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New surgical devices and ethical challenges: A collection of perspectives and panel discussion

An FDA perspective on device regulation

By Daniel Schultz, MD

As a surgeon, I know that not making a decision actually amounts to a decision in itself. In my current work with the Center for Devices and Radiological Health (CDRH) at the US Food and Drug Administration (FDA), there are times when we may not have all the information that we feel we need to make a decision but we are obligated to make one anyway. We try to apply a risk-based approach that makes the most sense for patients and for public health. Surgeons probably appreciate this method better than most people do, as they do risk-benefit analyses many times a day and do so almost subconsciously. In the government we have to do so in a more transparent and explainable way.

■ FDA MISSION ADDRESSES THE FULL PRODUCT LIFE CYCLE

The CDRH mission encompasses the entire life cycle of a device, from encouraging product development, to ensuring postmarket safety, to enabling access to innovation. Our mission is threefold, as outlined below:

- **To get safe and effective devices to market as quickly as possible.** This is a balancing act. On one hand, some people feel that “as quickly as possible” is not fast enough, yet safety and efficacy obviously need to be established. On the other hand, if we wait to be absolutely certain that a new device is safe and

effective, large numbers of patients may miss out on potentially benefiting from it in the interim. We try to analyze risks and benefits, and also to bring some common sense to the analysis. Our review process draws on whatever mix of expertise is necessary for evaluating a given product, so we consult with statisticians, engineers, physicians, and other experts as needed. In addition, the CDRH has a medical device fellowship program that brings in experts from academic settings—including physicians, biomedical engineers, computer scientists, statisticians, and law and policy experts—to contribute expertise in the evaluation of cutting-edge technologies.¹

The CDRH attempts to work with companies prior to submission to understand their technology, what they intend to do, and the population for which they intend their product. We aim for clarification rather than overregulation: our goal is to make the pathway as clear as possible to increase the likelihood that we will get the information we need to make a decision, to give companies a good sense of what to expect, and to promote mutual understanding.

- **To ensure that devices currently on the market remain safe and effective.** We are all well aware of cases in which questions are raised about safety or efficacy after a product has gone to market. From the FDA’s perspective, interpreting and dealing with postmarket data can be very complex.

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- **To provide the public with accurate, science-based information about devices.** Communicating postmarket data to the public adds another level of complexity. For example, not long ago questions arose about serious adverse events related to implantable cardioverter-defibrillators (ICDs). Because of publicity about these questions, many people who needed an ICD did not get one and many others had their ICDs replaced with a different model. Subsequently, a study in Canada showed that the risk of ICD replacement far outweighed any risk that was inherent in the product.

We can all agree that transparency and timely sharing of information are important, but exactly how to carry these things out is a challenge. When the FDA, as a government agency, makes a statement, it carries additional weight, so we try to be very careful about sending the right message to physicians and to patients.

Finally, we use the information that we gain in the postmarketing period to guide our regulation of the next generation of products, which contributes to all three broad aspects of our mission.

■ AS DEVICES GET MORE COMPLEX, NEW REGULATORY QUESTIONS AROUND

It used to be that when people thought of medical devices, they pictured mechanical tools. Now, however, we deal with a huge variety of different types of technology, including computer-related technology, molecular medicine, robotics, minimally invasive techniques, micro-electromechanical systems, nanotechnology, organ replacement, and wireless systems.

Not only is the technology new, but the way in which it is used is increasingly novel: devices are being used more and more in nontraditional settings, such as home care, and by nonclinicians who do not normally use medical devices. Can decisions about regulating a medical device that is safe and effective when used by a physician in the hospital be applied to its use by a relative caring for a 90-year-old patient in the home?

In addition, we now see combination products that increasingly blur the distinctions between medical devices and drugs. Genetic biomarkers have implications for the development of new drugs and for the refined use of existing drugs. One example is a test—already in existence—to assess individual

patients' sensitivity to the anticoagulant warfarin. There are also drug–diagnostic combinations in which a drug is developed along with a companion diagnostic test.

We are probably seeing just the beginning of these combined diagnostic and therapeutic systems as we move toward the concept of personalized medicine. When we consider the current challenges in designing appropriate clinical trials for specific populations and for off-label uses, it begs the question of how much more difficult trial design will be as technology moves closer and closer to individualized therapies for each patient.

■ FDA'S APPROACH TO MEDICAL DEVICE REGULATION

Our approach to medical device regulation is based on a number of objectives and principles:

- Basing the degree of control or oversight on the amount of risk with a given device
 - Weighing risks and benefits to determine safety and effectiveness
 - Using valid scientific evidence, which involves looking at clinical outcomes while recognizing that our mandate is not to regulate the practice of medicine
 - Considering the “least burdensome means”—ie, being open to any of several acceptable approaches that answer the pertinent regulatory questions (not, however, giving license to cut corners in submissions)
 - Providing “reasonable assurance,” recognizing that “reasonable” is in the eye of the beholder and that the agency and applicants may not always agree on its meaning.

If the FDA waits to be absolutely certain that a device is safe and effective before approving it, many patients may miss out on its potential benefits in the interim.

—Dr. Daniel Schultz

Other key elements: Intended use, adequate labeling

Beyond these principles, the FDA's approach to regulating device safety and effectiveness gives priority to at least two other key elements: specifying a well-defined intended use and ensuring adequate labeling. Sometimes applicants who are proposing a new device are very excited about their new technology but are not very specific about exactly how it will be applied to patients, so we need to focus them on clearly defining the intended population and the expected impact on patients. Similarly, device labeling must be developed to contain as much information as possible to help physicians make good choices without overpromoting the product or going beyond the submitted data.

Classifying devices

To ensure that appropriate oversight is applied to different types of medical devices, the CDRH uses a product classification system that differs from that used for drugs and biologics. It breaks down as follows:

- Class I devices, which are very simple (eg, gloves) and most of which are exempt from premarket submission
- Class II devices, which are subject to some special controls and require premarket notification (510[k] submissions)
- Class III devices, which are the highest risk and tend to be the most cutting edge. They require premarket application and approval.

There are two additional classifications:

- **De novo devices**, which have never been marketed in the United States but have a safety profile and technology that are reasonably well understood. Prior to the creation of this classification, a cutting-edge technology would have automatically been deemed Class III and required to go through the premarket approval process. Now a novel product may be recognized as lower risk and can be placed into its appropriate classification immediately.

- **Humanitarian device exemption**, for devices that address orphan diseases (conditions that affect fewer than 4,000 patients per year in the United States and thus may not offer an economic incentive for technology development). The motivation here is to help facilitate getting products to market for underserved niche patient populations with the understanding that some regulatory controls may be added.

Postmarket surveillance

The CDRH is working to make postmarket surveillance a stronger part of our program. In the past, people questioned whether the required postapproval studies for devices were actually getting done. Over the last few years, epidemiology staff from our premarket approval area helped design better postmarket studies, and we then transferred tracking and follow-up to the postmarket staff. In 2006, we issued a final guidance to manufacturers about how to submit follow-up reports and we developed a public Web site containing the postmarket studies that are required, including start dates, when reports are due, and whether studies are on schedule.² This helps us to have a transparent process and also prompts companies to follow through with agreements.

■ RISK/BENEFIT ASSESSMENT: REAL-WORLD EXAMPLES

The risk/benefit assessments undertaken by the FDA range from straightforward to highly complex. Devices that are life-sustaining have much potential for significant benefit, which makes most people willing to accept more risk. On the other hand, it can be difficult to quantify the benefit of cosmetic procedures (many of which we regulate), and people are less willing to tolerate risk for these procedures. Consider the handful of examples below.

Drug-eluting stents

When the CDRH first evaluated drug-eluting coronary stents, the data showed a greater than 50% reduction in the need for repeat interventions compared with bare metal stents, as well as low rates of complications. People asked us, “Why is it taking the FDA so long to approve them?” Soon after their approval, drug-eluting stents became the standard of care for about 60% of patients undergoing percutaneous coronary intervention.

Five years later, studies started showing some long-term complications, although the absolute risks and benefits are still not known with certainty. If we had spent another 5 to 10 years studying these devices, a lot of these questions might have been answered, but at what cost to those patients who actually benefited from this technology in the interim?

We are probably seeing just the beginning of these combined diagnostic and therapeutic systems as we move toward personalized medicine.

—Dr. Daniel Schultz

Cardiac occluder

Although studies showed that the muscular ventricular septal defect occluder had a high procedural success rate (81%), the adverse event rate was also very high: 44%. But because this device is for patients who have no treatment alternatives other than open-heart surgery but are considered to be at high risk from surgery, the risk/benefit assessment favored approval in this case.

Total artificial heart

The total artificial heart went through the humanitarian device exemption process. It is intended for patients with severe biventricular end-stage heart disease who are not candidates for transplant or a left ventricular assist device and are thus essentially at the end of life with no other treatment options.

Although studies showed that the device helped extend life, whether quality of life improved enough to support approval was in question. The device is

clearly not benign: out of 12 patients studied, support was withdrawn secondary to cerebrovascular accident in 6 of the patients. Four patients died of multiorgan failure or sepsis, and all patients had bleeding complications. However, 10 of the patients were able to interact with family members and 4 patients were able to have out-of-hospital activities.

How does one balance this ability to extend life for perhaps a few months—allowing patients to have additional time with their family, maybe to see a grandchild's birthday or attend a wedding—against all of these attendant adverse events?

Breast implants

Saline-filled and silicone gel-filled breast implants are designed for breast augmentation and breast reconstruction. Two saline-filled implants were approved in 2000 and two silicone-filled implants were approved in 2006, but only after complicated regulatory histories. Breast implants were first marketed in the early 1960s and were later “grandfathered” into the FDA's regulatory scheme upon passage of the Medical Device Amendment of 1976. They were classified as Class III devices in 1988, and the FDA called for submission of a premarket approval application in 1991 after the emergence of many reports (but scant solid clinical data) of adverse events related to these devices.

Over this period, breast implants became a considerable regulatory, scientific, and political controversy, for good reason: they are not life-saving devices, yet

they involve a lifetime commitment. How much clinical data and how much follow-up should be required? What should be the end points for studies? The FDA cannot determine the value that a woman puts on breast reconstruction or augmentation. What is clear is that adequate informed consent is critical, including a thorough explanation to patients of the benefits, the risks, and the nature of their commitment.

■ **DILEMMAS MOVING FORWARD**

Several dilemmas arise out of the FDA's mandates. Although our mission is to ensure product safety and effectiveness, what about patient autonomy? What about the rights of patients to be able to choose the therapies they want? While we are required to protect the public health, what if that conflicts with making products available?

Advertisements are another big challenge. We recently held a panel meeting on the LASIK eye procedure that included some very heart-wrenching stories told by patients who have had bad experiences. Part of the problem is how such procedures are advertised, without a balanced message about potential risks and benefits. People end up with the impression that the procedure is almost like getting their hair cut. Advertisements in newspapers and on Web sites tout a special price “for this month only,” exhorting patients to get the procedure done immediately. The surgeons who place such ads are at least as responsible for the problem as industry is, if not more so.

Responsibilities of the media, FDA, and professional societies

By Mary H. McGrath, MD, MPH

My experience with the FDA during the regulatory controversies over breast implants, mentioned above by Dr. Schultz, was the crucible in which my views about devices and the ethics of surgical innovation were forged. My comments here will focus on observations from that experience and then on the function of journalism in these issues, the role of the FDA, and the positive part that professional societies can play as we grapple with emerging technologies.

■ **BREAST IMPLANTS: A CASE STUDY IN REGULATORY COMPLEXITY**

A long and winding path to approval

Although breast implants had been on the market in the United States since the early 1960s, they did

not fully come onto the FDA's radar screen until 1991. The FDA had not been authorized by Congress to regulate medical devices until 1976, and at that point, other devices had higher priority. By the time of the first FDA panel hearings on breast implants, in November 1991, an estimated 1 million women in the United States had breast implants.

The 1991 hearings were driven largely by anecdotal reports in the literature suggesting a possible association between breast implants and rheumatoid and autoimmune disorders. As a plastic surgeon who specialized in breast reconstruction, I was a member of the panel for the hearings. The wave of public concern and the paucity of evidence in support of safety led then-FDA commissioner David Kessler to call for a moratorium on the use of breast implants in January 1992. Three

months later, the FDA ruled that implants would be limited to use only in clinical trials.

These actions produced a panicked response from the public, with silicone gel-filled breast implants being removed from more than 100,000 US women in the ensuing 2 to 3 years. People do not often consider the risk created by patients going back for surgery based on the fear resulting from a ban.

A huge class action lawsuit was brought against implant manufacturers, which culminated in Dow Corning—the largest manufacturer of implants at the time—abandoning the implant business and settling the suit for millions of dollars. Only two of five manufacturers continued to make breast implants, both of which manufacture them outside the United States.

Meanwhile, subsequent studies required by the FDA were gradually completed, leading the agency to approve saline-filled implants for marketing in 2000. In 2006, the agency approved silicone gel-filled implants after reviewing 553 studies that collectively demonstrated no association between these implants and systemic disorders. Both types of implants are marketed today, yet FDA approval carried some special conditions. Core study patients were to continue to be followed with magnetic resonance imaging screening through at least 9 years. Implant manufacturers were required to submit annual reports to the FDA, and a device retrieval program was set up. An implant registry also was established for postmarket surveillance. The registry was developed in collaboration with the FDA and professional societies, which also have developed content for formal patient education and professional training programs mandated as conditions of marketing approval.

Interest groups and the media: Fully in the mix

A multitude of interest groups were present and vocal throughout this entire episode, from the hearings in 1991-92 through the hearings leading up to the most recent approvals in recent years. In addition to obvious stakeholders, such as manufacturers, surgeons, and patients, the media packed the large hearing rooms and interviewed a wide range of interested parties, including investment fund managers, patients, and implant opponents. Groups such as “Fathers Against Breast Implants” typified the frustration that people felt about the sexualization of the culture. Every day, the panel hearings became front-page news.

FDA approval had an immediate market effect,

and implant sales surged. At the same time, the media raised questions about whether the FDA’s regulatory approach of requiring reasonable assurance of safety was sufficient and whether a higher level of evidence for safety and efficacy should be required for this type of device. News stories also examined societal ethics about quality of life and how much medical risk people should be allowed to accept for the sake of cosmetic procedures.³⁻⁵

■ THE ROLE OF THE PUBLIC—AND JOURNALISM

The case of breast implants illustrates the important role that the media can play in how emerging medical technologies are greeted, but this role should be viewed in the broader context of the key relationships involved in the development and use of surgical devices. Central to device development and use, of course, is collaboration between the medical profession and industry, as discussed at length earlier in this conference. I would like to focus now on two other major players that influence device development and use—the public and regulatory bodies (ie, the FDA).

Medical professionals have a responsibility to educate the public about emerging technology.

—Dr. Mary McGrath

Medical journalism falls short on two core principles

A key determinant of public views of new devices and other medical technologies is the discussion of those technologies in the media. Medical science has become increasingly publicized in both print and electronic media in recent years in response to high levels of public interest in medical news. In 1998, the *New England Journal of Medicine* published a lecture by medical journalist Dr. Timothy Johnson on the relationship between medicine, the media, and the public with regard to emerging devices and other products.⁶ Johnson argued that in the rush to satisfy the public hunger for medical news—and also to promote themselves—journalists and medical scientists have failed to adhere to some core principles: that science examines collective data over anecdotal data, and that getting a story right is better than getting it first. Moreover, weakened adherence to these principles has been exacerbated by the proliferation of business-related medical communications (press releases, press conferences, advertising infomercials, and the like) from biomedical product manufacturers, medical centers, and even individual practitioners as they try to increase their market share in today’s competitive environment.

Johnson pointed out that whereas journalists used to

present opposing viewpoints based on multiple sources, they now too often strive to be the first to report a medical story and to make it as forceful and dramatic as they can. Medical stories get more attention from the public, he noted, if they are unambiguous and use an anecdotal account to add “human interest.”⁶ These developments have been aided by the explosion in the number and type of news sources and the eclipse of journalists by public relations firms and—I would add from our 2008 perspective—bloggers.

Despite the challenge, potential solutions are at hand

Johnson argued that such excesses in the media are not in the public interest. Just as general news is based on facts, sources, and opinions, medical news should be based on data, probabilities, and conclusions. He proposed that medical reporters be required to undergo credentialing to demonstrate a background in biostatistics and epidemiology. Although this idea may seem radical, it has a precedent: meteorologists must be scientifically trained before reporting the weather forecast, a topic that is certainly no more important than medicine.

My view is that medical professionals have a responsibility to educate the public about emerging technology. Although we still do not require credentialing of medical reporters, we see more physicians contributing to the better broadcast and print media outlets. Some medical schools now offer training in medical journalism. In addition, the FDA has robustly implemented a directive to make public education a priority on its Web site.

Another hopeful sign is that some medical professional societies have begun to respond to issues like these through their codes of ethics. For instance, the society for my specialty—the American Society of Plastic Surgeons—has long had injunctions against false and deceptive advertising but now also bans exaggeration of one’s skills or claims to have been the first to use a new procedure or device, whether in an advertisement or, notably, in a media interview. Members who commit such transgressions can be brought before our ethics committee and asked to account for them.

■ THE ROLE OF THE FDA—AND AN OPPORTUNITY FOR PROFESSIONAL SOCIETIES

Let me turn to the other major player in device development beyond manufacturers and the medical profession—the FDA.

The FDA’s relationship is with the manufacturer; it has never been empowered to regulate the practice of medicine or the conduct of surgery. The FDA cannot dictate how a device is used (except via the manufacturer’s product labeling) or which physician specialties may use it. Physicians may use a device off label, but a manufacturer that deliberately markets a device for an off-label use (outside of the conditions outlined by Rebecca Dresser in the previous session in this conference; see pages S63–S64) is subject to regulatory penalties.

Increasing need for training requirements in device approvals

In the last few years, however, barriers preventing the FDA from regulating surgical practice have begun to break down as it has become increasingly obvious that a surgeon’s use of a device affects the performance of that device. For this reason, training in the use of a device must be integral not only to early development and clinical investigation but also to eventual use.

Until about 8 years ago, neither device manufacturers nor the FDA required end-user training. When such a requirement was first discussed, it was seen as an invalid effort to regulate medical practice. But a couple of gaps in this thinking eventually became obvious:

- Premarket clinical trials of a device are conducted at only a few institutions and by surgeons who tend to be very familiar with the product.

This raises real questions about how transferable the resulting data are to broader clinical practice.

- Mishandling of modern devices, which are increasingly complex and delicate, can easily result in product failure, a problem that can be very costly and damaging to the manufacturer.

Recognition of such problems has prompted the requirement for physician training in the labeling of an increasing number of devices. For instance, tracking done by the American College of Surgeons showed that 2 years ago, 8 of 13 FDA-approved devices for use in general surgery were approved with training requirements. The details of these prescribed training processes have not been very specific, however, and even the general requirement for training raises a host of resulting questions:

- Who should do the training—the device manufacturer, hospitals, or professional societies?

The American Society of Plastic Surgeons now bans its members from exaggerating their skills or claiming to have been the first to use a new procedure when they give media interviews.

—Dr. Mary McGrath

- What should training consist of—a course? Should there be a certificate upon completion?
- Who can take the training? Should it be confined to specific surgical specialties?
- Who designs the curriculum? Who evaluates the quality of the training? Who determines if the trainees are adequately prepared at the end?

Lessons from the American College of Surgeons

I would like to address some of these issues by drawing from the recent experience of the American College of Surgeons, which formed its Committee on Emerging Surgical Technology and Education (CESTE) about 8 years ago. The charge of CESTE was to formulate a comprehensive approach to questions like these and develop guidelines and mechanisms for a threefold mission: assessing new technologies, educating surgeons on new procedures and technology in their postresidency years, and verifying that this training results in actual acquisition of new skills.

Technology assessment. Technology assessment has proved to be the Achilles' heel of the CESTE efforts, because it is a difficult and costly long-term proposition. This is particularly true of device assessment, as devices are frequently modified to introduce incremental improvements over time.

The American College of Surgeons has sponsored only one randomized clinical trial—a collaboration 12 years ago with the Veterans Administration to evaluate open versus closed hernia repair. The study was very successful, eventually producing 42 published papers. However, by the time the follow-up was finished, the research question was moot, as everybody knew that closed hernia repair was a fine and acceptable approach. Firsthand experience with the complexity, the expense, and the 10 years needed to complete this surgical technology trial convinced

CESTE that undertaking primary assessment was beyond its scope. It has instead focused on becoming a clearinghouse for identifying new devices and procedures that are on the horizon and preparing surgeons for their arrival via its education mission.

Education. Education has been CESTE's greatest success. The committee has articulated goals for its courses with content and syllabi and has developed formats, instructors, and testing. Partnering with industry, CESTE has set up a number of skill centers around the country that involve cost-sharing, identifying learning needs, approving curricula and content, and assessing and verifying trainees.

Verification. Verification of education and training is necessary—documentation may be important for surgeons when requesting privileges—but is not always easy to do. Some components of training are easily verifiable: one can document that a physician attended a course, or one can ensure that didactic information was learned by using a written test. But demonstrating that someone actually acquired new skills is more difficult, and CESTE is just beginning to apply this level of verification to some of its courses. Ideally, CESTE will one day have a proctoring measure at trainees' home institutions to observe trainees actually applying their new skills in supervised clinical cases.

The first 8 years of the CESTE initiatives have been a learning process with more than a few challenges, but I believe the American College of Surgeons should be applauded for vigorously taking on the responsibility for training postgraduate surgeons in new and innovative technologies. I share its belief that professional organizations should serve this role, and this type of leadership from other medical and surgical societies will help address many of the challenges discussed earlier in this conference.

Promoting swift, safe, and smart innovation

By Thomas H. Murray, PhD

After listening to previous speakers at this conference, I am coming away with the message that we want a system for surgical innovation that is swift, safe, and smart.

In his keynote address, Dr. Thomas Fogarty, who will join us in this session's panel discussion, mentioned that people who want to develop a new technology need to actually talk with those who are working in and familiar with the field. That observation

is a fundamental insight behind the interdisciplinary methodology at the Hastings Center, where we identify issues in bioethics, develop relevant questions, and seek out people with various kinds of knowledge and insight to provide as comprehensive an understanding of those issues as possible.

The Hastings Center draws from people who make public policy, from people who interpret policy (such as those at the FDA), and from innovators. Two mem-

bers of our board are biotech entrepreneurs who have created companies that make products that they hope will help many people. I have never found a shortage of people willing to talk to you. The real shortage is of people who are actually willing to listen. So we try to encourage that as well.

In his keynote, Dr. Fogarty also brought up some controversial issues surrounding conflict of interest. The Association of American Medical Colleges (AAMC) report⁷ that he criticized was written by a committee that included me as well as leaders from the pharmaceutical and device industries, researchers who were developing new drugs and surgical devices, medical school deans, legal scholars, and ethicists. I stand behind that report and believe that it made a fundamental distinction between drug development and device development. This distinction—which has been pointed out earlier in this conference—is that drug development involves a lot of preclinical and clinical work but results in a product that can simply be given to a patient with simple instructions, whereas device development involves continuous innovation and improvement even after preclinical and clinical testing, and typically requires special expertise and training for proper clinical use.

■ WHAT DOES INNOVATION REALLY COME DOWN TO?

I see the challenge of innovation as a challenge to balance a number of things that we value: innovation itself, access to that innovation, respect for the human subjects who are part of the testing process, and regard for the patients who will ultimately benefit.

We also need to acknowledge the realities of how innovative surgical devices and procedures are created and to foster a culture of innovation that incorporates every bit of wisdom we can gather. This includes insight into what motivates inventors, such as royalties, with which there is nothing wrong in principle. It also includes insight into how to bring helpful innovations to patients. For instance, what do investors look for before they put money into a company or a particular development? We also need insights into how institutions and bureaucracies work—including the dreaded committees, to allude again to Dr. Fogar-

ty's keynote. I think we can all agree with the widely held insight, "Among democracy's many virtues, efficiency is not high."

■ A PERSONAL TAKE ON SUCCESSFUL INNOVATION

Last month marked the 25th anniversary of my Starr-Edwards valve, which replaced a Hancock porcine valve that calcified about 8 years after it was sewn into my heart. I would like to thank prior panelist Michael Mussallem of Edwards Lifesciences for his company's product, which has extended my life and the lives of many others. I am grateful to innovators and determined to ensure a healthy and vigorous culture of innovation in this country.

And I want that innovation to be swift, safe, and smart, though there are always tensions between these three values. The first two—swiftness and safety—are fairly straightforward: we should encourage creativity and innovation as much as possible, and we must respect the human subjects in whom we test new devices and the patients in whom we ultimately use them. But how can we ensure that innovation is smart? We must insist on a base of evidence that is as solid as possible while still being flexible. We also must learn which devices are the best matches for each patient.

Newborn screening is an example of one area that I have recently examined where innovation is fast proceeding in a way that might not be very smart. Recently we have seen a sudden and rapid expansion of the conditions for which newborns are screened. In many

cases we do not know what action to take if test results are positive, and in some cases we have no known effective therapies. I have criticisms of the process by which this expansion was decided upon, but most experts—even those supportive of the expansion—agree that we need to become much smarter about systematically studying the new conditions being screened for. Similarly, we need to make our system of surgical innovation as smart as we can in terms of how we gather evidence.

Dr. Joseph Fins opened this conference by declaring, "Let the conversation begin." I will conclude it by saying, "Let the conversation continue, and let it be vigorous, candid, and respectful, with unflinching regard for evidence."

The challenge is to balance a number of things we value: innovation itself, access to innovation, and respect for both the human subjects who are part of the testing process and the patients who will ultimately benefit.

—Dr. Thomas Murray

Panel discussion

Moderated by Roy K. Greenberg, MD

■ SHOULD INNOVATORS BE BARRED FROM USE OF THEIR INVENTIONS?

Dr. Roy Greenberg: Let us begin this roundtable portion of the session with any comments that our one additional panelist, earlier keynote speaker Dr. Thomas Fogarty, may have. Dr. Fogarty?

Dr. Thomas Fogarty: I agree with most of what was said, but one problem I have with the AAMC report that Dr. Murray refers to⁷ is the implication that those who develop a technology cannot treat patients with it. If a physician knows more than anybody else about a device, and a patient is referred to that physician, he or she is obliged to take care of that patient. The patient cannot be referred to somebody else who doesn't know anything about the technology—they haven't done the bench testing or the animal testing or the cadaver testing. Sending a patient to someone with no experience in the technology needed for treatment is a gross violation of the Hippocratic oath.

Dr. Thomas Murray: As I understand the AAMC report, what you just described would not be prohibited at all. In fact, under the proper circumstances, the innovator could be involved in testing and further development of the device. I am not familiar with the details of any policies related to this at Stanford, where you are affiliated.

Dr. Fogarty: Perhaps the restriction that I described is particular to Stanford, where it is still imposed. In any case, I think that type of restriction is improper.

■ INNOVATION VS REGULATION: HOW DOES AMERICA STACK UP GLOBALLY?

Dr. Greenberg: I would like to explore innovation in the United States compared with the rest of the world. On one hand, the United States has the reputation among scientists and companies abroad of having the most robust and respected studies, with the best follow-up and the most trusted results. On the other hand, we have an almost paralyzing regulatory system in which to get a study done. So devices become available in Europe, Australia, and elsewhere long before they come to the United States, and American

patients complain that they should not have to go to Europe to obtain a device. At the same time, some devices that are available elsewhere should probably never be used in patients. What are the panelists' thoughts on innovation and regulation in the United States in relation to the rest of the world?

Dr. Daniel Schultz: We probably are somewhere in the middle. The European system is much more *laissez-faire* than ours, especially with regard to devices. They primarily have third-party inspecting facilities, and if they show that the facility is safe and that the company has a manufacturing plan, most devices can go to market without any significant requirement for clinical efficacy. They may require some safety data, but in my mind it is difficult to establish safety if you do not know something about effectiveness. In

contrast, many consider the Japanese system far more rigorous and in some ways more inefficient than ours.

The FDA and its counterparts in other countries are trying to harmonize regulatory approaches around the world, recognizing that diseases—and companies—do not have borders. But value systems and public expectations differ a lot between different countries, so I doubt we will ever have a perfectly harmonized system.

Dr. Mary McGrath: As a longtime member of the FDA's General and Plastic Surgery Devices Panel, I have seen a lot of FDA applications that are not ready for prime time. Studies may be incomplete, the data may not reach statistical significance, or the manufacturers may have overlooked important consequences of the data. Some of the critics of the slowness of the FDA review process seem to assume that the minute an application reaches the agency, it is ready for analysis and a determination. In reality, applications often must be sent back for further work, which slows the process considerably.

With regard to other countries, I think it is decreasingly the case that our standards are much more stringent than those of the European Union, which has made great strides in trying to catch up with the US regulatory environment. I know of several devices in plastic surgery, including breast implants, on which the European Union would not rule until they had learned how the FDA ruled, and then they based

Sending a patient to someone with no experience in the technology needed for treatment is a gross violation of the Hippocratic oath.

—Dr. Thomas Fogarty

their decision on what they heard from our country because they had confidence in our process.

Dr. Murray: Although I do not have a comprehensive viewpoint on this question, I served on an FDA panel—the Cellular, Tissue, and Gene Therapies Advisory Committee—and found the FDA professionals and the members of the panel to be incredibly serious about the work they were undertaking to provide good feedback to the applicants. Although most of the applications in this cutting-edge area were not ready for prime time, the applicants needed good scientific advice about how to proceed, and I think they got some valuable feedback.

We need to recognize, however, that we can never achieve a perfect system. We will always have a tension between the values of swiftness, safety, and smartness. All three cannot be maximized at the same time. We have to keep adjusting and looking for the appropriate balance. A forum such as this one—where innovators, companies, ethicists, legal experts, and clinicians are present—is the right way to examine these issues, and we need to encourage more forums like this.

Dr. Fogarty: My experience with the FDA goes back to the initial device legislation; I was at the National Institutes of Health when we were asked by the FDA to help categorize devices in terms of risk. I have found that people in the upper levels of the FDA, especially those who have been practicing physicians, understand issues of safety and efficacy very well.

One challenging issue, however, is the goal of the “least burdensome means” in negotiating the regulatory process. Who determines the least burdensome means? It should not be an individual FDA reviewer. Input from patients and doctors is essential, since a reviewer may have a very different perception of burden than a patient or a treating physician does.

I agree that slowdowns often occur at the FDA because of inadequate preparation on the part of physicians or institutions. Applicants should not be going to the agency with inadequate data. But sometimes reviewers change, and one reviewer may emphasize different end points than his predecessor did, which makes the process less predictable. There should be a guarantee that nobody is going to change a study requirement midstream; often that leads to starting over, which can be very expensive, especially if ran-

domized, double-blind, prospective trials are involved. If a midstream study change is required for a product that serves only a small population, the developers will not pursue it further.

I think all of the issues I have mentioned can be resolved with frank, open conversations between the FDA and the physicians, institutions, and companies that it deals with. Beyond those issues, the FDA also can be subject to political influence, which is a different matter and which should not be the case.

■ WHERE DOES THE IRB FIT IN?

Question from audience: Could you clarify what the role of institutional review boards (IRBs) is in relation to the role of the FDA in approving and implementing studies of new devices in human subjects?

Dr. Schultz: For medical devices, the FDA has a process called an investigational device exemption that allows a clinical study to be performed for the collection of safety and effectiveness data, provided that certain requirements are met. These requirements include appropriate premarket or preclinical testing, evidence that the product is biocompatible and is manufactured appropriately, and other evidence that the product generally reaches a level where we think testing in patients is appropriate. At that point there are essentially two pathways: “significant risk studies” and “nonsignificant risk studies.” For products requiring significant risk studies, the study protocol must be reviewed

and approved by both the FDA and the relevant IRB before a trial can be initiated in humans, amounting to a sort of dual oversight. For nonsignificant risk studies, the protocol is approved solely by the IRB, which the FDA essentially uses as a surrogate for oversight in these less risky settings. Regardless of the type of study, the review of data resulting from the clinical study is done by the FDA, not the IRB.

■ WHO SHOULD MAKE CALLS ABOUT COST-EFFECTIVENESS?

Comment from audience: I found it interesting that when Dr. Schultz discussed the total artificial heart, no information was presented on cost. In the previous session, Dr. Peter Ubel asserted that we should be considering cost as an important feature of product assessment and that the FDA does not do so and in fact is not is not legally allowed to. I would like Dr. Murray to comment on the ethics of that.

The United States has the reputation of having both the most respected regulatory studies and an almost paralyzing regulatory system in which to get a study done.

—Dr. Roy Greenberg

Dr. Murray: If you want to see what I think about how to take costs into consideration in a general sense, take a look at an article I just published in the *Hastings Center Report*.⁸

To address your specific request, I agree with Dr. Ubel: to have a health care system that delivers the optimum care to people, you have to be mindful of the costs of care, the trade-offs, and the opportunity costs being incurred. But that does not preclude innovation; innovation can actually lower costs. Innovation can lead to delivering more care to more people at a lower price—look at what has happened in the semiconductor industry. You always have to be mindful of the policy choices, and cost is an inescapable factor.

Dr. Greenberg: I think Dr. Ubel used the term “psychological quirks” when he described the values that people bring to bear when they look at health care costs. Really, the most cost-effective way to deal with someone who needs an artificial heart is to let him die. For a lot of diseases, that is actually the most cost-effective way, but we have to somehow ascribe some value to what we are doing.

Dr. Murray: That may be the cheapest way, but it might not be the most cost-effective way. As an ethicist—not an economist, mind you—I think we must recognize that with the health care system we have in the United States, which is the most expensive in the world and gets middling results at best, we need to encourage innovation but we also need to think about effectiveness.

Being mindful of the costs of care does not preclude innovation; innovation can actually lower costs.

—Dr. Thomas Murray

Prior commenter from audience: I do not dispute that we need to think about cost-effectiveness. But individual physicians at the bedside should not be the ones who do that. We need a more sophisticated approach.

Dr. Murray: I absolutely agree; after all, doctors are not economists. We want them to focus on providing for patients the best they can. Decisions about cost-effectiveness need to be reached at a policy level and incorporated into medical training.

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