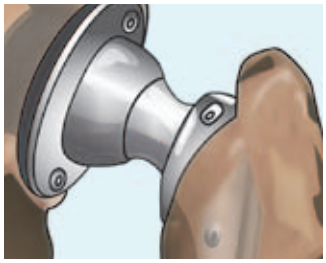




THE TRUTH ABOUT MEDICAL DEVICES

In today's *BMJ* we raise serious concerns about the regulation of high risk medical devices and how well they are tested before they come to market. There are thousands of devices on the market, and the industry worldwide is worth over £200bn a year, however, the approval process is far less stringent than for drugs, particularly in Europe, as Professor Nick Freemantle says (p 1129).

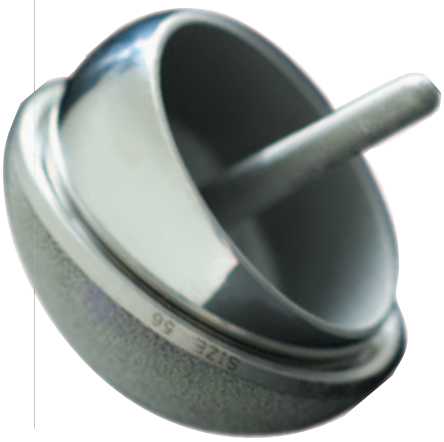
Makers may issue voluntary recalls, but they don't always act on emerging problems, finds Deborah Cohen's investigation (p 1116). The maker of articular surface replacement (ASR) metal hip implants, Depuy, waited till 2010 to fully recall its hip despite repeated warnings from doctors as early as 2007.

The British Orthopaedic Association has recently said that some metal on metal hip replacements should not be performed until more is known about their failure, say John Skinner and Peter Kay (p 1123).

A publicly available central register of adverse effects would allow early detection of emerging problems, suggest Deborah Cohen and Matthew Billingsley (p 1124), and Matthew Thompson and colleagues try to quantify recalls in the United Kingdom and the lack of information about safety and effectiveness (p 1131).

Carlo Di Mario and colleagues suggest (p 1128) that although there is room for improvement, uniformly increasing the hurdles in the regulatory process risks raising costs without improving patient safety, but Alan Fraser and colleagues argue (p 1130), despite official protestations, that standards for approving devices are less rigorous in Europe than in the United States.

In an accompanying editorial (p 1093) Peter Wilmshurst says that the problem of competing interests is far worse for medical devices than it is for drug prescribing.



More on bmj.com

Watch supplementary videos on bmj.com to accompany this series of articles, including a clip showing a patient who has received an ASR replacement hip, and an interview with Stephen Graves (pictured top right), orthopaedic surgeon and director of the Australian National Joint Replacement Registry.

- Read additional commentaries on bmj.com, including one from Stefan James and colleagues on use of registers
- Research from *BMJ Open*: Medical device recalls in the UK and device regulation process (doi:10.1136/bmjopen-2011-000155)
- Respond to these articles at bmj.com

OUT OF JOINT

Why did it take so long to recall from the market a hip implant after it became apparent that it was causing pain and disability in patients. In an investigation for the *BMJ*, **Deborah Cohen** describes how companies dictate the fate of their own devices and exert an unduly strong hold over surgeons

It is one of the biggest disasters in orthopaedic history, according to one senior surgeon. On 24 August 2010, DePuy, a subsidiary of American giant Johnson and Johnson, recalled its ASR (articular surface replacement) hip prostheses from the market. The recall followed years of denial by the company that the ASR implants had caused pain and disability in patients. In a statement to the *BMJ*, DePuy claim that "given the available information, we believe we made the appropriate decision to recall at the appropriate time."

Pathologically, the failing prosthesis had several effects. Metal debris from wear of the implant led to a reaction that destroyed the soft tissues surrounding the joint, leaving some patients with long term disability. Ions of cobalt and chromium—the metals from which the implant was made—were also released into the blood and cerebral spinal fluid in some patients.[1]

The long term effects are uncertain. But the US Food and Drug Administration recommends that patients should be monitored for systemic effects, particularly cardiovascular, neurological, renal, and thyroid signs and symptoms.[1]

With more than 93 000 ASR implants sold and ongoing litigation in many countries, the situation may prove costly for DePuy. And if lessons are not learnt from this latest episode in the chequered history of hip implant failures, it may also prove costly for the reputations of the regulators and the orthopaedic community.

The ASR is not the first hip implant to be recalled—there have been many others. One such recall in the late 1990s—the 3M Capital Hip—prompted questions about European device regulation[2] and a parliamentary investigation by then health minister, Lord Hunt.[3] But nor may it be the last—concerns are now being raised about the failure rates of other metal on metal hip implants.[4]

Metal on metal

The ASR is a "metal on metal" hip—the head at the top and the lining of the cup it fits into are made of cobalt chrome metal rather than ceramic or polyethylene. The devices come in different sizes according to the existing anatomy, and there are forms for both total hip replacement (ASR XL) and hip resurfacing (ASR resurfacing).

The conventional total hip replacement consists of a metal head with a polyethylene cup. But these joints don't last forever. Over time the plastic cup wears away against the hard metal head. Younger, more active people are especially likely to require early revision surgery to replace the worn out joint. [5]

In search of a more durable option, surgeons turned their attention to the development of joints using a metal head against a metal cup. Not only would metal be much harder wearing, but advancements in manufacturing meant that the metal could be produced with incredibly smooth surfaces. Complicated physical phenomena dictate that these smooth bearing surfaces trap a layer of fluid between them. So in perfect circumstances, the metal surfaces do not touch and the surfaces wear very little. And, in theory, the more quickly the patient moves the thicker this fluid layer becomes, ensuring even less wear.[6 7]

Competition between manufacturers spurred DePuy to develop the ASR. A new hip prosthesis called the Birmingham Hip Resurfacing (BHR), designed by UK surgeon Derek McMinn, had entered the European market in 1997 (the FDA approved it in 2006), and was proving popular. Smith and Nephew acquired it, and DePuy had to design a better product so that it didn't lose market share. The attempt to prise surgeons away from the BHR led to fractious competition between the companies, which was reflected in their marketing campaigns.

Simulator testing for ASR resurfacing

Both forms of the DePuy ASR came on to the market in Europe in 2003. At the time, resurfacing prostheses were classed as a class IIb device, which meant they didn't need to be tested in patients before entering the EU market.

DePuy followed and met the European standards. These provide guidance on how to conduct simulator studies to test how well the implant wears. According to DePuy, it conducted laboratory testing "including tests on simulators that evaluate how the device wears over time, the materials used in the device and device strength."

But exactly what information the company submitted is not open to public scrutiny—the scientific rationale is held by the company and by the notified body—one of several private organisations that do the premarket approval on behalf of EU governments.[8] In this case the notified body was the British company BSI.[9]

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) says that clinical studies may be too small and short to detect problems for premarket approval purposes. But clinical tests with relatively short follow-up may have picked up problems with the ASR. According to David Langton, a surgical researcher at the University Hospital of North Tees and Newcastle University who has been studying the ASR, problems in some patients first emerged about two years after implantation.[10]

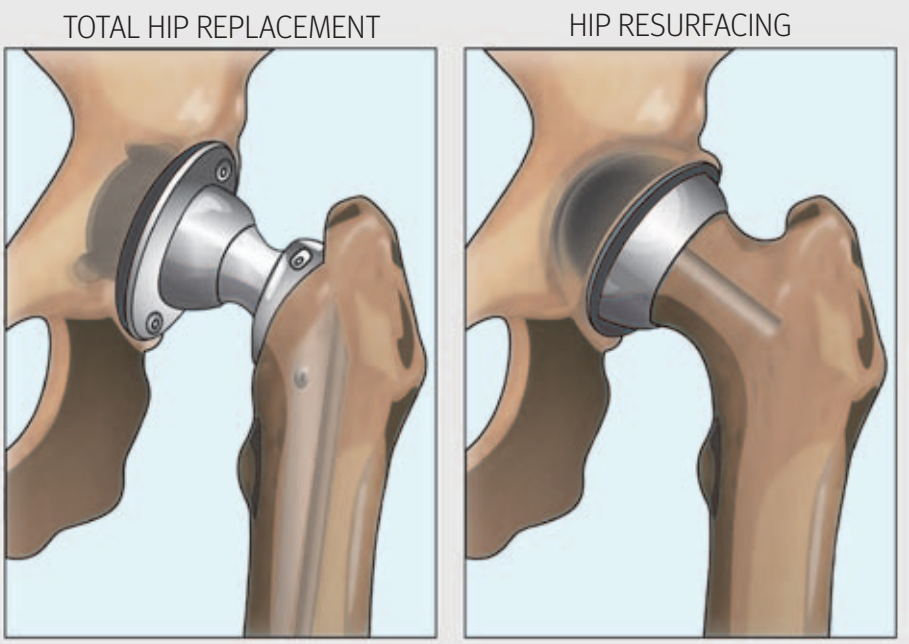
The absence of any clinical studies of implants in patients before approval remains a cause for concern—much like it was over 10 years ago with the 3M Capital hip.[2]

"The reason they get on to the market is that they look and smell like a joint replacement,"

says Stephen Graves, orthopaedic surgeon and director of the Australian National Joint Replacement Registry. Professor Graves thinks that simulator testing should not be relied on entirely to see if a device will function well when you use it in a person. Indeed, a recent Smith and Nephew backed paper suggests that simulators do not really represent the biological environment.[11]

"Before a hip or knee replacement is placed on to the market it should have been used in a limited number of people who had been monitored very carefully for a number of years," Professor Graves says, adding, "the outcome of that monitoring would indicate that the device is actually working very satisfactorily in that small group of patients."

Professor Graves thinks this would protect not only patients but also the company. "They [clinical studies] may well prevent a situation where they have a device that is not performing anywhere near as well as they would have hoped," he says.



HIP SURGERY

Total hip replacement surgery—The femoral head is removed and replaced with a prosthetic ball made of metal or ceramic, and the acetabulum is replaced with a prosthetic cup. The cup consists of one or two components made of metal, ceramic, or plastic. A stem is also placed in the femur to support the femoral head

Hip resurfacing surgery—The femoral head is trimmed and capped with a metal covering. Any damaged bone and cartilage within the acetabulum are removed and replaced with a metal cup

Problems emerge

Although the ASR resurfacing made it on to the European market, it was not approved in the US. Resurfacing was a new technique and so the implant had to go through the FDA's more rigorous premarket approval process. This requires manufacturers to submit their product to clinical testing to prove it is both safe and—unlike the European process—effective for its intended use. The FDA asked DePuy to perform a clinical study called an investigational device exemption (IDE).

Tony Nargol, an orthopaedic surgeon at the University Hospital of North Tees, was one of the surgeons involved in the studies for the American market. But not everything was going to plan. As DePuy's internal emails show in 2007, he reported problems with fractures in some of his patients. The FDA sent detailed questions to the company.

"You have not provided any explanation why this experienced investigator may have had a higher femoral neck fracture rate in this IDE study. It is concerning that an experienced surgeon who is familiar with patient selection criteria and surgical technique would have the highest neck fracture rate," it said.

So problems were being picked up in the premarket clinical study—despite some insisting that these studies are too small for this purpose. Surgeons experienced in the resurfacing technique should not have a fracture rate of more than 1% a year.[12] Yet according to a June 2008 document from the French health agency Haute Autorité de Santé, this two year follow-up study had a 4.9% fracture rate in the ASR resurfacing arm. And the two year survival of the implant was 95.9% (95% confidence interval 93.5% to 99.9%) when only 25.6% of people in the group were women—who typically fared worse with the prosthesis.[9] The French agency concluded in 2008 that given the data and the alternatives it would not fund the ASR resurfacing. But it was still being used in the NHS.

DePuy's response to the FDA questions shows its close relationship with the surgeons it chooses to participate in its regulatory studies and the hold it believes it has over them. The company assigned the list of questions to one of its marketing representatives with experience in regulatory affairs. It asked the representative to formulate the answers and ask Mr Nargol to sign the document if needed. In the end the company withdrew its application and the ASR resurfacing was never approved by the FDA.

But this did not stop US surgeons from using it "off label." Rita Redberg, editor of *Archives in Internal Medicine* and a cardiologist, has studied the US device regulatory system and testified to recent Congressional hearings.

"Patients have a right to know what the risks and benefits of any procedure are for them. If a device is used off label, it generally means there are not good data to support its use for that indication. That is information that should be discussed in the informed consent process. These discussions are particularly important for an implanted device, which cannot easily be removed," she says.

Similar equivalence—a flawed approach

Although the FDA's premarketing approval process requiring a clinical study may have protected patients from the widespread uptake of the failing ASR resurfacing prosthesis, the same could not be said about ASR XL, the total hip replacement. This passed through the FDA's 510(k) clearance process via the "similar equivalence" route, whereby companies need to show only that their product is similar to something else on the market. Even a small change in design can have a substantial effect on long term outcome.[13]

Critics say that the similar equivalence route is not nearly stringent enough.[14] Yet this is how 90% of devices gain US approval.[15] Companies say that toughening up the approval process will be bad for patients—they will be denied access to new improved technologies that are available elsewhere. But can this be true in a market saturated with hip prostheses? Isn't there an argument that the bar for market entry should be raised? According to data from the 2010 Australian Joint Registry report, there are more than 1539 stem and acetabular combinations for total hip replacement, but only 72 are commonly used (defined as having been used in more than 400 recorded procedures).[16]

Yet, companies scarcely let a year go by without introducing a "new improved" joint

replacement that "offers undreamt of (and unproven) advantages over the older designs."[17]

The same is true in other fields. Alan Fraser, an interventional cardiologist at Cardiff University, says: "I think any doctor who is treating patients is keen to try to stay up to date and use the most recent advances. And indeed, I think there is a tendency for doctors to want to use whatever the latest new technology is, and perhaps not always to be critical as to whether or not it's really been thoroughly evaluated."

The desire to use something newer, smaller, and shinier might well trump the evidence base. Nearly 20 years ago an editorial in the *BMJ* warned that this "fashion trade" in joint replacements is costing the health service many millions of pounds each year and, even more importantly, is causing patients unnecessary pain and distress through early failure of unproven implants.[17] And judging from the recent history of joint failures, it seems not much has changed.

Surgeons and the company

Surgeons involved in the design of a device can make large sums of money. One of the surgeons involved in the design of the ASR, Thomas Schmalzried, medical director of the Joint Replacement Institute in Los Angeles, received just under $3m (£1.9m; €2.1m) in royalties during 2009-10 alone. In the same period, another of the designers, Thomas Vail, University of California San Francisco professor, received just over $500 000. Figures are not available for the other designers—their respective countries do not have the same legislation about transparency of company payments as the US.

Royalties are legal, as are consultancies, research fees, and stock options. But some companies have been in trouble for providing other kinds of payment.

Four years ago, four of the major orthopaedic companies in the US were fined about $311m for paying doctors to use their products.[18] And last month, DePuy was ordered by the UK court to pay almost £5m for similar unlawful payments. [19] Johnson and Johnson was fined $21.4m by the US court for making "improper payments to publicly employed health care providers in Greece, Poland and Romania in order to induce the purchase of medical devices and pharmaceuticals" made by their subsidiaries—including DePuy.[20]

Charles Rosen, professor of orthopaedic surgery at the University of California, Irvine, School of Medicine, says companies try to find a relationship to keep you using that product. "It could be in the form of maybe having you as a consultant with the company for a certain amount per year and then you feel obligated to continue using that product. Or have you lead courses in how to use that drug or that device and reimburse you for that and tie you up to become an advocate as well as a user of that product," he says.

At the time of the launch of the ASR in 2003, DePuy was behind in the sales stakes, and it would have to turn to its design surgeons. The ASR's design surgeons located in several different countries acted as key opinion leaders, promoting the new device. They led educational programmes, published papers in journals, spoke at company dinners, and presented at conferences promoting the ASR.

Marketing campaign

A successful marketing campaign would be crucial to persuading surgeons to change from the BHR to the ASR resurfacing in Europe. Among its many strategies, DePuy ran simulator tests on its prosthesis and its competitor. The pictures appeared to show that the ASR produced less metal wear debris than the BHR—the ASR fluid was clear whereas the BHR was sitting in a dark metallic stained fluid. An accompanying journal article indicated that the ASR fluid had been changed and the pictures of the two devices had been taken at different time points.[21 22] Yet these pictures were used by sales representatives for marketing purposes divorced from the accompanying article and might have been misleading.[23] When we put this to DePuy, it said that it would not respond to "speculation."

But in the absence of publicly available data and no independent assessment of study summaries in Europe, manufacturers are able to interpret and promote their studies as they wish. This is in stark contrast to the US, where devices can be marketed only for a clinical claim that is included in labelling that has been reviewed by the FDA. Even the MHRA does not routinely collect any premarket clinical data. This means that clinical claims are difficult to verify.

Tony Nargol was one of the surgeons who was persuaded to change from the Birmingham hip after being shown the pictures by DePuy in 2004. As internal emails show, the company targeted him because he was known to be a big user of the BHR.

"They said the ASR would last considerably longer than a Birmingham [Hip Resurfacing],"

1993
An editorial in the *BMJ* warns of the a "fashion trade" in joint replacements that is costing the health service many millions of pounds each year and is causing patients unnecessary pain and distress through early failure of unproved implants.


Designer hips

1997
Birmingham Hip Resurfacing (BHR)comes on to the market in the EU (the FDA approved it in 2006).

1998
3M Capital Hip recalled prompting questions about European device regulation and a parliamentary investigation by then health minister Lord Hunt.

2002
National Joint Registry set up following the failure of the 3M Capital Hip

Major litigation against a hip manufacturer, Sulzer, which results in a payout of roughly $1bn and a major net loss that year for the company.

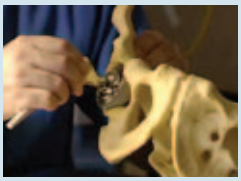
2003
The BSI gives Depuy's ASR market approval in the EU.

2004
Consultant orthopaedic surgeon Tony Nargol is persuaded to change from the BHR to the ASR on the back of pictures comparing the two.

2005
Derek McMinn, designer of the BHR, highlights what he sees as the design flaws of the ASR at a debate.

2006
An expert advisory group at the MHRA discusses metal on metal hips. "There is evidence to suggest that some metal on metal hip replacements may be associated with increased DNA-changes, which might result in genotoxicity in patients."

2007
An FDA email shows concern about fractures in a DePuy ASR resurfacing study for its approval process. This unpublished study shows a two year survival of the implant was 95.9%.



Mr Nargol starts to notice problems with the ASR XL. Some of his patients reported groin pain and difficulty walking. "The soft tissues and muscles around the hip were destroyed."

He raises concerns with DePuy. But company managers pass this off as a failure of surgical technique.

One of DePuy's engineers presents a two year follow-up study showing 30% of women and 7.5% of men had markedly raised metal ion concentrations in their blood.

The Australian National Joint Replacement Registry reports that the ASR had a high revision rate. DePuy sends out a "white paper" by one of the ASR design surgeons, Professor Vail, explaining how to interpret the Australian data.

Four of the major orthopaedic companies in the US are fined about $311m for paying doctors to use their products.

Mr Nargol said. He described the simulator test he was shown. "After a while the BHR went all black. It looked like metal had come off the bearing and it looked abnormal. And there's a clear difference between the two and it was very persuasive. And I know a lot of surgeons round the world were very persuaded by this."

Device failure or surgical technique?

A few years later, Mr Nargol started to notice problems with the ASR. In early 2007, some of his patients reported groin pain and difficulty walking. He got a shock when he opened them up to revise their prostheses. "The soft tissues and muscles around the hip were destroyed." He noticed a pus-like fluid coming from the capsule. Initially he put it down to infection. But cultures were negative. "And then we went on to find cases where the bone was starting to get destroyed as well," Mr Nargol said.

Other surgeons also mentioned problems with the device. But according to Mr Nargol, some of those with ties to DePuy declined to report what they were seeing and simply stopped using the device.

He raised his concerns with the company, and asked whether anyone else was having problems. As internal emails show, company managers hoped to pass this off as a failure of surgical technique—even though he was an experienced resurfacing surgeon. "I'm sure that the complications that Tony has experienced are wholly related to interoperative surgical technique compromises and I'm sure if managed effectively we can ensure that the published presented data from North Tees draws this conclusion and more critically clearly illustrates that it is not a device related complication," an email said.

Professor Graves says this response is not wholly surprising. "There's a natural tendency for companies [to think] it's probably factors other than a device, because they have invested a lot of time in it . . . It does take some time on occasions to convince a company that there may be problems with the device."

"I think there is a tendency for doctors to want to use whatever the latest new technology is, and perhaps not always to be critical as to whether or not it's really been thoroughly evaluated"

The high revision rate of the ASR XL should not have come as a surprise to the company or to the regulators. In 2005, Mr McMinn—designer of the Birmingham Hip Resurfacing—participated in a debate in Helsinki pitching the prosthesis he had created against the ASR. While Mr McMinn's arguments primarily focused on his prosthesis, he described in detail what he perceived to be the ASR's design flaws that would later lead to its demise.[11 24-29]

He criticised the shallowness and the rim on the inside of the cup and the manufacturing processes used, all of which, he said, could lead to increased wear. The design changes, he said, would mean the prosthesis would be less forgiving of surgeon technique—something which, some argue, should be factored into the design of a successful device.[30]

Mr McMinn says DePuy were "certainly aware of this lecture," and the "president wrote to me in a non-friendly tone 'advising' me to remove this talk from my website." He declined to remove it and it's been there ever since. DePuy chose not to comment on this allegation.

The company was also aware of raised blood levels of metal ions. At a conference in Dallas in 2007 one of DePuy's engineers gave a presentation, seen by this investigation, of two year follow-up data that showed 30% of women and 7.5% of men had markedly raised metal ion concentrations in their blood. Even though the procedures in the study had been performed by the design surgeons—who would be expected to position the device with the most precision—the presentation concluded that surgical technique was to blame.

In 2008, Mr David Langton, who had been analysing both the ASR and the BHR, gave a presentation at the British Orthopaedic Association conference in Liverpool describing the problems caused by the shallowness of the ASR cup. This, he said, was leading to increased wear as the edge of the cup rubbed against the head. DePuy representatives were at the meeting.

Registry data also dismissed

In 2007, individual surgeons were not the only people noticing problems. The Australian National Joint Replacement Registry reported that the ASR had a high revision rate. The registry was set up to spot "outliers"—prostheses that have twice the rate of revision of others in their class. All hip prostheses fail in some patients,

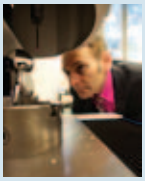
2008

Surgical researcher David Langton (below) gives a presentation at the British Orthopaedic Association conference in Liverpool describing the problems caused by the shallowness of the ASR cup.

Haute Autorité de Santé in France says that given the data and the alternatives it would not fund the ASR resurfacing.

The Australian National Joint Replacement Registry again reports that the ASR had a high revision rate.

Mr Langton and Mr Nargol give a presentation in Norwich reporting the cases of 10 women with soft tissue reactions who have significantly increased metal ion concentrations in their blood and high joint fluid metal ions. Representatives of both DePuy and the MHRA attend.



A paper shows that several of the ASR patients have raised chromium and cobalt concentrations in their blood. In some patients, these concentrations are 100 times greater than normal physiological values.

2009

The Australian National Joint Replacement Registry again reports that the ASR had a high revision rate.

Depuy issues a voluntary recall of the ASR in Australia for commercial reasons.

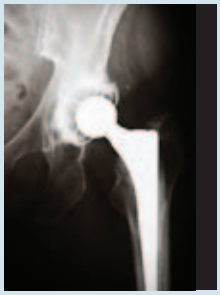
2010

A team from University Hospital of North Tees directly approaches the MHRA to force it to acknowledge the problems associated with the ASR.

National Joint Registry sees a rapid rise in the number of revisions. It notifies the MHRA.

Depuy issues a "voluntary recall" of the ASR globally. At the time of recall, the company tells sales representatives to offer other Depuy options—including the Pinnacle, another cobalt chrome metal on metal implant.

2011



The British Orthopaedic Association says the use of large diameter metal on metal bearings in primary total hip replacement should be "carefully considered and possibly avoided."

DePuy is ordered by the UK court to pay almost £5m for unlawful payments in Greece between 1998 and 2006, and Johnson and Johnson are fined $21.4m by the US court for making "improper payments to publicly employed health care providers."

Two year follow-up study in 144 patients shows an incremental increase in metal ion levels over the study period in a range of large head metal on metal implants made by manufacturers such as Zimmer, Biomet, DePuy, and Smith and Nephew.

but it is expected that the rate will be about 1% a year. The Australian data showed a 5.16% (95% confidence interval 3.50% to 7.56%) revision rate at two years.[31]

The registry uses revision as the primary outcome to identify implants that aren't performing as well as they should. Of course, it's only one measure of how well a joint performs, but according to Professor Graves, it's an "unambiguous end point—nobody can argue about [it]."

But that's precisely what DePuy did. According to Professor Graves, when the registry first notified DePuy about the high revision rate, the company released a safety warning to surgeons saying that positioning was important.

Over the next three years, DePuy used a range of techniques and arguments to try to assuage fears arising from the evidence generated repeatedly by the Australian registry and surgeons themselves.[16 31 32]

According to a presentation Professor Graves gave at a meeting in Glasgow, the Australian joint registry warned the Australian regulators and DePuy 17 times about problems with the ASR between 2007 and 2009.

But, according to internal company documents, concerns were explained away and sales representatives were instructed to keep on marketing the product. To counter the Australian registry's findings, internal documents show that DePuy sent out a "white paper" by one of the ASR design surgeons, Professor Vail, explaining how to interpret the Australian data.

It said that the Australian data did not account for the surgeons' learning curve with resurfacing. The Australian rates were almost double those of the "international surgeon design team at two years," it added. In order to "set the record straight" the sales representatives were told to tell surgeons about a paper detailing the American experience with the BHR, which reported an adverse event rate of 4.9%, which they claimed was higher than for the ASR.[33] Their marketing team also quibbled with the exact definition of the term "revision" used by the Australian registry.

"Why is the first response not to suspend the implantation [of a device] when legitimate concerns are raised?"

Surgeons carrying out a lot of operations had the same failure rates as those doing only a few, Professor Graves says. So their findings totally contradicted DePuy's assertion that surgical experience and patient selection were to blame. "We were quite strong in our conclusion," says Professor Graves. "We thought it was the device."

Meanwhile the North Tees team—including Mr Nargol and Mr Langton—were keeping DePuy updated about the problems they were finding and their data, as internal emails show. At a meeting in Norwich in 2008, they gave a presentation reporting the cases of 10 women with soft tissue reactions who had significantly increased metal ion concentrations in their blood and high joint fluid metal ions. Representatives of both DePuy and the MHRA attended.

Before presenting the data, Mr Langton had sought advice from a senior surgeon—who, according to internal emails, had instructed DePuy on promoting the ASR. He advised Mr Langton to keep quiet. "He told me, 'you have great data which will allow you to travel the world. But my advice would be not to present it at the Hip Society. I would go to DePuy and suggest a consultancy role with them. You can earn a lot of money just for doing nothing. I have done this a couple of times in the past with previous research,'" Mr Langton said he didn't take the advice.

Targeting women

One paper—published in mid-2008 and seen by DePuy before submission—showed that several of the ASR patients had raised chromium and cobalt concentrations in their blood. In some patients, these concentrations were 100 times greater than normal physiological values.[34]

It was also clear from these data that patients implanted with smaller ASRs, used mainly in women, were more likely to develop higher metal ion concentrations—as DePuy's own presentation in Dallas the year before had shown.

Yet this was the group of patients targeted by DePuy in an "advertorial" in the *Daily Telegraph* on 21 February 2008. Featuring quotes from the UK design surgeon Andrew Cobb and a young woman, Penny Brown, who said her life had been changed by the ASR, the advertorial "aimed to educate patients on their treatment options and demonstrate the unique advantages that the DePuy ASR can provide to the right patients." Unlike prescription drugs, there is no European legislation preventing direct to consumer advertising of devices.

According to John Nolan, orthopaedic surgeon at Norfolk and Norwich Hospital, patients were keen to have resurfacing. They would see adverts for it on the internet. "The emergence of resurfacing hip surgery coincided with the increased use of the internet to advertise hip replacement surgery on websites that were not peer reviewed. As a result, patients would request resurfacing surgery when it was not appropriate. I believe the surgeon has a professional responsibility to advise the patient accordingly and to decline the procedure when the correct indications are not present," he said.

And rather than advise surgeons not to use the ASR in women, DePuy merely instructed surgeons to be careful how they put the cup part of the implant in—again refusing to believe that it might be the device that was giving rise to the large increases in chromium and cobalt concentrations. Mr Langton was even told by a DePuy sales representative that good sources had told them that an illegal chromium ship unloaded its cargo in the river Tees a couple of years earlier and that was the reason for the raised chromium and cobalt levels he was finding in patients' blood. DePuy declined to comment on this allegation.

But it was the threat of losing a valued surgeon to their rival that made DePuy really start to take note. Panic started to set in in early 2009. In an email written in capitals, a local sales representative wrote: "Tony Nargol has said he will no longer use ASR at Hartlepool and instead will use BHR." The company had calculated the value of his custom—over a quarter of a million pounds in 2008. The representative said they would "work as closely as possible with Tony and to move him to Silent [another DePuy implant] as soon as possible to brickwall the account against competitors."

Later that year, DePuy was still in denial about the extent of the problems and was providing a counter argument to any concerning data. An internal email from March 2009 reported on outreach to surgeons. "All major XL users have been seen over recent weeks and are happy with their results."

Reporting adverse events

But not all surgeons were happy, and their revision rates were far higher than they ought to be. Shouldn't the regulators have stepped in to remove the product from the market and stop those who were purportedly happy to continue to implant the ASR?

In the UK the onus is on manufacturers, doctors, and patients to report problems directly to the MHRA—and the MHRA itself has been critical of the deficiencies in postmarket clinical follow-up.[35] According to the Association of British Healthcare Industries, manufacturers capture and analyse information from a variety of sources—clinical follow-up, registries, published and unpublished literature, expert meetings, and complaints.

The MHRA told the *BMJ* that it is the "manufacturer's responsibility to monitor the performance of their devices, for as long as they are in use, and to ensure these devices continue to be safe and suitable for clinical use. If in the light

David Langton, surgical researcher at Newcastle University, was advised by another surgeon to keep quiet about finding high levels of metal ions in patients

Stephen Graves, director of the Australian National Joint Replacement Registry, says how devices come on to the market needs to be reconsidered

Tony Nargol, orthopaedic surgeon at North Tees, warned Depuy several times that he was experiencing problems with the ASR

Alan Fraser, cardiologist at Cardiff University, says doctors are not always critical as to whether a device has been evaluated

Charles Rosen, a orthopaedic surgeon from Los Angeles, says companies try to find a relationship to keep you using that product

of this evaluation, the manufacturer establishes that products should not be used, the manufacturer should take the necessary steps to ensure patient safety."

But, in the case of the ASR, they chose which evidence to believe. And we have no way of knowing whether doctors and patients reported adverse events to the regulator or what kind of postmarketing surveillance was required of the company.

The *BMJ* and Channel 4's *Dispatches* filed a Freedom of Information request asking the MHRA for reports of adverse reactions to the ASR. This was declined under medical directive legislation that keeps all device regulatory affairs confidential. Nor could we access documents that would show what kinds of discussions the MHRA or the notified body were having with the company.

Role of MHRA

They knew that there were concerns about the risks of metal debris from wear of orthopaedic metal implants. In March 2006, an expert advisory group at the MHRA discussed the issue. "There is evidence to suggest that some metal on metal hip replacements may be associated with increased DNA-changes, which might result in genotoxicity in patients."[36] But it was not known whether there were any clinical implications of the findings. "The benefits of such implants are real. Whereas the discussed risk is theoretical and unquantifiable, but definitely low," it said.

But the agency knew it was a sensitive topic. Before the paper was presented, the chairman stressed the importance of confidentiality, adding that "anyone who felt they were unable to keep this matter completely confidential was asked to leave the room."

Despite the raft of data being published in both the medical literature and as formal registry reports over a number of years, the ASR was left on the market. No one from the MHRA contacted Mr Nargol and Mr Langton to follow-up their data despite the MHRA having a group specifically to look at metal on metal concerns for several years.

At the end of 2009, DePuy voluntarily recalled the ASR in Australia. But, according to Professor Graves, their registry reports had influenced the practice of the Australian surgeons, and the number implanted had already dropped.

But it remained on the market in the rest of the world. Confused by the apparent inaction of the MHRA, in April 2010 a team from University Hospital of North Tees directly approached the agency to force it to acknowledge the problems associated with the ASR. By this time they were seeing a 15% revision rate at five years, and almost all patients had tissue damage to some extent.

Mr Nargol told the investigation that the MHRA officials stopped the team's presentation halfway through, saying they believed the team and asking what they wanted. But when Mr Nargol and Mr Langton said the ASR should be banned, the MHRA officials said they couldn't do that as they would be sued. Instead, the MHRA sent out a medical device alert warning about all metal on metal hip implants. However, a spokesperson for the MHRA said that, "the MHRA would never be influenced by the threat or possibility of legal challenge in not taking regulatory action it thought to be appropriate."

Shortly after, the UK National Joint Registry (NJR) saw a rapid rise in the number of revisions. Up until this point there had been a rate of 7.5%. But this increased and they notified the MHRA. Internal company documents show that DePuy had decided to phase out the ASR globally by the end of 2010 for "commercial performance" reasons. In a statement to the investigation DePuy said that this decision "was not related to any concerns about product safety."

"At the time of the decision, data available to DePuy indicated that the revision rate of the ASR Hip System was similar to that reported for other large diameter metal on metal monoblock and resurfacing hip devices, " the company said. "Because the decision was based on business factors, not safety concerns, the timing to discontinue sales differed from country to country."

Recall of the ASR

But in the end, DePuy "voluntarily recalled" the ASR in August 2010, saying the recall was due to unpublished NJR data showing a 12% revision rate for resurfacing at five years and an ASR XL revision rate of 13%. "Early revision of poorly performing hip replacements that generate metal debris should give a better revision outcome," it added on the field safety notice—the means by which manufacturers alert people that a product is being recalled.

But revision of a destroyed joint is not straightforward. Not only are patients put at anaesthetic risk once again, the revisions have a higher risk of failure.[37]

And although DePuy states that it is "committed to addressing reasonable and customary costs of testing and treatment" for patients who might need revision after the recall of ASR, "including revision surgery if necessary," there is a cost to the NHS—in some centres primary hip procedures are being put back to accommodate urgent revisions.

But the delay in the recall might serve as a lesson to other companies. Not only will DePuy have to pay for the cost of revision in the NHS, there is global litigation that, if successful, may cost the company many billions of dollars. The last major litigation against a hip manufacturer was against Sulzer in 2002, which resulted in a roughly $1bn payout and a major net loss that year for the company.[38]

But even while DePuy was offering to pay revision costs, it again used the opportunity to promote its products. An internal presentation the day before the recall went out—seen by the *BMJ* and Channel 4's *Dispatches*—said that since the ASR system was no longer available, none of the components should be used for revision. However, it said that "DePuy offers a full line of both revision and primary acetabular and femoral implants and instruments to meet individual patient needs." For revision of both ASR resurfacing and ASR it recommends a total hip replacement. "DePuy option: Pinnacle," it said—

including the cobalt chrome metal implant. And in a briefing to the sales force it said the "Pinnacle is an alternative for the majority of patients."

According to Mr Nolan, this probably wasn't the wisest thing to do. "I don't think it is advisable, in the presence of an adverse soft tissue reaction to a cobalt chrome implant, to revise the hip replacement by using another implant made of cobalt chrome. I feel strongly that all cobalt chrome should be removed from the affected joint," he said.

But a much more widespread problem may be looming involving a range of other makes and models. And once again it illustrates the delicate trade-off between innovation and safety. Like resurfacing, the use of large head metal on metal total hip implants has followed another surgical trend. Heads have got larger to make them less likely to dislocate. But with this comes associated corrosion problems where the head meets the stem. "Some cemented, stemmed, metal on metal implants have shown marked corrosion of the stem and some large diameter head, stemmed implants have shown corrosion at the taper junction of the head/stem," Mr Nolan says.

A two year follow-up study in 144 patients published at the beginning of May this year shows an incremental increase in metal ion levels over the study period in a range of large head metal on metal implants made by manufacturers such as Zimmer, Biomet, DePuy, and Smith and Nephew.[39] A letter from the British Orthopaedics Association sent out to members at the end of March says the use of large diameter metal on metal bearings in primary total hip replacement should be "carefully considered and possibly avoided." Data now show a higher than expected early failure rate, it said. "These range from 21% revision rate at 4 years (potentially rising to 35% if all currently known painful implants progress to revision) to 49% at 6 years for the ASR XL device. Other devices have a revision or impending revision rate of 12-15% at 5 years," it added.

And there continues to be debate within the orthopaedic community about what constitutes a large head—one or two centres are seeing problems that others are not. As Mr Langton asked in a presentation to the British Hip Society this year: "Why is the first response not to suspend the implantation [of a device] when legitimate concerns are raised?"

Lack of regulator power

The story of the ASR shows the power that companies have in deciding the fate of their devices, their hold over surgeons, and the lack of regulatory power in Europe.

The failure of the 3M hip over 12 years ago prompted calls for a device regulatory system analogous to that set up for drugs, involving clinical trials, a licensing process, and postmarketing surveillance. Some new products will always have rare and unwanted consequences—it's an inevitable consequence of innovation. The regulatory imperative is to ensure that these are limited in scale and picked up early. A good regulatory system will benefit everybody by ensuring patients are not exposed unnecessarily to risk and that manufacturers and others are not exposed to undue liabilities.

But will we learn from the story of the ASR and large head metal on metal prostheses? "I think we have to rethink the whole system of how devices come on to the market and whether we should be doing things a bit differently from what we are now," Professor Graves says.

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COMMENTARY John Skinner, Peter Kay

Metal on metal hips

Total hip replacement is one of the most successful operations of the 20th century and is currently performed in 70 000 patients a year in the UK,[1] 250 000 a year in the United States, and one million worldwide. To improve wear and to allow bone conservation through hip resurfacing, metal on metal bearings were re-introduced in the 1990s.[2] These are made of cobalt chromium alloys, and in some series hip resurfacing has shown excellent results in younger active patients.[3] Hip resurfacing became popular with patients through the internet as a younger person's solution to arthritis that allowed high activity levels. It was used in 10% of hip arthroplasties in the UK between 2006 and 2009 and in 50% of all hip replacements in patients younger than 50 years.[1]

Problems with hip resurfacing that were initially reported included raised blood cobalt and chromium ions,[4] loosening of components,[5] hip fracture,[6] and soft tissue reactions around the hip.[7] In an attempt to overcome the fracture problem and to extend the use of large diameter metal on metal bearings to those not suitable for hip resurfacing, metal resurfacing type bearings were introduced on total hip replacement stems.[8] These large diameter metal on metal total hip replacements had a lower theoretical rate of dislocation. In fact, metal on metal bearings were used in up to 35% of all total hip replacements in the United States in 2009.[9]

The commonest symptoms of adverse reactions to metal debris are pain, swellings around the hip, and loss of function with reduced exercise tolerance and onset of limp. Soft tissue swellings, fluid collections or "bursas" may be noticed in the groin, buttock, or laterally. Pain and symptoms in patients with metal on metal hips should be investigated and referred to an orthopaedic surgeon. Normal causes of pain should be excluded as for any hip replacement (infection, component loosening, lysis/wear, pain referred from another source). Full clinical assessment should be accompanied by radiographs, full blood count, erythrocyte sedimentation rate, and C-reactive protein. Cross sectional magnetic resonance imaging using metal artefact reduction sequences or ultrasound should also be performed to look for fluid collections (common) or solid masses (rare) around the implants. Hip aspiration and injection may be helpful.

Blood should be taken for cobalt and chromium ion measurements; again this is best done as part of an orthopaedic assessment. In asymptomatic patients with well functioning metal on metal implants, levels of these ions are low, typically around 2 parts per billion (µg/L or ng/mL).[4] In the UK, the Medicines and Healthcare products Regulatory Agency has suggested that patients with levels of cobalt or chromium ions above 7 parts per billion should be investigated and ion measurements repeated as part of closer follow-up.[10] But measurements may also need to be repeated in asymptomatic patients with levels between 3 and 7 parts per billion, particularly in those with large diameter metal on metal total hip replacements, perhaps at 6-12 months.[11] There is evidence that levels are higher in the first 6-12 months after insertion of a metal on metal bearing as it beds in and then they fall, in some patients.[12]

SOVEREIGN, ISM/SPL

As yet, the level of cobalt or chromium at which revision surgery is advised has not been clearly defined.[13] Blood metal ion levels are therefore an adjunct in assessing metal on metal hip function at present. Revision surgery should be performed in patients with substantial pain, worsening pain, limp, or poor function. Similarly, it should be considered in those with rising blood metal ions, increasing or large fluid collections or masses, around the hip.[13]

The risk to patients of failing metal on metal implants is a progressive inflammatory response leading to tissue necrosis around the hip. All joint replacements using conventional bearings of metal on polyethylene, ceramic on polyethylene, or ceramic on ceramic will wear and may fail, with debris generating different adverse responses. These include metallosis, osteolysis, loosening and dislocation.[14] The difference with metal on metal bearings seems to be the potential to develop necrosis and cell death in tissues around the hip. They can occur with all metal on metal bearings in both hip resurfacing and total hip replacements. They are more likely in women, with small component sizes (in hip resurfacing), with particular implants, with raised blood metal ions, and in components in suboptimal positions. If a painful metal on metal hip is revised before substantial soft tissue damage the outcome is likely to be excellent.[15] If substantial tissue damage occurs then revision surgery is associated with poorer function and higher rates of complication including limp and dislocation.[16]

Hip resurfacing with components that have proven track records are an effective and safe treatment in the active under-55 age group

In 2010, the ASR hip resurfacing and the ASR XL THR were recalled because of higher than expected rates of failure.[17] The company has agreed to fund all investigations and revision surgery. Not all patients know whether they have a metal on metal bearing; all patients with a hip resurfacing do and a minority of patients with total hip replacements do. This information is recorded at the hospital where the operation was performed and also centrally in the UK on the National Joint Register, which is accessible through the hospital.

In the absence of pain with a metal on metal bearing, no investigations are needed other than an annual assessment and the prompt reporting of new symptoms. The MHRA guidelines included four situations in which to test blood for metal ions: pain or symptoms associated with metal on metal bearings; radiological features associated with adverse outcomes including component position or small component size; concerns of the patient or surgeon about the bearing; and concerns about a cohort of patients with higher than expected failure rates.

The MHRA has suggested follow-up for five years for all metal on metal implants and for the life of the prosthesis in patients with the ASR/ASR XL. Patients who have painful metal on metal implants should be reviewed by their orthopaedic surgical team as above. The decision whether to revise the hip remains a clinical one between the patient and the surgeon, guided by the above investigations.

The British Orthopaedic Association and British Hip Society advice is that large diameter metal on metal total hip replacements should not be performed until more is known about their mode of failure (13% revision rate by 5 years on the UK NJR), except in exceptional circumstances.

Hip resurfacing with components that have proven track records are an effective and safe treatment in the active under-55 age group, with favourable hip anatomy with component survival rates of 97-98% at 10 years in men and slightly less in carefully selected women.[3]However, adverse metal reactions can still be seen in this group.

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EUROPEANS ARE LEFT TO THEIR OWN DEVICES

When it comes to the regulation of medical devices, Europeans seem to get a worse deal than Americans. **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, 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. Responding to a plastic surgeon's description of what happens in the EU, he said, "We don't use our people as guinea pigs in the US."[4]

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 tweaks are made.

Unknown quantity

The UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA), 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 80 000[7] in the UK and over 200 000[8] in Europe. Uncertainty surrounds the numbers because there is no publicly available list of devices being used day to day in healthcare settings. 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 ignorance is that decisions on market authorisation of high risk devices are made by privately run notified bodies rather than government agencies (box 1). Together with the manufacturers, they are therefore the most fundamental part of devices market approval and monitoring.[9] Notified bodies issue a certificate when a device has been approved. Companies can then affix a CE [Conformité Européenne] mark, the EU safety standard.

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]

The agency 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. An AMHRA meeting noted that there were discrepancies between the notified bodies: "Although the UK Notified Bodies are accredited to EN 13485 [conformity

Box 1 | 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—eg, 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 notified 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 needn't be randomised clinical trials or evaluate effectiveness.[8] A manufacturer need do no more than produce a comparative literature review if they are arguing that their device is similar to an existing (predicate) product.[8]

National regulators are 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.

John Wilkinson, chief executive of Eucomed, an industry trade association

The UK's Medicine and Healthcare Products Regulatory Agency

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

The European Medicines Agency based in Canary Wharf, London

Jeffrey Shuren, director of the US FDA's centre for devices and radiological health

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 for being secretive and opaque, but at least scientific rationale and study summaries are published along with 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. 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 there 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 2).

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 (box 3).

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—

Box 2 | 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 in 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 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 list the device and its manufacturer but no patient details. This database provides the agency with safety signals, which can provoke 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," Dr 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 who had issued a device's 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]

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 27 national databases duplicating their efforts.

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]

Recent changes won't increase transparency: the European Commission's database to share information about devices among the national regulators (Eudamed) came into full operation this month, but the data will not be publicly available.

Postmarketing problems

The European system relies more on postmarketing surveillance than it does on premarket testing. But what does this entail? For drugs, extensive phase IV trials and studies are usually mandated by the regulators to help identify 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,

Box 3 | FDA rejected devices that were CE marked in\ Europe

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 Prosthese (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.

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]

"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"

Company reporting—which is often slow—is supplemented by clinicians and patients reporting adverse reactions to any devices to the MHRA. However, we know that most adverse drug reactions are not reported,[27] although whether that's true of devices is unknown.

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 problems. Registers have been crucial in identifying problems with devices that have not gone through adequate premarket clinical testing, such as those occurring with metal hip implants.

Although no one wants to slow 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 protection of the public.

While an FDA style regulator for Europe has been advocated by some, 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 devices 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."[28]

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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COMMENTARY C Di Mario, S James, D Dudek, M Sabate, M Degertekin

The risk of over-regulation

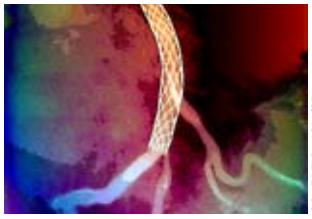
Regulatory bodies are expected to protect the public from the danger of inappropriately tested treatments—a shield against the vested interest of drug and device companies to sell products irrespective of their safety and effectiveness. The idea of the greedy industrialist focused on short term advantage and endangering lives with low quality components used to save manufacturing costs is familiar to the public and seems to justify stringent regulatory processes. But one person is forgotten in this equation—the doctor.

The doctor is directly accountable to the patient and is expected to have the competency and motivation to select appropriate devices and drugs. The personal ethical responsibility of every doctor towards his or her patient may get diluted in the impersonal setting of large hospitals run by governments or private health providers. Doctors have largely ceased to be independent professionals and became employees forced to follow rules aimed at maximising profit and containment of expenses. The medical industry is the main source of sponsorship for clinical trials and the main supporter of postgraduate medical education. This creates links with industry that have been overemphasised, depicting doctors like car dealers with a vested interest to "sell" products. The net result has been a shift of power in the decision making process about providing and regulating healthcare from the medical profession to administrative bodies. But have patients truly benefited from these changes and should we continue in this direction and strengthen the power of regulatory bodies policing the introduction and monitoring of new devices across Europe?

Lessons from interventional cardiology

Interventional cardiology, in which progress is strictly linked to technical development, is a goldmine of examples warning against the potential risks of over-regulation and showing that even the strictest regulatory process does not offer the full protection expected. We now know that coronary angioplasty saves the lives of patients with acute myocardial infarction and selected patients with acute coronary syndrome. But when Gruentzig and colleagues first described the technique in 1977,[1] it was not mature enough to be used for these challenging indications. Possibly the most widely applied "surgical" procedure in the world would have died in its infancy if powerful regulatory bodies had demanded demonstrations of equivalency or superiority to the other mechanical revascularisation technique available, coronary bypass surgery. It took more than 30 years and numerous trials of balloon angioplasty, bare metal stents, drug eluting stents versus surgery to have sufficient evidence for the representatives of the cardiology and cardiothoracic surgical associations to agree on common guidelines defining the relative merits and indications of the two strategies.[2]

New techniques introduced with more stringent regulatory processes risk being stopped before progressing to show their full potential and find their true indications. For a new transcatheter device to treat mitral insufficiency, the MitraClip, the Food and Drug Administration requested a randomised comparison with valve surgery, a mature technique benefiting from more than 30 years of experience. The result was not convincing enough for the FDA to grant approval. In Europe, where the device received a CE mark, doctors have used it not to replace reconstructive mitral valve surgery but to provide alternatives to the failure of medical therapy in inoperable patients and those with severe heart failure and secondary insufficiency—probably a more logical application for this technique than the comparison with surgery requested by the FDA. Even though the device is manufactured in the United States, it is available there only for restrictive compassionate use applications forcing patients to go abroad for treatment.



SOVEREIGN,ISM/SPL

Uniformly increasing the hurdles in the regulatory process risks raising costs without any real increase in patient safety

Middle Ground

Critics of the current European system argue that the system leads to inconsistency because of the variable attitudes of notified bodies and national regulators. Patients should enjoy the same protection everywhere in the world, and the standardisation recommended by Fraser and colleagues is desirable.[3] The number of drug eluting stents approved in Europe is 10 times greater than in the US, and many of those approved offer no advantage over bare metal stents for restenosis prevention or have much worse results than other drug eluting stents. This can be corrected by doctors, who can choose only well proved devices for their patients. Medical societies such as the European Society of Cardiology are also helping in the selection process, producing guidelines that recommend only devices with sufficient evidence.[2] Unfortunately, stents and other devices are increasingly selected by hospital managers based on their cost rather than performance.

Although there is room for improvement, uniformly increasing the hurdles in the regulatory process risks raising costs without improving patient safety. The approval process must acknowledge the varying requirements of different devices. It is illogical to have similar requirements for a new thrombectomy catheter and for a stent using a new drug and eluted by a novel fully biodegradable polymer. In the second situation clinical outcome measures are required. Number of patients should not be the only qualifying aspect of registration trials. We cannot expect that a trial in a selected subgroup of patients will apply to the wider population treated in clinical practice. Allcomers studies—started as the personal initiative of few European investigators[4-7]—should become a strict requirement for approval of truly new stents.

If a stringent scrutiny is applied to preregistration mechanical testing and clinical studies, unforeseen surprises are unlikely with wider clinical applications. But doctors and regulators still have a commitment to their patients to ensure that a sufficiently large and prolonged follow-up is available. The European Society of Cardiology's EurObservational research programme[8] is an ambitious project to monitor cardiac interventions, similar to the successful initiatives in Sweden.[9] Sponsorship of such registries for device surveillance and recommendation to the various national health authorities to enforce and police their applications are likely to be more effective ways of protecting patients than doubling the European Medicines Agency's offices, employees, and consultants to extend its competency over devices.

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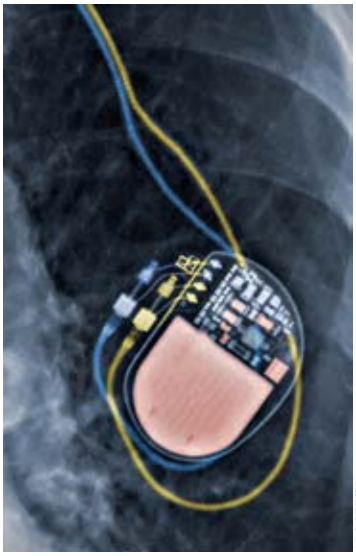
COMMENTARY Nick Freemantle

Evaluating and regulating device therapy

The current European regulatory framework—CE marking—might provide sufficient safeguards for electric toasters and kettles, but it is not adequate for treatments that can affect symptoms, health related quality of life, serious morbidity, and mortality.

There are many kinds of medical devices for myriad purposes in healthcare. All require an adequate regulatory framework to ensure that patients gain clear benefits and are not placed at unreasonable and avoidable risk. The so called class III devices have been defined by the US Food and Drug Administration as "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[1] Examples include pacemakers, stents, and prostheses. Class III devices share many of the challenges of drug treatments, which historically have had more regulatory attention and rigour.

The FDA evaluates the safety and effectiveness of class III devices in a process parallel to that of drugs, although differences exist that some people think are inappropriate.[2] In Europe, the process is different from that for drugs. Market access is granted if a device displays a CE mark. It is ultimately the manufacturer that decides whether to display the mark, which indicates that it is satisfied that its product conforms with the EU's quality standards and that "it is fit for its intended purpose."[3] Is the CE mark approach sufficient for a sophisticated clinical therapy?



APOGEE/SPL

Rather than devices being subject to an inferior regulatory model, we should extend and strengthen the approach taken for pharmaceuticals

Devices do present some additional challenges to regulatory agencies compared with drugs. Whereas the dose and formulation of drugs is fixed through the regulatory process, with marketing authorisation given to specific form and usage, devices may go through a more continuous development process characterised by a series of incremental steps in design and manufacture. Evolution may be helpful, although there is the risk that manufacturers may react to perverse incentives and aim for targets that are not in the best interests of patients or health systems. For example, manufacturers of sophisticated pacemakers have emphasised reducing device size rather than increasing battery life, which would benefit patients and health systems by reducing the frequency of explanting and reimplanting devices. Evolution also raises the prospect that a device used in practice may differ in some important aspect from that evaluated as part of the regulatory process.

Although the Medicines and Healthcare Products Regulatory Agency (MHRA) provides statistical guidance for device trials,[4] it is less methodologically sound than the related guidance available for drug trials.[5] MHRA guidance states explicitly that the trial programme for devices will not be adequately sized to address questions of safety,[4] a self-fulfilling prophecy that contrasts with drug regulation, where the randomised trial programme plays a key part in such evaluation.[5]

Long term data

Regulation is important since it drives the information available to inform clinicians and patients about the likely benefits and possible risks of treatment options. Cardiac resynchronisation devices for heart failure became available for use when only short term randomised trials were available; follow-up was 3-6 months, and all participants received devices but they were switched on according to randomisation.[6] Such trials cannot provide adequate evidence on the risks associated with implantation because all participants received devices, and evaluation of benefits was effectively limited to short term symptoms and quality of life. Class III devices should be evaluated using high quality randomised trials similar to those to which we aspire for drugs.

The manner in which industry sponsors trials of CE marked devices also contrasts with the situation for drugs. In drug trials, the investigational drug is paid for by the sponsor. However, in trials of devices, the experimental therapy may be funded indirectly by payments per patient (which may depend on the allocated treatment). This may not always fully cover the cost of the device. As contracts are complex and not generally in the public domain, this raises the risk of inadvertent public sponsorship of commercially organised trials.

Confirmatory trials that aim to establish the effect of a device on serious morbidity and mortality require adequate numbers of participants and sufficiently long follow-up, just as they do for drugs. Longer term follow-up trials of devices evaluating mortality and serious morbidity have often been of poor quality. Describing attempts to interpret one such device trial, a regulator commented that the trial was so challenged methodologically through loss to follow-up and device implantation in participants randomised to medical therapy alone as to be best interpretable as an observational study.

But high quality trials can be conducted. Bardy and colleagues compared placebo with amiodarone or an implantable cardioverter-defibrillator (ICD) in 2521 patients with a median follow up of 45.5 months and a primary outcome of all cause mortality.[7] Data on the primary outcome were available for all participants at the final planned visit. Despite the long follow-up, only 11% of participants randomised to placebo or amiodarone received an ICD during follow-up.[7]

Safety of devices must also be examined properly in the regulatory process. Thousands of patients receiving ICDs have experienced device malfunction,[8] with a substantial rate of complications, including death, associated with elective generator replacement of ICDs known to malfunction.[9] It is not clear that those responsible for regulating devices have dealt adequately with the challenges associated with device safety.

Class III devices share many characteristics with drugs and could be evaluated within a common framework examining efficacy, effectiveness, safety, and quality. Rather than devices being subject to an inferior regulatory model, we should extend and strengthen the approach taken for pharmaceuticals.

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COMMENTARY

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Standards need international collaboration

No implantable medical device is perfectly safe. It is the duty of manufacturers and regulators to minimise risks—and the purpose of evaluating and regulating devices is to ensure safety and effectiveness.

The product life cycle of many medical devices is short—often quoted as an average of two years or less—because of the rapid rate of technological change and because of frequent modifications (called iterative changes) to their design, manufacture, or programming. It would be desirable for all implantable devices to undergo long term clinical studies—but there is pressure from interventional specialists as well as from industry to base approval on shorter term studies with surrogate rather than clinical end points. This facilitates innovation but transfers responsibility for proof of safety and clinical efficacy to follow-up studies.

Regulatory approval in Europe hinges on the principle that as long as a device has been shown to perform its stated task, it can be approved if its potential benefits outweigh any expected risks. Approval on this basis can mean estimating benefit before clinical effectiveness has been confirmed, and it means accepting some risk as the trade-off for more rapid availability of devices. The system of approval by 74 notified bodies in the European Union (EU) requires manufacturers to evaluate the risks and propose how these should be addressed.[1] Official guidance published by the European Commission is vague. It relates to general principles, such as which details of a literature search should be included by the manufacturer in its clinical evaluation of a device, rather than to specific requirements for particular devices, such as upper limits for complication rates. It does not mandate when clinical trials are essential. This system means important questions about safety may be left unanswered.

In the United States, however, implantable devices are generally expected to undergo bench testing, animal studies, and clinical investigations before premarket authorisation. The burden of evidence varies with the category of risk and the degree of novelty, but the emphasis is on clinical effectiveness rather than the European principle of device performance.[1]

Despite official protestations to the contrary,[2] standards for approving medical devices are less rigorous in Europe than in the United States. One consequence is that devices are approved later in the US because of the time, work, and expense of providing data on human safety and outcomes for the Food and Drug Administration (FDA). Manufacturers often seek initial approval for their devices in Europe, where they can recoup some of their costs while gathering information about clinical effectiveness that they will submit later to the FDA.

As this example shows, different countries have responded to the common challenges of evaluating medical devices in different ways.[3] But it is not clear whether one system serves patients better than another. Although some populations may benefit earlier from new devices, they may also be exposed to greater risks. This is incompatible with the ethical principle that the risks associated with developing new devices should be equally shared worldwide. Patients everywhere should be protected by similar requirements for medical devices to be safe and effective.

Common standards

To try to overcome these problems, the Global Harmonization Task Force (GHTF)—an informal collaboration between regulatory authorities in Europe, North America, Japan, and Australia—has promoted common principles for evaluating devices, such as when clinical follow-up studies are indicated. Not all task force members have implemented its recommendations, however, and one third of countries still have no regulatory authority for medical devices.[4]

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The European Union is reviewing its system for approving medical devices. Since the EU is a member of the GHTF, it would be illogical if the planned recast of the medical device directives were to retain important differences from the regulations of other GHTF members. Equally, it would be inappropriate for higher levels of evidence to be required in Europe and North America than in parts of Africa and Asia. There should be no "region of least resistance" where devices could be approved more rapidly and on the basis of less evidence. Rather, efforts should be concentrated on developing a global approach. For each type of high risk device this should include a specific determination of how safe is "safe enough" relative to its therapeutic benefits.

The best way to use the limited pool of professional expertise concerning medical devices would be to develop global clinical standards for each class of medical device with moderate or high risks (classes II and III), specifying "objective performance criteria" and requirements for clinical evaluation and postmarketing surveillance. This is a task for all professional medical associations, the World Health Organization,[5] and others. The medical profession should accept some responsibility for the dearth of detailed clinical standards that regulators can apply. Too few physicians have taken an interest in the regulatory processes governing medical devices.

If international collaborations can lead to common standards, it might be possible to negotiate mutual recognition of approval processes between regulatory authorities without undermining essential aspects of individual national jurisdictions. A device that is evaluated and approved in Europe might then also be considered for approval in the US or Japan, or vice versa. The prospect of a single application leading to worldwide marketing authorisation would compensate for increased investment in premarket clinical studies. This could make the regulatory system less cumbersome and more efficient, as well as safer for patients. Where once this vision could have been characterised as a remote and idealistic dream, current global device clinical trials, developing international regulatory collaborations,[6] and advances in information technology now make it feasible.

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