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Medical Devices

Europeans are left to their own devices

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When it comes to medical devices, it seems that Europeans get a worse deal than US patients, and even that their safety could be being compromised. **Deborah Cohen** and **Matthew Billingsley** compare the regulatory systems

Slick and efficient or opaque and patchy—these are two of the views about the European medical device regulatory system expressed during a recent US Congress debate. But unlike the case with say, consumer drug advertising or other marketing incentives, the devices industry argues that conditions are more favourable in Europe.

“European regs are driven by one key goal: innovation,” one industry report suggests.⁽¹⁾ And another says that the conditions in Europe favour medical technology companies—they can obtain regulatory approval more quickly, generate revenues faster, and “engage patients and providers in the cycle of innovation to advance their products and services.”⁽²⁾

John Wilkinson, chief executive of Eucomed (a European medical device industry trade association), said in a report: “The current EU regulatory system makes innovative medical technology available to people the fastest in the world while ensuring the highest safety standards.”⁽³⁾

But although the conditions might be more favourable to industry, not everyone agrees that this is the best for patients—and that includes the director of the US Food and Drug Administration’s centre for devices and radiological health, Jeffrey Shuren. Quoting a plastic surgeon as saying that under the EU system, the public are being used as guinea pigs, he gave a stinging rebuke to the Europeans. “We don’t use our people as guinea pigs in the US,”⁽⁴⁾ he said.

A similar debate is being conducted within the European Commission—and on some levels the Europeans agree. Medical device regulation falls under EU directives, which in turn are

implemented by each member state’s national regulator. But the EU claimed earlier this year that there was a need to “adapt the European regulatory framework in order to secure patients’ safety while favouring innovation.”⁽⁵⁾ However, it is uncertain how much its proposals will actually change the current system—financial constraints may mean that only superficial tweaks are made.

Unknown quantity

The UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA), also has concerns about the current system, saying that “the evidence on safety and efficacy of new devices and new procedures at the time they are introduced into UK practice is very variable.” It has also suggested that the evidence base for most devices was poor.⁽⁶⁾

The number of different types of devices on the market is about 80<thin>000⁽⁷⁾ in the UK and there are over 200<thin>000⁽⁸⁾ in Europe. We can’t be certain about the numbers because not only is there no publicly available list of devices being used day to day in healthcare settings but the MHRA does not know precisely which class III devices (the most risky) have been cleared for use in the UK or Europe. Such devices include stents, prosthetic heart valves, hip implants, and pacemakers.

One reason for the lack of knowledge at both UK and European level is that the decision on market authorisation of high risk devices is made by privately run notified bodies rather than government agencies (box). They, together with the manufacturers, are therefore the most fundamental part of devices market approval and monitoring.⁽⁹⁾ Notified bodies issue a certificate when a device

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has been approved. Companies can then affix a CE [Conformité Européenne] mark, the EU safety standard.

Notified bodies and EU approval process

Decisions about marketing a new medical device are made by notified bodies. These organisations are accredited by national regulators—the MHRA in the UK—as being competent to make independent judgments about whether a product complies with the CE marking directive. Currently, there are 76 notified bodies in Europe and six in the UK, including BSI, SGS, and Intertek.⁽¹⁰⁾

A manufacturer must demonstrate to the notifying body that the safety of the device complies with the legal requirements in the EU medical device directives⁽¹¹⁾ and submit a precise definition of the intended use of a device.

For the highest risk devices (class III), the manufacturer must conduct some human clinical investigations, but these don't have to be randomised clinical trials or even evaluate effectiveness.⁽⁸⁾ And we have no way of knowing what they have done. A manufacturer can also just produce a comparative literature review if they are arguing that their device is similar to an existing (predicate) product.⁽⁸⁾

The national regulator is responsible for auditing the notified body. If a medical device needs to be removed from the market, it is the responsibility of the notified body to suspend its certificate and of the notified body and the manufacturer to let the regulator know.

In the UK the knowledge problem is compounded by the fact that NHS procedures are poorly coded⁽¹²⁾—although in future all medical devices should have a barcode.⁽⁶⁾ So, while we can get detailed information about which drugs are being used in the NHS, the same does not apply to devices.

The MHRA told the *BMJ* and Channel 4 *Dispatches* that a “list of class III devices would not be helpful or beneficial.” But MHRA documents suggest otherwise.

“Once CE marked, devices can enter widespread use without any organised monitoring of the outcomes of their use. Long term outcomes of implanted devices are a particular concern,” it says.⁽⁶⁾

Instead, the MHRA told us that it relies on a “statutory vigilance or voluntary adverse incident reporting system” to regulate—in other words, governmental regulation really starts when devices are already on the market.

The FDA takes a different tack. Each class III device that has either been approved or cleared through its regulatory mechanisms is on its website together with the scientific rationale for the device being on the market. In the US, devices can only be marketed for a clinical claim that is included in labelling that has been reviewed by the FDA.

Variable standards

There are agreed European standards for medical devices. But there's concern that these standards are not uniformly applied. A MHRA meeting noted that there were discrepancies between the notified bodies: “Although the UK Notified Bodies are accredited to EN 13485 [conformity to the EU quality and safety standard] by UKAS [United Kingdom Accreditation Service], there are some Notified Bodies in Europe with only two or three staff, and these may be operating to different standards.”⁽¹³⁾ In other words, some of the key organisations appointed to control what enters the European market might not be rigorous enough in checking how safe or well a device works.

It's something that concerns the Association of British Healthcare Industries. “We need to improve the performance of the notified bodies so that they are all checking these requirements to the same high level,” it said.

Manufacturers can choose the notified body to which they submit their application. In his testimony to Congress, Dr Shuren said that the system allows them to pick the notified body that they think will put their device through the least stringent checks.

Despite these concerns, the decision making process is kept behind closed doors. There is no publicly available summary describing the basis for granting a CE mark and neither is this available to genuine clinical academic researchers.

When we contacted 192 manufacturers requesting evidence of the clinical data used to approve their devices,⁽¹⁴⁾ they denied us access, claiming that “clinical data is proprietary information,” that it was “company confidential information,” and that they could discuss only “publicly available information.”

Likewise, when we asked the relevant notified bodies for the scientific rationale for approval of various devices that had been recalled, the results were stark. This information was classed as confidential because notified bodies were working as a client on behalf of the manufacturers—not the people who have them implanted in their bodies. But, as Dr Shuren put it: “For the public in the EU, there is no transparency. The approval [requirements] are just what deal is cut between the device company and the private [notified body].”⁽¹⁵⁾

But is this an acceptable situation? It's not a line that the FDA follows.

The FDA publishes information on its website about the basis for its approval decisions. The Office of In Vitro Diagnostics publishes a summary of the basis for its 510(k) clearance decisions for in vitro diagnostic tests. It also publishes a summary of safety and effectiveness data for original postmarket approvals. The Office of Device Evaluation, which reviews all other medical devices, is moving towards providing the same information

"We find great value in being as transparent as possible. It helps patients and health care practitioners use a device safely and correctly, and it builds trust between patients, practitioners, and the government. Clinicians need to be able to evaluate a device's risks and benefits, how to use it appropriately, and for which patients. It can help clinicians and patients make better informed decisions," Dr Shuren told the *BMJ*.

Nor does the same apply to medicines approved by the European Medicines Agency. The EMA has come under attack in the past for being secretive and opaque, but at least scientific rationale and study summaries are published along with submitted updates about the evidence detailing clinical claims for a drug.

Doctors and patients should know what a device has been approved to do. And here's the rub—in Europe the highest risk devices have to go through tests to establish their safety and performance. They do not have to prove any effect on clinical outcomes, even when a new technology is being introduced.

As Dr Shuren told the US Congress: "If a manufacturer wishes to market a laser to incise heart tissue to treat arrhythmia (abnormal heart rhythm) in the EU, the manufacturer must show that the laser incises heart tissue only. In the US, however, the manufacturers must show that the laser incises heart tissue and also treats the arrhythmia."⁽¹⁶⁾

This is also something that the EU has raised as an issue. A 2005 report says: "Questions have arisen on the evaluation of the design of a product and, in particular, the absence of clear rules on design evaluation, including verifying the sufficiency and adequacy of clinical data."⁽⁹⁾

Again this is unlike the expectations before drugs gain market approval—and some commentators argue that manufacturers of devices used in medicine "have the same ethical responsibilities to the individual patient as those companies which manufacture and sell drugs."⁽⁸⁾

Safety questions

Earlier this year, Rita Redberg, editor of *Archives of Internal Medicine* and a cardiologist,

told Congress: "I can't help but wonder why clinical trials are widely accepted by the pharmaceutical industry as essential to ensure patient safety, but not by the device industry."⁽¹⁷⁾ Drug regulation is a much older discipline than device regulation—any legislation on device regulation came into being only in the early 1990s. Yet in the past 10-20 years the number and complexity of medical devices has exploded, particularly in cardiology and orthopaedics. Dr Redberg added: "In contrast to most devices in the 1970s, the newer products pose substantially greater risks—even life threatening risks—to patients. For example, many new medical devices are permanently implanted in a patient's body and can be moved or changed, if at all, only with great risk to the patient."⁽¹⁷⁾

In the US here are currently two ways for a class III device to get on to the market—through the premarket authorisation route (PMA) or the less stringent 510(k) process (box).

FDA processes

Premarket authorisation (PMA)—The most stringent type of approval of devices and similar to processes for drug regulation. Manufacturers must submit their product to extensive testing to prove it is both "safe and effective for its intended use." It was developed as a pathway for the approval of devices that "support or sustain human life, are of substantial importance of preventing impairment of human health, or which prevent a potential, unreasonable risk of illness or injury."⁽¹⁸⁾

510(k)—This is sometimes referred to as the "substantial equivalence" route for class III devices. Initially intended for the likes of surgical gloves and less invasive instruments, it is now used to enable manufacturers to make tweaks to existing products without having to go through the extensive PMA route. Companies also use it if there is an existing product on the market (known as a predicate device). In this case manufacturers have only to show that their new product is "substantially equivalent" to the predicate device.⁽¹⁹⁾

Although 90% of devices in the US are approved through the 510(k) route,⁽²⁾ Dr Shuren says that the FDA approach is more protective to the public than the European one. "The US system has served patients well by preventing EU approved devices that were later shown to be unsafe or ineffective from harming American consumers," he said in his testimony to Congress.

The *BMJ* and Channel 4 *Dispatches* were sent a document listing six devices that were recently on the market in Europe but were rejected by the FDA

after going through the PMA approval process—so contrary to some opinion in Europe premarket clinical studies in a small number of people can pick up problems (box).

EU approved devices that the FDA rejected

Covidien PleuraSeal lung sealant system

This device went on the EU market in November 2007 and is used during elective pulmonary resection as an adjunct to standard closure techniques for visceral pleural air leaks. It has been approved for use on the dura and spine in the US. However, the Investigational Device Exemption (IDE) study (a clinical study for FDA regulatory purposes) produced unexpected interim results. In October 2010 Covidien announced a worldwide recall of all PleuraSeal lung sealant systems

Medtronic Chronicle

The Chronicle is an implanted system designed to measure and record haemodynamic variables continuously. In March 2007, an FDA panel refused to approve the device, citing statistically insignificant results as “lack of clinical effectiveness.” It was nonetheless approved in Europe, raising questions about the cost and necessity of the procedure.

PIP breast implants

In 1991, breast implants manufactured by Poly Implant Prothese (PIP) received a CE mark for its silicone breast implants. But in 2001 they changed the gel, so that it was different from the one described in the CE marking file.⁽²⁰⁾ This modification led to rupture rates higher than silicone implants made by other manufacturers.⁽²¹⁾ On 30 March 2010, the French regulator—AFSSAPS—issued a recall of all pre-filled silicone breast implants manufactured by PIP, affecting an estimated 35,000–45,000 women worldwide. In April 2011, the AFSSAPS had found that there is no link between the PIP and genotoxicity but that “test results have confirmed that the gel inside can bleed through the pocket of the implant.”⁽²²⁾

Trilucent breast implants

First marketed in the UK in 1995 by LipMatrix, Trilucent implants were recalled and withdrawn from the market in 1999. The filler of the implants, which was derived from soybean oil, broke down in the body and leaked through the shell, causing ruptures. The breakdown of the filler was significantly different from that predicted during preclinical testing, and many patients had to have implants removed.

Conor CoStar drug eluting stent

CoStar is a cobalt, chromium, paclitaxel eluting coronary stent and received EU approval in 2006.

In May 2007, Johnson and Johnson announced that a pivotal clinical study of the device had failed to find a significant difference on the primary end point, possibly because patients got a suboptimal therapeutic dose of paclitaxel. The trial did not identify safety issues. As a result of this trial, Conor terminated ongoing clinical trials and chose not to conclude the submission of its US premarketing approval. Conor discontinued the sale of the stent in Europe, Asia, and Latin America.

Most of the problems in the US have been with devices approved through the 510(k) route. During 2005 to 2009, there were 113 device recalls that the FDA classified as high risk. Eighty (71%) of these were cleared through the 510(k) route—although only 13 (12%) were class III devices. However, some major devices, such as hip and knee implants, fell into class IIb.⁽²³⁾

The FDA also maintains a database of reported adverse events and device malfunctions (called MAUDE). The reports are stripped of any information related to the individual patient or physician involved in the report, but the device and its manufacturer are included. This database has some limitations, but it provides the agency with safety signals, which can indicate the need for further and deeper investigation.

“By publishing device safety and effectiveness information, experts, industry and the public can do their own analysis. In fact, it keeps the FDA in check. Device problems have been highlighted to us by other people going through the reports and drawing our attention to an issue,” De Shuren says.

However, in Europe, it’s almost impossible for independent researchers to assess the extent of the health problems posed by recalled devices.⁽¹⁴⁾ Because information is confidential, companies would often not tell us where a device had got its CE mark or what class the device was approved as. Furthermore, neither lists of devices on the market nor the number of adverse event reports for each device is publicly available, meaning that rates of safety problems cannot be accurately calculated.

It’s something that companies acknowledge—although from a slightly different angle. A trade group that lobbies for the medical device industry said in a report: “The reasonable question has been raised whether greater regulatory efficiency in the EU has been achieved at the expense of patient safety. However, no information is available to suggest that patient safety in Europe has been compromised.”⁽²⁴⁾ “They don’t have enough data to make a firm comparison, but we do have evidence to suggest that our system provides great value,” Dr Shuren said.⁽¹⁵⁾

The Association of British Healthcare Industries agrees that the lack of transparency leads to misunderstanding and mistrust. “Today it is very

hard for anyone, even manufacturers and authorities, let alone citizens, to find out what products are approved to be on the market. We would like to see enhanced transparency and information to patients, citizens, and all EU government authorities.” It proposes a central EU database to avoid the potential of 27 national databases essentially all repeating the same thing.

Even the Freedom of Information Act is of no use in obtaining information on adverse events. The *BMJ*/Channel 4 Dispatches attempts to get access to adverse incident reports for the Pinnacle and ASR hip implants and the HighRes 90k cochlear implants from the MHRA through the act were thwarted because it is overridden by medical device legislation. Article 15 of the EU Medical Devices Directive states: “Member States shall ensure that all the parties involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks.”⁽²⁵⁾

And future plans to share adverse event data will be similarly opaque. The European Commission has plans to create a database to share this information between the national regulators—but it will not be publicly available.

Postmarketing problems

This shroud of secrecy occurs despite the European system relying more on post-marketing surveillance than it does on premarket testing. But what exactly is required in terms of postmarketing surveillance? For drugs, extensive phase IV trials and studies are usually mandated by the regulators, who help companies with their study design to enable them to spot potential adverse reactions. And the FDA mandates postmarketing surveillance studies for class III devices and some class II devices as a condition of approval. In Europe, however, manufacturers of devices are obliged to implement a “medical device vigilance system” to monitor their products once they are on the market. This is monitored by the notified bodies and audited by the MHRA in the UK.

But how manufacturers do this is not mandated. Rather than have large postmarketing studies, manufacturers may rely simply on feedback from users. Steve Owen, head of Devices Policy, European and Regulatory Affairs at the MHRA, has stated that he finds it “staggering” how many manufacturers fail to fully fulfil their legal responsibility to collect product data once their device is on the market.⁽²⁶⁾ And according to an MHRA report: “Post-market surveillance has not been addressed sufficiently in the past, as many manufacturers do not focus on this area, and it is not ‘policed’ vigorously enough by Notified Bodies.”⁽⁶⁾

The MHRA had hoped that this would change with the recent amendments of the medical device

directives, The MHRA currently relies on manufacturers and clinicians to report problems to it. But in the past manufacturers have been slow to respond to problems with a device.

In 2005, certain implantable cardiac defibrillators made by Guidant were recalled from the market following deaths due to internal short circuiting. This resulted in failure to deliver a shock when needed.⁽²⁷⁾ However, following an investigation, Guidant pleaded guilty to withholding information from the FDA regarding “catastrophic failures” in some of its lifesaving devices four years later.^{(28) (29)}

Recently, Medtronic has had lawsuits filed against it alleging that it delayed disclosing information about lead fractures that occurred in its Sprint Fidelis implantable cardiac defibrillators.⁽³⁰⁾ Medtronic settled for a total payment of \$268m—although they did not admit any liability.⁽³¹⁾

Company reporting is supplemented by clinicians and patients reporting adverse reactions to any devices to the MHRA. But clinicians often fail to report adverse reactions for all sorts of reasons. One systematic review found that the median under-reporting rate across the 37 studies included in the review was 94% (interquartile range 82%–98%).⁽³²⁾ In other words, most adverse drug reactions were not reported—although it’s hard to know if this can be extrapolated to devices.

One way to capture problems with devices is to use a register. Although registers are not a replacement for clinical trials, they can provide data on long term safety, performance, and reliability and allow early identification of emerging problems. Registers have been central to spotting problems with devices that have not gone through adequate premarket clinical testing, such as the problems with some metal in metal hip implants.

Although no-one wants to halt the pace of innovation—it has brought dramatic improvements to people’s quality of life—the system needs fine tuning. Given past problems and the rapid pace of innovation over the past 20 years, the EU’s propensity to support innovation needs to be balanced with better means of protecting the public.

An FDA style regulator for Europe has been advocated by some—but it’s unlikely to happen. But having one agency that regulates devices and drugs has had its benefits in the US—institutional memory is collective and experts from both the device and the drug centres can share expertise and information easily. And data obtained through postmarketing studies, adverse event reporting, and premarket applications from other manufacturers can inform the questions asked about new devices submitted for approval and the decision subsequently made. “It’s much harder to learn if you don’t get all the information,” Dr Shuren says.

And there are calls for drugs and class to be put more on an equal footing in terms of evaluation. Jürgen Windeler, director of the Institute for Quality and Efficiency in Health Care in Germany, agrees that the current process of device approval does not address the same level of detail as that for drugs: “I agree with the CE marking, but it’s not enough,” he said. He also added that we need “some kind of proof of benefit before bringing medtech products onto the market, just as for drugs.”⁽³³⁾

As Dr Redberg said about the situation in the US, this needs to be through the “proper use of evidence-based medicine and well-designed clinical tests before the devices are approved and clinical registries to track outcomes in real time after they are approved.”⁽¹⁷⁾

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