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Review Article

Medical Device Regulation: A Comparison of the United States and the European Union

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| Travis G. Maak, MD  James D. Wylie, MD, MHS |  |
| Abstract  Medical device regulation is a controversial topic in both the United States and the European Union. Many physicians and innovators in the United States cite a restrictive US FDA regulatory process as the reason for earlier and more rapid clinical advances in Europe. The FDA approval process mandates that a device be proved efficacious compared with a control or be substantially equivalent to a predicate device, whereas the European Union approval process mandates that the device perform its intended function. Stringent, peer-reviewed safety data have not been reported. However, after recent high-profile device failures, political pressure in both the United States and the European Union has favored more restrictive approval processes.  Substantial reforms of the European Union process within the next 5 to 10 years will result in a more stringent approach to device  regulation, similar to that of the FDA. Changes in the FDA  regulatory process have been suggested but are not imminent. |

From the Department of Orthopaedics, University of Utah School of Medicine, Salt Lake City, UT.

Dr. Maak or an immediate family member is a member of a speakers’ bureau or has made paid presentations on behalf of Arthrex and serves as a board member, owner, officer, or committee member of the American Orthopaedic Society for Sports Medicine. Neither Dr. Wylie nor any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article.

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edical devices are essential to the practice of orthopaedic surgery. The medical device industry is an economic driver in both the United States and the global econ- omy. The US medical device market is the largest in the world and is ex- pected to reach $133 billion in annual sales by 2016.1 Orthopaedic devices made up the largest segment of this

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market (21%) in 2013.1

The regulation of medical devices throughout the world evolved at dif- ferent times as the result of societal pressures. In the United States, regula- tion began in the 1970s after a gov- ernment report cited .10,000 injuries from medical devices. During this same era, the Dalkon Shield intrauterine device caused .200 septic second- trimester abortions and 11 maternal deaths.2 These events led to the Med- ical Device Amendments of 1976, which gave the US FDA the authority

to regulate medical devices.3 In the European Union (EU), the Medical Device Directives were passed in the 1990s. Before this legislation, the European medical device regulatory process varied among countries.4 Recently, the FDA has been criticized for delays in approval, whereas the EU system has been criticized for lax device approval and the inability to gather meaningful data.5

# US Food and Drug Administration Regulatory Process

Regulatory Structure

In the United States, medical devices are regulated by the Center for Devices and Radiological Health in the FDA. The FDA oversees all aspects of device regulation, including approval and postmarket surveillance. The FDA is a



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large governmental agency, and the device-regulating aspect of the agency was created for the purpose of pro- tecting the public’s health.6

# Device Classification

Most devices are classified according to their level of risk, ranging from class I (lowest risk) to class III (highest risk). One exception, the humanitar- ian device exemption, applies to devices designed for a market with

,4,000 patients per year in the United States and no comparable device and/or other pathway for the device to be introduced to the mar- ket. These devices must be consid- ered likely to be safe, and their probable benefits must outweigh their probable risks. An institution using a device classified under the humanitarian device exemption must have a study of its use approved by the Institutional Review Board, and data on its use should be col- lected in a manner similar to the collection of data in a clinical trial.

Class I devices include low-risk devices, such as stethoscopes and tongue depressors. They are assumed to be safe and effective if the tenets of good manufacturing practices, proper labeling, and adequate pack- aging and storage are followed. Class II devices are medium-risk devices, such as sutures and bone wax. They are more complex and must be proved to perform as expected. They generally are approved through a premarket notification requirement known as 510(k) clearance (after the section of the Food, Drug, and Cos- metic Act that requires this clearance). These devices must meet performance standards, and the manufacturer must conduct postmarket surveillance. Class III devices are high-risk devices that require stringent safety and efficacy data for FDA approval unless they can be proved to be substantially equiva- lent to a predicate device (ie, a device in use before 1976 or with proved safety

and efficacy). Examples of class III devices include joint arthroplasty implants and spinal implants.

# Device Approval

Because of their low risk, class I devices are approved without any clinical or preclinical data on the basis of their assumed safety and efficacy. Class II devices are approved through the 510(k) clearance process. These devices commonly have pre- clinical data that demonstrate that they perform their intended function, but clinical efficacy data often are not available. Class III devices require premarket authorization (PMA). This process requires an investiga- tional new device (IND) application and a small safety trial. The key aspect of the IND application is a prospective clinical trial in which the IND is compared with the standard of care. These trials are typically ran- domized, can cost millions of dollars, and can require several years to complete. However, if high-risk devices are deemed substantially equivalent to an existing device, they can be approved through the 510(k) clearance pathway. Most device applications are processed through the 510(k) pathway, which receives 4,000 applications per year, compared with

,100 PMA applications per year.7 The mean cost from concept to approval reported in an industry survey was $31 million for devices approved through the 510(k) process and $94 million for devices approved through PMA,8 demonstrating the motivation for companies to have devices deemed substantially equiva- lent and therefore eligible for 510(k) clearance. Devices that have no predicate device and are a new device type are automatically classified as class III and can be approved through the so-called de novo classification process. This process provides a pathway to classification as class I or class II if the determination can be

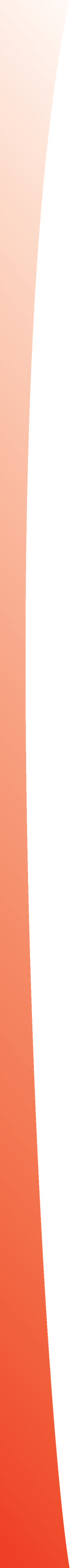
made that general controls, such as a 510(k), or general plus special con- trols, such as a 510(k) plus a specific guideline for use or special labeling, provide reasonable assurance of the safety and effectiveness of the device.9

# Postmarket Surveillance

Postmarket surveillance was outlined in the Safe Medical Devices Act of

1990.10 This act required healthcare facilities to report serious device- related injuries or deaths to manu- facturers and the FDA. It also allowed the FDA to mandate device tracking or a postmarket registry or clinical trial if deemed necessary. The FDA receives 80,000 to 120,000 adverse-event reports annually.7,11 Because the reporting system is vol- untary for healthcare providers and consumers, adverse events are thought to be substantially under- reported. Patients, providers, and other healthcare workers can report adverse events through the FDA MedWatch reporting program.12-14 MedWatch receives approximately 5,000 reports annually, with nurses being the most common reporters at 25% and physicians providing only 8% of reports.7 FDA investigations based on these reporting systems can lead to public health advisories, safety alerts, and product suspen- sions or withdrawals.

An interesting group of products commonly used in orthopaedics is allograft tissue. These products are termed “361” products because they are defined in section 361 of the Public Health Service Act. These tis- sues are minimally processed and intended for homologous use. They cannot be a cell or tissue combined with another tissue that would raise safety concerns. They cannot be combined with another drug, device, or biologic agent or tissue. They cannot rely on living cells for function and cannot have a systemic effect.15 If these conditions are met, they are not



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subject to the PMA process.16 Therefore, data on clinical efficacy of these products are generally limited to independent postmarket clinical stud- ies. Motivation is limited for manu- facturers to investigate efficacy because these products can be approved for use without efficacy data provided that they meet the previously stated requirements. Examples of these products commonly used in ortho- paedics are tendon grafts for ligament reconstruction, allograft bone and demineralized bone matrix products, particulate juvenile articular cartilage allograft, and fresh osteochondral allografts.

# European Union Regulatory Process

Regulatory Structure

The regulatory structure in the European Union is fundamentally different from that in the United States. The current uniform process

has been in place since the 1990s and

devices are those deemed relatively low risk to humans. Examples of class IIa devices include intravenous pumps and electronic wheelchairs. Class IIb devices pose a relatively high risk of harm to the human body. Class III devices are deemed the highest risk of harm to patients and endanger the patient’s life or involve electricity to function.

# Device Approval

In a process similar to that of the US FDA system, class I devices are approved in the European Union on the basis of the manufacturer’s declaration of conformity with essential require- ments, including good manufacturing practices, proper labeling, and ade- quate packaging and storage. Class IIa devices require a submission to a notified body. For class IIa devices, the notified body commonly requires a literature review combined with pre- clinical data demonstrating that the device performs its intended function. However, the specific notified body

determines the requirements. Gener-

postmarket surveillance of safety. Since 2011, inclusion of all adverse events in the European Databank on Medical Devices (Eudamed) has been mandatory. Eudamed also lists the manufacturers of approved devices; the history of certificates issued, revised, withdrawn, or refused; and ongoing clinical investigations of the device. The notified body can require companies to perform postmarket studies as part of the CE mark certi- fication if the long-term safety of the device is unknown.

# High-profile Medical Device Failures

Recent high-profile medical device failures in both the United States and the European Union have brought medical device legislation to the forefront of efforts to ensure patient safety and have been widely reported in the press. One prominent recent example in orthopaedics is the metal- on-metal hip arthroplasty implant.

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was established to encourage inno-

ally, class IIa devices take 1 to 3 months

Ardaugh et al

detailed the 510(k)

vation and to strengthen the industrial process across Europe. Private com- panies called notified bodies regulate device approval.17 The European Union certifies the notified bodies, and .70 notified bodies are currently functioning. These for-profit compa- nies engage in contracts with device companies to regulate device approval. They grant the Conformité Européenne (CE) mark, which allows the device to be marketed in all EU countries.17 Postmarket surveillance of safety is regulated by national competent authorities, which are government agencies in each of the countries of the European Union.

# Device Classification

Device classification in the European Union is similar to that of the US FDA system. Class I devices are those with minimal risk of harm. Class IIa

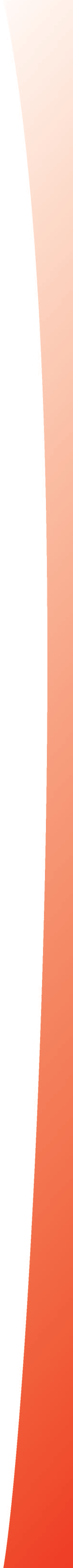
to obtain approval. Class IIb, which encompasses most orthopaedic devices, and class III also require a submission to a notified body. These submissions include clinical and preclinical evidence supporting the device’s safety and performance. The supporting evidence typically includes a literature review of similar approved devices along with clinical data supporting the safety and performance of the device. The clinical studies are typically nonrandomized single-arm case series with historic control subjects. For all device approvals in the European Union, the specific notified body that is contracted by the device manufacturer within the approving country determines the specific requirements.

# Postmarket Surveillance

The competent authorities in each of the EU countries are in charge of

clearance ancestry of the DePuy

ASR metal-on-metal hip arthro- plasty system, which was approved without clinical safety or efficacy data. The authors compared the implant to 95 different, previously marketed devices to justify that the characteristics of the implant were substantially equivalent to those of predicate devices. Although the implant was approved through this process, it had substantially higher revision rates than other contempo- rary hip implants that also had proceeded to the market without a clinical trial proving safety or effi- cacy. Metal-on-metal hip arthro- plasty implants had a similar fate in the European Union, where they were also approved without clinical trials demonstrating safety or efficacy. Implantation of these devices led to a 5-year revision rate more than four times that of other contemporary hip



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arthroplasty implants and a sub- sequent global recall of the product.18 Other devices that gained the CE mark in the European Union were unable to gain approval from the US FDA. One example is an elbow implant for the treatment of radial head fractures.19 The FDA voiced concerns to the company on review of the application for FDA approval because of the concern of implant fracture. The company subsequently withdrew the FDA application and received a CE mark in Europe. After the implant reached the market, clin- ical evidence of fracture rates led to its removal from the EU market.19 These orthopaedic devices are examples of device failures that have led the pop- ular press and the public to question the safety of medical device regulation.

# Comparison of the Regulatory Systems of the United States and the European Union

The differences between the US and EU regulatory systems start with their inception. The Medical Device Amendments of 1976 and the FDA regulation of devices were motivated by patient safety concerns in the 1970s in the United States. The Medical Device Directives in the European Union were motivated by the unifica- tion of the EU market, which aimed to strengthen innovation and the indus- trial process across Europe. Whereas the US FDA process requires that companies deal directly with the gov- ernmental regulatory body charged with protecting the public’s health, the EU system requires device manufac- turers to work with private notified bodies. Some authors have questioned whether the notified bodies are more interested in getting devices to market than in protecting the health and safety of the public.4,20-22

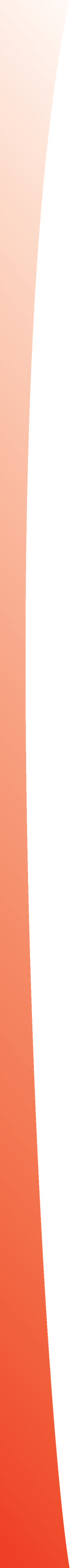
The largest apparent difference between the systems is the potential

opportunity to shepherd novel devices to patients more quickly in the EU system than in the US system.8 Historically, devices have had an easier path to approval in the Euro- pean Union than in the United States because of the difference between the evidence required to obtain a CE mark and that required to obtain US FDA PMA approval. The CE mark requires proof of the device’s performance, whereas US FDA approval of a PMA application requires proof of the device’s safety and efficacy.4 The EU requirement of proof of performance can be accomplished with a single-arm case series, whereas the FDA requirement of proof of efficacy requires large studies involving comparison of patients treated with the device to a control group representing the cur- rent standard of care. Although not an orthopaedic device, an excellent example of this difference is the GuardWire (Medtronic) device.23 To receive the CE mark, the manufac- turer used a 22-patient case series to prove that the device could perform the function of aspirating embolic debris distal to an angioplasty pro- cedure in a saphenous vein graft. Conversely, proof of efficacy for FDA approval required an 800- patient randomized, controlled clinical trial demonstrating that the use of the device reduced 30-day embolic complications of angio- plasty of a saphenous vein graft.24 The cost difference between the studies required in the United States and in the European Union is dra- matic and possibly prohibitive to companies desiring approval in the United States.

In addition to being more expensive than the EU process, the US FDA process takes a much longer time because of the need to complete these studies; therefore, the time to get the device to patients is longer. An industry survey published in 2010 reported that the average time to US

FDA approval was 31 months through the 510(k) pathway and 54 months through the PMA pathway, from first contact with the FDA to device approval.8 In the EU system, approval of similar devices took 7 months and 11 months, respectively.8 This survey was not published in the peer-reviewed literature and was fur- ther restricted by a 20% response rate among device manufacturers.8 The low response rate may represent a substantial selection bias in the com- panies that responded to the survey. Nonetheless, the substantial cost and time constraints result in large barriers to innovation and device availability in the United States.

Despite the longer time to market, no definitive studies prove that the US FDA process is safer than the EU pro- cess. The only report comparing recalls in the two systems was a non–peer- reviewed report funded by AdvaMed, a trade association representing the medical device industry. This report suggested that FDA-approved and EU-approved devices had no differ- ence in device recalls between 2005 and 2009.25 The study of device safety has been hindered by the fact that the European Union had no central reporting of device recalls and safety- related events before Eudamed was established in 2011. In a study done in the United Kingdom, Heneghan et al26 reported that the number of field safety notices increased from 62 in 2006 to 757 in 2010. The authors attempted to determine differences in the approval of these devices but found it difficult to procure data from device manufacturers in the EU system because only 2% of the man- ufacturers provided approval and review data when asked, as a result of the lack of legal requirement.26 Whereas the FDA process for device regulation is relatively transparent, the EU system requires only a contract between the device manufacturer and a notified body with no requirement of public access to device approval



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decisions. The FDA recently published a list of devices that did not obtain FDA approval but were approved and subsequently recalled in the European Union.19 To date, no thorough peer- reviewed studies have compared the safety of the US FDA and EU systems. Nevertheless, multiple orthopaedic devices that have proved to be effi- cacious and safe in extensive experi- ence in the European Union, such as devices for matrix-assisted cartilage repair, are unavailable in the United States.27,28

Although the CE mark is most commonly compared with the US FDA PMA process, most medical devices in the United States are approved through 510(k) clearance. Because the 510(k) clearance process requires little or no clinical data, most device recalls (71%) in the United States are of 510(k) products.5 Among these device recalls, 16% were of class III prod- ucts.5 The Institute of Medicine stated that the 510(k) process does not ensure safety or efficacy and recom- mended a new regulatory framework for medical devices.29 The fact that most devices do not go through the PMA process in the US FDA system may contribute to the difficulty of finding differences in safety or recalls between the US system and the cur- rent EU system. Table 1 outlines the major differences between the two systems.

# Upcoming Changes to the Regulatory Process of the European Union

The high-profile device failures in the European Union have resulted in a recent push for changes to the EU regulatory system. A report from the United Kingdom’s Committee on the Safety of Devices concluded that, in the European Union, devices reach patients without clinical trials proving safety and efficacy.30 The report sug- gested that more centralized regulation

of the notified bodies that approve devices would improve the current system. Other groups have also ques- tioned the role of the notified bodies in the approval process and have identi- fied the notified bodies as the weakest link in the EU system.20 In fact, an investigative report found that a ficti- tious hip implant with very poor per- formance properties was approved through certain notified bodies in the EU system.21

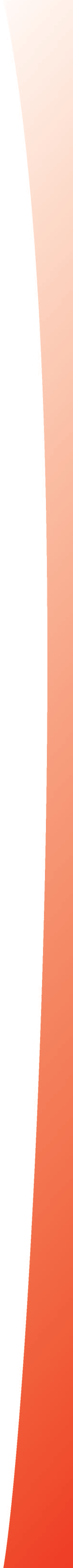
The call for change has led to the drafting of new European medical device regulations for future im- plementation within the next 5 to 10 years, which will represent a sweeping change in regulatory approval in the European Union.31 The im- plementation of these changes will rectify many of the fundamental dif- ferences between the US and EU sys- tems. The European Commission will be able to review all applications for the CE mark before approval. Only newly created, special notified bodies will be able to approve high-risk devices and implants. The govern- mental competent authorities will be able to audit notified bodies, and notified bodies will be able to audit device manufacturers. Unique device identification will become a part of Eudamed to allow tracking of the outcomes of implanted devices.31 Because preliminary data from devices previously approved in the European Union are commonly used to justify device approval in the United States, these reforms may subsequently affect device availability in the United States, as well.

# Clinical Problems Encountered in Orthopaedics

The practicing orthopaedic surgeon does not commonly interact with the device regulation system; however, clinical questions related to device approval can arise. For example, how

would a surgeon obtain approval for a custom-made implant that is not approved by the FDA? Physicians can order a custom patient-centric or physician-centric device from a manufacturer. Patient-centric custom devices in orthopaedics include implants for patients with abnormal anatomy, such as custom joint implants specifically constructed for patients with skeletal dysplasia. Physician-centric custom devices include devices or machines that the physician uses to provide care for patients. An example of a physician- centric custom device would be a surgical instrument that is custom made to accommodate deformity of a surgeon’s hand. Section 520(b) of the Food, Drug, and Cosmetic Act reg- ulates the use of custom devices in the United States. For a product to be considered a custom device, the conditions detailed in Table 2 must be met. Both new devices and mod- ifications of existing devices can qualify as custom devices. Companies are not permitted to market these devices because they are custom built on the basis of the physician’s order. An annual report submitted to the FDA each year must include the number of all custom devices distrib- uted, the number of patients who received a custom device or had one revised, and a report of any custom devices returned or destroyed. The annual report must also justify why each custom device was needed and how it meets all of the parameters in Table 2.

Another clinical situation that may arise in orthopaedic practice is the need for implants that are used in other areas of the world but are not FDA approved for use in the United States. This situation may arise when a device that was implanted elsewhere requires a partial revision in the United States. For example, a polyethylene liner in a joint implant that is not FDA approved and is otherwise functioning well may require replacement. This clinical



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Table 1

Differences in Device Regulation in the United States and the European Union

Factor United States European Union

Purpose/structure The FDA is a government agency

mandated to protect the public’s health.

Centralization The FDA regulates device approval and surveillance under one umbrella.

Funding Federal appropriations provide .80% of funding. User fees provide approximately 20% of funding.

Notified bodies regulate device approval as private companies. Competent authorities are government agencies that regulate postmarket surveillance of safety and facilitate trade among countries of the European Union.

More than 70 notified bodies regulate device approval separately. A competent authority in each of the countries of the European Union is tasked with device safety and surveillance.

Notified bodies are completely funded by contracts with device manufacturers. Funding of competent authorities varies by country.

Data requirement for approval

A device must prove to be safe and efficacious through premarket authorization approval or prove to be substantially equivalent to a predicate device through 510(k) clearance.

Proof is required that the device can perform its intended function.

Premarket transparency Proprietary limits exist on the sharing of

information, but safety and approval data are shared through the FDA.

Device surveillance Reporting by manufacturers and

healthcare institutions to the FDA is mandatory. Reporting by healthcare professionals and consumers is voluntary. The FDA can issue public

health advisories, safety alerts, and

product suspensions or withdrawals.

Approval decisions of the notified bodies are not made public.

Manufacturers must submit adverse events to competent authorities. All adverse events have been required to be submitted to the European Databank on Medical Devices since 2011. Postmarket data are shared among competent authorities but not with the public. Competent authorities can issue adverse-event reports and field safety notices or device recalls.

Table 2

US FDA Conditions for Custom Devices

that is unregulated or not legally marketed. In this scenario, the phy-

sician assumes full responsibility for

The device must be created or modified because of an order from a physician.

The device must not be generally available in the United States.

The device must be designed to treat a unique pathology or physiologic condition that no other device is domestically available to treat.

The device must treat a condition that is sufficiently rare that clinical investigation would be impractical.

No more than five units of the device are used per year.

The manufacturer must submit an annual report of the device to the FDA.

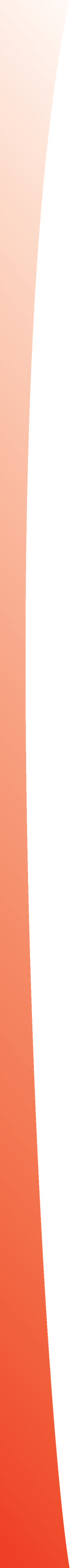
the decision. Because of the potential for substantial legal ramifications, this circumstance typically requires approval on a case-by-case basis by the treating physician’s hospital, Institutional Review Board, and/or practice.

scenario falls under the “practice of medicine” regulated by section 1006 of the Food, Drug, and Cosmetic Act.32 In this situation, the physician is permitted to use an implant that is not FDA approved to partially revise the implant that was placed elsewhere. However, state laws on the use of nonapproved medical devices differ,

and clinicians should investigate the applicable laws before proceeding with the use of these devices. If state law allows, the medical professional can use a nonmedical device, which is a device that is not classified or cur- rently used in medicine but may address a specific medical/surgical need or purpose, or a medical device

# Summary

The medical device industry is a strong economic driver worldwide. The approval processes for medical devices have historically differed between the US FDA and the EU system, although postmarket surveillance programs are similar. A difference in safety between the two systems has not been



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demonstrated, likely because most devices approved by the FDA in the United States go through the 510(k) clearance process and not the more stringent PMA process and because the availability of safety data in the EU system is limited. However, in response to recent high-profile device failures, political pressures have driven substantial reforms of the device approval system that will likely be im- plemented in the European Union within the next 5 to 10 years. The effect of these reforms on device availability and innovation worldwide remains unclear. Calls for reforms in the US FDA device approval process, specifi- cally in the 510(k) clearance process, have not led to discernible changes in device regulation. For patients with rare conditions, custom devices or devices available under the humani- tarian device exemption can be ob- tained if certain conditions are met. More research is needed to understand the safety and efficacy of both the US FDA and EU regulatory systems.

# References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, reference 1 is a level I study. References 5, 22, 25, and 27 are level IV studies. Refer- ences 1, 2, 4, 6, 7, 9-17, 19-21, 26,

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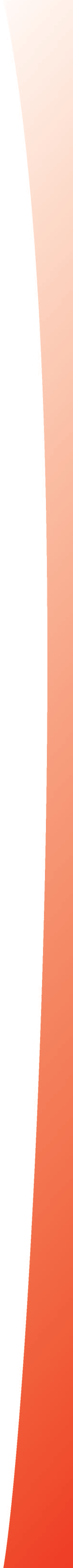
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