



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

May 2012

Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US



Table of Contents

| | |
|---|-----------|
| Executive Summary | 3 |
| Introduction | 5 |
| <hr/> | |
| List of Dangerous and Ineffective Devices | 7 |
| I PleuraSeal to Seal Lung Incisions | 8 |
| II Trilucent Breast Implants | 8 |
| III AAA Stent Grafts to Repair Aneurysms | 8 |
| IV Elbow Implant | 9 |
| V Cardiac Constraint Device Technologies for Treatment of Heart Failure | 9 |
| VI Injected Dermal Fillers for Cosmetic Use | 10 |
| VII Pendra for Monitoring Blood Glucose Levels in Diabetes | 10 |
| VIII PFO Occluders to Prevent Stroke | 11 |
| IX CoSTAR Drug-Eluting Stent to Open Arteries | 12 |
| X Biofield Device to Detect Breast Cancer | 12 |
| XI RoboDoc for Hip Surgery | 12 |
| XII Zephyr for Emphysema | 13 |
| <hr/> | |
| Conclusion | 14 |
| Endnotes | 15 |

Executive Summary

The recent revelation that over 80,000 women in the European Union (EU) received dangerous breast implants containing industrial-grade silicone has drawn attention to weaknesses in the EU’s regulation of medical devices. This report examines 12 additional high-risk devices that were approved in the EU and later found to be dangerous or ineffective. Most of these devices were ultimately withdrawn from the EU market, but only after thousands of patients were harmed. In many cases, the device’s risks or ineffectiveness were discovered only as a result of studies conducted for approval in the US. None of the dangerous and ineffective devices described in this report were approved here, and US patients were spared significant harm.

A sound approval system for high-risk medical devices should make sure that patients receive devices that improve their lives without subjecting them to unnecessary risks. At the same time, it should provide access to important therapies without unnecessary delay. According to industry figures, US patients already have access to low- and moderate-risk devices, which account for

80% of all devices, at least as early as EU patients. For high-risk devices, however, the EU’s lower approval standard and private third-party review (see Box 1) have meant that high-risk devices are more often approved first in the EU. (Lengthy reimbursement reviews in some of the biggest EU markets may nevertheless delay patient access long beyond the date of EU approval.)

US law requires sufficient valid scientific evidence in humans that high-risk devices are both safe and effective—that is, that they provide a real benefit to patients in actual use, and that their risks are well-defined. In contrast, EU approval is conducted by private companies and based on more limited evidence, often without significant studies in humans, that high-risk devices are safe and that they are mechanically fit to perform the job they are labeled to do. There is no requirement in the EU that a high-risk device provide an actual treatment benefit to patients. As shown in this report, the limited testing required in the EU can fail to predict dangerous risks and lack of effectiveness in actual use.

Box 1. Regulation of High-Risk Devices in the US and EU

| | US | EU |
|--|--|---|
| Standard for approval | Safety Effectiveness: proof of actual benefit to patients | Safety Technical performance, not benefit to patients |
| Evidence required | Valid clinical trials—generally randomized and controlled | Limited data, which may be laboratory testing, literature reviews or small clinical trials |
| Approval granted by | Central regulatory authority: FDA | Notified bodies: private, for-profit organizations chosen and hired by the manufacturer. Approval by any notified body authorizes marketing throughout EU |
| Transparency of approval decisions | Approvals and their evidentiary basis disclosed to public | Neither approvals nor evidentiary basis disclosed to public |
| Post-approval reporting requirements and transparency | Side effects and recalls must be reported to FDA and are publicly disclosed on its website | Reported side effects and recalls are not publicly disclosed. |

The EU system for approving devices has come under criticism from the European medical community because of the number of approved devices that have turned out to be dangerous or ineffective, inconsistent review standards, and the secrecy surrounding the

device approval process there. The 12 high-risk devices described here (see Box 2) demonstrate the serious risks to patients and high cost to the health care system when high-risk devices are marketed without adequate evidence of safety and effectiveness.

Box 2. Examples of dangerous or ineffective devices approved in the EU

| |
|---|
| <p>I. PleuraSeal to seal lung incisions was approved in the EU with minimal testing. Claimed to be superior to stitches in preventing air leaks and subsequent lung collapse, Pleuraseal was withdrawn worldwide after a US study showed that 3 times as many Pleura-Seal patients had air leaks as those with stitches.</p> |
| <p>II. Trilucent breast implants were approved in the EU without human testing and implanted in more than 8,000 women. After the soybean filler was found to break down into toxic compounds, causing rupture, disfigurement, and potentially cancer and birth defects, the implants were withdrawn.</p> |
| <p>III. Stent grafts to repair aortic aneurysms made by many manufacturers were approved in the EU with limited testing. When US approval was sought, FDA found that many of the devices approved in the EU presented severe risks to patients, including blood clots, graft failure, and aneurysm rupture.</p> |
| <p>IV. An elbow implant was approved in the EU after FDA told the manufacturer that it had been inadequately tested and was prone to fracture. Once marketed in the EU, many reports of implant fractures caused the manufacturer to withdraw it</p> |
| <p>V. Cardiac constraint devices to treat heart failure were approved in the EU based on limited testing. Testing to support US approval showed that the devices were no better than prescription drug therapy, but subjected patients to invasive surgery, a higher risk of operative death, and precluded necessary bypass surgery for some patients.</p> |
| <p>VI. Over 160 injected dermal fillers containing poorly tested substances have been approved in the EU, causing high rates of disfigurement, nerve damage and severe allergic reactions.</p> |
| <p>VII. The Pendra glucose monitor sensor, approved in Europe as the first noninvasive blood glucose monitoring system, was withdrawn after later studies showed that the device was inaccurate and failed to warn of dangerous blood sugar levels.</p> |
| <p>VIII. At least 12 PFO Occluders implanted in the heart to prevent strokes have been approved in the EU. Later studies conducted for US approval showed that that a PFO Occluder marketed in the EU is no more effective no more effective for stroke than blood thinning medications but, unlike blood thinning medications, cause heart perforation and other serious complications.</p> |
| <p>IX. The CoSTAR drug-eluting stent, approved in the EU with limited testing, was withdrawn from the EU when a study for US approval showed that patients more often need repeat procedures and suffered heart attacks with CoSTAR than another similar available stent.</p> |
| <p>X. The Biofield device, claimed to detect breast cancer better than mammography was approved in the EU with limited testing. FDA review showed that the company's studies failed to demonstrate that the device did, or even could, work. It was not marketed in the EU.</p> |
| <p>XI. RoboDoc, a robotic device to drill the femur for hip replacement, was approved in the EU with limited data. Later studies showed that the device caused serious complications, including tendon rupture, nerve injury, and hip implant failure.</p> |
| <p>XII. Zephyr, a valve implanted in the lung to treat emphysema, was approved in the EU to replace surgery. A later study for US approval showed that Zephyr was no more effective than surgery, but resulted in more deaths and serious complications.</p> |

The FDA believes strongly in the goal of timely and predictable access to new devices and is working to improve the efficiency of its device approval process. Timely approvals serve patients, manufacturers, and the public health, and can be achieved without sacrificing safety and effectiveness. A recent report on the success of the FDA's new drug review program shows we can have an efficient, well-funded

approval process that is a world leader in both speed of approvals and in assuring safety and effectiveness. The FDA has begun to implement changes in policy and practice that, joined with adequate resources, can greatly improve the speed and predictability of the FDA's review of devices, and expedite the availability of innovative devices.

Introduction

This report examines a series of high-risk devices that were approved in the European Union (EU) on the basis of limited scientific data and were later found to be dangerous or ineffective. The devices include:

- Inadequately tested stents for repairing life-threatening defects in blood vessels, which turned out to present severe risks to patients;
- Breast implants and cosmetic dermal fillers made from untested substances that were found to cause serious complications and require additional surgeries to repair the damage; and
- Devices to treat heart failure and emphysema that turned out to cause more deaths and injuries than standard, less-risky treatments.

Most of these devices were ultimately withdrawn from the EU market, but only after thousands of patients were harmed. In many cases, the device's risks or ineffectiveness were only discovered as the result of studies conducted to support approval in the US. None of the dangerous and ineffective devices described in this report were approved in the US.

US approval standards for devices, established by Congress in the Medical Device Amendments of 1976,¹ help to ensure that the devices available to American patients can make a real difference in their health and are not dangerous or ineffective. But the FDA's responsibility to

the public health goes farther than that. The FDA must also help make sure that patients have access to safe and effective devices as early as possible, and that innovative new devices continue to be developed. FDA's success in providing timely access has often been measured by looking at when a device becomes available in the EU compared to the US.

According to industry figures, US patients already have access to low and moderate risk devices, which constitute 80% of all devices, at least as early as EU patients. That is, these devices came on the market at an earlier date in the US than in the EU in a majority of cases.² Nevertheless, maintaining a balance between ensuring safety and effectiveness on one hand, and speed of access on the other, can be challenging. Different approaches to the balance between safety and access in the US and EU approval regimes for high-risk devices illustrate these challenges most clearly.

US law requires sufficient valid scientific evidence in humans that high-risk devices are both safe and effective—that is, that they provide a real benefit to patients in actual use, and that their risks are well-defined. The evidence of safety and effectiveness is reviewed for each device by the FDA, and the approval and the evidence relied on are publicly available. In addition, the FDA maintains a publicly available database of all reported side effects and recalls.

In contrast, the EU requires more limited evidence, often without significant studies in humans, that high-risk devices are safe and that they are mechanically fit to perform the job they are labeled to do. There is no requirement in the EU that a high-risk device provide an actual treatment benefit to patients. For example, a manufacturer might have to establish that a coronary stent to open clogged arteries was technically capable of enlarging an artery. But the manufacturer would not have to show that the stent was effective in reducing heart attacks or angina (see IX. CoSTAR Drug-Eluting Stent to Open Arteries, page 12). Because different stents perform differently in actual use, the lack of effectiveness data prevents physicians from knowing which stents will benefit their patients and which will not, and can result in the unknowing use of stents that are not as effective as others on the market.

In addition, review and approval of devices in the EU is conducted by private for-profit third-parties—*notified bodies*—chosen and hired by the manufacturer. There is no oversight by a central government authority. Approval by a notified body in any country authorizes marketing throughout the EU. Neither the approvals nor the evidence relied on by the notified bodies are publicly available. There is also no central collection of information on device side effects and those that are reported to the manufacturer and notified body after approval are generally not disclosed to the public.³

Because of the EU's lower approval standard and degree of oversight, high-risk devices are more often approved first in the EU than in the US. The lack of valid evidence of effectiveness has several negative effects on patients, however. As shown in this report, the EU's reliance on limited testing, generally without significant testing in humans, can fail to predict dangerous risks and ineffective treatment in actual use. As a result, approval of devices without a valid demonstration of effectiveness has permitted the marketing of products in the EU that turned out to cause severe

harm to patients, either because the testing was inadequate to reveal the device's risks or because use of an ineffective device denied patients access to effective treatments for serious diseases. In addition, the lack of valid data on effectiveness has caused some of the biggest EU countries to delay reimbursement for some approved high-risk devices until a second, sometimes lengthy cost-effectiveness review is completed.⁴ In those cases, EU approval of a device does not necessarily mean that it is available to patients there.

The EU system for approving devices has now also come under criticism from the European medical community because of the number of devices that have turned out to be dangerous or ineffective. The medical community has also expressed dissatisfaction with the inconsistent review standards of the private bodies that approve devices in the EU and the secrecy surrounding the device approval process there.

Concerns about device oversight in the EU have further increased with the recent revelations about the PIP breast implant, which was approved in the EU and implanted in over 80,000 women there.⁵ After approval, it was discovered that the manufacturer was using industrial-grade silicone, rather than medical-grade, causing the implants to rupture and spill the unsafe chemical into women's bodies.⁶ EU health care groups are calling on the EU to adopt a more US-like model for high-risk devices that would require a demonstration of clinical benefit to patients as well as more accountability and transparency in the approval process.⁷ The European Commission has undertaken a process to "recast" medical device regulation. Opposition by the device industry to significant changes, as well as financial constraints, may limit the changes that are made.⁸

List of Dangerous and Ineffective Devices

The following is a list of some of the devices that were approved in the EU and later discovered to be dangerous or ineffective. We developed this list using information made publicly available by manufacturers. A full list of dangerous and withdrawn devices is not possible for two reasons. First, there is no central, publicly available source of information on EU device approvals, recalls, side effects, or other relevant information about approved devices, as there is in the US. Only the manufacturers, and to a lesser extent, the applicable notified body, have complete information about a specific device and most of

it is not publicly available in any form. Second, EU requirements for reporting post-approval safety problems and recalls and for conducting post-market studies are very limited. The lack of reporting and of transparency make it difficult for anyone to gather the information necessary to determine whether a device approved in the EU is unsafe or ineffective in actual use.⁹ This partial list of dangerous and withdrawn devices nevertheless highlights the serious risks to patients when high-risk devices are approved without being required to demonstrate safety and effectiveness on the basis of adequate data.

Glossary of Terms

| |
|--|
| EU The European Union: a political and economic union of 27 independent European member states. |
| EU Approval There is no centralized EU authority that grants approval of medical devices. Instead private third parties, called notified bodies, are hired by each manufacturer to determine whether its device meets safety and performance requirements, and to bestow a “CE Mark” on the device. A CE Mark, once granted, allows marketing in all EU countries. |
| PMA Premarket Approval Application: the application to FDA for approval of high-risk medical devices. The manufacturer must demonstrate safety and effectiveness to gain approval of a PMA. |
| 510(k) An application to FDA for market clearance of medium-risk devices. The manufacturer must demonstrate that the device is “substantially equivalent” to an already marketed device. (Low-risk devices are generally exempt from premarket review.) |
| Preclinical Trial Testing that device manufacturers conduct that does not involve human subjects. This includes testing in the laboratory or in animals to see how the device functions when put under stress, how the materials affect the body, and how the device holds up over time. |
| Clinical Trial A study of a device in humans. |
| Pivotal Clinical Trial The clinical study upon which an FDA decision whether to approve a high-risk device depends—often a randomized, blinded, and controlled study. These features of a study provide more reliable results than non-randomized, unblinded, or uncontrolled studies. |

I. PleuraSeal to Seal Lung Incisions

In September 2006, the PleuraSeal Lung Sealant System received an EU approval to seal incisions following lung surgery. The device's primary purpose was to prevent persistent air leaks. This is critical after lung surgery because if a lung incision is not adequately sealed, persistent air leaks can cause the lung to collapse. PleuraSeal was already approved under a different brand name (DuraSeal) to aid in closing incisions for brain and spinal surgery. In seeking the EU approval for sealing lung incisions, the manufacturer proposed to use the same technology and claimed that the device would help to seal an incision in the lung better than the standard of care—stitches—alone. The device was marketed in the EU beginning in November 2007.

In 2007, the manufacturer also began a clinical study to support US approval of PleuraSeal. The study was designed to demonstrate its claim that PleuraSeal worked better than stitches to seal lung incisions following surgery. Instead, an early analysis of the study results found that the device was unsafe and ineffective: three times more patients who received PleuraSeal had persistent air leaks than patients whose incisions were closed using standard stitching techniques.

In October 2010, when the adverse results of the US study were revealed, the manufacturer announced a worldwide recall of all PleuraSeal lung sealant systems. PleuraSeal was removed from the market in the EU and the US study was terminated.

II. Trilucent Breast Implants

Trilucent breast implants received EU approval in 1995. Unlike the more common silicone or saline implants, the Trilucent implants used a filler derived from soybean oil, touted as safer than silicone implants because they were "natural." The EU approval was based on preclinical safety data only.

In the same year as its EU approval, the

manufacturer began a clinical study in the US to determine whether Trilucent breast implants were safe and effective. While the study was ongoing, adverse events reported in the UK revealed that the soybean oil filler breaks down in the body and leaks through the shell of the implant, causing it to rupture. This was not predicted during the preclinical testing of the device.

When the leakage and rupture problem was discovered in 1999, the US study was terminated and Trilucent breast implants were pulled from the UK market. In 2000, it was discovered that the soybean filler broke down into compounds that could cause cancer and birth defects. At that point, the UK health authority recommended that women with Trilucent implants have them surgically removed. Between 1995 and 1999, it is estimated that at least 8,000 women in the UK and other European countries received Trilucent breast implants. Many of these patients suffered severe cosmetic consequences and other adverse health effects. Trilucent breast implants were never approved in the US.

III. AAA Stent Grafts to Repair Aneurysms

An abdominal aortic aneurysm (AAA) is caused by a weakened area in the aorta, the main vessel that supplies blood from the heart to the rest of the body. When blood flows through the aorta, the pressure of the blood beats against the weakened wall, which causes it to bulge like a balloon. The larger the bulge, the more likely it is to burst, which can cause severe, often fatal, complications. AAAs can be repaired with AAA stent grafts, which are used to create new walls in the weakened area of the artery. A number of different AAA stent grafts have been approved in the EU since 1997, in each case generally before FDA received a marketing submission for the product.

FDA began to receive requests to study AAA stent grafts in the early 1990's. Although some of these devices were shown to be safe and effective in US clinical trials and subsequently

approved, FDA found during its premarket review that structural characteristics of nine of the devices already marketed in the EU presented severe dangers to patients. For these nine AAA stent grafts, the manufacturers had to suspend the ongoing study, redesign the device, initiate new studies and/or abandon the device in the US. For example, the Aptus stent graft, which incorporated a novel staple technology, was found during the US clinical trial to produce blood clots in the legs of patients. This problem had not been predicted by the testing conducted to support EU approval. During the US study of the Vanguard stent graft, the device was discovered to develop wear holes. Based on these results, the US study was terminated and the device was withdrawn in the EU.

At the same time that problems with specific stent grafts were being discovered in the US clinical trials, post-market reports in the EU identified serious consequences to patients from some of the devices on the EU market, including late rupture of the aneurysm, persistence of leaks (indicating a graft failure), continued AAA enlargement, graft obstruction, fracture, migration and kinking. Six AAA stent grafts have been permanently discontinued in the EU due to complications and three were redesigned and reintroduced.

There are currently six AAA stent grafts approved by FDA on the US market, none of which has shown the failures identified in the EU-approved devices. No FDA-approved AAA stent graft has been withdrawn from the US market for safety or effectiveness reasons.

IV. Elbow Implant

In the mid 2000s, FDA received a submission for an implanted device to be used in the repair of elbow fractures. The device used a new material and new design not previously seen in elbow implants. FDA concluded that the manufacturer had not conducted enough preclinical testing to assess safety or

effectiveness of the device for repairing elbow fractures. FDA informed the manufacturer that it believed the device could be prone to fracturing, and requested additional laboratory testing. After discussions with FDA, the manufacturer withdrew the submission from consideration.

The manufacturer proceeded to obtain an EU approval. After the elbow implant was placed on the market in the EU, the device began fracturing in patients. The fractures were caused by the parts of the device the FDA had identified as prone to fracturing and for which FDA had requested additional laboratory testing. After many reports of device fractures, the manufacturer removed the implant from the EU market.

V. Cardiac Constraint Device Technologies for Treatment of Heart Failure

Congestive heart failure is a debilitating chronic illness in which a patient's heart is unable to pump blood adequately, resulting in enlargement of the heart, worsening heart function, shortness of breath, and fatigue. Cardiac constraint devices are surgically implanted mesh coverings for the heart intended to: (1) prevent the heart from enlarging further as a result of progressive heart failure, and (2) reduce stress on the walls of the heart.

Two companies received EU approval in 2000 and 2004 for the CorCap and Paracor cardiac constraint devices based on encouraging preclinical results but little clinical data. Both companies then sought FDA approval. When the results of the completed pivotal clinical trials required for FDA approval of these devices were announced, however, they showed that cardiac constraint devices did not convincingly improve patient outcomes over the existing standard of care (non-invasive prescription drug therapy) and were associated with an increased surgical death rate. In addition, patients who had the device

implanted were not able to undergo coronary bypass surgery in the future if they needed it.

These devices were never allowed on the US market. Although they remain on the EU market they are no longer widely used there. During the course of FDA's review of the trial results, the device was presented to an Advisory Panel that also shared these concerns. In addition, this application was further reviewed by the Medical Devices Dispute Resolution Panel that voted to uphold the FDA's decision not to approve the technology. In the case of Paracor, the pivotal trial was stopped early due to futility for the primary effectiveness endpoint, which included a composite of functional status and quality of life measures important to heart failure patients.

VI. Injected Dermal Fillers for Cosmetic Use

Dermal fillers are substances injected under the skin to fill scars and wrinkles or to increase lip size. Serious complications from dermal fillers can range from cosmetic disfigurement due to movement or hardening of the filler to facial necrosis (dead tissue), nerve damage and anaphylactic shock (a severe, sometimes fatal, allergic reaction). There are currently 10 dermal fillers on the market in the US, all of which have gone through the controlled clinical testing for safety and effectiveness required for high-risk devices. Premarket testing is carried out on an average of 120 patients, and many products are also subject to long-term safety studies after marketing. Dermal fillers are approved for use in the US only by prescription.

To obtain an EU approval, dermal fillers are studied in only 10 – 20 patients with a six-month follow-up. There are currently over 160 EU-approved dermal fillers on the market in the UK alone and they can be administered by anyone from a dental hygienist to an aesthetician.

Evidence shows that a substantial number of UK patients suffer serious complications from EU-approved dermal fillers. In a survey

conducted by the British Association of Aesthetic Plastic Surgeons (BAAPS):

- Two in five plastic surgeons (38.5%) in the UK reported seeing patients in that year who had experienced complications with permanent facial fillers; and
- Almost a quarter (23%) of plastic surgeons in the UK reported having patients in that year who required surgery to correct the complications caused by permanent fillers.¹⁰

BAAPS says that the device approval standards for dermal fillers are so low in the UK that these products are less regulated than tattooing, acupuncture, and cosmetic piercing.¹¹ BAAPS members said one of the main reasons for complications from EU-approved dermal fillers was a lack of regulation which has allowed “unproven substances” to be used in the UK. They recommended that patients who want dermal fillers use only the products that have been approved in the US and make sure they are administered by a medical professional. 96% of the BAAPS membership agrees that dermal fillers should be regulated in the UK to meet the same standards as are required in the US.¹²

VII. Pendra for Monitoring Blood Glucose Levels in Diabetes

Portable blood glucose monitoring devices are used to monitor blood sugar (glucose) levels in people with diabetes. Used at home, these devices allow individuals to measure and treat fluctuations in their blood glucose levels daily. Most approved blood glucose monitoring devices require the user to draw a small blood sample. Patients and scientists, however, have long sought noninvasive methods of measuring blood glucose so patients could avoid the constant drawing of blood. Unfortunately, it has been extremely difficult to develop a device which can indirectly but accurately measure blood glucose levels. There is currently one US-approved noninvasive blood glucose monitoring system, which pulls body fluid

from the skin using small electric currents. Because it is not sufficiently accurate, however, it cannot be used by itself as a substitute for actual blood measurement. It is approved only for use in conjunction with devices that measure glucose levels from a blood sample. The Pendra glucose monitor sensor was developed in Europe as a noninvasive blood glucose monitoring system worn on the wrist and resembling a digital watch. It was supposed to produce blood glucose values through a process called impedance spectroscopy. In 2003, the Pendra received an EU approval.

The Pendra was first marketed in the Netherlands. Prior to the official launch, the company briefly marketed the device directly to Dutch patients. When a post-marketing validation study was conducted, it showed that the Pendra device had very poor accuracy, and in some cases failed to alert patients to dangerous blood glucose levels. The manufacturer withdrew the Pendra device from the EU market and acknowledged the limitations in the current design, and the considerable improvements needed to enable safe and effective patient use. Several Dutch diabetes experts published an article arguing that the Pendra approval showed that the EU approval process for blood glucose monitors needed to be strengthened with more rigorous data requirements to prevent exposing patients to potentially dangerous situations.¹⁴

The Pendra was never approved in the US.

VIII. PFO Occluders to Prevent Stroke

Patent foramen ovale (PFO) occurs when the opening that exists between the two upper chambers of the heart during fetal development fails to close after birth. PFO exists in about 20% of the population but usually does not lead to adverse health outcomes. It is thought that in rare cases PFO is the cause of unexplained stroke. In these cases, a blood clot forms in the legs or pelvis, dislodges and travels to the heart, through the

PFO, to the brain. Drugs that thin the blood, like aspirin and warfarin, are the standard of care for this condition.

PFO Occluders are tiny umbrella-like devices that are designed to be inserted into the PFO and expanded to cover the opening, thus preventing a blood clot from reaching the brain. There are at least 12 PFO Occluders approved in the EU since the 1990s for prevention of recurrent stroke of unknown cause, and tens of thousands have been implanted in patients there.

Between 1999 and 2002, FDA approved 2 PFO Occluders under Humanitarian Device Exemptions (HDEs). Under US law, an HDE is an alternative approval mechanism available only for a device that will be used in fewer than 4,000 patients. Because of the small patient population, the manufacturer does not need to show that the device is effective before obtaining an HDE. Instead, the manufacturer must show that the probable benefit to health outweighs the risk of illness or injury. The HDE indication for PFO Occluders was limited to patients with recurrent stroke of unknown cause who had failed conventional drug therapy. In 2006, both manufacturers voluntarily withdrew their HDEs for PFO Occluders after FDA determined that the patient population far exceeded 4,000 patients.¹⁵

The manufacturers have recently completed two pivotal clinical trials on the safety and effectiveness of PFO Occluders conducted to support their applications for FDA approval. Only the results of the first trial have been released by the manufacturer. These studies evaluated a PFO Occluder plus drug therapy with blood thinners against drug therapy alone. In the first of these studies, the PFO Occluder plus blood thinning medications was no better than aspirin or warfarin alone, meaning that the device provided no additional benefit to patients. In addition, patients who had the device implanted suffered blood clots, device fracture, heart perforation, fluid

around the heart, and abnormal heart rhythms that they would not have been exposed to with blood thinning medications alone. Consequently, patients who had the devices implanted endured serious risks without any demonstrated benefits. FDA did not approve these devices.

PFO Occluders remain on the market in the EU.

IX. CoSTAR Drug-Eluting Stent to Open Arteries

Coronary stents are wire-mesh tubes that are implanted in narrowed or blocked arteries in the heart with the goal of reopening the arteries to prevent heart attacks and other serious cardiac events. Drug-eluting stents are coated with a drug intended to keep the artery from reclosing. Initial small clinical studies of the CoSTAR drug-eluting stent conducted outside the US appeared to indicate that this stent would perform as well as other marketed stents. On this basis, the stent received an EU approval in 2006 and was widely used in Europe, even though other drug-eluting stents that had been shown in US studies to be safe and effective were also on the market in the EU.

A pivotal clinical trial of 1700 patients was conducted in the US to support an application for FDA approval. The results of the study, announced in May, 2007, clearly demonstrated that the CoSTAR drug-eluting stent was not as effective as another available similar product. Patients who received the CoSTAR stent more often needed repeat procedures, suffered heart attacks and died than patients who received the approved stent. Following the publication of these results, the stent was withdrawn from the European market. It was never approved in the US.

X. Biofield Device to Detect Breast Cancer

The Biofield Breast Cancer Diagnostic System is claimed by its manufacturer to detect breast cancer better than X-ray mammography. The device does not produce images but instead

measures the flow of electricity across the surface of the skin and provides results by recording variations in the number of millivolts. The device is said to indicate the likelihood of cancer by relying on differences in the ways pre-cancerous and cancerous cells in the breast conduct electricity compared to non-cancerous cells.

This device was granted EU approval in 1998. Biofield sought US approval of the device with what appeared to be promising clinical data. Several fundamental problems were discovered, however, and the manufacturer was unable to demonstrate that the device did, or even could, work. First, the manufacturer could not explain how cancer cells in breast tissue can generate enough current for the device to work. In addition, the clinical data was based on a very small sample of patients, so the positive results could have arisen simply by chance.

Most importantly, the data offered by the company that the device could detect breast cancer as well or better than mammography was scientifically invalid. The manufacturer contended that by plugging the results of each patient's test (in millivolts) into a mathematical formula (algorithm), the formula reliably identified the patients whose cells were later shown by biopsy to be cancerous. The company, however, selected the formula from several after it already knew the results of the biopsies in its trial, picking the formula that best fit with those results. To be scientifically valid, however, the formula must also be independently validated; that is, the formula must be shown to predict correctly which cells are cancerous where the biopsy results are not known ahead of time. The company failed to validate the formula, so there was no valid scientific evidence that the Biofield test could reliably detect breast cancer.

FDA requested that Biofield conduct a new prospective study, which was never carried out. The device has not been approved in the US. Biofield has apparently not marketed the

device in Europe, but is currently working to enter Asian markets.¹⁶ The consequences for women of replacing mammography with unproven technology are potentially very serious, including higher rates of false negatives resulting in unnecessary deaths, and false positives resulting in unnecessary surgeries.

XI. RoboDoc for Hip Surgery

RoboDoc is a computer-assisted robotic milling machine for use in hip implant surgeries. It is used to drill out the femur to make a hole for the hip implant, a procedure traditionally carried out by the surgeon manually. RoboDoc received an EU approval in 1996 and was put on the EU market. The manufacturer sought US marketing clearance, but the FDA did not clear the device at that time because clinical data demonstrating the safety and effectiveness of the device was lacking.

Papers published in the EU after its marketing there showed that RoboDoc was associated with a high rate of complications compared to manual implantation.¹⁷ Some of the complications were very serious, resulting in a series of lawsuits by patients. Complications included tendon rupture, nerve injury, infection, higher rates of device failure, recurrent hip dislocation, and need for reoperation. At the same time, the RoboDoc-assisted surgeries did not have better outcomes than manually assisted surgeries.¹⁸ There were also reports that use of the device in hip replacements was associated with post-operative gait abnormalities. Usage of RoboDoc in the EU dropped significantly following these reports.

In August 2008, after the FDA determined that a series of software updates had resulted in improved device performance, a new-generation RoboDoc received FDA marketing clearance.

XII. Zephyr for Emphysema

Emphysema is a chronic, debilitating disease that causes difficulty breathing. In emphysema

patients, the small airways in the lungs collapse during exhalation. As a result, airflow is blocked and air becomes trapped in the lungs. The Zephyr device is a removable one-way valve that is implanted into the diseased lobe(s) of the lungs of emphysema patients. The Zephyr valve is intended to limit the amount of air entering the diseased portion of the lungs while still allowing trapped air to escape. It was created as an alternative to the option of lung volume reduction surgery, which was considered riskier.

The Zephyr received an EU approval in 2003 and its manufacturer launched the product in the EU on a limited basis. The company then sought FDA approval in 2007, based on the results of a pivotal clinical trial in 221 patients. The trial compared safety and effectiveness of the Zephyr to surgery, which is the standard treatment. The clinical trial results showed that the patients receiving the Zephyr valve had much less improvement than expected over the surgical patients at 6-months post surgery and no increased benefit at all over the traditional surgical patients at 1 year. At the same time that they received no additional benefit from the device, patients in whom the device was implanted had an increased risk of death, serious adverse events, and hospitalizations compared to patients receiving traditional surgery.

In 2008, an FDA Advisory Panel recommended against approval of the Zephyr because the marginal benefits did not outweigh the substantial risks to patients. The FDA denied approval for the Zephyr in 2009.

The manufacturer plans to resubmit a new version of the Zephyr for FDA approval after performing a new pivotal clinical trial addressing the deficiencies identified by FDA and the Advisory Panel.

The Zephyr remains on the market in select EU countries.

Conclusion

A sound approval system for high-risk medical devices should ideally provide two benefits to patients. First, it should make sure that patients receive devices that improve their lives without subjecting them to unnecessary risks. Second, it should provide access to important therapies without unnecessary delay. Because it takes time to produce sound evidence that a device is beneficial and that its benefits outweigh its risks, requiring evidence of safety and effectiveness and providing early access are sometimes in tension. This tension raises questions about the value to patients and society of pre-approval substantiation of safety and effectiveness and of whether producing this evidence as a prerequisite to marketing constitutes an “unnecessary delay.” The US and the EU systems approach these questions differently. US law requires that solid evidence showing the benefits and risks of a high-risk device be weighed before it is widely marketed, while EU law requires far less evidence.

This report examines actual cases to help answer the question of what can happen when high-risk devices are allowed to be marketed without substantiation of safety and effectiveness. The 12 high-risk devices described here were approved in Europe under the EU’s less rigorous approval standards and then later found to be dangerous and/or ineffective after they were marketed.

All were approved relatively quickly because little or no clinical data was required and the manufacturers were allowed to market them without first showing that the devices benefited patients. For these devices, however, the cost of quick approval was much higher than expected and was borne by patients and by the health care system. Devices like the withdrawn AAA stents for aneurysms, the cardiac constraint devices for heart failure, and the CoSTAR stent

to open heart vessels cost European patients’ lives without providing any health benefits. Others like the Trilucent breast implant, the elbow implant, and the RoboDoc for hip surgery inflicted serious injuries and required costly additional surgeries to repair the damage they caused.

In many cases, the dangers of these EU-approved devices were not discovered until the manufacturers had to conduct the clinical studies needed to support US approval of a high-risk device. These scientifically robust studies revealed what the limited studies relied on for EU approval could not:

- That the testing to show the devices’ technical performance did not accurately predict whether the devices would provide a benefit to patients in actual use; and
- That patients who received the devices were dying or being injured at higher rates than those patients receiving better-established treatments.

For some of these devices, even the widespread marketing of these devices and exposure of thousands of patients did not reveal their dangers—the dangers were discovered only when the devices were subjected to valid studies in the US. This is because it is difficult to discern the true benefits and risks of a device when there is no control group to make valid comparisons.

The FDA believes strongly in the goal of timely and predictable access to important new devices and recognizes the need to improve the efficiency of its device approval process. Timely approvals serve patients, manufacturers, and the public health, and can be accomplished without sacrificing safety and effectiveness. The experiences described in this report show

that lowering standards of approval for devices in order to speed access can jeopardize patient health and impose high but often hidden costs on both patients and the health care system. However, other changes in policy and practice that do not jeopardize patient health, together with adequate resources, can substantially improve the speed and predictability of the FDA's review of high-risk devices, and expedite the availability of important new devices. As recently described in a report on innovative drug approvals, the FDA's program for review of new drugs provides an example of an efficient, well-funded approval process that is both the fastest in the world and a world leader in assuring safety and effectiveness.¹⁹

The FDA has already proposed or implemented a series of policies and practices enhance the timeliness and predictability of the device approval process and support innovation.²⁰ These actions are designed to:

- Improve transparency, interaction, and collaboration during device review;
- Assure appropriate balancing of benefits and risks in deciding whether to approve individual devices;
- Implement efficient processes and use of resources to speed reviews; and
- Assure predictable and consistent recommendations, decision making, and application of the least burdensome principle.

In 2011, the FDA published an ambitious series of relevant draft guidances and standard operating procedures (SOPs). For example, draft guidances and SOPs were issued:

- Creating a patient-centric framework for benefit-risk determinations
- Allowing early clinical trials to start sooner in the US;
- Assuring that prior advice given to a manufacturer is not changed midstream without supervisory approval;
- Clarifying how manufacturers can appeal device decisions,
- Providing device-specific guidance designed to facilitate the development of such forward-looking devices as mobile applications and artificial pancreas systems; and
- Exempting 30 types of in vitro diagnostics and radiology devices from having to submit 510(k)s.

These actions—geared toward a system of smart regulation—have already started to have a visible, positive impact on our pre-market programs, and we expect that positive trend to continue as we proceed to implement the improvements we have committed to make. With adequate resources and a system of smart regulation, the US can have a timely, predictable review process without sacrificing patient health or safety.

Endnotes

1. See ... *(insert reference text here ... OEA will provide)* ... for a brief summary of the US regulatory system for low, moderate, and high-risk medical devices.
2. California Healthcare Institute and The Boston Consulting Group, "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry," Fig. 15 (Feb. 2011), available online at <http://www.bcg.com/documents/file72060.pdf>.
3. See, Cohen D, "Medical Devices: Europeans are left to their own devices," *British Medical Journal* 2011;342:d2748, available online at <http://www.bmj.com/content/342/bmj.d2748.full.pdf>.
4. See [Medicaldevice-network.com](http://www.medicaldevice-network.com), Payback Time, Dec. 10, 2008, available online at <http://www.medicaldevice-network.com/features/feature48597/>: (In Germany, decisions permitting reimbursement for many innovative devices "take years". In France, some innovative devices cannot be marketed until they are included on a reimbursement list and this process can take "three to four years." In Italy, payment for new devices is generally delayed by "500-800 days.") See also International Society for Pharmacoeconomics and Outcomes Research, ISPOR Global Health Care Systems Road Map, available online at <http://www.ispor.org/htaroadmaps/FranceMD.asp>.

5. European Commission Press Release, Medical Devices: European Commission asks for further scientific study and draws first lessons from the recent fraud on breast implants, Feb. 2, 2012, available online at <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/12/96&format=HTML&aged=0&language=EN>.
6. Bloomberg Businessweek, "Faulty French Breast Implants May Upend U.S. Device Debate," Jan. 19, 2012, available online at <http://www.businessweek.com/news/2012-01-19/faulty-french-breast-implants-may-upend-u-s-device-debate.html>.
7. See Editorial, "Offline: The scandal of device regulation in the UK." *The Lancet*, published on line January 18, 2012, DOI:10.1016/S0140-6736(12)60070-1, available online at [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(12\)60070-1/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60070-1/fulltext). Fraser, et al, "Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform," *European Heart Journal*, May 2011, available online at <http://eurheartj.oxfordjournals.org/content/32/13/1673.full.pdf> "Medical Devices: European Patients Are Left to Their Own Devices," *supra*, *British Medical Journal* 2011; 342:d2748; see also Fiona Godlee, "Editorial: The Trouble With Medical Devices," *British Medical Journal* 2011; 342:d3123, available at <http://www.bmj.com/content/342/bmj.d3123.full>; Carl Heneghan et al., "Medical-Device Recalls in the UK and the Device-Regulation Process: Retrospective Review of Safety Notices and Alerts," *BMJ Open* (May 2011), available at <http://bmjopen.bmj.com/content/early/2011/05/12/bmjopen-2011-000155.full.pdf>; "The pre-market clinical evaluation of innovative high-risk medical devices," KCE reports 158C, Belgian Health Care Knowledge Centre, 2011, available at http://www.kce.fgov.be/index_en.aspx?SGREF=202677.
8. "Europeans are left to their own devices," *supra*, *BMJ* 2011;342:d2748; Manthei et al, "Future Medical Device Regulation in the European Union: Prospects for Reform," *Medical Device and Diagnostic Industry*, Oct. 19, 2011, available online at <http://www.mddionline.com/article/future-regulation-medical-devices-european-union-prospects-reform>.
9. Thompson et al, Analysis: Medical device recalls and transparency in the UK, *British Medical Journal*, 2011;342:d2973 (May 14, 2011), available online at <http://www.bmj.com/content/342/bmj.d2973>.
10. BAAPS, 1 in 4 surgeons fixing botched permanent filler ops, *British Association of Aesthetic Plastic Surgeons Offers Safety Guidelines for Injectables* (June 2009), available online at <http://www.baaps.org.uk/about-us/press-releases/491-1-in-4-surgeons-fixing-botched-permanent-filler-ops>.
11. BAAPS, Surgeons' demands published in *British Medical Journal: Fillers Less Regulated than Tattooing and Acupuncture - Call to Make Them Prescription* (July 2009), available online at <http://www.baaps.org.uk/about-us/press-releases/498-surgeons-demands-published-in-british-medical-journal>.
12. *Id.*
13. Shareholder letter of Pendragon Medical AG (2004), available online at <http://www.progressnow.com/news/default.asp?page=4&order=news%5Fstart%5Fdate&cat>; Statement concerning the report in "10 vor 10" on 2 September 2004 on Pendragon Medical AG, a portfolio company of ProgressNow! invest AG (2004) <http://www.progressnow.com/news/default.asp?page=3&order=news%5Fstart%5Fdate&cat>.
14. Wentholt IM, Hoekstra JB, Zwart A, DeVries JH, Pendra goes Dutch: lessons for the CE mark in Europe. *Diabetologia*, 2005 Jun;48(6):1055-8. Epub 2005 May 4, available online at <http://www.ncbi.nlm.nih.gov/pubmed/15871008>.
15. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm135747.htm>.
16. Biofield Corporation's 51% Owned Subsidiary Agrees to Deal Appointing McKinley infocapital as Korean Exclusive Distributor of Breast Cancer Diagnostic System, April 8, 2011, http://www.mackaylifesciences.com/v2/index.php?option=com_content&view=article&id=149:biofield-corporations-51-owned-subsidiary-agrees-to-deal-appointing-mckinley-infocapital-as-korean-exclusive-distributor-of-breast-cancer-diagnostic-system-contract-has-potential-value-of-up-to-153-million&catid=42:newsroom&Itemid=176.
17. Honi, M et al, Comparison of Robotic-Assisted and Manual Implantation of a Primary Total Hip Replacement: A Prospective Study. *J Bone & Joint Surgery*, 2003; 85:1470-1478; Schulz AP, Seide K, Queitsch C, et al. Results of total hip replacement using the Robodoc surgical assistant system: clinical outcome and evaluation of complications for 97 procedures. *Int J Med Robot*. 2007 Dec;3(4):301-6; Schrader P. Consequence of evidence-based medicine and individual case appraisal of the Robodoc method for MDK and the malpractice management of insurance funds and the principles of managing innovations. *Gesundheitswesen* 2005; 67(6):389-395.
18. *Id.*
19. FDA, FY 2011 Innovative Drug Approvals, Nov. 2011, available online at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm>.
20. FDA, Medical Device Pre-Market Programs: An Overview of FDA Actions, Oct. 19, 2011, available online at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM276332.pdf>.