

Watching over the medical device industry

Although all new drugs have to be tested to get regulatory approval, the same is not necessarily true for medical devices.

Jeanne Lenzer reports on loopholes that leave patients at risk

Lana Keeton was 54 when a surgeon used a synthetic mesh to create a pubovaginal sling to treat her for stress urinary incontinence. After her surgery in 2001, Ms Keeton developed a necrotising soft tissue infection at the operative site. Surgeons later found that the mesh had migrated and eroded through her bladder wall. During the past eight years, Ms Keeton has had numerous procedures and operations to remove pieces of the mesh and to treat recurrent urinary tract infections and pain. In October 2008, the US Food and Drug Administration warned that surgical meshes made by nine manufacturers, including the manufacturer of the mesh implanted in Ms Keeton, have been associated with serious complications, including bowel and bladder perforations, infections, and pain.¹ Because of a little known loophole in the device approval process, the FDA did not require the manufacturers to submit safety or efficacy data before receiving approval to market their products.

And it is not just surgical mesh that gets a free ride. An investigation conducted at the request of Congress by the US Government Accountability Office in January 2009, found that the FDA has never clinically reviewed many devices currently on the market, including some of the highest risk implantable devices.² Another investigation, published in February 2009 by the US watchdog Project on Government Oversight, concluded

that the device industry operates in an environment akin to the “Wild West days, when manufacturers were free to set their own rules and standards without interference from the FDA.”³

Even when devices undergo the most rigorous level of FDA review, known as premarket approval, some FDA scientists say the process has been corrupted. On 2 April, nine FDA scientists, whose names have not been revealed publicly, wrote to President Barack Obama, complaining that senior managers

have approved several medical devices despite the strenuous and sometimes unanimous objections of agency scientists.⁴ In one instance cited, the scientists’ unanimous recommendation against approval of a digital mammography machine was over-

turned, allegedly after a call to the director of the Office of Device Evaluation from Congressman Christopher Shays, a claim Congressman Shays disputes. Congressman Shays represented the district where equipment for the device is manufactured. He told the *New York Times* that he called the FDA to demand a final decision—not to force approval.⁵ The FDA scientists asked the president to put an end to a “culture of wrongdoing and cover-up” at the agency.

The device industry, according to several experts and external assessments, operates in a disturbingly lax regulatory environment that is riddled with conflicts of interest. As a result,



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the safety and efficacy of many of the highest risk devices on the market today have never been adequately tested—or tested at all.^{2,3,6} This problem, combined with misleading promotional practices, loose post-market surveillance, and “pre-emption” or legal immunity from personal injury lawsuits for device manufacturers, have led to calls for tighter control over an industry that some say is out of control.^{3,6-8}

Approval regulations

While there is little doubt that many devices have provided enormous benefits to the public and that the regulatory agencies have been central to the safety of many products, the global reach of today’s companies, combined with the rapid uptake of drugs and devices, means that the scope for harm is enormous. For example, in 2005, Medtronic reported potentially lethal problems with its pacemakers and implantable defibrillators that had been implanted in over 100 000 patients worldwide, according to a Medtronic spokeswoman.⁹ That same year, Guidant recalled defective implantable defibrillators that were in use by 50 000 patients worldwide.^{10,11}

Thomas O McGarity, author of a book on the effects of competing interests on public health research,⁸ says the divergent timelines of drug and device development have led to important differences in how the two industries are regulated in the US. The drug industry came under substantive regulatory control with the passage of the 1938 Federal Food, Drug, and Cosmetic Act, which was passed in the wake of the 1937 sulphanilamide-ethylene glycol disaster that caused 106 deaths. However, regulations for the device

THE FDA RISK CATEGORIES

Low risk (class I)

Devices include items such as tongue depressors and bandages

Medium risk (class II)

Devices include endoscopes and infusion pumps

High risk (class III)

Devices include cardiac pacemakers, implanted defibrillators, and heart valves



STEPHEN SAVOIA/AP/PA

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industry, the Medical Device Amendments, were not introduced until 1976. By this time, device manufacturers, like drug manufacturers, had grown into multinational corporate behemoths, capable of bringing enormous economic and political pressure to bear. According to McGarity, the device industry was able to wrest important concessions in the device amendments—including certain exemptions from the proposed premarket approval mechanism and a key concession known as “pre-emption,” which protects manufacturers from personal injury liability if the FDA gives their product full premarket approval.

The FDA classifies devices into three risk categories: low risk (class I) devices include items such as tongue depressors and band-aids; medium risk (class II) devices include endoscopes and infusion pumps, and high risk (class III) devices include cardiac pacemakers, implanted defibrillators, and heart valves. Most class I and some class II devices are exempt from clearance or approval and can simply be registered with the FDA. For the remaining devices in classes I and II the manufacturer simply has to notify the FDA of the product's class and its intent to market the device 90 days before distribution. The process, known as 510(k), does not require clinical trials.

Class III or high risk devices are generally expected to undergo a premarketing approval process in which the manufacturer must provide evidence of clinical safety and efficacy. However, one of the concessions won by industry was an allowance that all devices, including high risk devices, on the market before 1976 could be sold under the 510(k) provision. In addition, any new devices that the manufacturer deems to be “substantially

equivalent” to a device (which is known as a predicate device) that was on the market before 1976, can also win approval under the 510(k) process. Even devices that are substantially equivalent to other substantially equivalent devices can be approved under 510(k) for potentially infinite iterations.²

During fiscal years 2003 through 2007, exemptions have allowed the majority of original applications for high risk devices to be approved through the 510(k) process—without clinical testing.^{2,3} During the same period, 1458 devices of unknown class were approved under 510(k), according to the FDA's own records.² It isn't known how many of those devices are high risk devices, according to Marcia Crosse, director of health care at the Government Accountability Office.

According to the Project On Government Oversight, the problem with the 510k exemption is that it is based on two, potentially false assumptions—“that the predicate device is truly safe and effective, and that manufacturer's claim of ‘substantial equivalence’ means that the new device is at least as safe and effective as the predicate device.”³ The report notes that a US court of appeal judgment in 1995 held that 510(k) approval “standing alone, is not a finding of safety and effectiveness,” and that this was affirmed in 1996 by the Supreme Court: “Since the 510(k) process is focused on equivalence, not safety, substantial equivalence determinations provide little protection to the public.”³

The court's findings foreshadowed Ms Keeton's case described above. The vaginal mesh sling she was treated with won 510(k) approval when the manufacturer cited two predicate devices, one of which had already

been recalled as “adulterated and misbranded.” The sling has now been removed from the market and dozens of women are suing the manufacturer.¹ The FDA, asked why it would allow approval to be based on a recalled, adulterated device, responded in an email to the *New York Times*: “Any legally marketed device can serve as a predicate for a premarket submission.”¹² Johnson and Johnson said it did not comment on ongoing litigation.

Scope for compensation

On 20 February 2008, the US Supreme Court dealt a blow to patients seeking redress for injuries from medical devices, even if they have full market approval. In *Riegel v Medtronic* the Court ruled that the 1976 Medical Device Amendments protects manufacturers from personal injury liability if their product received premarket approval from the FDA.¹³ The case resolved a suit against Medtronic, the manufacturer of a balloon catheter that ruptured while Mr Riegel was having angioplasty. The Riegels contended that the catheter was defective and had caused severe and permanent injuries to Mr Riegel. Justice Antonin Scalia, writing for the 8-to-1 majority, said the 1976 amendments prohibit states (where personal injury lawsuits are filed) from imposing different or additional requirements from the federal requirements imposed by the amendments.¹⁴

Justice Scalia said that the 1200 hours spent by the FDA reviewing premarket approvals offers “reasonable assurance” that devices are safe and effective. However, FDA reviews are generally based on small clinical trials that may fail to detect rare but serious adverse events, problems that might only be picked up

during postmarketing surveillance.⁸ The ruling also treats the device industry differently from the drug industry: In *Wyeth v Levine*, the US Supreme Court ruled against pre-emption and held in its February 2009 ruling that manufacturers can be held liable for personal injury caused by FDA-approved drugs.

The FDA has chosen not to oppose pre-emption for devices, despite its earlier opposition, stating, “The Supreme Court’s decision in *Riegel v Medtronic* establishes the applicable federal law. FDA applies the law as decided by the Court.”

Surveillance: is anyone looking?

Surveillance and monitoring systems are intended to pick up serious safety issues that may not be apparent during the approval process. But experts like former National Institutes of Health scientist Ned Feder say the surveillance system is an empty shell without active analysis by the FDA. Dr Feder, currently a staff scientist with the Project on Government Oversight, says the case of Kyle Pacheco, is emblematic of systemic problems at the FDA.

Pacheco was injured after using prefilled heparin syringes manufactured by AM2PAT in Angier, North Carolina. He subsequently developed sepsis, went into a month long coma, and emerged brain damaged, unable to walk, and in need of full time nursing care.

Pacheco was just one of hundreds of patients who were admitted to hospital during November 2007, at least five of whom died, after using the prefilled syringes. In December 2007, the Centers for Disease Control and Prevention in Atlanta, announced that a number of AM2PAT’s unopened devices were contaminated with *Serratia marcescens*.¹⁵ Federal prosecutors filed charges against the company’s executive officers in April 2008 for selling adulterated devices. Two of the officers are now in prison and the AM2PAT plant in Angier is shut.

But safety problems were evident long before Pacheco and others were infected. In June 2005, an FDA inspection of the Angier plant found unsanitary conditions and multiple violations of good manufacturing processes. On 15 November 2005 the FDA received a complaint that particles were seen floating in the syringe fluid. Eventually, dozens of complaints of contamination were filed in the FDA’s manufacturer and user facility device experience (MAUDE) database that tracks device related adverse events.

FDA inaction after the reports were filed raises questions about its surveillance. According to Dr Feder, even when inspections detect serious violations that pose potentially lethal threats, the FDA rarely takes any action more severe than issuing a warning letter. The FDA should not rely on factory managers to correct serious problems, says Dr Feder, “without close continuing surveillance by the FDA.”

Dr Feder is also sceptical that the MAUDE database is being used appropriately. “It’s not enough to collect data,” said Dr Feder. If the FDA doesn’t have the staff to look at the data and decide which devices should be investigated, he said, “it really doesn’t matter if the reports are sitting inside the FDA’s files.”

Device approvals, politicians, retaliation

A history of industry influence and intimidation has left the device approval and surveillance systems in a shambles, according to prominent spinal surgery researcher Richard Deyo. In the early 1990s, Dr Deyo and his colleagues incurred the wrath of the North

American Spine Society after they published several studies suggesting that spinal fusion surgery was often ineffective and sometimes harmful.¹⁶ The society, which is heavily funded by companies

that make the plates and screws used in spinal fusion surgery, attacked Dr Deyo and his sponsor, the Federal Agency for Health Care Policy and Research, now renamed the Agency for Healthcare Research and Quality. Members of the society lobbied key members of Congress who, in 1994, voted to eliminate the agency’s budget. Only intensive efforts by the American Medical Association and the American Hospital Association restored 75% of the original budget. But the damage was done: the agency stopped issuing comparative effectiveness guidelines.

Since then Dr Deyo says spinal fusion operations have increased “dramatically” and new surgical devices have proliferated. Despite the increase in surgery, there is little evidence of benefit for many patients: three of four randomised controlled trials in Europe found “very little advantage over rigorous rehabilitation for back pain due to worn-out discs,” says Dr Deyo.

The value of the FDA’s MAUDE database as an early warning system is undermined by two key problems: under-reporting of the numerator (the number of adverse events), and the lack of a denominator (the total number of exposures). One cause of under-reporting

is that manufacturers do not have to report serious adverse events, including deaths, if they decide that the event is not related to the device. Jerome Hoffman, an expert in clinical epidemiology at the University of California, Los Angeles, is critical of the FDA’s policy of allowing manufacturers to make that determination. “The manufacturer has a powerful motive to find an alternative explanation for an adverse event. There’s always the possibility of a separate cause.” Dr Hoffman says that the agency should insist on independent adjudication of serious adverse events.

The database’s value could be further improved, says Dr Hoffman, by including denominator data. “It’s often claimed that even when bad events occur, they have to be relatively rare, given the huge number of exposures. That certainly may be true in some cases. But it’s hard to know for sure in any individual instance, because the FDA doesn’t track the number of exposures. It shouldn’t be that hard. . . considering that WalMart can apparently track every head of lettuce they sell, at every point of its existence. Of course the FDA would have to require that companies submit data on the quantity of devices sold, and in use.”

Ultimately, says Dr Hoffman, the process of ensuring device safety will continue to be compromised unless the thorny problem of interference from politicians and industry is tackled. “None of this occurs in a vacuum, of course. If we want to see fewer of these debacles in the future, it seems only logical that we’re going to have to look to root causes, such as how campaigns are financed, and how the wealthy and powerful get to have so much more influence on laws, regulations and policies, than do scientists and others who would advocate for making the public health more important than corporate profit.”

However, it is not clear that Dr Hoffman’s wish that scientists have greater influence on regulation than industry is likely to be realised any time soon. President Obama has appointed Margaret Hamburg as FDA commissioner. She has stepped down as director with Henry Schein—the largest supplier of medical devices in North America and Europe. Hamburg and her husband, who is a hedge fund executive, reported their 2008 income at \$10m.¹⁷ She said last week that she plans to take a “hard look” at the agency’s 510(k) process that allows manufacturers to market many of the devices in use.¹⁸

Jeanne Lenzer medical investigative journalist, New York jeanne.lenzer@gmail.com

Competing interests: None declared.

References are on bmj.com

Cite this as: *BMJ* 2009;338:b2321