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TRANSLATIONAL TOOLBOX

Drugs and Devices

Comparison of European and U.S. Approval Processes

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SUMMARY

The regulation of medical drugs and devices involves competing goals of assuring safety and efficacy while providing rapid movement of innovative therapies through the investigative and regulatory processes as quickly as possible. The United States and the European Union approach these challenges in different ways. Whereas the United States has always relied on a strictly centralized process through 1 agency, the Food and Drug Administration (FDA), the European Commission synchronized the regulations of 28 different countries as they combined to create the European Union. The FDA historically developed as a consumer protection agency, whereas the regulations from the European Commission arose out of a need to harmonize inter-state commercial interests while preserving national "autonomy." Thus, whereas the FDA has the advantages of centralization and common rules, the European Union regulates medical drug and device approvals through a network of centralized and decentralized agencies throughout its member states. This study explores some of the similarities and differences in European and U.S. regulation of drugs and devices, and discusses challenges facing each. (J Am Coll Cardiol Basic Trans Science 2016;1:399–412)

Regulation of the development and dissemination of medical drugs and/or devices (DADs) involves competing interests: ensuring that agents are both safe and effective, while facilitating the movement of innovative therapies as rapidly as possible through the investigative process to public use. Balancing these goals falls globally in large measure to the Federal Food and Drug Administration (FDA) in the United States, and to regional and centralized regulatory bodies in the European Union (EU) (1).

Controversy persists about the differences in U.S. and EU regulatory processes, costs, and the time it can take for a DAD to proceed from concept to approval under the regulations of each. A frequently held assertion is that slower FDA approval processes deprive American citizens of effective DADs that are available to Europeans (2), and critics have characterized FDA processes as "slow, risk averse, and expensive" (3). However, the Institute of Medicine determined that current FDA pre-marketing procedures for medical devices are insufficient to assure device safety, particularly those approved largely on their similarity to previously cleared "predicate" devices, rather than on prospective, randomized clinical trials (4). In the EU, concerns abound that DADs may be approved too quickly, to the detriment of patient safety. In recent years, there have been calls to tighten approval processes and to establish regulatory consistency between the FDA and the EU. Efforts include recent legislation in the U.S. Congress to facilitate release in the United States of drugs that have already achieved European approval (5). Proposed changes to regulations of the European Commission (EC) regarding device approval are under discussion (6), but are vigorously opposed by both industry and patient groups insisting that it will impede availability of innovative therapies to the public.

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ABBREVIATIONS AND ACRONYMS

BMJ = *British Medical Journal*

CE = Conformité Européenne

DAD = drugs and devices

EC = European Commission

EMA = European Medicines Agency

EU = European Union

FDA = Food and Drug Administration

MHRA = Medicines and Healthcare Products Regulatory Agency

NB = Notified Bodies

PMA = pre-market approval

A 2-part series published earlier in *JACC: Basic to Translational Science* provided an overview of FDA approval processes for drugs and medical devices in the United States (7,8). This review compares European processes with those of the FDA, and discusses some of the challenges facing each.

BACKGROUND

The FDA was an outgrowth of a division of the U.S. Patent Office in the mid-19th century, initially charged with ensuring that medications on the public market were effective as advertised. The Federal Food, Drug and Cosmetics Act of 1938 subsequently invested the agency with more rigorous powers to ensure that drugs were not only effective, but "safe" (9), and the FDA was ultimately given authority to regulate medical devices in 1976 (10) through legislation that was later amended in the Medical Device User Fee and Modernization Act of 2002 (11). Although regulatory amendments have been implemented to facilitate DAD transit from concept to market, the powers and processes of the FDA have stayed largely consistent since the 1970s, and are authoritative for all 50 states.

The evolution of European regulation of DADs, by contrast, is much more recent, with significant changes after the formation of the EU in 1993. Before that, regulation and marketing approval for DADs fell to its (now) member states. Differences in regulations among the states often impeded marketing and disbursement of DADs across Europe, and in some cases fostered "protectionist" legislation within states to shield sovereign nations' companies from fierce market competition. Among the current 28 member states, many interstate agencies have been reorganized. Clinical trial applications are generally handled in the member state, whereas marketing applications are approved by both state and central agencies in accordance with regulations set forth by the EC.

EUROPEAN REGULATION OF DRUGS

Efforts to standardize European regulations regarding drug approval first came to fruition before the formation of the EU, with the passage of EC Directive 65/65/EEC in 1965 (12). The directive defined a medical product as "any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting, or modifying physiological functions in human beings or in animals." Under the directive, any medicinal product marketed in the member states would first pass approval in the originating state (1,12,13). The directive established consistent guidelines throughout the member states regarding the information that must be submitted for approval: these items parallel regulations of the FDA regarding investigational new drug applications and new drug approval applications.

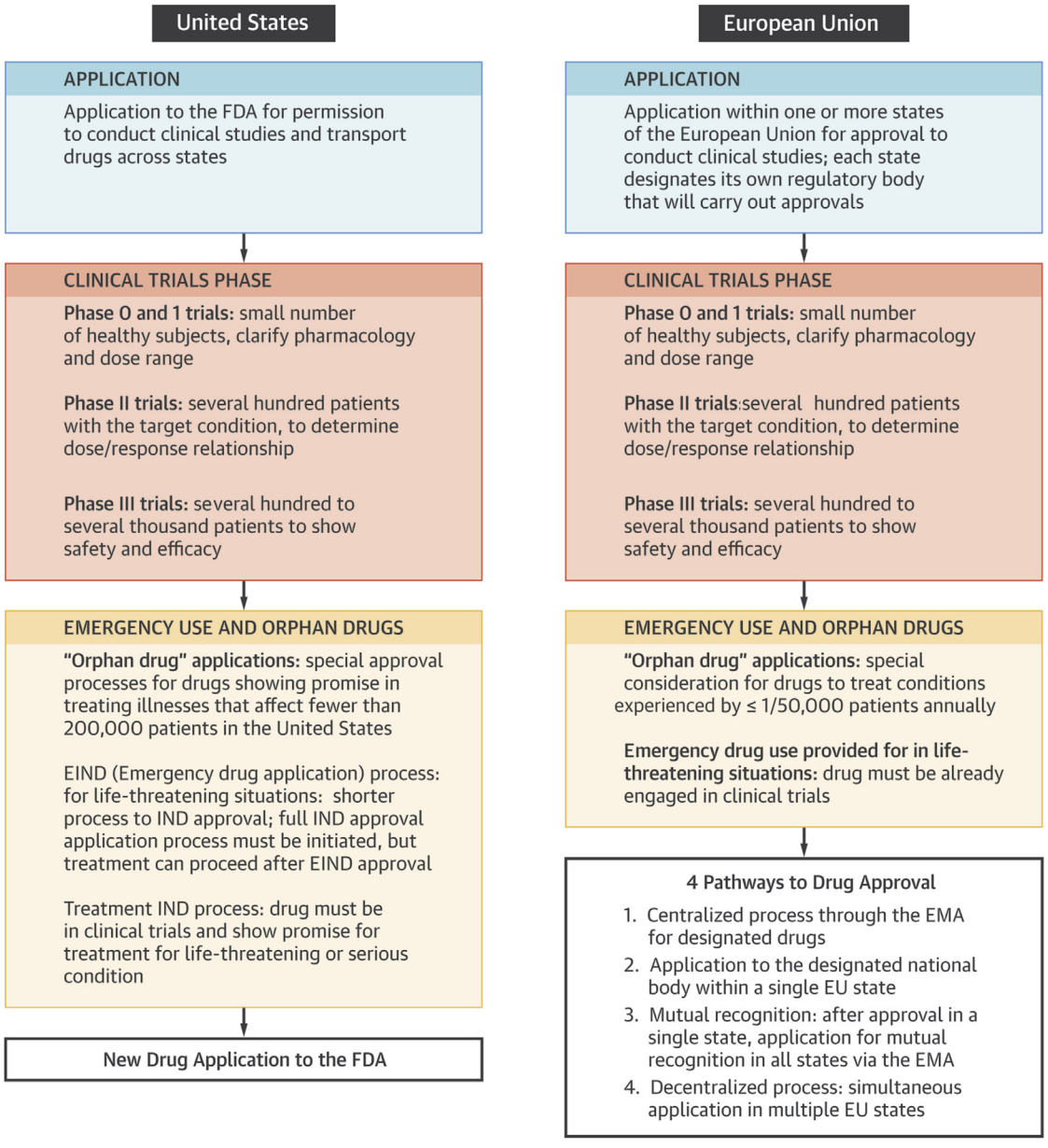
DRUG APPROVAL PROCESSES. Many of the processes to approve drugs in the EU are similar to those of the FDA (**Figure 1**). An investigator of a proposed pharmaceutical first obtains pre-authorization for use of the drug in clinical trials. All European clinical trials were regulated under the Clinical Trials Directive of the European Commission (2001/20/EC) (14), later repealed and replaced in 2014 by Regulation No. 536/2014 of the European Parliament (15).

The drug then progresses through sequential studies analogous to those in the United States: Phase I trials conducted in a small number of healthy subjects to clarify pharmacology and dose range, Phase II trials conducted in several hundred patients with the target condition to investigate the dose-response relationship, and Phase III confirmatory trials in several hundred to several thousand patients to substantiate safety and efficacy. As in the United States, the EC provides means for approving "orphan drugs," or those that treat conditions that affect so few people that randomized controlled trials may be impossible to complete (16,17). There are also methods for obtaining conditional approval for drugs to be used in emergency conditions, or other conditional approvals (18).

The European Medicines Agency (EMA) was formed in 1995 with funding from the EU, pharmaceutical industry, and member states (19). The EMA was charged with harmonizing processes in the member state regulatory agencies to reduce annual costs to drug companies (that previously were required to obtain separate approvals in each member state) as well as to eliminate competition-restricting regulation in sovereign states. However, the EMA does not oversee all drug approvals the way the FDA does in the United States. In Europe, there are 4 routes by which a drug can be approved, depending on the drug class and manufacturer preference (6).

CENTRALIZED PROCESS. The centralized process is controlled through the EMA. Every member state of the EU is represented on the EMA Committee for Medicinal Products, which issues a single license valid in all EU member states. This route of approval is mandatory for some classes of drugs, such as treatments for HIV/AIDS, oncology, diabetes, neurodegenerative disorders, autoimmune disease, and viral diseases.

FIGURE 1 Comparison of Drug Approval Processes in the United States and EU



After clinical trials, FDA drug approvals follow a centralized path, whereas European approval can occur through 4 different paths, depending on the nature of the drug and the preference of the manufacturer. EIND = emergency investigational new drug; EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; IND = investigational new drug.

NATIONAL PROCESS. Each EU state can have its own procedures for approving drugs that fall outside of those required to undergo the centralized process.

MUTUAL RECOGNITION. Drugs approved in one EU state via that state's national process can obtain marketing authorization in another EU member state.

DECENTRALIZED PROCEDURE. Manufacturers can apply for simultaneous approval in more than 1 EU state for products that have not yet been authorized in any EU state and do not fall under the mandatory centralized process. This route now manages by far the largest number of applications for approval: in 2008, there were 1,400 decentralized applications,

compared with 100 applications via the centralized process (6).

CONTRASTS IN FDA AND EU DRUG APPROVAL PROCESSES

Comparisons and contrasts between the U.S. and European processes for drug approval are plentiful, but 2 issues have elicited particular scrutiny: the time required for drug approvals, and transparency of nonpublished drug trials data.

TIME FROM CONCEPT TO MARKET. Shortening time from concept to market is not only important to patients. During that period in a drug or device's life, it generates costs rather than revenue for its sponsor. For drugs, most of that time, in both Europe and the United States, is spent in clinical trials that can consume years and generate costs in the millions or even billions of dollars (7). Thus, some proposals in Europe have called for earlier market release of drugs once they have completed Phase II clinical trials, with post-market surveillance thereafter to continually assess patient safety and drug efficacy (20).

Another determinant of the concept to market period is the time it takes the regulatory agencies to conduct their reviews. It is commonly asserted that FDA processes are significantly slower than those of the EMA, and that FDA processes should be loosened to facilitate drug approval and equalize drug availability in Europe and the United States. Closer examination shows that, in fact, drug review times are significantly *shorter* at the FDA than the EMA. One study demonstrated that for similar drugs, the median times of initial reviews were 303 and 366 days, respectively, and for full reviews was 322 days compared with 366 days, respectively (21). For drugs that were brought to market in both the United States and EU, 63.7% were brought to market first in the United States, and were available a median of 90 days sooner. Comparing first-to-market times between the United States and Canada, 85.7% of drugs were available first in the United States, and a median of 355 days sooner (21). Roberts et al. (22) found that for cancer drugs, review times were even more abbreviated—by about 6 months in the United States. All of the drugs that were approved by both the FDA and EMA were available sooner to patients in the United States, in part because of consistently shorter review times at the FDA. Furthermore, during the same period of time, the FDA approved a larger number of cancer drugs than the EMA (35 vs. 29, respectively) (22).

TRANSPARENCY OF DRUG APPROVAL DATA. Not all data generated for drug approval is ultimately submitted for peer review and publication, and this can be a significant source of publication bias (23). Transparency of trial data is an issue for both the FDA and EMA, which poses challenges to the production of systematic reviews and meta-analyses that may be critical to public safety and health. At the FDA, nonpublished data included in new drug applications is available for review online (24) and by request. MacLean et al. (25) found the methodological quality of these studies generally comparable to that of published trials, and confirm they can be invaluable in systematic reviews. In contrast to the FDA, at the EMA, nonpublished data is considered "commercially sensitive" and not available to the public unless there is an overriding public interest. Gøtzsche and Jørgensen (26) detailed their years-long struggle to obtain unpublished trial data from the EMA in 2011.

EUROPEAN REGULATION OF DEVICES

Approval processes for medical devices also followed a path of "harmonization" in Europe with establishment of the EU, but medical device regulation also does not fall solely to any one agency.

Three EC directives that have been subject to periodic amendment address approval of medical devices: 1) implantable devices are regulated under directive 90/385/EC; 2) most other devices are regulated under directive 93/42/EC; and 3) in vitro diagnostic devices (i.e., used on substances produced by the body) are regulated under 98/79/EC (27,28). Under Directive 93/42/EC, the definition of a medical device is "any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means" (29).

In the EU, every marketed medical device must carry a Conformité Européenne (CE) mark indicating that it conforms to relevant directives set forth in the EC Medical Device Directives of the EU. A device with a CE mark can be marketed in any EU member state. Medical devices that are non-implantable and considered low risk are "self-marked," meaning that the manufacturer itself simply certifies compliance

and applies a CE mark (30). High-risk devices must undergo a more extensive outside review.

Through a complex system of legislation, high-risk medical device approval applications can be filed in any member state and reviewed by a "Notified Body" (NB) established within that state and authorized by that state's Competent Authority, or health agency, to assess and assure conformity with requirements of the relevant EC directive (27). NBs are private companies that contract with manufacturers to supply these certifications for a fee, and there are currently around 76 NBs in the EU. Once the NB agrees that the device meets requirements for conformity, the NB issues a CE mark, and the device can then be marketed in EU member states (31).

Until recently, the CE mark authorized marketing "without further controls and no further evaluation" (32), but new regulations in 2010 tightened requirements for approval of devices based on their similarity to previous "predicate" devices. They also required "proactive post-market surveillance" of devices by their manufacturers (33). Post-marketing surveillance events (e.g., alerts, modifications, recall, and withdrawal of products) are required in the new regulations to be reported to a central database (Eudamed) to facilitate dissemination of information of adverse events throughout Europe. The database is currently available only to the EC and Competent Authorities, not to the public (30,34). According to Emergo, a global medical device consulting firm, the "Future Eudamed Steering Committee" met in January of 2016 and discussed widening Eudamed accessibility to NBs, manufacturers, experts, non-European Competent Authorities, medical institutions, the public, and the press (35).

COMPARISON OF U.S. AND EU DEVICE APPROVAL. Approval of medical devices in both the EU and the United States share some similarities (**Figure 2**). The FDA assigns devices to 3 main regulatory classes: low risk or Class I, moderate risk or Class II, and high risk or Class III (**Table 1**). In the United States, a Class I device requires merely a Premarket Notification without clinical trials, whereas Class III devices require clinical trials and/or other evidence, unless they are not substantially different from an already-marketed Class III device. If they are similar to a previously approved predicate device, they can usually forgo clinical testing, or undergo only limited clinical investigations. About 75% of Class II devices in the United States require some form of clinical trials to demonstrate their safety and that they perform as expected, although the level of evidence required for approval is often less rigorous than that for new drug approval (8). Randomized controlled trials, for example, are uncommon because of difficulties in randomization and blinding, and many devices are approved based on small observational studies (36).

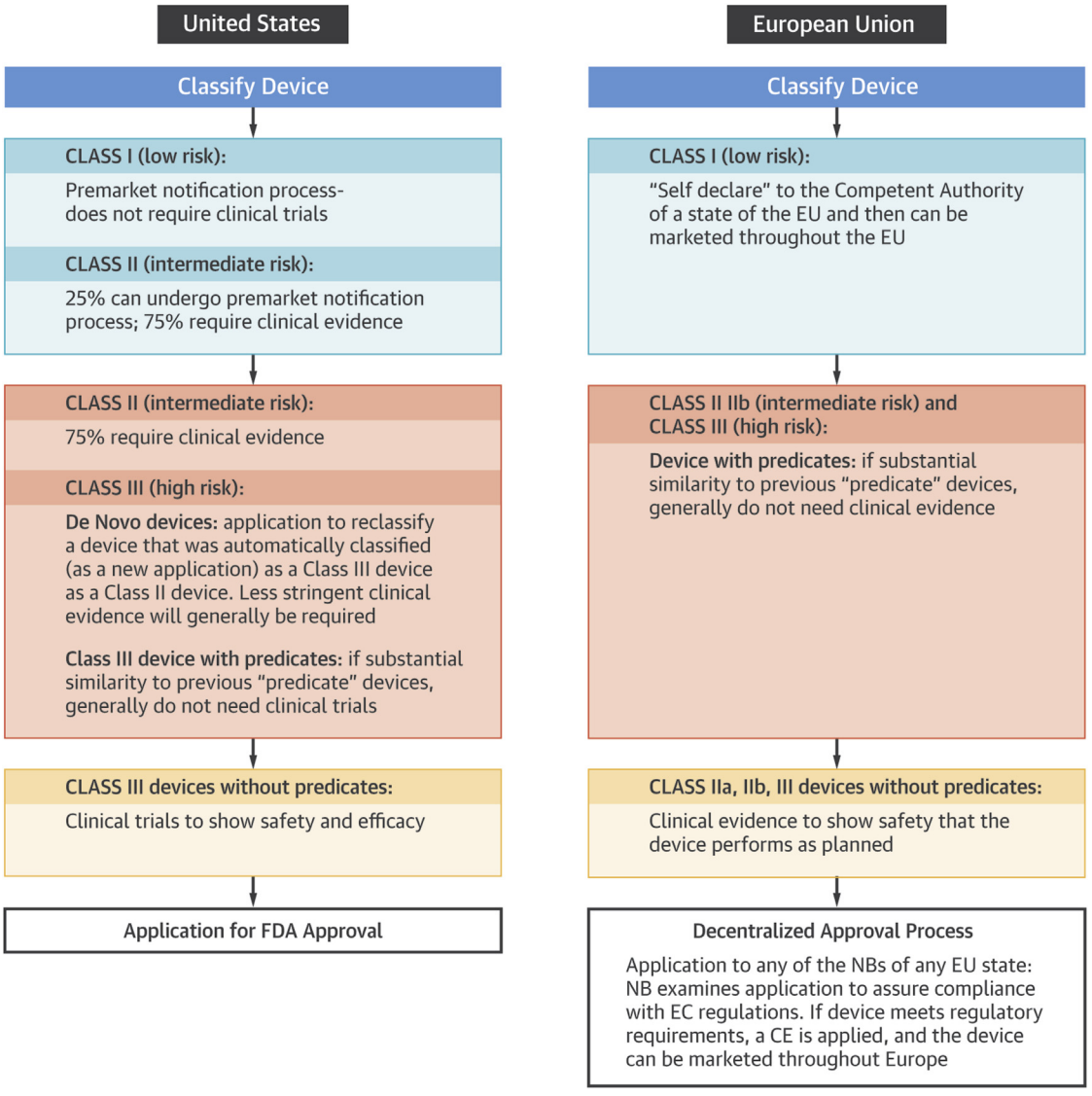
In Europe, the European Council New Approach Directives (3,28) defined "Essential Requirements" that apply to all countries to ensure devices' safety and performance. The EC assigns devices into 4 classes (**Table 1**). Class I or low risk devices need only "self-declare" that they conform with the Essential Requirements to the national Competent Authority in their country of origin (30,37). In the United Kingdom, for example, the Competent Authority is the Medicines and Healthcare Products Regulatory Agency (MHRA).

Moderate- and high-risk devices (Classes IIa, IIb, and III) require clinical and/or nonclinical evidence to support approval. As in the United States, if a device is shown to be substantially similar to an already approved device, data from the predicate device may be used to support approval, and new clinical testing may not be needed (38).

DIFFERENCES IN THE FDA AND EU DEVICE APPROVAL PROCESSES. Although drug review and approval processes are in many ways similar between the United States and Europe, critical differences exist between the approaches to device approval, largely rooted in the historical origins and commissions of the agencies responsible.

The FDA was established as a central answer to the problem of the increasing marketing of health products for which benefits were unproven, nonexistent, or minimal, and products that were frankly harmful (7). By contrast, the European system of NBs was developed out of initiatives to foster innovation and commercial and industrial policies in Europe, and not as a public health or consumer protection agency. Protection of the public health in Europe is the commission of the Competent Authority established in each of the member states, and their roles and authority vary widely depending on the state. Indeed, as an employee of ITC, one of the NBs in the Czech Republic stated, NBs are "on the side of the manufacturer and their products, not on the side of patients" (39). Although the CE mark is often mistakenly equated to being a seal of quality, in fact achieving a CE mark merely indicates that the device in question is in full compliance with European legislation. A report to the U.S. Congress of the Global Legal Research Center points out that "The legal value of the CE marking lies in its proof that the medical device concerned is in full compliance with applicable legislation. On the other hand, the CE marking does

FIGURE 2 Comparison of Device Approval Processes in the United States and EU



The FDA processes for device approvals are centralized within 1 agency, but allow device approvals based on clinical trials, or based on predicate devices. European processes for device approval follow decentralized paths in each of the member states and also allow for approval based on predicate devices. CE = Conformité Européenne; NB = Notifying Body; other abbreviations as in Figure 1.

not represent quality, even though consumers often assume that products bearing the CE marking are of better quality than others" (37).

Before approval of a medical device in the United States, a device must not only be shown to be safe, but efficacious (3). Medical devices approved in Europe need only to demonstrate safety and performance, that is, that they perform or, in the case devices approved based on predicates rather than clinical trials, will probably perform as designed and that potential benefits outweigh potential risks. They are not required to demonstrate clinical efficacy. A collateral effect of more "commercially sensitive" regulations in Europe is that initial approval of U.S. company-backed devices is increasingly being sought in the EU before application in the United States (40).

Another challenge for EU processes is that, whereas only 1 organization (the FDA) oversees medical device development and approval in the United States, a complex mesh of organizations with various

allegiances are responsible for oversight in the EU—including government agencies (Competent Authorities) and private, for-profit companies (NBs). In the United States, the single authority system presumably allows for better coordination and enforcement, but may result in a less flexible, lengthy, and expensive process (30). The EU process, by contrast, may provide more flexibility and more rapid approval of devices, but its rules are more difficult to define and enforce. Standards among the NBs differ, and this provides manufacturers with loopholes to expedite approval by seeking a CE mark from the least rigorous NB and those that charge the lowest fees (39,41). NBs as private companies not only compete from a pricing standpoint for approval contracts, but may be reluctant to disapprove devices for fear of losing an ongoing relationship with a manufacturer who hires them. A lack of centralization makes safety data more difficult to collate, and in any case, data submitted for high-risk devices to the NBs is considered "commercially confidential," and is not available to the public (2,41,42).

The FDA must approve all high-risk medical devices in the United States, but in Europe, some high-risk devices, such as those that are not intended for "distribution and/or use on the Community Market," are not approved under the Medical Devices Directive. A device produced "in house"—for example, in an academic medical center—could theoretically be distributed for widespread use throughout that academic system and its associated entities without having ever undergone scrutiny for safety and performance, and it would not require a CE mark (28).

Cohen (39) from the *British Medical Journal* (BMJ) demonstrated some of the loopholes in the EU process for device approval. The BMJ investigators pursued EU approval for the Changi TMH (total metal hip), an entirely fictitious metal-on-metal hip prosthesis deliberately modeled (on paper) on a predicate product that had been recalled for unacceptable failure rates. Although the fictitious BMJ product data also indicated that their proposed prosthesis produced potentially toxic levels of metal ions in the body, the NB to which the investigators finally submitted their application raised no significant issues with regard to product design.

The investigators learned that few devices actually fail approval, with at least 1 NB explicitly offering a "100% success rate." Furthermore, the actual country of manufacture of devices was easy as well as legal to conceal; the NB office approached by the investigators was located in South Korea (allowed under EU regulations), and the NB suggested they establish a European distribution hub so that the product could carry package labeling indicating it was from the EU (also legal under EU regulations) even though it would be manufactured in Asia (39,43).

TABLE 1 Risk Classification of Medical Devices in the United States and Europe

United States	European Union
Class I: low risk of illness or injury, e.g., gauze, toothbrushes	Class I: low risk; e.g., sterile dressings, gloves
Class II: moderate risk of illness or injury, e.g., suture, needles	Class IIa: low-medium risk; e.g., surgical blades, suction equipment Class IIb: medium to high risk; e.g., ventilators, some implants, radiotherapy equipment
Class III: significant risk of illness or injury; e.g., pacemakers, implantable defibrillators	Class III: high risk; e.g., drug-eluting cardiac stents, pacemakers, implantable defibrillators

Differences in DAD approval processes in the United States and Europe cannot entirely be attributed to the regulators or even the manufacturers. Product liability lawsuits are less common in Europe than in the United States. This may reflect differences in liability laws, as well as differences in how comfortable European patients are with clinical risks, compared with those in the United States.

TIMELINES TO DEVICE APPROVAL AND USE. The biotech industry is vocal in asserting that U.S. DAD approval is much slower than in Europe, and that European patients enjoy earlier access to innovative drugs and technology over U.S. patients. Independent analysis of device "lag times" between the EU and the United States is difficult, because there is no central European clearinghouse for such information, and applications for device approvals seldom occur simultaneously in Europe and the United States. A "device lag" of 3 years between the EU and United States approval is frequently quoted from a 2012 report of the Boston Consulting Group, which was hired by the biotech industry to support changes in European regulations for device approval (44). Kramer et al. (45) examined comparisons in device approval timing between the FDA and the EU, and found that whereas devices approved via the more stringent FDA pre-market approval (PMA) approval process did indeed lag about 3 years behind EU approvals, devices approved via the FDA 501(k) approval process only differed by about 18 days as of 2010. In a subset of devices cleared via the 501(k) process that did not require clinical evidence, FDA approval was faster than EU approval. Since 2006, the vast majority of Class III devices are approved in the United States via the 501(k) process (46).

In addition, approval does not equate with availability to patients. Analysis shows that although time for regulatory reviews may be longer in the United States, the timeline from application to clinical

availability of devices in the United States is similar to or shorter than in the EU. This is largely because in Europe, once a device is approved it is still subject to reimbursement approval before becoming available for patient use, and reimbursement decisions take considerably longer in the EU than in the United States (47).

Approval and adoption timelines do not tell the whole story, nor even possibly the most important part of the story regarding device availability to patients. Critical questions are: 1) does faster DAD approval equate with greater availability of "innovative" and better clinical therapies; and 2) is there evidence that patients have been or would be harmed by reducing regulatory hurdles to DAD approval?

The evidence that faster approvals for either drugs or devices improve availability of significantly better DADs is lacking. Only 3 in 20 new drug approvals in Germany in 2011 were deemed improvements over previous therapies (48). Di Mario et al. (49) assert that, even though over 10 times as many drug-eluting coronary stents are now approved in the EU than in the United States, many do not offer significant advantages, or actually have worse outcomes than existing devices. In the words of Rita Redberg, editor of *JAMA Internal Medicine*"…we need to be more specific about 'innovation'. Most new devices are not innovative" (44).

Wild et al. (2) reviewed 10 high-risk cardiovascular devices (for arterial and coronary artery angioplasty, renal denervation, endovascular aortic repair, atrial appendage closure, and others uses) already approved in Austria and marketed in the EU, that were then subjected to FDA application. They asked whether more rigorous clinical investigation or further investigation would have changed perspectives on these devices. For 4 devices, application to the FDA was suspended or withdrawn due to safety concerns, 2 devices either failed to show improved efficacy over existing devices or had unknown efficacy, and clinical trials for another device (for endovascular aortic repair) were subsequently suspended due to an unexpected high number of reinterventions. Time lag between approval in Europe to approval in the United States (for those that were able to obtain FDA approval) was 3 to 7 years. Analysis of the quality of clinical evidence in the Wild study (2) was limited because no data on clinical evidence used for CE marking were available due to confidentiality regulations.

Early device release and adoption does not always predict benefits for patients, whether approved in the United States or Europe. Renal artery stenting widely adopted in the 1980s, was debunked by the ASTRAL (Angioplasty and Stent for Renal Artery Lesions) trial, which demonstrated no efficacy over drug therapy, and high rates of serious complications, including amputations and death (50). The Cerecyte coil (Micrus Endovascular, San Jose, California), a treatment of intracranial aneurysms, was approved in the United States via the less stringent 501(k) process on the basis of predicate devices, and the manufacturer was able to charge a premium for the coil without having to supply prospective clinical data. Post-market clinical trials proved efficacy, but nonsuperiority over other less expensive existing devices (51).

CONTINUING CHALLENGES TO DRUG AND DEVICE REGULATION AND APPROVAL

The EU and United States face some common challenges in balancing the mandate to ensure DAD safety and efficacy against the pressure from industry and the public to expedite the transit of new DADs to market.

SAFETY AND EFFICACY EVIDENCE REQUIREMENTS. Appropriate and effective evidentiary requirements for device approval is a serious problem for both the United States and EU. In the United States, only about 2% of medical devices approved in the last 10 to 12 years have undergone Premarket Applications, the most rigorous process for FDA device approval (52). A 2006 report states that only 10% to 15% of FDA device submissions contain any clinical data *at all* (30). Approximately 71% of devices in 1 study had been cleared through the less rigorous 501(k) process, and another 7% were exempted entirely from review (53). These statistics do not begin to address quality issues plaguing product applications, which the FDA itself has determined to occur in more than one-half of submissions (54).

When clinical trials are required for devices, they frequently do not meet the same strict standards for clinical evidence that are required for drugs; they are often nonrandomized, nonblinded, do not have active control groups and lack hard endpoints (30). In fact, such rigorous clinical trials may not always be feasible—randomization and blinding of patients or physicians for implantable devices is nearly impossible. But device approval based on predicates raises serious doubts about safety assurances, and both the Institute of Medicine (4) and the U.S. Congress, under the 1990 Safe Medical Devices Act (55), have pushed to have this pathway for approval of devices curtailed. Nevertheless, 19 types of Class III devices were still allowed as of 2013 to reach patients via an FDA clearance based on predicates (56). It is worrisome that predicates can include devices that were on the

market before regulatory requirements to prove safety and efficacy existed, and even voluntarily recalled devices (52,53,57). Thus, it is not uncommon for a medical device to reach the market in the United States without ever having been tested in humans. Such was the case with the DePuy ASR LX Acetabular Cup System, a metal-on-metal hip replacement product that later suffered an unacceptable high rate of failure and was recalled (8).

In the EU, in contrast with the United States, regulations do not require rigorous clinical studies to support clinical efficacy for any devices, even those without predicates, but merely evidence to support safety and performance. Often, evidence takes the form of laboratory testing or very limited clinical trials (58). This raises the risk that a device will be approved that offers no substantial advantages or benefits over existing products, or else that the general public will be exposed to serious adverse effects that were not detected in limited clinical experience. In 2009, the chief executive officer of the French drug agency stood squarely in sympathy with industry when he stated in the preface for a book distributed by Medtronic Corporation that "rapid obsolescence of the products…is hardly compatible with the delay necessary for clinical trials, particularly morbidity and mortality data." He suggested that "predictive equivalence" should replace clinical testing—referring to a chapter in the book that suggests predictive equivalence can be based on merely a successful bench test of a medical device (50,59).

In both the United States and the EU, the lack of requirement for rigorous new clinical evidence to approve the majority of medical devices and the use of predicate data can furthermore have a palling effect on the motivation of industry to conduct expensive trials to demonstrate clinical efficacy or superiority, as well as on the pursuit of truly new innovation (60).

POST-MARKET SAFETY AND EFFICACY SURVEILLANCE. In the United States, physicians, manufacturers, and patients have the ability to report adverse events involving DADs to the FDA, which centrally collects and reviews adverse event data. The FDA has the power to condition approval of DADs on the completion of post-marketing studies, and may even determine what the design of such studies should be. Ultimately, if an after-market drug or device is found to be unsafe, the FDA can withdraw its marketing approval and require the manufacturer to withdraw/recall it; the different classes of recall are summarized in **Table 2**. Failure to recall a device would then constitute a federal crime. Reports and actions taken by the FDA are publically available (61). Discovery of inherent flaws in the theory, design, manufacture, or marketing of a DAD exposes the manufacturer, as well as medical establishments and physicians, to the full force of the American civil liabilities laws. Manufacturers may also be subject to criminal charges, as when Guidant LLC was charged in 2010 for allegedly concealing information regarding catastrophic failures of implantable cardioverter-defibrillator devices (62). A recent review of FDA drug recalls from 2004 to 2011 demonstrated that most Class I recalls (in which product defects had the greatest likelihood of causing patient harm) were due to contamination or wrong dose or release mechanisms. Five recalls were initiated due to patient adverse events (63).

European drug safety regulation relies heavily on post-market surveillance, through "vigilance systems" required under the 2012 EC pharmacovigilance legislation (EU/20/2012) (64,65). Adverse drug reactions are reported to the Competent Authority of each member nation, or their authorized surrogate: in the United Kingdom, for example, that is the MHRA. The 2012 legislation provided significant new powers to the EMA to ask for post-marketing safety and

TABLE 2 Classes of FDA Recalls and Alerts*

Class I recall	Reasonable probability that use or exposure to a device will result in serious adverse health consequences or death	Examples: defective implantable defibrillator; critical labeling error on a drug
Class II recall	Use or exposure may cause temporary or medically reversible adverse health consequences; probability of serious adverse health consequences is remote	Examples: a drug that is understrength, but not used to treat a serious illness
Class III recall	Use or exposure is unlikely to cause adverse health consequences	Examples: unlikely to cause health effects, but violate FDA labeling or manufacturing laws, such as a lack of English labeling on a retail food
Market withdrawal	Manufacturer-initiated: product has a minor violation that would not be subject to FDA action	Examples: routine updates and equipment adjustments and repairs. This differs from a voluntary "recall" in that a recall involves a violation that would be subject to FDA action
Medical device safety alert	Advisory that a medical device may present an unreasonable risk of substantial harm; in some cases, such alerts are also considered recalls	Example: notification to the public of a serious defect in an implantable defibrillator

*From the U.S. Food and Drug Administration (FDA), available at: http://www.fda.gov/Safety/Recalls/ucm165546.htm. Accessed June 17, 2016.

efficacy studies. The specific methods for collecting and analyzing reports are left to each state's Competent Authority.

Some proposals have called for quicker drug approvals based on Phase II clinical studies, coupled with heavier reliance on post-marketing surveillance, as a way of balancing availability and safety (20). However, this approach presents several problems. Almost one-half of drugs fail in Phase III clinical trials due to safety and efficacy concerns (66,67). Quicker approval based on more exploratory clinical studies, therefore, virtually guarantees that patients will be exposed to drugs that later prove to have little clinical benefit, or worse, potential serious harm. Such was the case with gefitinib (Iressa, AstraZeneca, London, United Kingdom), which achieved accelerated approval on the basis of Phase II clinical trials, but was later restricted by the FDA on the basis of randomized double-blind study results (68). Another problem is the fact that for the majority of accelerated drug approvals that have been "conditional" on the completion of post-market studies by the FDA, post-market safety and efficacy studies were not actually completed (69).

A review of conditional approvals by the EMA also reveals problems; in one review of 26 conditionally approved medications (70), over one-half were converted to standard approval processes, and 5 had already exceeded deadlines for meeting conditions at the time of the review. Average time to address the obligations of the conditional approval was 4 years, but ranged as high as 7.7 years. Conditional approvals were most often offered to cancer drugs and orphan drugs. The investigators commented that a recently proposed "adaptive pathway" or "live licensing" that would open up conditional approval (requiring much lower levels of clinical evidence) to more drugs "could pave the way to further marketing authorization strategies allowing access to medicines whose clinical value is still not fully established" (70).

Finally, approval of drugs based on Phase II studies may reduce the willingness of patients to even enroll in randomized controlled trials that might restrict their access to new drugs, making safety and efficacy studies more difficult or impossible to accomplish (68).

In Europe, the mixture of government and private processes makes post-market surveillance challenging (36), and although device manufacturers are responsible for reporting adverse effects, it is not clear how diligently they are required to look for product defects, nor to search for adverse events (71). The post-marketing surveillance plan that was accepted for the BMJ's factitious hip prosthesis consisted solely of listing the phone number of an employee of the "manufacturer" as a contact on their brochures (39).

Calls for reform in the European process for device approval and post-market surveillance were fueled in 2010 after Poly Implant Prosthèse (PIP), a French company that manufactured silicone breast implants under a CE mark issued in 1991, was found to have switched to industrial silicone rather than medical grade material in their implants. Over 30,000 women received PIP implants, which were implicated in cases of systemic toxicity, as well as cancer (72). Before PIP changed to lower grade components (sometime in 2001), their implant had been refused approved for marketing in the United States on the basis of a post-market surveillance process. In 1992, the FDA began requiring follow-up of all patients receiving breast implants through post-market clinical trials. When higher than expected complication rates were found, the FDA required all breast implants to undergo evaluation via the stringent PMA approval process. PIP's PMA application failed in 2000, based on an FDA inspection of their manufacturing plant (which resulted in a warning letter to the company) and clinical and safety data that the FDA determined was insufficient (72,73).

Despite success regarding defective breast implants, FDA post-market surveillance processes and FDA and manufacturer recalls are fraught with deficiencies. For example, it took more than 3 years to recognize safety issues and recall the Sprint Fidelis (Medtronic, Minneapolis, Minnesota) implantable cardioverter-defibrillator, which had a high propensity for lead fracture that lead to patient deaths. Over 268,000 patients received the device, and had to consider whether they should undergo removal of the device with its attendant risks (74). In another case, concerns were raised regarding the Riata ST defibrillator leads (St. Jude Medical, Sylmar, California), which was prone to a type of "inside-out" conductor erosion that would predispose to lead failure. The company concluded, based on product analysis and complaints, that the risk of insulation abrasion was 0.63%, of which only about 15% might cause a clinical problem. However, several small clinical studies indicated that "inside-out" insulation erosion occurred in up to 30% of implanted leads (75). The leads were withdrawn from the market in 2011, more than 10 years after market release, following reports of alarming rates of lead erosion (15%) and lead failures (76). A later analysis conducted by Hauser et al. (77) identified 71 deaths in patients with Riata leads, 22 of which were confirmed in Riata or Riata ST leads to be lead-related. Comparing the experiences with

the Spring Fidelis and Riata leads, Liu et al. (76) commented that, despite "early identical patterns," reasons for the delay in the Riata lead recall compared with that of the Spring Fidelis were unclear, and speculated that it might be in part due to failures in the manufacturer-to-FDA reporting system.

Reliance on post-marketing surveillance to assess the experience with devices and device safety relies on the accuracy and quantity of data reported by manufacturers, which, as Kaszala and Ellenbogen (75) point out, "is not adjudicated by the Food and Drug Administration." Post-market data are furthermore subject to underreporting of clinical events to the manufacturer by health care providers. In the words of Hauser (78), "our current passive post-marketing surveillance system fails to detect significant device defects before large patient populations have been exposed."

European law requires the manufacturer to report adverse events that they know about to the member state in which the CE mark was obtained (28), and the individual states have the responsibility for restricting or withdrawing the device. Failure of a manufacturer to comply can result in criminal penalties. Penalties for noncompliance differ significantly, depending on the member states. Extrapolating from several reports, in the United Kingdom, this might result in a fine of £5,000 ($7,257.50) and imprisonment of up to 6 months, France can impose fines of up to approximately €48,000 ($65,760) and imprisonment of up to 3 years, and Germany can impose unlimited fines and prison terms of 3 to 5 years (28). Individuals harmed by a defective medical device have 3 courses of action in Europe: actions in contract or negligence, both of which are subject to individual laws and processes of the member state, and action under the Product Liability Directive 85/374/EC (79). However, the complexity of bringing suit in the maze of agencies, offices, distributers and manufacturers is daunting.

The lack of transparency regarding data submitted for clinical approval, and the lack of a central "clearing house" in the EU to manage device approval make it nearly impossible to make accurate comparisons of EU and U.S. rates and industrial interventions for unsafe and inferior medical devices. Kramer et al. (3) state that "studies in the EU regarding the premarket features of devices that are subject to recalls have proved impossible to conduct." One study of device recalls and safety alerts reported to the MHRA in the United Kingdom showed that a large number of medical device safety alerts were related to cardiovascular devices, and 44% of all device safety alerts lead to recall. But many manufacturers would not supply requested details about the recall, and frequently simply did not respond to such requests at all (80). For the United States, one report estimates that 6 to 8 devices are removed from the U.S. market annually due to safety concerns (81). Another analysis of cardiovascular and noncardiovascular device recalls in the United States indicated that device recall rates were relatively constant over an 8-year period at approximately 30 per year. The largest proportion of recalls were for cardiovascular devices (27%). In the last year of the study, recall rates for devices approved under the 501(k) "predicate" approval process doubled from 0.65% to 1.39% (82), reinforcing concerns about the 501(k) process.

Many have called for centralizing processes for device approval in the EU, similar to the way in which approval is accomplished with the FDA; this would facilitate standardization of regulations, decrease variance of pricing and processes, restrict questionable practices by the NBs, and reduce conflicts of interest in the approval process. But the price for standardization would likely be increased cost, increased time to approval, and decreased flexibility for industry. Industry has responded vigorously to proposals to tighten regulations and processes, calling them "Kafkaesque" and "harmful to patients" (44).

THE FUTURE. Recognizing a common goal of patient safety, in the wake of the 2012 vigilance legislation, the EMA and the FDA announced a program of collaboration to reinforce efforts in medication safety by holding regular teleconference meetings to discuss "areas that have been identified as requiring an intensified exchange of information and collaboration" (83).

A 2012 proposal for amendments to the EC's regulations on medical devices (37,84) that would involve the EMA in device regulation and final review after NB approval and before release, tighten quality controls over NBs and require stricter clinical evidence for device approval, among other changes. The measure has been the subject of ongoing debate, and initial hopes for adoption of new rules by 2014 were not met. It remains to be seen whether they will be passed by the end of 2017.

SUMMARY

Globally, the largest share of medical DADs are investigated and approved in the United States and in the EU. Although the regulatory processes in the United States and Europe share common goals and have many similarities, the different histories of DAD

regulation in both regions contribute to significant regulatory dissimilarities. Whereas the FDA was founded as a centralized consumer protection agency, the current European systems were driven out of a need to standardize commercial rules across the European member states. As a result, the FDA is sometimes seen as overplaying safety concerns at the cost of commercial enterprise, whereas the European systems are sometimes characterized as being primarily concerned with preserving commercial interests to the detriment of patient safety. Despite assertions that drugs are approved more slowly in the United States, analysis indicates that they actually reach the public more quickly in the United States than Europe. Whether there is a true "device lag" between Europe and the United States is less clear. Nevertheless, device safety concerns and device failures on both sides of the "pond" have lead both the United States and EU to seek greater mutual cooperation, and to explore tightening regulation regarding device approvals. Legislative efforts in both the United States and EU are currently underway to promote transparency and mutual standardization of DAD approval processes.

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REFERENCES

1. Kashyap UN, Gupta V, Raghunandan HV. Comparison of drug approval process in United States and Europe. J Pharm Sci Res 2013;5:131–6.

2. Wild C, Erdos J, Zechmeister I. Contrasting clinical evidence for market authorisation of cardio-vascular devices in Europe and the USA: a systematic analysis of 10 devices based on Austrian pre-reimbursement assessments. BMC Cardiovasc Disord 2014;14:154.

3. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. N Engl J Med 2012;366:848–55.

4. Institute of Medicine. Medical Devices and the Public's Health: the FDA 510(k) Clearance Process at 35 Years. Washington, DC: National Academies Press, 2011. Available at: http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years/510k%20Clearance%20Process%202011%20Report%20Brief.pdf. Accessed June 3, 2016.

5. Gaffney A. Bill Wants Drugs Approved in Europe to Be Available More Quickly to US Patients. Regulatory Focus March 15, 2015. Regulatory Professional Affairs Society. Available at: http://www.raps.org/Regulatory-Focus/News/2015/03/20/21778/Bill-Wants-Drugs-Approved-in-Europe-to-be-Available-More-Quickly-to-US-Patients/. Accessed May 28, 2016.

6. Parvisi N, Woods K. Regulation of medicines and medical devices: contrasts and similarities. Clin Med 2014;14:6–12.

7. Van Norman GA. Drugs, devices and the FDA: an overview of approval processes. Part 1 FDA approval processes for drugs. J Am Coll Cardiol Basic Trans Science 2016;1:170–9.

8. Van Norman GA. Drugs, devices and the FDA: an overview of approval processes. Part 2 FDA approval of medical devices. J Am Coll Cardiol Basic Trans Science 2016;1:277–87.

9. U.S. Food and Drug Administration. History. Available at: http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm. Accessed March 4, 2016.

10. U.S. Government Accountability Office. Classes of Devices. Publication No. 21 USC 360c(a);2006 ed. Washington, DC: U.S. Government Printing Office, 2006.

11. U.S. Food and Drug Administration. Medical Device User Fee and Modernization Act (MDUFA). Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm. Accessed June 3, 2016.

12. Council Directive 65/65/EEC of 26 January 1965 on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Proprietary Medicinal Products. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31965L0065 Accessed May 27, 2016.

13. U.S. Food and Drug Administration. A Look at the European Medicines Agency. Available at: http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm246776.htm. Accessed June 3, 2016.

14. European Commission. Clinical Trials – Directive 2001/20/EC. Available at http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm. Accessed June 3, 2016.

15. European Commission. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Accessed June 17, 2016.

16. European Medicine's Agency. Orphan Designation. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp. Accessed June 3, 2016.

17. U.S. Food and Drug Administration. Developing Products for Rare Diseases & Conditions. Available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm. Accessed June 17, 2016.

18. European Medicines Agency. Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation (EC) No 726/2004. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf. Accessed June 3, 2016.

19. European Medicines Agency. About Us. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid. Accessed June 3, 2016.

20. Cooksey DA. Review of UK Health Research Funding. London, UK: Her Majesty's Stationery Office, 2006, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf. Accessed June 3, 2016.

21. Downing NS, Aminawung JA, Shah N, et al. Regulatory review of novel therapeutics—comparison of three regulatory agencies. N Engl J Med 2012;366:2284–93.

22. Roberts SA, Allen JD, Sigal EV. Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. Health Aff (Millwood) 2011;30:1375–81.

23. Begg CB, Berlin JA. Publication bias: a problem in interpreting medical data. J R Stat Soc 1988;151:419–63.

24. U.S. Food and Drug Administration. Drugs @ FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed June 3, 2016.

25. MacLean CH, Morton SC, Ofman JJ, Roth EA, Shekelle PG. How useful are unpublished data from the Food and Drug Administration in meta-analysis? J Clin Epidem 2003;56:44–51.

26. Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011;342:d2686.

27. Campbell B. Regulation and safe adoption of new medical devices and procedures. Brit Med Bull 2013;107:5–18.

28. Bright J. European medical device regulatory law and product liability. J Hosp Infect 1999;43:169–73.

29. EUR-Lex. Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31993L0042. Accessed May 27, 2016.

30. Sorenson C, Drummond M. Improving medical device regulation: the United States and Europe in perspective. Milbank Qrtly 2014;92:114–30.

31. Boulton AJM. Registration and regulation of medical devices used in diabetes in Europe: need for radical reform. Lancet Diabetes Endocrinol 2013;1:270–2.

32. Jefferys DB. The regulation of medical devices and the role of the Medical Devices Agency. Br J Clin Pharmacol 2001;52:229–35.

33. McKenna C. Understanding the medical device directive changes. Biomed Instrum Technol 2009;43:319–20.

34. European Commission. Market Surveillance and Vigilance. Eudamed—European Databank on Medical Devices. Available at http://ec.europa.eu/growth/sectors/medical-devices/market-surveillance/index_en.htm. Accessed June 3, 2016.

35. Boumans R. The Future of Eudamed—Better, Bigger, Riskier. EmergoGroup blog, February 1, 2016. Available at: http://www.emergogroup.com/blog/2016/02/future-eudamed-better-bigger-riskier. Accessed June 3, 2016.

36. Altenstetter C. EU and member state medical device regulation. Int J Tech Assess Health Care 2003;19:228–48.

37. Global Legal Research Center. Approval of Medical Devices. The Law Library of Congress. September 2014. Available at: https://www.loc.gov/law/help/medical-devices/approval-of-medical-devices.pdf. Accessed on June 3, 2016.

38. European Commission. Guidelines on Medical Devices: Guidelines on Clinical Investigations; Guide for Manufacturers and Notified Bodies. MEDDEV 2.7/4. Available at: http://ec.europa.eu/DocsRoom/documents/10336/attachments/1/translations. Accessed June 3, 2016.

39. Cohen D. How a fake hip showed up failings in the European device regulation. BMJ 2012;345:e7090.

40. Kaplan AV, Baim DS, Smith JJ, et al. Medical device development: from prototype to regulatory approval. Circulation 2004;109:3068–72.

41. Cohen D, Billingsley M. Europeans are left to their own devices. BMJ 2011;342:d2952.

42. McCulloch P. The EU's system for regulating medical devices: now is the time for radical change. BMJ 2012;345:e7126.

43. Cohen D. The truth behind "made in Europe" labels on medical devices. BMJ 2012;345:e7193.

44. Cohen D. Devices and desires: industry fights toughening of medical device regulation in Europe. BMJ 2013;347:f6204.

45. Kramer DB, Xu S, Kesselheim AS. How does medical device approval regulation perform in the United States and the European Union? A systematic review. PLos Med 2012;9:e1001276.

46. Resnic FS, Normand SLT. Postmarketing surveillance of medical devices—filling in the gaps. N Engl J Med 2012;366:875–7.

47. Basu S, Hassenplug JC. Patient access to medical devices—a comparison of U.S. and European review processes. N Engl J Med 2012;367:485–8.

48. Stafford N. Only 3 in 20 new drugs approved in Germany in 2011 were an improvement, report says. BMJ 2014;348:g2657.

49. Di Mario C, James S, Dudek D, Sabagte M, Degertekin M. Commentary: the risk of over-regulation. BMJ 2011;342:d3021.

50. Braillon A. Medical devices and the approval processes: United States vs. France. Arch Intern Med 2010;170:2040–1.

51. Fargen KM, Frei D, Fiorella D, et al. The FDA approval process for medical devices: an inherently flawed system or a valuable pathway for innovation? J Neurointerv Surg 2013;5:269–75.

52. Sweet BV, Schwemm AK, Parsons DM. Review of the processes for FDA oversight of drugs, medical devices and combination products. J Manage Care Pharm 2011;17:40–50.

53. Zuckerman DM, Brown P, Nissen SE. Medical device recalls and the FDA approval process. Arch Intern Med 2011;171:1006–11.

54. U.S. Food and Drug Administration. Understanding Barriers to Medical Device Quality. Available at: http://google2.fda.gov/search?q=understanding+barriers+to+medical+device+quality&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&requiredfields=-archive%3AYes&output=xml_no_dtd&getfields=*. Accessed June 3, 2016.

55. H.R. 3095 Safe Medical Devices Act of 1990. Congress.gov Available at: https://www.congress.gov/bill/101st-congress/house-bill/3095. Accessed June 3, 2016.

56. Ardaugh BM, Graves SE, Redberg RF. The 501(k) ancestry of a metal-on-metal hip implant. N Engl J Med 2013;368:97–100.

57. U.S. Food and Drug Administration. How to Find and Effectively Use Predicate Devices. Available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/ucm134571.htm. Accessed June 3, 2016.

58. U.S. Food and Drug Administration. Unsafe and Ineffective Devices Approved in the EU That Were Not Approved in the US. Silver Spring, MD: U.S. FDA, 2012. Available at: http://www.elsevierbi.com/~/media/Supporting%20Documents/The%20Gray%20Sheet/38/20/FDA_EU_Devices_Report.pdf. Accessed June 3, 2016.

59. Audry A, Ghislain JC. Le Dispositif Médical. Paris, France: Presses Universitaires de France, 2009:55–7.

60. Curfman GD, Redberg RF. Medical devices–balancing regulation and innovation. N Engl J Med 2011;365:975–7.

61. U.S. Food and Drug Administration. Recall, Market Withdrawals and Safety Alerts. Available at: http://www.fda.gov/Safety/Recalls/default.htm. Accessed June 3, 2016.

62. Wang B, Gagne JJ, Choudry NK. The epidemiology of drug recalls in the United States. Arch Intern Med 2012;172:1109–10.

63. U.S. Food and Drug Administration. February 25, 2010: Medical Device Manufacturer Guidant Charged in Failure to Report Defibrillator Safety Problems to FDA. Available at: http://www.fda.gov/ICECI/CriminalInvestigations/ucm272226.htm. Accessed June 19, 2016.

64. Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF. Accessed June 3, 2016.

65. European Commission. Medicinal Products for Human Use: The EU Pharmacovigilance System. Available at: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm. Accessed June 3, 2016.

66. Arrowsmith J. Trial watch: phase II and submission failures 2007-2010. Nat Rev Drug Discov 2011;10:87.

67. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3:711–5.

68. Eichler HG, Pgnatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008;7:818–26.

69. Ajorn J. Paying for drug approval—who's using whom? N Engl J Med 2007;356:1697–700.

70. Banzi R, Gerardi C, Bertele V, Garattini S. Approvals of drugs with uncertain benefit-risk profiles in Europe. Eur J Int Med 2015;26:572–84.

71. Randall H. Post marketing surveillance and vigilance for medical devices: the European approach. Drug Safety 2001;24:869–72.

72. Greco C. The Poly Implant Prosthèse breast prosthesis scandal: embodied risk and social suffering. Soc Sci Med 2014;147:150–7.

73. Heneghan C. The saga of Poly Implant Prosthèse breast implants. BMJ 2012;344:e306.

74. Dhruva SS, Redberg RF. Medical device regulation: time to improve performance. PLoS Med 2012;9:e1001277.

75. Kaszala K, Ellenbogen KA. In search of the shocking truth. Heart Rhythm 2012;9:1236–8.

76. Liu J, Brumber G, Rattan R, Jain S, Saba S. Class I recall of defibrillator leads: a comparison of the Sprint Fidelis and Riata families. Heart Rhythm 2012;9:1251–5.

77. Hauser RG, Abdelhadi R, McGriff D, Retel LK. Deaths caused by failure of Riata and Riata ST implantable cardioverter-defibrillator leads. Heart Rhythm 2012;9:1227–35.

78. Hause RG. Here we go again—another failure of postmarketing device surveillance. N Engl J Med 2012;366:873–5.

79. European Commission. Directive 85/374/EC: Liability for Defective Products. Available at: http://www.seio.gov.rs/upload/documents/skrining/eksplanatorni/prezentacije/pg28/28_3.pdf. Accessed June 3, 2016.

80. Heneghan C, Thompson M, Billingsley M, Cohen D. Medical-device recalls in the UK and the device regulation process: retrospective review of safety notices and recalls. BMJ Open 2011;1:e000155.

81. Schoonmaker M. The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison With the Drug Model. Order Code RL 32826. Congressional Research Service (CRS) Report for Congress. March 23, 2005. University of Maryland School of Law. Available at: http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3282603232005.pdf. Accessed December 1, 2010.

82. Somberg JC, McEwen P, Molnar J. Assessment of cardiovascular and non-cardiovascular medical device recalls. Am J Cardiol 2014;113:1899–903.

83. Dal Pan GJ, Arlett PR. The US Food and Drug Administration-European Medicines Agency collaboration in pharmacovigilance: common objectives and common challenges. Drug Saf 2015;38:13–5.

84. European Commission. Proposal for a Regulation of the European Parliament and of the Council on Medical Devices and Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. Available at: http://data.consilium.europa.eu/doc/document/ST-9769-2015-INIT/en/pdf. Accessed June 3, 2016.

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