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Outside the operating room—economic, regulatory, and legal challenges

A collection of perspectives and panel discussion

Preface

By Lawrence K. Altman, MD (Moderator)

Early in the history of the United States, physicians commonly discussed medical issues in newspapers and other public forums. But a remark attributed to Osler, "Never trust anything you read in a newspaper…and if you do, immediately doubt it at once," was used by the medical profession for decades to justify avoiding public discussion of medical issues. This retreat by physicians from the public discourse was particularly harmful in that it overlapped with the period when the public began paying for most medical research via federal research funding. Recently the medical profession has again started to discuss medical matters openly with the public, but this step has been taken reluctantly, in response to public pressure.

This resurgence in physicians' engagement with the public has come not a moment too soon, as factors and players outside the operating room—economic forces, regulators, legislators, lawyers, and others—today may have as much influence on what goes on in US operating rooms as do the surgeons, nurses, and technicians who work there. Our panel will address some of these influences on surgical innovation from outside the operating room, touching on historical and current examples of attempts to regulate innovation as well as the points of view of device companies, investors, lawyers, government, and health economists.

A device company perspective: Serving patients is the key to sustainable success

By Michael A. Mussallem

I am honored to be here to represent industry. Although medical technology companies compete fiercely with one another in the marketplace, we also have a broad common interest: we want to develop innovations to help patients.

DEVICE AND DRUG DEVELOPMENT DIFFER

Discussing ethical challenges involving industry is easier in the context of pharmaceutical development, for a number of reasons. The pharmaceutical industry is so large that it tends to dominate the discussion. But medical devices, which are primarily what is involved when we speak of surgical innovation, differ from pharmaceuticals in key ways.

The physician-company relationship is central

First, medical devices are not used directly by patients but are tools for physicians, which makes the relation-

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ship between industry and physicians more closely intertwined when devices are involved.

An iterative process by nature

Second, it takes years of development and enormous sums of money before a drug is finally approved. The final product then has a market life of 10 or 20 years. In contrast, device development is an inherently iterative process. After Thomas Edison developed the light bulb, attempts to improve the product were immediate and constant: "Can the light be made softer? The bulb smaller? Can it be turned off?" The same type of continuous improvement process happens with medical devices, which typically are refined every 12 to 18 months. Occasional breakthroughs occur and open up a whole new way of thinking, but far more often device innovation is about incremental modifications and improvements.

SUCCESS BREEDS CONFLICTS… AND REGULATION

The development of medical devices is an American success story; we tend to be better at it than any other country. Our system works well and rewards risks and innovation. When technology is racing forward to address an unmet patient need, a tremendous amount of value is created in the form of patients living longer and healthier lives. People pay for that value, which can create substantial payoffs for successful innovators and companies. I believe that six of the companies in the Fortune 500 are medical device companies, and the medical device industry has a $450 billion market capitalization in total.

I refuse to believe that raising ethical standards requires pulling apart companies, engineers, scientists, and physicians. Instead, we need to find ways for these various players to engage together.
—Michael Mussallem

The medical device business is like an ecosystem with many interacting components. Someone with a bright idea puts a physician and an engineer together, starts a company, attracts some capital, and develops a product. Because they need startup money for production, they might offer physicians a share of the company and some stock options, and immediately an opportunity for conflict of interest arises.

As a result of these many interacting components and the conflicts they can create, medical device companies today are highly regulated by a long list of entities, including the Securities and Exchange Commission, the Food and Drug Administration (FDA), the Department of Justice, the Internal Revenue Service, the Environmental Protection Agency, the New York and NASDAQ stock exchanges, the Office of the Inspector General, and the Foreign Practices Act. This degree of regulation makes every part of the medical device development process more time-consuming and expensive.

LONG-TERM SUCCESS REQUIRES THAT COMPANIES SERVE PATIENTS

The motivation of medical technology companies is often called into question. Medical device companies are certainly motivated to make money, and they certainly have obligations to shareholders. But for a company to be successful for many years, it cannot be single-minded about the constituencies that it serves. Great medical device companies have employees who want to work for them, physicians who want to buy products from them, communities that welcome them, and shareholders who want to own their stock, but the primary goal is always to serve patients: if that is done really well over the long term, the company can count on those other success factors being present. To have a sustainable competitive advantage, one must think beyond the next quarter and run a highly respectable business on an ongoing basis.

It is true that there are outlier medical device companies who do not always operate with full integrity, as there are in any industry. The challenge, both for the medical technology industry and for the broader health care community, is to raise the standards and encourage everyone to operate at a highly ethical level. I refuse to believe that doing so requires pulling apart companies, engineers, scientists, and physicians. Instead, we need to find ways for these various players to engage together.

A good start may be the revised Physician Payments Sunshine Act, proposed by US Senator Charles Grassley. This legislation, which is supported by the Advanced Medical Technology Association (AdvaMed), would establish a national registry of payments made to physicians by medical device, medical supply, and pharmaceutical companies, and seems to make a lot of sense. As we move forward on this and other efforts to raise the ethical bar in health care innovation, it is important that there be a place at the table for everyone involved.

A regulatory and legal perspective: Issues in off-label device use

By Rebecca Dresser, JD

My comments will focus on off-label use of medical devices, which is a topic rife with ethical questions. I will begin by reviewing recent experience with drug-eluting coronary stents, which are regulated by the FDA as Class III devices, as this experience touches on many of the challenges that arise from off-label product use.

CASE STUDY: DRUG-ELUTING STENTS

The earliest coronary stents were made of bare metal. Over time, arteries treated with these stents tend to become blocked again, requiring patients to return for repeat revascularization. Drug-eluting stents were developed to extend the time that the artery stays open.

Earlier this decade, a couple of device manufacturers sought FDA approval to market their drug-eluting stents. Each manufacturer submitted data from randomized clinical trials in otherwise healthy patients with small, newly diagnosed heart blockages. The trials showed that patients who had received drug-eluting stents had reduced reclogging rates after 9 months compared with those who had received bare metal stents. Risks appeared to be similar between the two types of stents. On the basis of this evidence, the FDA approved the initial drug-eluting stents for marketing in 2003 and 2004.[1]

The few courts that have addressed off-label use ruled that physicians have no obligation to specifically inform patients of off-label status.

—Rebecca Dresser

Soon after they were approved, drug-eluting stents were being used in about 80% of patients who received coronary stents. However, although these new stents had been tested and approved for use in otherwise healthy patients with small, newly diagnosed heart blockages, about 60% of their real-world use was off label—specifically, in patients with large blockages or additional health problems such as diabetes.

Reports of adverse events with drug-eluting stents began to emerge, so the FDA issued a statement of concern in September 2006 and subsequently convened an advisory panel of outside experts to review the data and make recommendations. In January 2007, that advisory panel concluded that off-label use of drug-eluting stents is associated with an increased risk of thrombosis, death, or myocardial infarction compared with on-label use. The panel noted, however, that data on off-label use were limited and that additional studies were needed to determine optimal treatments for more complex patients.[2]

So research on the safety of off-label use of drug-eluting stents continues. Recent data—including studies published in the *New England Journal of Medicine* and *JAMA* earlier this year[3,4]—suggest that some off-label uses are safe and effective, but much uncertainty remains.

PHYSICIANS SHOULDER THE ETHICAL BURDEN

The story of drug-eluting stents illustrates some of the issues that can arise with off-label use of devices. Currently, the FDA gives physicians discretion to prescribe approved products for uses that deviate from the products' FDA-approved package inserts. Although the FDA is imperfect, it provides the most thorough and systematic review we have of medical product safety and efficacy. However, an FDA review typically addresses the risks and benefits of a product in only one context or patient population, which might not apply to another context or population. For instance, children and the elderly are generally not well studied in clinical trials, so off-label use of therapies is particularly common in these populations. Of course, patients can be harmed if off-label use presents unappreciated risks or does not provide an adequate benefit. Even if no adverse effects result from off-label therapy, other harms are possible: an alternative therapy might have been superior or the treatment may simply be a waste of money.

In this absence of regulation, the questions of whether and when to prescribe off label—and what the guiding ethical standards should be—fall to physicians. A few professional groups provide some guidance. The American Medical Association states that off-label use is justified when "based upon sound scientific evidence and sound medical opinion."[5] The American Academy of Pediatrics (AAP) has issued what is perhaps the best statement[6] (although it focuses on drugs, its principles can be applied to devices as well). The AAP maintains that off-label use should be based on "sound scientific evidence, expert medical judgment, or published literature" and notes that physicians who prescribe off label have "a public and professional responsibility to assist in the systematic development of the information" about a particular off-label use. The AAP also advocates that prescribers consider discussing with patients (or their

parents) the off-label status of a therapy and the degree of the therapy's acceptance among physicians for the proposed off-label use.

SPECIFIC ETHICAL ISSUES

How to evaluate evidence about off-label use?

The justification for off-label use is not to advance knowledge but to best meet the needs of an individual patient. But how can a physician know that a therapy is best for a proposed use when it has not been through the FDA approval process for that use or for the particular type of patient at hand? Some off-label uses are supported by strong data while others are not. Physicians have the responsibility to evaluate the available evidence with integrity and to promote rigorous research when the available evidence is inadequate.

Healthy skepticism of industry promotion warranted

One problem is that the pharmaceutical and device industries are heavily involved in communicating about off-label uses of products. Since 1997, the FDA has permitted drug and device companies to engage in limited promotion of off-label product uses through distribution of "enduring materials" such as textbook chapters and peer-reviewed articles. Industry has also been allowed to sponsor education sessions about off-label uses so long as an independent continuing medical education provider is involved in planning the sessions. The authorization for such off-label promotion expired recently, however, and was not renewed in the FDA reauthorization law passed in the fall of 2007. The FDA has since proposed a similar rule regarding off-label promotion,[7] but it has been criticized for being a bit more lenient toward such promotion.

Concerns about off-label promotion and communication remain. Manufacturers sometimes violate the spirit of the rules that require independence, for example, through compensating physicians who speak favorably about off-label uses. Similarly, manufacturers sometimes design studies of off-label uses of therapies so that the results are especially likely to turn out favorably.

Data collection: Easier said than done

The aim of promoting information gathering and systematic research on off-label uses may be viewed as a professional duty,[6] but in practice this duty is complicated by the question of who will pay for it. Often product manufacturers are already making plenty of money from an off-label use and therefore have little financial incentive to conduct trials to obtain FDA approval to add a new indication or population to the label. At the same time, there is very little money available in the public sector for such studies.

No consensus on patient consent

The principle of informing patients about off-label use is also controversial. Not much litigation has been brought on this issue. The few courts that have addressed it have ruled that no obligation exists to specifically inform patients of off-label status and that physicians are obliged only to inform patients about risks, anticipated benefits, and alternatives to an off-label treatment. Some writers think that most patients do not understand the concept of off-label use and that informing patients will only confuse them. Others argue that off-label uses ought to be disclosed, especially in situations involving very innovative off-label applications or when insurers may not provide coverage. Interestingly, a recent Harris Interactive poll found that about half of the US public feels that doctors should only be allowed to prescribe drugs for diseases for which they are FDA-approved.[8]

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WHAT SHOULD BE DONE?

Some people argue that the regulatory approach to off-label use already works well. Others want more government oversight. Probably no one would argue that every variation from the label should be subjected to the FDA approval process. There is debate over exactly how to define an off-label use—ie, how different it must be from the approved use to legitimately warrant the "off label" title. This is similar to the question of how to define when a change in surgical technique is innovative enough to require formal evaluation.

Some argue that better postmarketing surveillance is needed to assess the effects of off-label device use in patients. Additional help could come from a 2007 amendment to federal law that strengthens requirements to make clinical trial information publicly available through clinical trial registries. This will make it difficult for sponsors to conceal unfavorable data from trials involving off-label uses. More information exchange and independent assessments of off-label uses are also needed to promote better and safer off-label use of medical devices.

A historical perspective: The more things change, the more they remain the same

By Paul A. Lombardo, PhD, JD

As a historian and a lawyer, I tend to look back to established precedents, a tendency that often leads to a conservative and cautious perspective. This kind of temperament is slow to reach sweeping conclusions, slow to push for change, and slow to believe that anything is really very new. This temperament is in stark contrast to that of the successful surgeon, who tends—again, speaking in stereotypes—to be aggressive, bold, courageous, pathbreaking, and, at the best moments, even heroic.

This contrast in temperaments may bring a different and perhaps helpful perspective to the task I have at hand—to look to the past for examples of ethical challenges in surgical innovation. In gathering these examples I was struck by how many of the foundational ethical issues that surgeons have faced over the years remain with us today.

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—Dr. Paul Lombardo

CASE 1, 1649: 'STANDARD OF CARE' CONCEPT ARTICULATED

In 1649, an ordinance passed by the Massachusetts Bay Colony made it a crime to operate on a person without consent. It also stated that no person employed as a surgeon may perform any act contrary to "the known approved rules of the art" as laid out by one's medical peers. The ordinance pointed out that this rule was meant not to discourage "the legal use of the skills of healers" but rather to inhibit those who might not be restrained from "the presumptuous arrogance of their own skill."

This law mandated three things that are a foundation of what we think of as surgical ethics today:

- The notion of a standard of care ("the known approved rules of the art")
- Peer review (the need to consult preoperatively with peers regarding that standard)
- Patient consent.

Interestingly, this ordinance was adopted at a time when most surgery was performed on visible pathologies or deformities, and elective surgery was all but unknown. Only about 150 years later did surgeons open a body cavity on a regular basis.

CASE 2, 1809: INNOVATION IN THE FACE OF CONDEMNATION

In 1809, Ephraim McDowell, a Kentucky surgeon, described the desperation of his patients as a motive for attempting a new procedure to fix a problem that was otherwise incurable. In his most famous case, McDowell reported visiting a woman some 60 miles from his home who thought she was pregnant but who actually had a large ovarian tumor. McDowell told her that there was no cure but invited her to come to his home if she were willing to undergo an experiment. He thought she would not make the trip, but, to his surprise, she arrived on Christmas Day in 1809.

As McDowell prepared for surgery, his nephew, who was a physician and his partner, argued that the procedure was a terrible thing to try. McDowell was also condemned from the pulpit by a preacher, who declared that the surgery was tantamount to murder if it failed.

While his patient recited psalms from the Bible, McDowell removed a 22-pound lump of tissue without anesthetic or antisepsis. The patient returned home about a month later and lived for more than 30 more years.

After having performed this oophorectomy procedure three times, McDowell deemed it less perilous than any other mode of treatment and the only certain cure for diseased ovaries. Later, surgeons in England who read about his work criticized McDowell for not explaining the operation sufficiently for others to replicate it, although he denied this charge.

In pioneering oophorectomy, McDowell did something quite innovative in the face of considerable professional and community opposition. Moreover, he took care to obtain patient consent and to include his patient in decision making.

CASE 3, MID-1800s: J. MARION SIMS AND 'THERAPEUTIC MISCONCEPTION'

J. Marion Sims, considered the father of American gynecologic surgery, is famous not only for his technique as a surgeon but also for inventing several instruments, including the speculum. Yet he is criticized by historians and ethicists, primarily because he often performed experimental procedures on slaves, who probably were not in a position to give true consent. He kept patients as boarders for many months, doing a variety of experiments on them, and described in his writings how much pain his patients endured from his mistakes or from the prolonged operations.

Sims' work is an example of "therapeutic mis-

conception": while he told his patients that he was going to cure them, he often had no idea whether he could. Thus, his patients believed that the operations were primarily for their benefit although he seems, as critical colleagues came to believe over time, to have sometimes been simply experimenting on patients who were uniquely vulnerable.

CASE 4, 1903: EARLY EXAMPLE OF MODERN INFORMED CONSENT

In contrast to the record of Sims, some 50 years later Dr. Franklin Martin described the painstaking approach he took to advising a patient who would undergo one of the first ovarian transplants, performed around 1903. Martin wrote:

> I carefully explained to her the difficulties which we had to surmount…. I also clearly informed her that the operation must be looked upon entirely in the light of an experiment, and that she must be prepared to assume all responsibility with regard to failure in the outcome. Being a woman of unusual intelligence and one who was thoroughly in earnest in her efforts to regain her normal condition, these preliminaries were very easily settled.[9]

Without being required to do so, 100 years ago Martin went through a process equal to any informed consent disclosure that one might encounter today.

Even a century ago, "giving the donors what they want" was seen as a prerequisite for hospitals' ability to raise the funds needed to care for the poor.
—Dr. Paul Lombardo

CASE 5, EARLY 1900s: A CALL FOR RESTRAINT IN EXPERIMENTATION

Around the same time, at the beginning of the 20th century, a surgeon writing in the *Boston Medical and Surgical Journal* condemned "over-confidence in the benefits to be derived from mechanical interference and an unrestrained enthusiasm for doing something tangible and heroic."[10] He urged his colleagues to "be brave enough to refrain from the mutilation and suffering caused by too late and hopeless operations."[10] He noted the habit of experimentation with new methods, arguing that advances in surgery led to a disproportionate focus on surgery as an art and too little attention to surgery as a science.

These arguments from a century ago make clear that today's debates about the evidence required to move forward with innovative procedures are certainly not new.

CASE 6, 1913: COMPLEX INSTITUTIONAL MOTIVATIONS

In his 1913 book, *The Modern Hospital: Its Inspiration, Its Architecture, Its Equipment, Its Operation*, Dr. John Allen Hornsby wrote:

> Benefactors of institutions, before giving their money, will want to know just what care the poor… are actually receiving at the hands of the institutions asking for their aid….Yet there must be a difference between the service given to a millionaire and a pauper, but that service should be wholly of the luxuries. The pauper need not have broiled quail and asparagus tips for dinner, and he need not have a private room with adjoining bath, with roses on every stand and the odor of perfumes scenting the room; but these extras should be the only ones that the man of millions should have that the pauper should not have; and patrons of wealth and refinement and of humanitarian instincts will give thousands annually to the institution where they know the poor are getting everything a rich man can get that is needful, where they will give begrudgingly a few paltry dollars to the institution that they know is neglecting the wants and welfare of the poor.[11]

While this excerpt is notable for Hornsby's eloquence in arguing for meeting a standard of care for the poor, it is just as notable for demonstrating how complex Hornsby's motivations were. Not only should we care for the poor, but we have to do it right or the institution will not get money from the rich. In other words, "give the donors what they want." Then, as now, it took large sums of money to run institutions, as well as to put new innovations in place. And then, as now, institutions had to grapple with complicated motives.

SAME ISSUES, NEW CONTEXTS

This historical review makes clear that the ethical issues we face today are not new. The foundational questions about the ethics of biomedical research as applied to surgery consistently revolve around consent, how thoroughly to inform patients, the use of vulnerable populations as research subjects, distinguishing between experimentation and therapy, and, of course, money and the best use of resources. Variations on these questions continue to loom for surgeons and other physicians.

An economic value perspective: Setting limits on health care can be ethical

By Peter A. Ubel, MD

I am a fan of innovation: my patients benefit from it every day. But I am also concerned about the cost of health care. In the Veterans Affairs health system, I see patients who cannot afford their medications and who cannot afford to get private insurance; such problems are largely due to the high cost of health care.

As an example, consider a new pharmaceutical innovation, bevacizumab (Avastin), which costs approximately $106,000 per year when used to treat lung cancer.[12] On average, the treatment leads to a 2-month increase in survival, making the cost of this intervention more than $600,000 per quality-adjusted life-year. Or consider the use of a left ventricular assist device rather than medical management for patients with congestive heart failure who are not eligible for transplantation. The estimated cost is approximately $900,000 per quality-adjusted life-year.

These examples illustrate that some benefits to patients can come at a very high cost. For this reason, I believe that we need to set limits in (ie, ration) health care. I will outline here why we need to do so and why third-party payors—both government and private insurance companies—need to consider the cost-effectiveness of health care interventions in deciding whether to pay for them. In the process, I will discuss common thresholds for defining the price of life and explore whether special moral considerations are required for life-saving treatments—ie, whether the price of life should be higher for severely ill patients.

We hate making difficult decisions, both as individuals and as a society.
—Dr. Peter Ubel

WHY IS IT TIME TO RATION MEDICAL CARE?

Spending on health care in the United States has risen steadily in the last few decades both in real dollars and as a percentage of the gross domestic product. One important reason for setting limits on health care spending is that we have other things to spend our money on. Medicare budgets compete with tax cuts, education, military spending, homeland security, and many other national interests. Economics teaches us that we have to make difficult choices: when we spend more on health care, we have less money to spend on other things.

Cost-effectiveness analysis provides insight on why it is important to set limits. When I trained at the Mayo Clinic, we used to send patients home with six fecal occult blood test cards to screen for colon cancer. (Patients smear stool on a card and mail it to the laboratory, where it is tested for blood; if blood is present, the patient needs a colonoscopy. The six card samples are taken and mailed at periodic intervals to maximize sensitivity.) What is the cost-effectiveness of the sixth card? The answer is surprising: although the cards cost only a couple of dollars, the cost per life saved is an estimated $26 million, which most would agree is more than we can afford to spend to save a life from cancer.

Why is the sixth card so expensive? If any of the first five cards shows blood, the sixth card is worthless, as it provides no new information. On the other hand, if none of the first five cards shows blood, the chance is minuscule that the sixth card will show blood that actually comes from a precancerous lesion that can be removed and save a person's life.

This example illustrates that cost-effectiveness does not apply only to expensive new therapies like Avastin; it also applies to really inexpensive items like fecal occult blood test cards.

WHAT IS A YEAR OF LIFE WORTH?

If our own child were sick, we would say that a year's life is worth an infinite amount of money; we would do anything we could to save our child's life. But the job of the cost-effectiveness community is to address this question from a societal perspective, and they have a different answer. The most commonly cited view among experts in cost-effectiveness analysis is about $50,000 per quality-adjusted life-year, although it typically ranges up to $100,000.[13]

This figure has not risen with inflation, and it probably should not. If enough new technologies were developed at the threshold of $50,000 per quality-adjusted life-year, the entire budget of the country would quickly be used up.[14] Making payment decisions based on a certain cost-effectiveness threshold sets no real limit on health care spending. The threshold is not meant to be a realistic number but should illustrate the kind of thinking required about how much we want to spend on health care relative to other things. The aim is to help us decide how much "bang for the buck" we should expect from our dollars spent on health care.

WHAT DO PEOPLE VALUE WHEN SETTING LIMITS?

In light of the above, how do we set limits when trying to decide what the price of life is? Might our limit-setting be changed if we are facing a desperately ill patient? Examination of questions like these reveals that people value other factors beyond just economic efficiency, as can be illustrated with a couple of theoretical policy dilemmas.

Dilemma 1: Cost-effectiveness vs fairness

Imagine that the Medicaid program decides to screen for colon cancer. They have enough money either to offer an inexpensive test ("Test 1") to everyone and save 1,000 lives or to offer a more expensive test ("Test 2") to half the population (selected randomly) and save 1,100 lives.

If the decision were made according to rational cost-effectiveness principles, the choice would be to go with Test 2 in half the population, as it saves 10% more lives and thus maximizes the average health of the population. However, a survey found that the option of offering Test 1 to everyone was favored by 55% of the general US public, as well as by 55% of medical ethicists and even by 45% of cost-effectiveness experts, all of whom were willing to give up some cost-effectiveness for fairness.[15]

Resistance to limiting treatments that are not cost-effective is psychological and political, but it is not ethical.

—Dr. Peter Ubel

This tendency to favor fairness suggests that moral considerations affect health policy decisions in important ways. Yet further analysis raises questions about the extent to which these considerations are based truly on moral values as opposed to psychological quirks.

For instance, my colleagues and I presented this same choice of colon cancer testing scenarios to a separate survey sample, and again a highly similar rate of respondents—56%—favored offering Test 1 to the full population as opposed to offering Test 2 to half the population. However, to test whether this preference for equity over efficiency persists when neither test can be offered to the entire population, we changed the scenarios for a separate group of randomly selected participants. In one version of the scenario, we told participants that only 90% of the population could receive Test 1 and only 40% could receive Test 2. (As in the original scenario, we indicated that Test 1 saves 1,000 lives, whereas Test 2 saves 1,100 lives.) With just this small variation in test availability, the proportion of respondents favoring Test 1 plummeted to 27%. Similarly, we randomly selected another group of participants to receive a third version of the scenario, in which 50% of the population could receive Test 1 and 25% could receive Test 2, saving 1,000 and 1,100 lives, respectively. Once again, the proportion of the respondents favoring Test 1 remained low (28%).[16]

These results suggest that people's preference for equity versus efficiency depends, in large part, on whether the more equitable option can be offered to everyone in a population. But people's preferences are actually not nearly that coherent. Consider a follow-up study in which we repeated the scenario again for each respondent, but with a twist.

In one group, we began with our original scenario: 100% of the population can receive Test 1, saving 1,000 lives, or 50% can receive Test 2, saving 1,100 lives. As expected, 60% of participants chose Test 1. But then we told this same group of participants that the number of people qualifying for Medicaid had doubled, so that the tests could be offered to only 50% and 25% of the population, respectively (still saving 1,000 and 1,100 lives, of course, since the population was now twice as large). Remember that when people were *initially* presented with this 50% versus 25% option (without any other scenario being presented first), the preference for Test 1 plummeted. In this case, however, almost no one changed their mind: the majority (60%) still favored Test 1.[17]

People's preferences for how to allocate scarce health care resources—the moral values that they believe should guide our health system choices—are often disturbingly arbitrary.[18]

Dilemma 2: Targeting severe vs moderate illness

Now imagine a new scenario. A treatment is available that will help patients with an illness that causes severe health problems, but it provides only modest benefit. Another treatment helps patients with an illness that causes moderate health problems, and it provides considerable benefit. The cost of the two treatments is the same. How should funding be allocated?

Although a majority (60%) of survey respondents say that most funding should go toward treating the moderate illness where considerable benefit is expected, a sizeable share of people (40%) favor devoting most funding to the severe illness despite the more modest benefit.[19] This is another instance where moral values seem to come into play, as a large minority will favor helping the severely ill even at the expense of efficiency.

A variation of this dilemma illustrates another salient point—that people like "easy outs." When we present people with an additional option—"How about spending money equally between the two treatments?"—the vast majority (75%) choose that "compromise" option over the option of devoting most funds to either of the individual illnesses.[19] The lesson is that we hate making difficult decisions, both as individuals and as a society.

COST-EFFECTIVENESS IS THE MOST RATIONAL AND ETHICAL WAY TO SET LIMITS

These surveys make clear that many of the moral values that people express are fragile at best or even psychological quirks. I have heard no compelling moral arguments to support treatments that cost more than $500,000 per quality-adjusted life-year, which leads me to conclude that many new medical interventions are unaffordable. The resistance to limiting such treatments is psychological and political, but it is not ethical.

The appropriate response is for third-party payors, such as Medicare and insurance companies, to let industry know that cost-effectiveness matters. If a treatment is not cost-effective, it should be limited to people who pay out of pocket or for experimental purposes. To make this happen, we need cost-effectiveness analyses of new technologies. Because such studies are expensive and time-consuming, we should develop new incentives to motivate companies to conduct such studies of their products, perhaps by extending patent protection for products that are shown to be cost-effective. We need to work with industry on how to implement such a plan. But continuing to ignore the cost-effectiveness of interventions when they come to market is harming patients who can no longer afford insurance, which has real consequences on people's health and well-being.

An industry perspective: Proactive self-regulation through an industry code of ethics

By Christopher L. White, Esq

I serve as general counsel of the Advanced Medical Technology Association (AdvaMed), a Washington (DC)-based trade association that advocates on behalf of the medical device innovation community. Most of the approximately 1,600 companies we represent are small, having fewer than 100 employees. All of our member companies have a great interest in creating an environment that will sustain innovation to fuel additional benefits in patient care.

PHYSICIANS AND THE DEVICE INDUSTRY: INTERACTIONS ARE MANY, VARIED, ESSENTIAL

As noted earlier in this session by Mike Mussallem, who serves as chairman of AdvaMed's board of directors, the medical device industry is very different from the pharmaceutical industry. Device innovation requires a great deal of collaboration with physicians in the field. Moreover, devices are not simply prescribed—they are *used*. That is, many of the inventions are an extension of the surgeon's hand, such that technique influences how devices are deployed and used. As a result, with each incremental innovation, there is often a need for retraining.

Physicians wear many hats in their relationships with the medical device industry. Not only are they purchasers of products but they are collaborators, inventors, trainers, and trainees. They are also recipients of charitable contributions and of research grants. We recognize that these multiple relationships can become intertwined and, from a distance, can arouse confusion or suspicion. But simply because these relationships exist does not mean that there is a conflict of interest—there may be dualities of interest. In most cases we have a common interest and are working toward a common objective: to provide care in the best interest of the patient.

THE ADVAMED CODE OF ETHICS

The key question from industry's perspective is how best to manage these relationships with physicians and any potential conflicts of interest. To that end, AdvaMed has developed a code of ethics to provide guidance relevant to the most common interactions between device manufacturers and health care professionals.[20] The AdvaMed code has been adopted by international device trade associations and embraced or cross-referenced by physician specialty societies.

Although the AdvaMed code has become a "gold standard," it is a living document, and we are in the process of reviewing and revising it in an effort to address challenging new issues such as royalty payments, among others, which have become the focus of public questions and scrutiny.

MOVING FORWARD AFTER THE JUSTICE DEPARTMENT DEFERRED PROSECUTION AGREEMENTS

Recently, five orthopedic hip and knee implant manufacturers entered into novel deferred prosecu-

tion and non-prosecution agreements with the US Department of Justice following a Justice Department investigation into financial relationships and consulting agreements between these companies and orthopedic surgeons. The agreements include the appointment of federal monitors to review virtually every transaction that these companies have with physicians. These agreements impose a level of governmental review over the device industry that has never been seen before.

The agreements also require the five companies to disclose on their public Web sites all payments made to physicians. The disclosures must follow a specified format listing each physician's name and location, the amount of the payments, and limited information regarding the purpose of the payments (eg, for consulting, royalties, charitable contributions, research grants). This requirement has created much interest as well as a good deal of confusion.

If passed, the Physician Payments Sunshine Act would require that virtually all payments from industry to physicians be reported to a federal database.
—Christopher White

These developments have also spurred AdvaMed to work aggressively on federal and state legislative efforts. We are taking a proactive position on the disclosure of financial arrangements between industry and physicians in the context of the proposed Physician Payments Sunshine Act mentioned earlier by Mike Mussallem. If passed, this legislation would change the landscape by requiring that all pharmaceutical and device companies report to a single federal database all transfers of value or other payments, subject to certain exceptions, from industry to physicians. Similar to the federal agreements with the orthopedic implant manufacturers, the bill would require that the name and location of the physicians receiving payments be disclosed, along with the payment amount, but with greater context regarding the purpose of the payment. AdvaMed has been advocating for providing detailed explanations of this context so that everyone, including the public, can understand why such payments are made and how they can be beneficial.

Panel discussion

Moderated by Lawrence K. Altman, MD

Dr. Lawrence Altman: Let us start by opening the discussion to the audience.

Comment from audience: Considerable discussion has focused on the conflict between regulation and innovation, but I find very little evidence that such a conflict actually exists. It was pointed out that the United States is by far the biggest producer and user of medical devices and has been since World War II. Economists estimate that 50% of the growth of the US economy since then has resulted directly from innovations in science and technology. During that same period, the regulatory apparatus—including the FDA—has vastly expanded. Apparently, innovation has not been stifled by regulation but actually seems to thrive in a regulated environment.

I speak often with venture capitalists who finance science technology. They know this history, and they know that regulation is inevitable. Rather than opposing it, they want clarity about regulation. For instance, many of them avoid financing human embryonic stem cell research because the rules around it are not clear, owing to the stigma and political controversy surrounding it.

Michael Mussallem: You make great points. People who invest in medical innovation would like an idea of the rules before they make investment decisions. And good, solid regulation—such as when the FDA pushes companies for the kind of science and evidence needed to clear a hurdle—is absolutely appropriate. But as regulation increases, the time and costs to bring an innovation to market increase. At the moment, the innovation equation is fragile. When too many obstacles are put in the way, the risk of failure becomes too high.

Keep in mind that the success rate in innovation is low. Although I have been in this field my entire career, it would be much easier for me to hit a major league fastball than it is to successfully innovate in medical technology. We are wrong many more times than we are right. For every success, there may be 9 failures, or 19 failures, or even 99 failures.

Rebecca Dresser: I agree that regulation sometimes does not effectively advance its goal. When that is the case, I think we need to be willing to negotiate rather than condemn; we need to show where regulation is not meeting agreed-upon goals (such as pro-

tecting patients) and figure out how to reach those goals more efficiently.

We also should keep in mind the cliché, "If professions do not adequately self-regulate, external regulation will come in." Perhaps that is what has happened. Professionals need to self-examine and organizations need to develop voluntary standards to help avoid stupid regulation.

Christopher White: We need to be mindful of the unique relationships that we have within this niche sector of the health care industry. Issues that might not appear to threaten us directly may have unanticipated implications. Some of the barriers that regulation can impose may not be immediately perceptible and can be masked by otherwise beneficial public policies. For example, we now have a patent reform debate on Capitol Hill promoted by the information technology industry as pro-innovation, but in the context of the life sciences industry, many of the proposed patent reforms threaten innovation by devaluing device improvements.

Also, much of the regulation the device industry confronts is responsive to dynamics in the pharmaceutical industry. For example, one house of the Massachusetts legislature recently passed a bill that would ban gifts to health care professionals and require licensure of pharmaceutical and device sales representatives who work in the state. The term "gift" is defined very broadly and could include not only meals and the other things that we read about regularly but also rebates, educational grants, and training. *[Editor's note: A modified version of this legislation was signed by Massachusetts' governor in August 2008 and will take effect January 1, 2009.]*

The success rate in innovation is low. Though I have been in this field my entire career, it would be much easier for me to hit a major league fastball than to successfully innovate in medical technology.
—Michael Mussallem

Question from audience: As a practicing surgeon, I think the major problem lies in the area of off-label use. If one accepts that the device manufacturer is well-intentioned and living up to the AdvaMed code of ethics, the system falls apart once the device has cleared the hurdle of FDA approval for a labeled indication. The product then reaches the broad market, where it is subject to commission-based sales. Whether or not to use the device in innovative ways is generally at the discretion of the physician, until it reaches the threshold of research and institutional review board approval. We have virtually no postmarket surveillance by the manufacturer. At what point is the manufacturer culpable for the off-label use of its product when patients are harmed and no surveillance exists until enough casualties occur that the problem becomes obvious?

Mr. Mussallem: Put yourself in the shoes of a physician who is facing a difficult situation that has not been studied and is outside the realm of any approved, "on-label" therapies. A classic case is for children with congenital heart defects. Since no one advances a medical device for such small patient populations, physicians treating such cases are forced to be creative. They take devices that were intended and tested for adults and apply them to a child. Do you punish those physicians? Do you punish the company that created the devices?

When you look at the question down at this level, where it becomes quite practical and quite personal, the issue of off-label use takes on a different color. In many ways, it comes down to how much we trust physicians and to what extent we think they should be regulated. I would want to give physicians the freedom to try to do what is best for their patients and to use their judgment to apply a device in a different way—one that they understand has not been tested or approved for that use. But I would also want transparency: I would want them to explain to the patient (or the parents) what is known and unknown about the situation. It is in the absence of that transparency that you enter dangerous ground.

Paul Lombardo: When a new law is passed or a new regulation comes down, it is usually in response to a scandal: something bad enough happened to scare everyone to death. If I were advising industry, I would tell them to go to any length to avoid the kind of scandals that we have seen that challenge the trust of the public. So I agree that transparency is critical. It is one thing to say, "I am trying to do what is best for my patients and trying new things because I do not have access to tools especially designed for children." But when we find out that a doctor or a manufacturer has hidden data about a method of using equipment that has never been approved, and is covertly pushing that use, the predictable result is that somebody will want to regulate it.

Ms. Dresser: Of course, malpractice suits are an option, but they will cover only a few cases, generally the most extreme ones. I think the greatest need

is for information gathering. The medical profession should think about how to encourage data collection for off-label use so that problems can be detected earlier than they are now. This type of data collection is also in device manufacturers' best interest, as it helps to avoid scandal.

Another approach is to extend the patent exclusivity of products whose manufacturers conduct trials in underserved patient populations, thus providing a financial incentive to do such studies. This approach has in fact been adopted in the case of pediatric trials and for orphan diseases. Interestingly, some pediatric trials prompted by this patent extension incentive have shown that certain medications or dosages previously accepted as standard medical practice turned out to be harmful in children once they were formally studied.

Dr. Altman: What about proposals to use published literature—which also is subject to abuse—as a criterion for off-label use?

Ms. Dresser: Peer-reviewed journals do not have access to raw data, which can be manipulated in a lot of ways, so they cannot completely substitute for FDA review. Recent articles in *JAMA* addressed these concerns.[21,22]

Comment from audience: There seems to be a misguided desire to look to our regulatory agencies to tell us how we should manage a patient. As a practicing surgeon who does minimally invasive procedures, I never look to regulatory agencies to tell me what the optimal therapy is for a patient; rather, I look to them to tell me whether a product is a therapeutic option for a patient, and then I use my judgment to decide whether it is the best option for this particular patient.

Consider how Britain's National Institute for Clinical Excellence (NICE) has approached drug-eluting stents. They looked specifically at off-label uses of these stents and determined that the stents confer a benefit in these off-label areas, based on subgroup analysis. But then they did a cost-effectiveness analysis and determined that the benefit was not great enough to offset the cost to society based on the quality-adjusted life-years gained. Well, that may be a fine theoretical discussion, but when I am sitting in front of a 75-year-old who I think will do better with a particular device, it is hard to be concerned about whether it is on label or off label, or does or does not meet cost-effectiveness criteria.

Some of the barriers to innovation that regulation can impose may not be immediately perceptible and can be masked by otherwise beneficial public policies.

—Christopher White

Mr. Mussallem: This comes back to the trust that we have in our physicians. Should product manufacturers be allowed to hand out peer-reviewed journal articles? If physicians are provided with those articles, does that provide too much information for them and steer them inappropriately? Well, if physicians single-mindedly made such articles the sole basis for a treatment pattern, then it absolutely would be inappropriate, but we should give physicians a little bit of credit. Their job is to take a tremendous amount of data—everything that they have learned through their own experiences, plus journal articles and other sources—and apply it to design the best course of treatment they can for a specific patient.

If we try to overprescribe how a physician behaves, we will find it is too complex to regulate or legislate from the top. We should have a lighter hand and design incentives appropriately so that physicians are first and foremost motivated to take care of the patient. We should not try to tell them too much about exactly how to practice; after all, a large study that finds that one treatment has a 62% chance of being superior does not prove that it is the best treatment for a specific patient. You always want to preserve physician judgment.

Dr. Peter Ubel: I agree, but if we are to avoid overmanaging the day-to-day decisions that doctors make, we doctors also have to think more broadly about our responsibilities. If our duty is only to the patient in front of us, we can ignore being told that a treatment offers only a very small benefit for the cost. If we doctors say that it is not our job to be mindful of costs, then somebody is eventually going to have the job of telling us when we can and cannot use those stents, as a way to rein in costs because no one can afford insurance anymore.

For physicians to maintain more room for our judgment in influencing clinical practice, we have to remember that we are stewards not just of individual patients but of the general health care system. The cost of technology plays a huge role in driving up the cost of medical care.

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