Is the World's Leading Innovator of Medical-Technological Advances Losing Its Edge?

Some say the conditions for medical innovation in this country have never been worse. What happened, and how do we fix it?

BY JAMES J. INCOLLINGO, CORRESPONDING EDITOR

It is common knowledge that the system is not working and that it has not been for some time. The complaints have been coming from inventors, manufacturers, venture capitalists, doctors, and patients. The gripes have been building in number and intensity for several years, and they recently merged into a chorus of consensus: the FDA's approval processes—both the 510(k) for most devices and the premarket approval (PMA) for most drugs—are too slow, too expensive, and fraught with uncertainty and difficulty. For many, the detrimental effects of this trend have become impossible to ignore—the progressive relocation overseas of the United States' medical-technological industry, a growing drag on the weakened US economy, patients' limited access to the latest therapeutic devices, and increasing doubts about the position of the United States as the world's leader in medical innovation, technology, and skill.

STRAINED RELATIONSHIPS

According to several business insiders, the conditions for the development of innovative medical technologies have never been worse in this country, and they say that relations between the FDA and the industry it regulates are often strained, sometimes even hostile. As one long-time observer and regulatory consultant told *Cataract & Refractive Surgery Today*, "There's a total lack of predictability in the regulatory process at FDA's Center for Devices and Radiological Health [CDRH]. It started getting really bad just as the financial markets went south in 2008, so it's a perfect storm of investors' taking a hit and then having to deal with longer review times and unexpected requirements from [the] FDA." The source, who is familiar with the FDA's approval process, asked not to be named.

> "We're losing our technological advantage, our engineering advantage, and our biomedical advantage, and it just makes me want to weep."
> *—a source familiar with the FDA's approval process*

More and more frequently, physicians are sending their patients overseas for treatments they cannot obtain here, while the manufacturers of new drugs

and devices move their studies, staff, and facilities abroad to finish their work in modern medical centers situated in less-regulated and less-costly environments.

Despite a real fear among those interviewed for this article that the United States is losing its edge, confidence remains that it is not gone completely. This country maintains several unique advantages, and one is the FDA itself. Even some of the agency's most pointed critics still praise the FDA's staff for its competence and its commitment to the agency's important mission and highest standards of scientific rigor.

Opinions on the FDA's leadership, however, are not as positive. Some individuals interviewed for this article believe that, after several recent notorious failures of approved devices, the administration's heads have been shell-shocked by the harsh rebukes from all sides and are now held to an impossible standard of perfec-

> "While the approval process is much longer in the United States, I don't think it protects Americans to any degree more effectively."
>
> —*Eric. D. Donnenfeld, MD*

Would Ophthalmology's Greatest Technological Breakthroughs Get Approved by Today's FDA?

With the approval process for new medical devices more difficult, expensive, and time-consuming than ever before, more than one observer has wondered aloud whether the innovations that propelled ophthalmology into the digital age would be approved in today's regulatory climate.

Before 1976, when device regulations were first implemented, there was nothing but malpractice lawsuits and the opprobrium of one's peers to prevent quackery in medical innovation. Looking back from 2011, the old days may resemble the Wild West more than an orderly system of technological development. Although there was certainly more freedom to experiment—on live subjects and otherwise—the old guard of medical practitioners and academics offered a remarkable amount of resistance and criticism to the mavericks who would break the bonds of rigid tradition and invent something new.

The soul-crushing experience of Charles D. Kelman, MD, while he developed phacoemulsification in the 1960s is well known, as is the determined pushback against the introduction of IOLs in the 1970s. The charge to introduce these lenses was led by Kenneth J. Hoffer, MD, and his newly formed American Intra-Ocular Implant Society. Some of the criticism they endured at the time still seems shocking today. Speaking with *Cataract & Refractive Surgery Today*, Dr. Hoffer recalled when detractors "went out of their way to publicly humiliate doctors who were doing phaco and IOLs. They were called 'intraocular time bombs,' and that phrase went around the world. It was out-and-out warfare to get rid of these IOLs and basically shut up people who were attempting to push them." Nevertheless, without regulatory law to prevent their use, these new technologies forced their way into practice by dint of their undeniable efficacy.

Developments such as IOLs, LASIK, and other game-changing techniques and technologies were radical for their times and were not initially viewed as obvious successes. They succeeded anyway, often thanks to the courage and tenacity of their inventors. Looking through today's FDA-approval prism, John Vukich, MD, worries that "the unintended consequence of this increased burden of proof for safety and efficacy is that we are now developing fewer things, or the things that we develop potentially have less risk and subsequently even less potential for being groundbreaking. We take small steps with things that we think are going to move incrementally instead of taking big steps we think are going to be dramatic. It's an insidious effect that is occurring in slow motion over time, but cumulatively, it's a change the consequences of which most people that work in new technology don't appreciate or understand."

Richard L. Lindstrom, MD, takes this thought experiment to its natural conclusion by imagining a world where ophthalmic technology stands still: "If we were trying to do 3.2 million cataract operations a year using intracapsular cataract extraction without intraocular lenses—fitting patients with soft contact lenses like we were when I started or aphakic spectacles—it would be impossible. Most of us believe, in the current regulatory environment, we would not have been able to get approval for any of the innovations that we take for granted today or certainly not at a cost that would attract the investment that allowed those things to happen. A lot of us believe it's going to be in our country's and our patients' best interest to go back a little bit [to] the way it was a few years ago."

tion, leaving them terrified of making another lethal, costly, or embarrassing mistake. To avoid such missteps, critics charge that CDRH Director Jeffrey Shuren enacted policies that have formalized an atmosphere of excessive risk aversion and hypervigilance.

THE FDA BEGINS TO RESPOND

With such a rising cacophony of criticism, it is comforting to know that the agency is not deaf. The FDA is well into the process of implementing a multiyear plan to reassess its relationship with its client base, streamline the PMA and 510(k) processes, and improve its "predictability, consistency, and transparency" for innovators and manufacturers, according to an open letter from Director Shuren dated January 19, 2011. The FDA's first substantive public response came in September 2009, when it established two working groups to study the problems with device approvals and recommend solutions. As part of their investigation, the working groups conducted a public outreach campaign that included town hall events and many smaller meetings with a range of stakeholders. In August 2010, the groups released a list of 55 suggested solutions. Based on those suggestions, the FDA announced a 25-point action plan in January of this year. Then, on August 15, it issued its Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff - Design Considerations for Pivotal Clinical Investigations for Medical Devices, which is open for public comment until mid-November. While hopes are high in all quarters that the FDA's efforts will pay off in tangible improvements, the task is daunting, and the problems are manifold.

HOW DID WE GET HERE?

The FDA's currently sluggish, unproductive approval process is fairly well recognized. How it got this way is murkier, and opinions vary. According to the anonymous source cited earlier who is familiar with the FDA's approval process, the problem is not entirely unexpected. "There were no device regulations until 1976, so if you think about it, we're just now getting into adulthood, but certainly not yet middle age, in terms of the regulation of devices." As for the specific causes of the growing pains, many believe they stem from a combination of administrative overreactions to highly publicized device failures and an associated aversion to taking risks. These factors are exacerbated by a public that expects perfection from an agency that is run by fallible humans. "They're paralyzed by risk aversion," the source said. "The big problem is they don't have enough capabilities, they don't have core competencies, and they often rely on outside clinicians who are not the best and brightest, because they can't have a conflict of interest."

An industry insider from a medical device company who also asked not to be named made more pointed comments to *CRSToday*: "You've got people who aren't as capable as they should be, and they're scared of their own shadows to make a decision. There's a lot of bureaucracy and a lot of stagnation, because people are afraid, and they don't know what they're doing."

Concerns over whether the FDA's staff is capable of meeting the challenges, although significant, are relatively rare. More prevalent is a widespread, even glowing, respect for the generally high caliber of the doctors, physicists, and researchers at the FDA who have been characterized as "bright, articulate, hardworking, dedicated, and idealistic." In a conversation with *CRSToday*, Mark Rosenberg, executive director of Barnet

> "We certainly need an FDA. None of us is saying we want to go without any regulation. We don't want to go back to the way it was in the 1800s."
> —*Richard L. Lindstrom, MD*

Dulaney Perkins Eye Center in Phoenix, talked about the FDA's staff and the system in which they work. "I don't think anybody comes to work trying to do a bad job," he said. "I don't think anybody at the FDA is intentionally trying to inhibit the advancement of medicine. On the other hand, we have a system that is clearly broken, because there are many proven technologies available worldwide that we're not able to access here."

Eric D. Donnenfeld, MD, a New York laser and cataract surgeon and educator, described the FDA's personnel as "very smart people who know how to run and evaluate a study" but who "need to be given a political push to move more quickly and in a less costly fashion." Dr. Donnenfeld is a chief medical editor of *CRSToday*.

Once completed to the FDA's satisfaction, approved studies are regarded as the best of the best. Stephen G. Slade, MD, sees such FDA studies as "an absolute, solid gold standard that is as close to perfect as it can get. They tend to be landmark studies that are valid for years, people compare to them, and they have the best follow-up, the best structure. The methodology of an FDA study results in an outstanding piece of research that is very valuable." Dr. Slade is a Houston-area ophthalmologist, a pioneer in the areas of devices and techniques, and an FDA presenter for several technologies, including the Crystalens (Bausch + Lomb, Rochester, NY), the Visian implantable collamer lens (STAAR Surgical Company, Monrovia, CA), and various lasers and algorithms. He is a chief medical editor of *CRSToday*.

A group of highly skilled and intelligent people, however, can unexpectedly find themselves in a systemic pickle.

DAMNED IF THEY DO, ETC.

Across the board, the people interviewed for this article agreed that the FDA is in a terrible position. The agency is rarely praised for approving things that work as intended, and CDRH processes roughly 3,000 new device submissions each year through the 510(k) approval path alone, as mentioned in Director Shuren's January 19, 2011, open letter. When mistakes inevitably occur, however, the FDA goes directly to the proverbial woodshed for a verbal lashing from doctors, patients, industry, and particularly elected representatives (whether they are grandstanding for political gain or earnestly striving to serve their constituents). Such treatment cannot be rewarding, especially for people who take very seriously their responsibility to protect the drug- and device-using public from ineffective or dangerous products.

Dr. Slade summed up the situation: "I have enormous respect for them, and they only get negative feedback. That's a tough environment to work in." Dr. Donnenfeld added, "There are very good people who work for the FDA, but there's no incentive for them to approve a drug or device. The result of that is that there's no fast-tracking, and devices and drugs are held up because there's no one moving them along quickly, because it's not to their advantage."

> "In the last decade ... the FDA approval process has been as cumbersome and slow as it's ever been in my career. It's been more challenging and harder than ever."
> —*William J. Link, PhD*

NOTORIOUS FAILURES

The fallout from recalled products such as implantable cardioverter defibrillators, pacemakers, and hip implants, among others, chastened the FDA. The source familiar with the FDA's approval process notes that, under such circumstances, "FDA is going to go underground," delaying approvals for pending technologies like corneal collagen cross-linking, the iStent (Glaukos Corporation, Laguna Hills, CA) to reduce IOP after cataract surgery, and the Visian toric implantable collamer lens (TICL; STAAR Surgical Company) to correct myopic astigmatism.

There are even elements of the FDA's constituency who want more restrictive regulations. In particular, they wish to address the "exception-creep" that has happened within the faster 510(k) approval pathway, which began accepting new technologies with new implications into a program that was originally designed to fast-track the review of minor modifica-

tions to existing devices.

The FDA's reaction to failures and criticism was somewhat predictable, but more than one critic has noted that these types of climate changes at the agency are cyclical. It just seems the pendulum may have swung a bit too far toward excessive caution this time. Those who take a long view are sanguine about a reversal. Perfection is an unrealistic standard for a government agency charged with promoting the dissemination of novel therapeutic technologies, and an inevitable turn back toward work-a-day practicality may lubricate the process without significantly raising risk. In Europe, under the European Conformity or CE Marking regime, patients receive access to a variety of new devices before US patients, and the former do not seem to suffer ill effects from excessive recalls. Richard L. Lindstrom, MD, founder of Minnesota Eye Consultants in Minneapolis, notes that "there's no evidence that patients are less safe in Sweden or Norway or Germany or France or Australia than they are in America, but the barriers to innovation are just two to three times higher here. It's hard to understand why all that extra time and money [are] necessary."

MANUFACTURERS, INVESTORS, PATIENTS, JOBS, AND MONEY GOING OVERSEAS

A simple consequence of liberal market capitalism is that, when companies can realize substantial savings in research, development, or manufacturing costs by moving their operations elsewhere, they do so. Delays in approval timelines cost money, and the nagging uncertainty built into the process can make the United States seem like an increasingly unattractive environment for venture capital in medical innovation and production. An example of products lost in seemingly ever-expanding approval timelines is the Visian TICL.

"Here's a technology that's been through clinical trials 6 or 7 years ago," Mr. Rosenberg told *CRSToday*. "There are patients who've had [these lenses] in their eyes for 10 years. Internationally, it's a standard of care, but we're not able to get these technologies here. I think it's important that the FDA serves its purpose, but when the process prevents good, proven technologies from being sold in the United States or is so onerous that it discourages some international companies from doing business in the United States, then clearly, I think we have overshot the mark." He added, "The FDA is actually inhibiting good medicine by interfering with the introduction of new technologies."

The result has been a quiet migration overseas—both of patients seeking treatment and companies seeking profits—to countries in Europe, Asia, South America, and even Canada and Mexico. Medical technology and pharmaceutical companies have sent entire research studies and development teams outside the United States to save money and time. This response to recent conditions here gained momentum when foreign laboratories and production facilities attained a level of quality commensurate with those in the United States. Now that some have surpassed US facilities in terms of their attractiveness to medical-technological business investors, the former have an increased pull on entrepreneurial talent, the industries it spawns, and the jobs created to make them work.

William J. Link, PhD, explained the trend to *CRSToday*. Dr. Link is cofounder of Versant Ventures (Menlo Park, CA) and founder of Chiron Vision. He has spent decades moving capital and building value in the

> "The industry and the FDA both have to be able to keep up with each other, because the questions get tougher."
>
> — *Ed Peterson*

medical device industry. "There is clearly a movement to taking innovation outside the United States," he said. "Our ability to get into human testing in the United States has [been] dramatically bogged down, and so we take a developing or developed technology outside the United States and do the initial human trials there in high-quality centers but in settings where the regulatory burden is less. Once we've advanced the innovation, and those technologies become commercial and available to patients and doctors outside the United States first—in Europe especially—then we begin the challenging process of putting the technology into the US market. So, there is quite a substantial delay, a multiyear delay, in access for patients and physicians to new, important technologies here in the States. And sometimes, it is the uncertainty [of] cost and time related to US FDA approval that is just too much, and those technologies never make it out to the United States. We've fallen behind in patient therapy."

Dr. Link is far from alone in his opinion. Cataract and refractive surgeon John Vukich of Madison, Wisconsin, has worked on FDA studies. "The process has become more detailed, and the burden of proof for establishing safety and efficacy has become more difficult to meet," he commented. "That has, in many instances, delayed the process of approval. What this has meant is that much of what we are looking at in terms of new technology, core concepts, patents, ideas, prototypes for devices which are developed in the United States, are no longer initially tried in the United States. The development of new technology is seen as something more efficiently, more cost-effectively, more rapidly done outside the United States. This would include the equivalent of phase 1 and phase 2 trials as well as actually some of the phase 3 data collection, and that really does lead back to both the regulatory environment and the length of time it takes to gain the necessary approval."

Anecdotal observations are supported by recent research, including a study by Split Rock Partners (Eden Prairie, MN) that shows a marked decrease in the rate of recent PMA approvals[1] and a Stanford University survey comparing perceptions of the timelines and relative difficulty between the approval processes here and in Europe.[2] In short, the process seems to be pointlessly tougher, slower, and more costly here, so overseas options become more attractive.

For patients who need treatments that are unavailable in this country, going abroad is a personal decision often undertaken at great expense and inconvenience. More than a few US doctors find irksome the fact that their patients need to go overseas for care, including Dr. Lindstrom, who has spent his career on ophthalmology's cutting edge and has witnessed the transition firsthand. "I really believe the American public would like to have broader access, and they're kind of proving that by flying around the world, away from America, to access drugs and devices that aren't available in the United States," he told *CRSToday*. "Medical tourism is becoming a major industry because of the lack of access to technologies [here]. The most classic example in ophthalmology today, and I could list many, is corneal collagen cross-linking. I have patients here every month flying off to Toronto, because they have keratoconus and need collagen cross-linking. It's been an approved treatment in Europe, Canada, and Mexico and more or less around the world for years, and we're probably years away from approval in the United States."

The United States used to attract large numbers of medical tourists from other countries, but those who continue to come here cite our reputation from years gone by as their chief motivation. Dr. Slade observed that "it's very rare these days for a doctor overseas to send a patient to a US doctor, because there's really nothing we have that they don't have. Now, we still get patients who self-refer from abroad, but that's because they have the perception that we're better doctors."

According to a 2008 forecast by the Deloitte Center for Health Solutions, medical tourism by US patients could multiply by a factor of 10 during the next decade, amounting to almost 16 million Americans heading abroad for treatment each year.[3] Leaving with them are jobs, the infrastructure of the medical-technological industry, and the perception that the United States is number one in health care.

SOLUTIONS?

Opinions on how to fix the problem tend to coalesce around a few general suggestions. Most commentators agree that exchanging "perfection" for a "reasonable" standard would be an important first step—both for the FDA and the American public's expectations. The

source familiar with the FDA's approval process believes that "people here should realize that no product is perfect and no physician or surgeon is perfect." The source added, "It's challenging in this country to have a meaningful discussion of benefit and risk." That conversation, and finding some appropriate middle ground on which to have it, seems long overdue.

Others argue that improving communication between the FDA and the sponsors of devices would go a long way toward streamlining the process. Dr. Donnenfeld notes that "dealing with the FDA is not a negotiation; you're dealing essentially with a dictatorship. There should be more give and take and discussion about approval processes." Those discussions should take place in real time, as opposed to the time-consuming tradition of exchanging letters.

Ed Peterson, president and CEO of device-maker AcuFocus (Irvine, CA), suggested to *CRSToday* that one potential improvement would be to "have one-on-one conversations with different people in the FDA in order to increase communication between the companies and the FDA, rather than have the written process with 30 days for them to respond. Writing things out is much like an e-mail; everyone who reads it interprets it [in his or her] own way. Spoken language going back and forth would enhance the process of full understanding of what the FDA wants and what the company is responding to."

The answers to the current problems may lurk in the FDA working groups' 55 recommendations from September 2010, its 25-point action plan from January 2011, or the draft guidance for medical device studies released on August 15 of this year. The people and industries dependent upon the FDA for their lives and livelihoods will likely echo the source familiar with the agency's approval process, who advises that, "in life, it's always hard to find middle ground, but FDA has to start working toward it and allowing innovation to move ahead." ■

Eric D. Donnenfeld, MD, is a consultant to numerous pharmaceutical and device manufacturers. Dr. Donnenfeld may be reached at (516) 766-2519; eddoph@aol.com.

Richard L. Lindstrom, MD, is a consultant to numerous pharmaceutical companies and device manufacturers. Dr. Lindstrom may be reached at (612) 813-3600; rllindstrom@mneye.com.

William J. Link, PhD, may be reached (949) 729-4500; bill@versantventures.com.

Ed Peterson may be reached at (949) 585-9511.

Mark Rosenberg acknowledged no financial interest in the products or companies mentioned herein. Mr. Rosenberg may be reached at (602) 508-4808; mrosenberg@bdpec.com.

Stephen G. Slade, MD, is a consultant to numerous pharmaceutical and device manufacturers. Dr. Slade may be reached at (713) 626-5544; sgs@visiontexas.com.

John A. Vukich, MD, is a consultant to numerous pharmaceutical and device manufacturers. Dr. Vukich may be reached at (608) 282-2000; javukich@facstaff.wisc.edu.

1. Link B. The high cost of regulatory compliance. Menlo Park, CA: Versant Ventures, Spring 2011.
2. Makower J. FDA Impact on US medical technology innovation: a survey of over 200 medical technology companies. http://www.nvca.org/index.php?option=com_docman&task=doc. Published November 2010. Accessed August 15, 2011.
3. Johnson LA. Americans look abroad to save on health care: medical tourism could jump tenfold in next decade. *San Francisco Chronicle*. August 3, 2008. http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2008/08/03/BUGA121GPF.DTL&type=health. Accessed August 15, 2011.