that the trust the public has for physicians is off-the-charts high, and the percentage of those who answer that they "don't trust physicians" is statistically insignificant. In such a situation, the duty to disclose is paramount.

As you said, however, we shouldn't think that this is all that is needed. For instance, the disclosure required by the Sarbanes-Oxley Act for conflict of interest between research analysts and investment banks involves multiple pages of tiny print that no one will read. As a result, I believe it has no impact whatsoever.

Dr. Miller: One positive but intangible aspect of disclosure is that faculty members are forced to regularly think, "Do I have something to disclose?" Being forced to disclose keeps the issue in front of everybody and helps to build an ethical culture.