Medical Devices — Protecting Patients and Promoting Innovation

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Many Americans benefit from the implantation of medical devices, such as artificial joints and lifesaving defibrillators. Tragically, many also suffer or even die from complications related to the same types of medical devices, some of which have never studied in clinical trials before being implanted in a large population of patients. As devices have evolved and become more complex, our device-approval system has become less capable of assuring safety and effectiveness. The system we use today was created 35 years ago in an era of much simpler and fewer devices, and it is now inadequate.

A recent, but not rare, example provides a cautionary tale about the challenges of ensuring that complex medical devices are both effective and safe. Osteoarthritis of the hip joint is a common and debilitating disorder. Each year, more than a quarter of a million patients with advanced painful arthritis receive a total hip replacement in the hope that it will restore mobility and improve their quality of life.[1] Conventional artificial hip implants consist of a metal ball inserted into a plastic cup. In 2005, a new metal-on-metal design was introduced in which both components were made from a metal alloy. The design was touted as a major innovation that would improve durability and reduce the risk of hip dislocation — advantages that were especially appealing to younger patients. However, these design innovations were never tested.

One metal-on-metal design is the DePuy (Johnson & Johnson) ASR XL Acetabular System, which was introduced into the U.S. market in 2005. The ASR was cleared by a Food and Drug Administration (FDA) process known as 510(k), which refers to the section of the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act that created it. Under that section, the criterion for clearance of a new medical device is that it be “substantially equivalent” to an already-marketed device (a “predicate”); clinical data are not required nor are data on safety and effectiveness.

The ASR was constructed by borrowing a metal alloy cup from a different hip device known as the ASR Hip Resurfacing System and retrofitting it onto a standard hip implant. The manufacturer successfully made the case that the re-engineered implant was "substantially equivalent" to a predicate device. Its marketing clearance was therefore based not on clinical trials or other clinical data but on bench testing in a laboratory, which was inadequate to simulate the stresses that would be placed on it in patients' bodies.

It soon became clear that the device failed at the astonishing rate of at least one in eight. According to a recent report presented at the British Hip Society Annual Conference, 21% of these hips have had to be replaced (revised) by 4 years after implantation, and the revision rate rises to 49% at 6 years, as compared with 12 to 15% at 5 years for other devices.[2] Failure appears to be due to erosion of the metal in the articular surfaces and migration of metallic particles into the surrounding tissues and the bloodstream. Thus, the innovation led to tragedy for many patients.[3] Before it was recalled in 2010, the ASR had been implanted in nearly 100,000 patients, and the result was a public health nightmare.

The ASR is a class III device — the FDA's highest risk classification. As a high-risk device, it should not be cleared (without clinical data) via the 510(k) process, especially as its design is novel and thus there is no predicate for a 510(k) clearance. Congress envisioned that class III devices would be approved through the more stringent premarket approval (PMA) process, which does require clinical testing, and the Safe Medical Devices Act of 1990 requires that the FDA either use the PMA process for class III devices or reclassify them in a lower-risk category. Despite the clear intent of Congress, a recent GAO report noted that most high-risk devices continue to slip by this requirement. In fact, a recently published study found that among high-risk device recalls from 2005 to 2009, nearly three-quarters had been cleared through the 510(k) process.[4]

The Wingspan endovascular stenting system provides yet another cautionary tale about the potential risks to human health of innovative medical devices. The Wingspan stent was designed to be placed into small blood vessels in the brain in patients at high risk of a

stroke, in order to re-open narrowed vessels to prevent a subsequent stroke from occurring. The Wingspan system was approved for use in both Europe and the U.S. in 2005. While in Europe the device received standard approval by a notified body, in the U.S. the FDA approved the device with a humanitarian device exemption (HDE), which requires a less stringent approval process than standard pre-market approval (PMA) and limits use to no more than 4000 patients per year. One phase I trial in 45 patients but no controls, which demonstrated angiographic benefit, served as the basis for HDE approval. On the basis of this phase I trial, the company optimistically referred to the device as a "groundbreaking system."

Just two months ago, and six years after the Wingspan was approved by the FDA, a phase III clinical trial (SAMMPRIS) comparing the device with intensive stroke-prevention medical therapy was published in the *New England Journal of Medicine*.[5] The study was investigator-initiated and funded by the National Institute of Neurological Disorders and Stroke (the commercial sponsor, Stryker Neurovascular [formerly Boston Scientific Neurovascular], donated the devices), and thus was paid for principally by taxpayer dollars. The hypothesis tested in the study was that the stenting system would improve patient outcomes, as measured by the primary endpoint of stroke or death within 30 days of enrollment. After just 451 patients had been enrolled, the study was terminated prematurely because of a serious adverse safety signal in the stent-treated group. The incidence of the primary endpoint (stroke or death) in the stent-treated group was two and a half times greater than in the medically-treated group (14.7 percent versus 5.8 percent), a worrisome result that was unanticipated by the investigators. The comparable figures at 1 year were 20.0 percent and 12.2 percent. Despite these worrisome outcomes, the device remains available in the U.S.

The disturbing experience with the Wingspan stent system, which harmed many patients, serves as a stark reminder that innovative medical devices, regardless of how promising they may first appear on the basis of preliminary studies, do not always prove to be successful when subjected to rigorous controlled clinical trials. Implantable medical

devices are complex pieces of engineering, and bypassing clinical testing to rigorously evaluate their function inside the human body can result in substantial harm to patients.

On July 20, 2011, the U.S. House Energy and Commerce Subcommittee on Oversight and Investigations held a hearing entitled "Medical Device Regulation: Impact on American Patients, Innovation, and Jobs." The subcommittee's chairman, Congressman Cliff Stearns (R-FL), argued that FDA regulation of medical devices is too burdensome, stifles innovation, and drives device manufacturers overseas. Since then a number of bills have been introduced in Congress that would diminish FDA's ability to assure safety and effectiveness of medical devices. But the disastrous outcomes of the use of DePuy ASRs and the Wingspan endovascular stenting system show that rushing untested and potentially dangerous medical devices into the marketplace carries serious risks; our regulators should not be in the business of creating jobs in the manufacture of dangerous devices.

On July 29, 2011, the Institute of Medicine (IOM) released an FDA-commissioned report on the 510(k) clearance process.[6,7] The report concluded that it was impossible for 510(k) clearance to assure safety and effectiveness, because it assesses neither, instead establishing only "substantial equivalence" to an existing device. The report therefore recommended that 510(k) clearance be eliminated. In addition, it recommended monitoring medical devices throughout their life cycle, especially during the postmarketing period. Despite its reasonable (and relatively modest) recommendations, the report has been aggressively attacked by the device industry and by politicians from states where device companies are located. In fact, the attacks began even before the report was released, which is highly unusual for an IOM report.

I believe that the IOM report is insightful, judicious, sensible, and long overdue. The 510(k) clearance process was established 35 years ago, and although it may have been a reasonable approach then, it surely is not today. The 510(k) process was never intended for use for clearing Class III medical devices, defined by the Code of Federal Regulations as products used for life-supporting or life-sustaining indications, for preventing impairment

of human health, or presenting a potentially unreasonable risk of illness or injury. I support the IOM committee's recommendation that the 510(k) process be replaced with an evaluation of safety and effectiveness. It is important to maintain and encourage innovation in medical devices. But true innovation requires that safety and effectiveness be proven by scientific study in clinical trials.

Under intense pressure from the device industry, the FDA leadership has already indicated that it does not intend to implement this key recommendation of the report, although it may be open to other changes. As the best long-term improvements are contemplated, there are important steps that the agency can take now.

First, the use of 510(k) clearance for class III devices should stop, as Congress made clear 20 years ago. A substantial equivalence standard for clearance of such complex devices is untenable. This recommendation was made previously in a report from the Government Accountability Office (GAO),[8] but it has not been fully implemented by the FDA.

Second, the use of multiple predicates in 510(k) clearance should be eliminated. Now a device may be cleared if it is found to be substantially equivalent to an existing device that was cleared, in turn, by being found substantially equivalent to another device, and so on. A device can receive 510(k) clearance by being substantially equivalent to a device that is no longer on the market. This tenuous process should be discontinued.

Third, if a substantial equivalence standard is to be retained for certain devices deemed not of high risk, there must be a clear definition of substantial equivalence including the authority of FDA to require the submission of clinical data to assess whether the new device meets the substantial equivalence definition.

Third, as was recommended by the IOM committee, a formal system of postmarketing surveillance for medical devices should be put in place. Strong, mandatory, and transparent postmarketing data, in registries, allow rapid identification of serious

problems that may emerge after approval. Careful tracking of every patient with a high-risk device is a crucial step for ensuring patient safety and avoiding nightmare scenarios. To this end, I hope that the FDA will soon finalize its rule about a system of Unique Device Identification (UDI), and then that the Centers for Medicare & Medicaid Services will require the UDI to be submitted with claims. That would allow safety surveillance for medical devices to be much more tractable.

Fourth, I strongly endorse the FDA's Sentinel Initiative and the associated Mini-Sentinel pilot program.[9] Through the Mini-Sentinel pilot program, capabilities are being developed for actively monitoring the safety of approved medical products using the electronic health information in claims systems, inpatient and outpatient medical records, and patient registries. Such a system will be an important step forward.

Fifth, I believe that the European medical device regulatory system, in which 82 privately run notified bodies rather than a government agency make decisions on market authorization for medical devices, is not a suitable model for the U.S. and would not be in the best interest of the American people. Notified bodies do not adhere to uniform standards, and device manufacturers can select the notified body that will put their device through the least stringent assessment of safety and performance. Most surprising, manufacturers do not have to demonstrate a beneficial effect on clinical outcomes.

I strongly believe that, in the interest of advancing human health, patients must have easy access to innovative medical devices and that the approval process needs to be sensible and efficient. But no one's interest is served by putting defective or untested medical devices onto the market where they cause harm to patients, waste health care dollars, and may kill jobs when they are withdrawn. It is essential that the FDA be adequately funded to carry out its mission to ensure the safety and effectiveness of medical devices. The IOM report charts a path that is right for the future, and despite well-financed outside pressures, I urge the FDA to initiate an action plan with congressional support to adopt these important recommendations.

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