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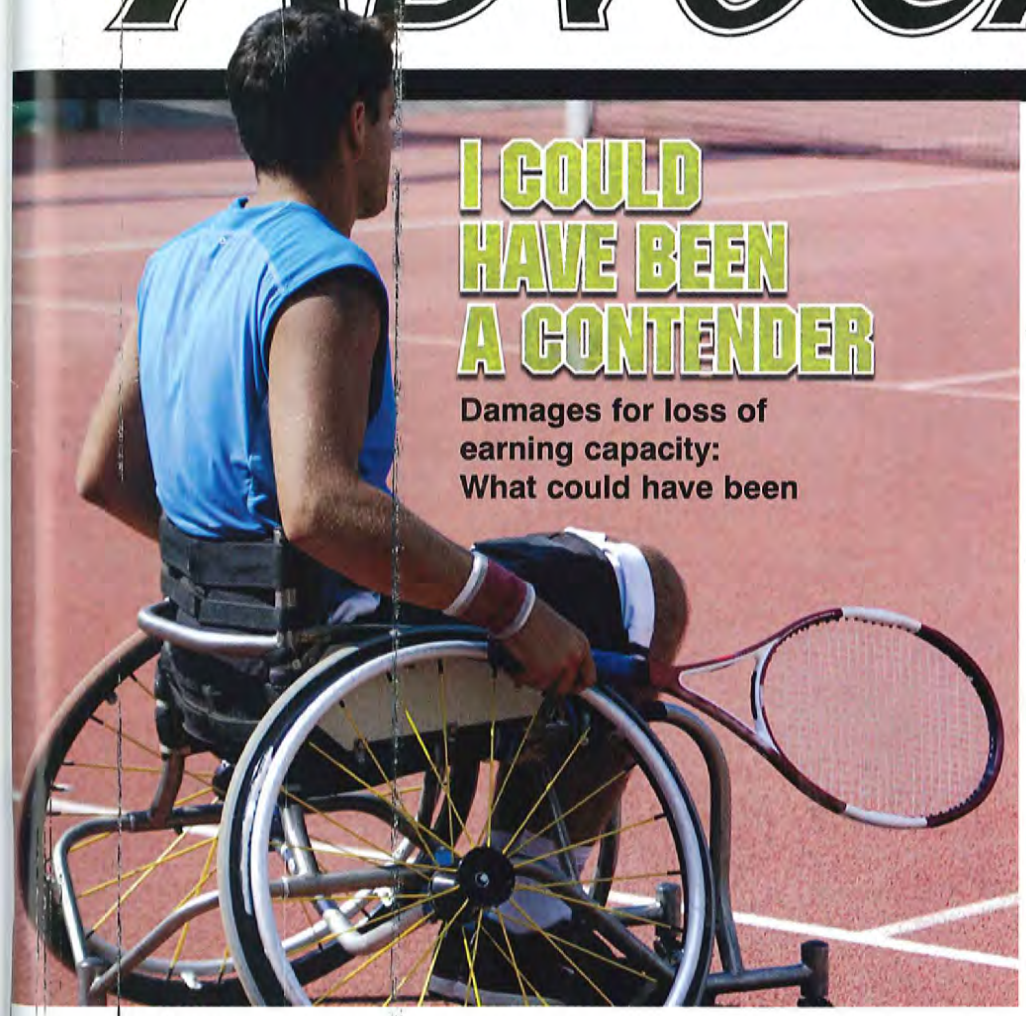

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Pete Kaufman

Products liability: Medical devices

A review of the FDA's approval process and a brief case study of the DePuy ASR hip implant

On August 24, 2010, DePuy Orthopaedics, Inc., a subsidiary of pharmaceutical giant Johnson & Johnson, Inc., withdrew its ASR hip implant device, a total metal joint-replacement device. Like most manufacturers of newer metal-on-metal hip implant devices, DePuy promised that the ASR hip would provide vast improvements over artificial hips using polyethylene or ceramic in the bearing surfaces. But after marketing the device for only five years, DePuy recalled the ASR, citing post-marketing safety data from around the world which showed the hip's untested design caused it to deposit metal debris at the implant site, leading to dangerously high circulating levels of cobalt and chromium, and requiring revision procedures far earlier than older, proven devices.

In 2011, the British Orthopaedic Association reported that the failure rate for the ASR hip was a staggering 49 percent within six years of implantation. (Updated guidance on large diameter metal on metal bearing total hip replacements. London: British Hip Society and British Orthopaedic Association, March 2011.) The "acceptable" failure rate for an artificial hip is one percent, per year.

So how did tens of thousands of hip patients get stuck with a device that failed so disastrously? How did the world's largest manufacturer of joint-replacement devices market a product without first determining whether it was at least as safe as those which were decades older? And, perhaps most critically, how did the U.S. Food & Drug Administration ("FDA") and regulatory bodies across the world, permit this product to be marketed without requiring clinical testing, which likely would have revealed the defect and avoided putting tens of thousands of patients at risk for revision surgeries?

Failed promises

The failed promise of the ASR hip implant is as stark an example as any in the recent history of medical devices, of the malfunctioning regulatory system in place in the U.S., and around the world. Instead of improving the lives of the patients who received the product, the ASR hip became one of the biggest disasters in orthopedic history. The consequences for DePuy will likely be dire as well. By the end of February 2012, more than 5,000 cases had been filed in the U.S., on behalf of patients who received an ASR hip which failed, or which – according to allegations – will fail, prematurely. Unhappily, the entire ordeal has served to create the impression that there is very little oversight of medical devices, even those which require major surgery for implantation. Remarkably, this impression – alarming as it may be – is largely accurate.

The challenge for attorneys handling defective medical device cases is to educate jurors about this sad state of affairs. As dramatic as the recent ASR debacle was, plaintiffs still must overcome a number of common misconceptions about the approval of medical devices. As often as not, prospective jurors arrive at the courthouse with a vague notion that the FDA monitors the drugs and devices that millions of patients rely on every day. Beyond that, little else is well known. The concept that there is an adequate regulatory framework in place to ensure the safety of medical devices exists as received wisdom. The overall impression is that medical devices are tested before they are made widely available; that there are clinical data supporting the use of these products; and that approval of a device by the FDA means that it is safe.

These misconceptions are consistently exploited by medical device defendants, who seek to avoid liability by leveraging the assumption that FDA approval is synonymous with safety. Often, the defense in these cases is focused simply on showing that the product was approved for the market. To this end, manufacturer employees (physicians, scientists and management alike) routinely testify that the company did all that was required under the applicable regulations. Defense experts opine that the current system ensures that only devices which are proven to be safe and effective make it to the market. And the import of all of this is that if it is good enough for the FDA, then it must be good enough for the jury.

Of course, to anyone paying attention, decades of litigation involving defective drugs and medical devices have shown that the FDA's ability to protect patients is – to say the very least – deeply flawed. With respect to medical devices in particular, the agency's record is strikingly poor. The framework which we assume protects the interests of patients is "subject to gaps, internal tensions, and conflicts of interest." (See *Deyo RA. Gaps, Tensions, and Conflicts in the FDA Approval Process*: Medical Device. J., Am Board Fam Med. 2004;17, at 1.) Contrary to the typical juror's typical assumptions, the FDA "rarely requires tests of clinical efficacy for new devices." (*Ibid.*) And practitioners should hardly be surprised that prospective jurors lack an accurate perspective concerning government regulation of medical devices. Indeed, there has been concern recently that even clinicians lack "realistic ideas about what FDA approval does and does not mean." (*Ibid.*) The conceit that safety is the agency's main focus is increasingly undermined, borne out by this sobering comment from former FDA commissioner David Kessler: "[T]he biggest fight between the industry, the Congress, and the FDA over the past decade [has been] getting products out fast." (*Id.*, at 5.)

Use of a regulatory expert: FDA Regulation of Medical Devices

In order to level the playing field in medical device cases, the plaintiff must provide for the jury a more accurate view of the FDA's oversight of the products. To that end, it is critical that the plaintiff's regulatory expert place the approval of the device in question within the appropriate context. The plaintiff must demonstrate, in his or her case, what approval means, and – more to the point – what it does not mean.

The regulation of new drugs and new medical devices varies to an astonishing degree. Nearly all new drugs – those approved via a *New Drug Application* – are treated identically. This is to say, some amount of real world, clinical data are required before they can be approved. The same cannot be said for new medical devices. Because of the quirks of the relevant statutory framework, subsequent changes thereto, and the development of ordinary FDA practices, many devices, including even the most complicated, are marketed without any safety review for years, if not – for all practical purposes – indefinitely. (Medical Devices and the Public's Health: The 510(k) Clearance Process at 35 Years. *Institute of Medicine* (*"IOM"*), July 2011, p. 30.)

Nominally, the FDA has regulated medical devices since shortly after its inception. But the present regulatory scheme dates from 1976, when Congress enacted the Medical Device Amendments (MDA). Prior to the enactment of the MDA, the agency lacked any real oversight, as decades-old regulations failed

increasingly to reflect the complexity of products on the market. Indeed, before the enactment of the MDA, most medical devices were not reviewed by the FDA at all prior to being introduced to the market.

The MDA was a response, in part, to public outcry over well-publicized device failures. The most prominent of these involved the Dalkon Shield, an intrauterine contraceptive device associated with serious infections. The MDA was intended to address dramatic changes to the technological landscape that had occurred since the FDA first regulated medical devices, in the 1930s. As the U.S. Supreme Court has observed: "As technologies advanced and medicine relied to an increasing degree on a vast array of medical equipment…policymakers and the public became concerned about the increasingly severe injuries that resulted from the failure of such devices." (*Medtronic, Inc. v. Lohr* (1996) 518 U.S. 470, 475-76.)

Classification of medical devices

The MDA is admirable in scope and design, if not in implementation. It classifies medical devices into three categories based on the risk that they pose to patients. Products which present "no unreasonable risk of illness or injury" are designated Class I and are subject only to minimal regulation by "general controls." (21 U.S.C. § 360c (a)(1)(A).) Devices that are potentially more harmful are designated Class II. These may be marketed without advance approval, but manufacturers must comply with federal performance regulations known as "special controls." (§ 360c (a)(1)(B).) Lastly, devices that either "presen[t] a potential unreasonable risk of illness or injury," or which are "purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," are designated Class III. (§ 360c (a)(1)(C).)

The approval requirement for Class III devices represented a considerable attempt to improve the safety of these high-risk products. Pursuant to the MDA, a Class III device may be approved for marketing only after the manufacturer has provided the FDA with a "reasonable assurance" that the device is both safe and effective. (§ 360e (d)(2).) The process of establishing this "reasonable assurance," known as the "premarket approval," or "PMA" process, is a rigorous one, requiring manufacturers to submit detailed information regarding the safety and efficacy of their devices, which the FDA then reviews, spending an average of 1,200 hours on each submission. (*Medtronic, Inc. v. Lohr*, at 477.) Because the PMA process is so comprehensive, common-law claims challenging the safety or effectiveness of a device that has received premarket approval from the FDA are barred via the preemption doctrine. (*Riegel v. Medtronic, Inc.* (2008) 552 U.S. 312.)

While the classification system outlined in the MDA is rational enough, it quickly became apparent that the legislative mandate far outstripped the abilities of the FDA to implement it. For example, while devices in existence at the time of the enactment of the MDA were ultimately to be classified according to the scheme, no substantive analysis of the safety and efficacy of these products was performed initially. Existing devices were simply "grandfathered in." (*IOM*, at 31.) And the 1976 Act hardly affected anything approaching expeditious change in the industry. The process of merely *classifying* existing devices into the new categories alone took eight years. (*Ibid.*)

Meanwhile, the vaunted goal of conducting thorough safety analyses for all existing and new Class III devices went largely unmet. In fact, nearly 40 years after the passage of the MDA, most Class III devices on the market have not been through the PMA process because of two statutory exceptions. Realizing that *existing* devices could not be withdrawn from the market while the FDA completed PMA analyses, Congress included a provision allowing pre-1976 devices to remain on the market without FDA approval until the requisite PMA was completed.

At the same time, there was concern that *new* devices not be disadvantaged by the gradual implementation of the MDA requirements. Thus, any device submitted post-amendment, which was "substantially equivalent" to either a pre-amendment or approved post-amendment device was permitted to be marketed until the FDA either established standards or demanded a formal PMA application for Class III devices. (*IOM*, at 32.) The manufacturer was simply required to give notice to the FDA that the new device was going to be marketed.

Obviously, these exceptions were intended merely as stopgap measures, as statutory requirements caught up with existing technology and practice. Still, read cynically, the MDA appears to open enormous loopholes for medical devices to be marketed without any substantive review of safety; if not indefinitely, then certainly for years, or longer. Comprehensive analyses of safety were to take place eventually, of course. The 1976 MDA directed the FDA to promulgate a rule calling for the manufacturers of Class III devices to submit PMAs but the resource constraints of the FDA delayed the calling of these applications. In 1990, Congress directed the agency to set a schedule for submissions of PMA applications, extending no later than December 1996, but this process is still not complete. As a consequence, most Class III devices are now subject to the same approval requirements as Class I devices: demonstration of substantial equivalence to a pre-amendment device. In effect, for example, implantable hip replacement devices are approved in the same manner as tongue depressors.

To make matters worse, the agency has long known that the MDA is, if not completely ineffective, then at least badly flawed. In 1992, an FDA committee performed a review of 24 PMA and 510(k) applications and found that they (1) failed to utilize appropriate controls; (2) used poorly defined historical controls; (3) used sample sizes inadequate to answer questions; (4) poorly characterized study subjects; (5) poorly assessed the comparability of patients in treatment and control groups; (6) failed to clearly and consistently define study endpoints; and (7) failed to have blind evaluation of subjective endpoints.

The 510(k) application

The shortcut to the comprehensive, though seldom used, PMA application is the so-called 510(k) approval (named for the statutory provision from which it derived). Pursuant to this process, manufacturers must submit an application, describing the new device, its material and design characteristics and intended use. The agency reviews the 510(k) to determine if the device is "substantially equivalent" to an existing approved device, and thereby giving it clearance for marketing.

The 510(k) notification process is by no means comparable to the PMA process; in contrast to the 1,200 hours necessary to complete a PMA review, the 510(k) review is completed in an average of only 20 hours. (*Medtronic, Inc. v. Lohr.*, at 478-79.) As one commentator noted: "The attraction of substantial equivalence to manufacturers is clear. [Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly." (*Adler*, The 1976 Medical Device Amendments: A Step in the Right Direction Needs Another Step in the Right Direction, 43 Food Drug Cosm. L.J. 511, 516 (1988).)

The central flaw of the abbreviated 510(k) process is the amorphous nature of the term "substantial equivalence." Precious little guidance as to the phrase's meaning is provided in the statute. It is not defined at all in the MDA, and the legislative history contains a one-paragraph discussion which has been described – charitably – as "ambiguous." (*IOM*, at 33.) But nature abhors a vacuum, and so statutory vagueness gradually combined with agency and industry practices, incrementally devaluing the phrase until it was rendered a bureaucratic rubberstamp. For example, the FDA initially permitted manufacturers to use multiple devices, like Russian nesting dolls, to find substantial equivalence to a pre-amendment (and so *quasi* approved) device. Thus, an applicant could argue that new Device A was substantially equivalent to Device B, which in turn was substantially equivalent to pre-amendment Device C. The practical effect of this was that the 510(k) application process evolved into one which found substantial equivalence far more often than not. In fact, between fiscal years 1976 and 2009, only 1 to 4 percent of 510(k) notifications submitted annually were found by the FDA to be not substantially equivalent. Over time, the easiest approach was for the agency simply to find substantial equivalence, and it tended to do so.

The trend toward lighter and lighter requirements for 510(k) approval has emanated not simply from the FDA and industry, either. In 1997, Congress took steps to restrict the Agency's authority with respect to the process, actually making it easier for manufacturers to obtain 510(k) clearance. When the FDA did have to make a determination about whether a technologically new device was as safe and effective as its predicate, it was directed by Congress not to request any evidence beyond the "least burdensome" means to determine equivalence. (*Ibid.*) Consequently, that FDA routinely permitted new technology to be marketed without any real effort to determine if it was safe and effective. This permissive approach at the legislative and agency levels yielded predictable results.

In 1990, the House reported that 80 percent of new Class III devices were being introduced to the market through the 510(k) process and without PMA review. (See *H.R.Rep.* No. 101-808, p. 14 (1990); see also *D. Kessler, S. Pape, & D. Sundwall*, The Federal Regulation of Medical Devices, 317 New England J. Med. 357, 359 (1987).) Between 1976 and 1998, nearly 98 percent of new devices entering the market in class II or III were approved through the 510(k) process. *(Ramsey SD, Luce BR, Deyo R, Franklin G.* The limited state of technology assessment for medical devices: facing the issues. Am J Manag Care 1998; 4 Spec No:SP188-99.)

In 2002, the FDA reported 41 premarket approvals and 3708 approvals through the 510(k) process. (FDA Center for Devices and Radiological Health. Office of Device Evaluation annual report 2002.)

Between fiscal years 2005 and 2007, about 15 percent of Class II and Class III 510(k) submissions for which the FDA reached a determination of substantial equivalence or nonsubstantial equivalence had new technologic characteristics. Some 99.5 percent received a determination of substantially equivalent. As of 2008, ninety percent of the medical devices on the market – over 120,000 devices – were cleared through the 510(k) process.

When one considers that there are more than 1,700 different types of medical devices, 70,000 different products for specific applications, and 7,000 companies who have FDA approval to market these products, one begins to get a sense of the enormity of the problem. (National Hospital Discharge Survey: National Bureau of Health Statistics; 1993.) As former commissioner Kessler put it, "the products that have been pushed through 510(k) are astonishing."(*Deyo*, at 4.)

A case study: DePuy's ASR hip-implant device

Perhaps more than any other product in recent history, the story of the ASR hip illustrates the hazards of the system of regulations applicable to medical devices. That this catastrophe occurred within this class of products should come as no surprise. Regrettably for tens of thousands of patients, hip replacement devices were positioned perfectly to fall through the cracks opened by the MDA, subsequent legislation, and agency and industry practices. This is so, principally, for two reasons: 1) the availability of predicate devices when the MDA was passed, in 1976; and 2) the high degree of competition among hip-implant manufacturers.

There were a handful of total-hip implants – including metal-on-metal devices – available before the 1976 passage of the MDA. As pre-amendment devices, these were grandfathered under the Act and permitted to remain on the market without any immediate analysis of safety and efficacy. Of course, the analysis was not supposed to be deferred in perpetuity, but essentially this is what happened. In the case of hip replacement devices, the FDA did not call for PMA submissions until September 1996, more than 20 years after the MDA was passed. And, not surprisingly, the process of grinding through the enormous number of hip replacement products has proceeded slowly. Indeed, as of February 2012, the PMA process has not been completed for any metal-on-metal hip device released since 2005.

Meanwhile, the market for total hip arthroplasty is large and growing. There are an estimated 200,000 primary hip replacements performed annually in the U.S. As a consequence, competition among manufacturers of artificial hips is especially keen, as designers cast about for any improvement – real or perceived – to help their product stand out from the crowd. Materials and component design are tweaked for a number of reasons, but the overarching concern is durability. All hip replacements have a limited life span and so many will ultimately require revision. Because of this, device manufacturers have focused intensely on ways in which to improve the life span of artificial joints.

This drive to improve has led to an explosion in the number of devices available on the market. According to the 2010 Australian Joint Registry, there are more than 1,500 stem and acetabular cup combinations for total hip replacement. As one commentator has observed, "companies scarcely let a year go by without introducing a 'new improved' joint replacement which 'offers undreamt of (and unproved) advantages over the older designs.'" (See *Bulstrode CJ, Murray DW, Carr AJ, Pynsent PB, Carter SR.* Designer hips. BMJ. 1993;306:732-3.)

The ASR hip implant was just such a device. Designed to compete with the Birmingham Hip system, DePuy hoped to position the ASR as a bestseller among younger, active patients. Originally, the ASR was designed solely as a hip-resurfacing system. Hip resurfacing devices differs from total hip joint replacement devices in the manner in which they are implanted at the femur. In a total hip replacement, the top of the femur is removed, and a metal stem is placed deep within the bone, on top of which the artificial femoral bearing is placed. In a hip resurfacing system, the existing femoral head is capped, instead of being removed.

The ASR resurfacing system was touted as a "major innovation." (*Curfman GD.* Medical Devices – Balancing Regulation and Innovation. N Engl J Med 2011; 365:975-7.) The device was first marketed in Europe in 2003, based solely on laboratory testing, which involved little more than simulator studies to test how well the implant wore. No clinical studies of the device's safety or efficacy were ever performed. But simulator studies are an imperfect method for determining the safety of a new device, as they do not represent the biological environment. And the total absence of clinical data left critical gaps in the manufacturer's understanding of the new device. As Stephen Graves, orthopedic surgeon and director of the Australian National Joint Replacement Registry, explains: "Before a hip or knee replacement is placed onto the market it should have been used in a limited number of people who had been monitored very carefully for a number of years," …[as]"the outcome of that monitoring would indicate that the device is actually working very satisfactorily in that small group of patients."

The ASR resurfacing system was not approved in the U.S. Because resurfacing was a new technique, it was subjected to PMA approval, and the FDA required DePuy to submit the product to clinical testing to demonstrate safety and efficacy. But the studies quickly produced negative data, as participating surgeons sent reports of adverse events to DePuy. In response, the FDA requested that DePuy provide explanations of the events. Exhibiting a pattern of obfuscation all too familiar in the industry, DePuy referred the Agency's questions to a sales representative, who formulated answers for the participating surgeon. Ultimately, DePuy withdrew its application for approval of the ASR resurfacing system.

But while regulatory scrutiny was sufficient to keep this new, unproven device from the market, it did not spare the tens of thousands of patients who later received much of the same unproven hardware as part of the ASR *total* hip implant. Because after DePuy abandoned the resurfacing configuration of the ASR, it simply coupled the device with an older femoral stem and sold it as a total hip replacement. And instead of continuing with the clinical studies which were producing less than promising results, the company submitted the device for approval using the 510(k) process, telling the FDA that the ASR – a product it would later describe to surgeons and patients as innovative – was substantially equivalent to an older product. After using patients around the United States and the world as *de facto* test subjects for five years, and as reports of premature failures mounted, with evidence that that ASR's design was causing harmful deposits of heavy metals leading to loss of tissue and bone, the company recalled the device in August 2010.

Conclusion

Unfortunately, the story of the ASR hip is not unique. The 510(k) approval process is used for nearly every new medical device, irrespective of class. Meanwhile, the FDA struggles through an enormous backlog of devices, for which PMAs should be called, but which are not for years, if not longer. That legislators and industry should be compelled to revamp the current system, as was recommended in the Institute of Medicine's 2011 report on the 510(k) process, is to state the obvious.

In the meantime, any liability presentation in a medical-device case will be utterly incomplete without an explanation of how new, and risky, products are approved. The effective regulatory expert will be able to describe the conditions which have permitted medical-device companies to speed unproven products to the market, with particular attention to the circumstances which have rendered FDA review of new devices essentially toothless.

Pete Kaufman is an attorney at Panish, Shea & Boyle *in Los Angeles specializing in drug and device litigation. He is a graduate of the University of Wisconsin-Madison and the University of Florida, Levin College of Law. He encourages you to bike to work at least once a month.*

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The challenge for attorneys handling defective medical device cases is to educate jurors about this sad state of affairs. As dramatic as the recent ASR debacle was, plaintiffs still must overcome a number of common misconceptions about the approval of medical devices. As often as not, prospective jurors arrive at the courthouse with a vague notion that the FDA monitors the drugs and devices that millions of patients rely on every day. Beyond that, little else is well known. The concept that there is an adequate regulatory framework in place to ensure the safety of medical devices exists as received wisdom. The overall impression is that medical devices are tested before they are made widely available; that there are clinical data supporting the use of these products; and that approval of a device by the FDA means that it is safe.

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Meanwhile, the vaunted goal of conducting thorough safety analyses for all existing and new Class III devices went largely unmet. In fact, nearly 40 years after the passage of the MDA, most Class III devices on the market have not been through the PMA process because of two statutory exceptions. Realizing that *existing* devices could not be withdrawn from the market while the FDA completed PMA analyses, Congress included a provision allowing pre-1976 devices to remain on the market without FDA approval until the requisite PMA was completed.

At the same time, there was concern that *new* devices not be disadvantaged by the gradual implementation of the MDA requirements. Thus, any device submitted post-amendment, which was "substantially equivalent" to either a pre-amendment or approved post-amendment device was permitted to be marketed until the FDA either established standards or demanded a formal PMA application for Class III devices. (*IOM*, at 32.) The manufacturer was simply required to give notice to the FDA that the new device was going to be marketed.

Obviously, these exceptions were intended merely as stopgap measures, as statutory requirements caught up with existing technology and practice. Still, read cynically, the MDA appears to open enormous loopholes for medical devices to be marketed without any substantive review of safety; if not indefinitely, then certainly for years, or longer. Comprehensive analyses of safety were to take place eventually, of course. The 1976 MDA directed the FDA to promulgate a rule calling for the manufacturers of Class III devices to submit PMAs but the resource constraints of the FDA delayed the calling of these applications. In 1990, Congress directed the agency to set a schedule for submissions of PMA applications, extending no later than December 1996, but this process is still not complete. As a consequence, most Class III devices are now subject to the same approval requirements as Class I devices: demonstration of substantial equivalence to a pre-amendment device. In effect, for example, implantable hip replacement devices are approved in the same manner as tongue depressors.

To make matters worse, the agency has long known that the MDA is, if not completely ineffective, then at least badly flawed. In 1992, an FDA committee performed a review of 24 PMA and 510(k) applications and found that they (1) failed to utilize appropriate controls; (2) used poorly defined historical controls; (3) used sample sizes inadequate to answer questions; (4) poorly characterized study subjects; (5) poorly assessed the comparability of patients in treatment and control groups; (6) failed to clearly and consistently define study endpoints; and (7) failed to have blind evaluation of subjective endpoints.

The 510(k) application

The shortcut to the comprehensive, though seldom used, PMA application is the so-called 510(k) approval (named for the statutory provision from which it derived). Pursuant to this process, manufacturers must submit an application, describing the new device, its material and design characteristics and intended use. The agency reviews the 510(k) to determine if the device is "substantially equivalent" to an existing approved device, and thereby giving it clearance for marketing.

The 510(k) notification process is by no means comparable to the PMA process; in contrast to the 1,200 hours necessary to complete a PMA review, the 510(k) review is completed in an average of only 20 hours. (*Medtronic, Inc. v. Lohr.*, at 478-79.) As one commentator noted: "The attraction of substantial equivalence to manufacturers is clear. [Section] 510(k) notification requires little information, rarely elicits a negative response from the FDA, and gets processed very quickly." (*Adler*, The 1976 Medical Device Amendments: A Step in the Right Direction Needs Another Step in the Right Direction, 43 Food Drug Cosm. L.J. 511, 516 (1988).)

The central flaw of the abbreviated 510(k) process is the amorphous nature of the term "substantial equivalence." Precious little guidance as to the phrase's meaning is provided in the statute. It is not defined at all in the MDA, and the legislative history contains a one-paragraph discussion which has been described – charitably – as "ambiguous." (*IOM*, at 33.) But nature abhors a vacuum, and so statutory vagueness gradually combined with agency and industry practices, incrementally devaluing the phrase until it was rendered a bureaucratic rubberstamp. For example, the FDA initially permitted manufacturers to use multiple devices, like Russian nesting dolls, to find substantial equivalence to a pre-amendment (and so *quasi* approved) device. Thus, an applicant could argue that new Device A was substantially equivalent to Device B, which in turn was substantially equivalent to pre-amendment Device C. The practical effect of this was that the 510(k) application process evolved into one which found substantial equivalence far more often than not. In fact, between fiscal years 1976 and 2009, only 1 to 4 percent of 510(k) notifications submitted annually were found by the FDA to be not substantially equivalent. Over time, the easiest approach was for the agency simply to find substantial equivalence, and it tended to do so.

The trend toward lighter and lighter requirements for 510(k) approval has emanated not simply from the FDA and industry, either. In 1997, Congress took steps to restrict the Agency's authority with respect to the process, actually making it easier for manufacturers to obtain 510(k) clearance. When the FDA did have to make a determination about whether a technologically new device was as safe and effective as its predicate, it was directed by Congress not to request any evidence beyond the "least burdensome" means to determine equivalence. (*Ibid.*) Consequently, that FDA routinely permitted new technology to be marketed without any real effort to determine if it was safe and effective. This permissive approach at the legislative and agency levels yielded predictable results.

In 1990, the House reported that 80 percent of new Class III devices were being introduced to the market through the 510(k) process and without PMA review. (See *H.R.Rep.* No. 101-808, p. 14 (1990); see also *D. Kessler, S. Pape, & D. Sundwall*, The Federal Regulation of Medical Devices, 317 New England J. Med. 357, 359 (1987).) Between 1976 and 1998, nearly 98 percent of new devices entering the market in class II or III were approved through the 510(k) process. (*Ramsey SD, Luce BR, Deyo R, Franklin G.* The limited state of technology

assessment for medical devices: facing the issues. Am J Manag Care 1998; 4 Spec No:SP188-99.)

In 2002, the FDA reported 41 premarket approvals and 3708 approvals through the 510(k) process. (FDA Center for Devices and Radiological Health. Office of Device Evaluation annual report 2002.)

Between fiscal years 2005 and 2007, about 15 percent of Class II and Class III 510(k) submissions for which the FDA reached a determination of substantial equivalence or nonsubstantial equivalence had new technologic characteristics. Some 99.5 percent received a determination of substantially equivalent. As of 2008, ninety percent of the medical devices on the market – over 120,000 devices – were cleared through the 510(k) process.

When one considers that there are more than 1,700 different types of medical devices, 70,000 different products for specific applications, and 7,000 companies who have FDA approval to market these products, one begins to get a sense of the enormity of the problem. (National Hospital Discharge Survey: National Bureau of Health Statistics; 1993.) As former commissioner Kessler put it, "the products that have been pushed through 510(k) are astonishing."(*Deyo*, at 4.)

A case study: DePuy's ASR hip-implant device

Perhaps more than any other product in recent history, the story of the ASR hip illustrates the hazards of the system of regulations applicable to medical devices. That this catastrophe occurred within this class of products should come as no surprise. Regrettably for tens of thousands of patients, hip replacement devices were positioned perfectly to fall through the cracks opened by the MDA, subsequent legislation, and agency and industry practices. This is so, principally, for two reasons: 1) the availability of predicate devices when the MDA was passed, in 1976; and 2) the high degree of competition among hip-implant manufacturers.

There were a handful of total-hip implants – including metal-on-metal devices – available before the 1976 passage of the MDA. As pre-amendment devices, these were grandfathered under the Act and permitted to remain on the market without any immediate analysis of safety and efficacy. Of course, the analysis was not supposed to be deferred in perpetuity, but essentially this is what happened. In the case of hip replacement devices, the FDA did not call for PMA submissions until September 1996, more than 20 years after the MDA was passed. And, not surprisingly, the process of grinding through the enormous number of hip replacement products has proceeded slowly. Indeed, as of February 2012, the PMA process has not been completed for any metal-on-metal hip device released since 2005.

Meanwhile, the market for total hip arthroplasty is large and growing. There are an estimated 200,000 primary hip replacements performed annually in the U.S. As a consequence, competition among manufacturers of artificial hips is especially keen, as designers cast about for any improvement – real or perceived – to help their product stand out from the crowd. Materials and component design are tweaked for a number of reasons, but the overarching concern is durability. All hip replacements have a limited life span and so many will ultimately require revision. Because of this, device manufacturers have focused intensely on ways in which to improve the life span of artificial joints.

This drive to improve has led to an explosion in the number of devices available on the market. According to the 2010 Australian Joint Registry, there are more than 1,500 stem and acetabular cup combinations for total hip replacement. As one commentator has observed, "companies scarcely let a year go by without introducing a 'new improved' joint replacement which 'offers undreamt of (and unproved) advantages over the older designs.'" (See *Bulstrode CJ, Murray DW, Carr AJ, Pynsent PB, Carter SR.* Designer hips. BMJ. 1993;306:732-3.)

The ASR hip implant was just such a device. Designed to compete with the Birmingham Hip system, DePuy hoped to position the ASR as a bestseller among younger, active patients. Originally, the ASR was designed solely as a hip-resurfacing system. Hip resurfacing devices differs from total hip joint replacement devices in the manner in which they are implanted at the femur. In a total hip replacement, the top of the femur is removed, and a metal stem is placed deep within the bone, on top of which the artificial femoral bearing is placed. In a hip resurfacing system, the existing femoral head is capped, instead of being removed.

The ASR resurfacing system was touted as a "major innovation." (*Curfman GD.* Medical Devices – Balancing Regulation and Innovation. N Engl J Med 2011; 365:975-7.) The device was first marketed in Europe in 2003, based solely on laboratory testing, which involved little more than simulator studies to test how well the implant wore. No clinical studies of the device's safety or efficacy were ever performed. But simulator studies are an imperfect method for determining the safety of a new device, as they do not represent the biological environment. And the total absence of clinical data left critical gaps in the manufacturer's understanding of the new device. As Stephen Graves, orthopedic surgeon and director of the Australian National Joint Replacement Registry,

explains: "Before a hip or knee replacement is placed onto the market it should have been used in a limited number of people who had been monitored very carefully for a number of years," ...[as]"the outcome of that monitoring would indicate that the device is actually working very satisfactorily in that small group of patients."

The ASR resurfacing system was not approved in the U.S. Because resurfacing was a new technique, it was subjected to PMA approval, and the FDA required DePuy to submit the product to clinical testing to demonstrate safety and efficacy. But the studies quickly produced negative data, as participating surgeons sent reports of adverse events to DePuy. In response, the FDA requested that DePuy provide explanations of the events. Exhibiting a pattern of obfuscation all too familiar in the industry, DePuy referred the Agency's questions to a sales representative, who formulated answers for the participating surgeon. Ultimately, DePuy withdrew its application for approval of the ASR resurfacing system.

But while regulatory scrutiny was sufficient to keep this new, unproven device from the market, it did not spare the tens of thousands of patients who later received much of the same unproven hardware as part of the ASR *total* hip implant. Because after DePuy abandoned the resurfacing configuration of the ASR, it simply coupled the device with an older femoral stem and sold it as a total hip replacement. And instead of continuing with the clinical studies which were producing less than promising results, the company submitted the device for approval using the 510(k) process, telling the FDA that the ASR – a product it would later describe to surgeons and patients as innovative – was substantially equivalent to an older product. After using patients around the United States and the world as *de facto* test subjects for five years, and as reports of premature failures mounted, with evidence that that ASR's design was causing harmful deposits of heavy metals leading to loss of tissue and bone, the company recalled the device in August 2010.

Conclusion

Unfortunately, the story of the ASR hip is not unique. The 510(k) approval process is used for nearly every new medical device, irrespective of class. Meanwhile, the FDA struggles through an enormous backlog of devices, for which PMAs should be called, but which are not for years, if not longer. That legislators and industry should be compelled to revamp the current system, as was recommended in the Institute of Medicine's 2011 report on the 510(k) process, is to state the obvious.

In the meantime, any liability presentation in a medical-device case will be utterly incomplete without an explanation of how new, and risky, products are approved. The effective regulatory expert will be able to describe the conditions which have permitted medical-device companies to speed unproven products to the market, with particular attention to the circumstances which have rendered FDA review of new devices essentially toothless.

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