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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?

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

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

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.

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

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,

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.

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

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 Elan 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

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.

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

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

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-

tury 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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