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REVIEW

Electrophysiology devices and the regulatory approval process within the U.S. FDA and abroad

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Abstract
Almost all electrophysiology (EP) devices need to obtain premarket approval before they can be commercially sold and available for use in the community. The US Food and Drug Administration (FDA) has different paths to market approval depending on the intended use and the associated risks of the device. The European Union and Japan have device approval processes that have many similarities as well as differences to the US regulatory system. This paper describes some of the history and background of the US device approval process with an emphasis on EP devices. It provides an overview of the different regulatory pathways in the USA that are currently being utilized and contrasts them to the procedures often used in the European Union and in Japan. It also touches on the impact of the twenty-first Century Cures Act and how the balance between premarket and postmarket regulatory oversight is continually being examined and refined.

Keywords FDA · Regulation · Premarket · Device · Approval · *De novo*

1 Introduction

The U.S. Food and Drug Administration (FDA) is an agency within the Department of Health and Human Services that oversees the regulation of medical devices as well as prescription and over-the-counter drugs, biologics, food, and tobacco. Within the FDA, the Center for Devices and Radiological Health (CDRH) is responsible for reviewing most of the medical device submissions and providing device manufacturers with regulatory pathways for these devices to be studied and authorized for marketing in the USA. Different regulatory pathways each have their own standard for what evidence is required to support approval. The Center focuses on ensuring that these standards are met when reviewing the various marketing applications. For most applications, this includes demonstration of a reasonable assurance of safety and effectiveness. Additionally, CDRH monitors a device's safety profile after it becomes available to the public. A priority for CDRH is finding the balance between enabling expedient patient access to new and developing technology, while maintaining public safety and confidence. Although many types of devices regulated by CDRH have seen many advances recently, the devices within the field of cardiac electrophysiology have had disruptive game-changing technological discoveries and device innovation for both cardiac implantable electronic devices and for catheter ablation. This has required CDRH and FDA to adapt and expand its premarket and postmarket efforts with respect to these devices.

2 History of device regulation in the USA

Various drugs and medical devices have been invented and sold to the public in the USA for centuries. Although the regulation of drugs began in the early 1900s, premarket regulation of medical devices did not begin until years later with the introduction of the Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938. Initially, device regulation was narrowly limited to pursuing action against harmful or defective devices being sold and against those making blatantly false claims about their devices [1]. The FDA did not gain the authority to review and assess medical devices prior to marketing to consumers until the 1976 Medical Device Amendments of the FD&C Act. This required device manufacturers to provide data to the FDA that supported a "reasonable assurance that the device is safe and effective for its intended use" to be

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allowed to market it [2]. This is now often referred to as the premarket review process. The FDA did not have the authority to require hospitals and other health care facilities to report incidents involving devices that resulted in patient harm or death until the Safe Medical Devices Act was passed in 1990. Importantly, this law also authorized the FDA to order recalls and other corrective actions based on the reports gathered on various medical devices. Subsequent legislation over the years, such as the Medical Device User Fee Amendments (MDUFA), detail the user fees that medical device companies must provide to FDA "whenever they submit an application or a notification to market a new medical device in the USA." [3]. MDUFA, which was first passed in 2002, was most recently reauthorized as MDUFA IV with the passage of the FDA Reauthorization Act of 2017. MDUFA legislation also details performance goals and commitments that the FDA must meet and demonstrate to Congress in the form of successive progress reports. The twenty-first Century Cures Act passed in 2016 and provides the FDA with additional tools to modernize and facilitate regulatory reviews to help accelerate the development and delivery of innovative devices to patients.

3 US regulatory premarket review process

In the U.S., medical devices are classified based on their risk profile and their controls, or regulatory stipulations, necessary to demonstrate reasonable assurance of safety and effectiveness. Class I is the lowest risk category, and Class III is the highest risk category, with Class II being moderate risk. As an example, steerable diagnostic catheters are Class II while ablation catheters are Class III. All implantable pacemakers and defibrillators as well as the programmers are Class III devices while implantable loop recorders are Class II [4]. The intended use of the device also impacts the classification process. For instance, a device that delivers radiofrequency energy that is used non-invasively on the skin for esthetics or for pain relief is typically designated as Class II [5]. Using a device to deliver radiofrequency energy on the myocardium can also be Class II such as the AtriCure multifunctional linear pen which is intended to be used only during open-heart cardiac surgery [6]. However, ablation catheters used to deliver radiofrequency energy to the myocardium are Class III devices given the increased risks associated with use of the device.

The classification of a device is important because it determines the regulatory requirements that apply to a device type including (1) the type of premarket submission that FDA requires and (2) what the postmarket obligations are. In general, Class II devices require a 510(k) submission and Class III devices require a premarket approval (PMA) application. PMAs typically provide more rigorous testing and performance data and are the most stringent type of device marketing application required by FDA. Certain class II devices may be subject to "special controls" which are generally device specific and can include adherence to international standards, performance testing such as bench testing or software validation testing, special labeling provisions, or postmarket surveillance requirements.

Additionally, there are products that are considered combination products when they combine a device with a drug or a biological product. The most common electrophysiology example of this is a pacing or defibrillation lead with steroid elution at the lead tip [7]. For these products, the lead testing and other premarket data must demonstrate sufficient performance for both the lead and the drug components.

3.1 The Premarket Approval (PMA) regulatory pathway

Many of the devices used in cardiac electrophysiology such as ablation catheters and most cardiac implantable electronic devices (CIEDs) are Class III, PMA-approved devices. If a Class III device is novel, clinical data will almost always be part of the PMA application.

Studying these devices in humans in a premarket clinical trial often, but not always, requires permission from FDA. For a medical device that is not legally marketed to be studied in a clinical trial in the USA, or for a legally-marketed device to be studied for a new intended use, FDA approval of an investigational device exemption (IDE) application is often required. The IDE application includes the early clinical and nonclinical data supporting the initiation of the study, as well as the proposed investigational plan. Prior to trial initiation, FDA and the device manufacturer typically agree upon the key elements of the study and protocol such as the sample size, primary and secondary endpoints, and type of study (i.e., randomized, cross-over, etc.). The FDA and the study sponsor will often discuss these aspects of the trial prior to the IDE submission using the presubmission process which can facilitate the eventual IDE review process [8]. Once the study is completed, the results can be assessed to determine whether, in totality, they provide a reasonable assurance of safety and effectiveness for the proposed use [9, 10], (Fig. 1). For example, the left atrial appendage closure device Watchman™ (Boston Scientific, Marlborough, MA) was studied under two IDE studies, known as the PROTECT AF and PREVAIL studies [11–13]. The results and analyses of these studies contributed to the PMA application. Another example is the leadless pacemaker Micra™ (Medtronic, Minneapolis, MN) which was studied under IDE and the results contributed to the PMA application [14]. Although single-chamber transvenous pacemakers are a well-known entity, the leadless pacemaker was considered novel and notably different in design and implantation, with a different set of risks that warranted the clinical study and the original PMA submission. Similarly, the subcutaneous ICD or S-ICD® (Cameron

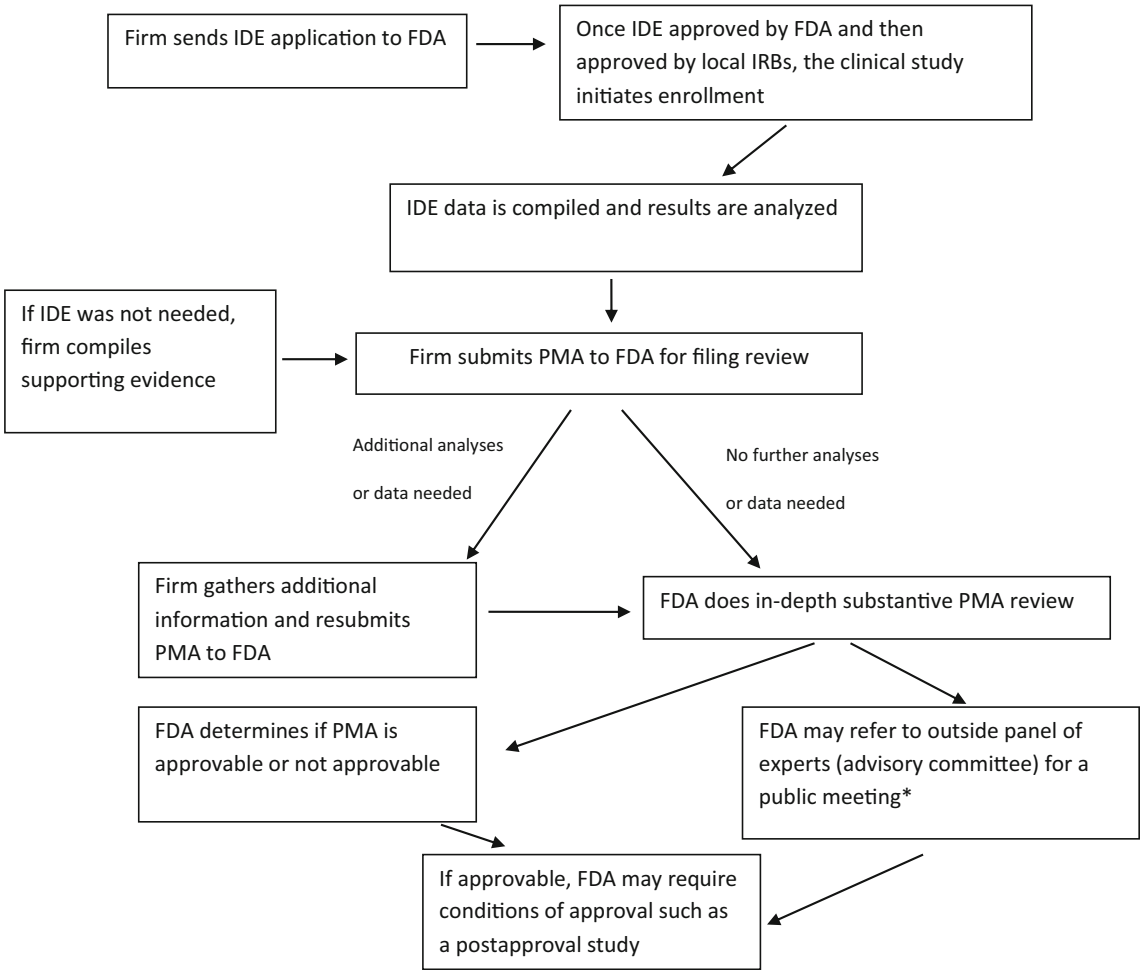

Fig. 1 PMA pathway. *EP devices referred to panel are typically brought before the CDRH Circulatory System Devices Panel of the Medical Devices Advisory Committee. CDRH, Center for Devices and Radiological Health; FDA, Food and Drug Administration; IDE, investigational device exemption; IRB, institutional review board; PMA, premarket application

Health, Inc., San Clemente, CA) was studied under IDE and the results were submitted to the FDA as part of an original PMA application because the S-ICD was novel and different from traditional transvenous defibrillators in terms of implantation technique and risk-benefit profile [15, 16].

There are also situations where a device, such as a pacemaker or defibrillator, already has an approved PMA and is commercially available but the manufacturer wants to add a diagnostic feature, such as a heart failure diagnostic, or make changes to a current feature, such as changing the out-of-the-box tachy detection and tachy therapy settings. These are iterative changes to make an improved next-generation version of an already approved device. If the proposed changes affect the safety and effectiveness of the device then a supplement to the PMA, rather than a new PMA, is often required to be reviewed and approved by the Agency [17]. There are different types of PMA supplements depending on the nature of the changes being proposed. Other examples requiring FDA review are changes to the device's circuits, components, software fixes, or design specification changes. The FDA and the CDRH in particular, considers this to be part of the "life cycle" of devices (called TPLC or total product life cycle). In a TPLC framework, knowledge gained from the postmarket data of a device helps inform manufacturers of possible design changes for the next generation of that device and provides FDA insight into the rationale and the clinical need for the proposed changes (Fig. 2). The review is to ensure that the new or enhanced feature itself demonstrates safety and effectiveness and that the safety and core, basic functionality of the device (i.e., detecting and treating arrhythmias in the case of ICDs) have not been adversely affected. Clinical data expectations for PMA supplements depend on the type and extent of the proposed change. Some examples of when a clinical study was conducted include various algorithms to help detect worsening heart failure such as CorVue® (the DEFEAT-PE study; St. Jude Medical, St. Paul, MN) and HeartLogic™ (the MultiSENSE study; Boston Scientific, Marlborough, MA) [18, 19]. Examples of PMA supplements that did not require clinical data were various defibrillator algorithms used to differentiate right ventricular lead noise from a true ventricular

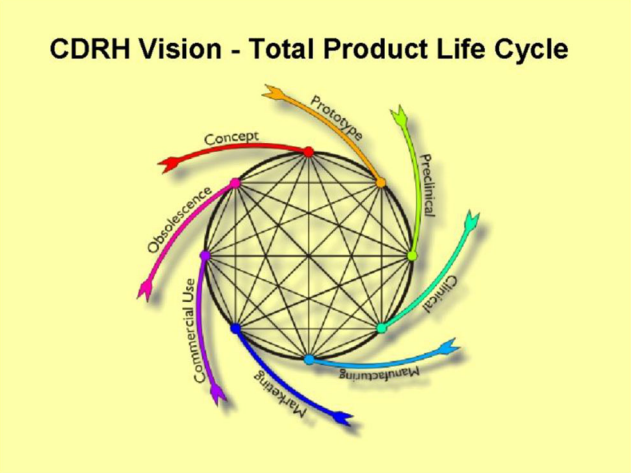

Fig. 2 The total product life cycle, known as TPLC, represents the FDA's vision for new device development. Prior devices help inform the devices of the future. CDRH, Center for Devices and Radiological Health; TPLC, the total product life cycle

arrhythmia such as the SecureSense Lead Failure Detection Algorithm™ (St. Jude Medical, St. Paul MN) [20]. Bench testing and algorithm verification testing were deemed adequate to characterize this technology. The question of whether new clinical data is needed is determined on a case by case basis and can be controversial given the tradeoff between quicker access to the latest technology and the added value of more data to evaluate safety. This can also bring to light the inherent tension that can result from the time needed for the collection of clinical data for various stakeholders, including patient and physician groups who may favor differing levels of assurance.

A PMA submission may also be required if the manufacturer wants to change the intended patient population or the intended use of the device without changing the device in any way. New clinical data may also be required to assess the safety profile and whether it is effective in the new patient group. A good example is the expansion of cardiac resynchronization therapy (CRT) devices to less sick heart failure patients. Medtronic (Minneapolis, MN) and Boston Scientific (Marlborough, MA) conducted randomized clinical trials comparing CRT-D with ICD therapy in class I and class II NYHA patients in order to expand their intended patient population to the less sick class I and II heart failure patients [21, 22]. Similarly, prior to 2009, atrial fibrillation (AF) ablations were often performed using ablation catheters approved for atrial flutter and supraventricular tachycardia such as the NaviStar™ ThermoCool® ablation catheter (Biosense Webster Inc., Irvine California). The manufacturer conducted a randomized controlled study comparing AF ablation using this catheter to antiarrhythmic drug therapy showing a large reduction in AF recurrence in the ablation arm compared with the drug arm and was able to submit these results to FDA to expand the catheter's labeling to include paroxysmal AF patients [23]. Devices, particularly if novel, may also be further studied in the postmarket setting. Although postapproval studies occur after the device is approved and available for clinical use, often the general building blocks are discussed prior to approval during the PMA process. The core questions of safety and effectiveness are answered premarket, and the postapproval study is conducted to answer relevant, clinically meaningful questions that remain after the pivotal study is completed or to provide longer-term follow-up. As an example, the current paradigm for all transvenous leads is a five-year duration postapproval study. The questions to be answered by the postapproval study are formulated along with sample size determination and how the data will be collected. For CIED systems, remote monitoring has enhanced the ability to collect long-term safety data without increasing the burden of frequent clinic visits to the patients and their physicians.

3.2 The 510(k) regulatory pathway

The 510(k) regulatory process is very different from the PMA process. Rather than submit data to FDA demonstrating the safety and effectiveness of the new proposed device on its own merits, the manufacturer submits data demonstrating that the device is "substantially equivalent" to a legally marketed predicate (a previously cleared device or a device that was marketed prior to the enactment of the 1976 Medical Device Amendments). The term "substantial equivalence" means that (1) the new device has the same intended use as the predicate device and (2) has either the same technological characteristics or different characteristics which do not raise different questions of safety and effectiveness. If the device is deemed to be substantially equivalent, then the new device is presumed to be as safe and effective as the specified predicate [24].

In contrast to the PMA pathway, in which devices or modifications to devices are assessed via a stand-alone demonstration of safety and effectiveness, the review process for a 510(k) hinges on establishing that an appropriate predicate device exists and then demonstrating that the device under review is similar to that prior device. If the predicate belongs to a different company, the information provided in the 510(k) can use publicly available data or comparative testing to compare the new device with the predicate device. This review process is termed "clearance" of a device which distinguishes it from "approval" of a device as with devices requiring PMA. More than semantics, this terminology is used to distinguish the different regulatory processes [25, 26], (Fig. 3).

In general, the vast majority of Class II devices require 510(k) notification prior to marketing and are not considered as high risk as Class III devices. An Institute of Medicine (IOM) report from 2011 showed that greater than 80% of 510(k) cleared devices between 1996 and 2009 were Class II and less than 2% were class III [18]. Some examples of EP devices that are Class II and cleared under 510(k) include arrhythmia monitoring devices such as event monitors,

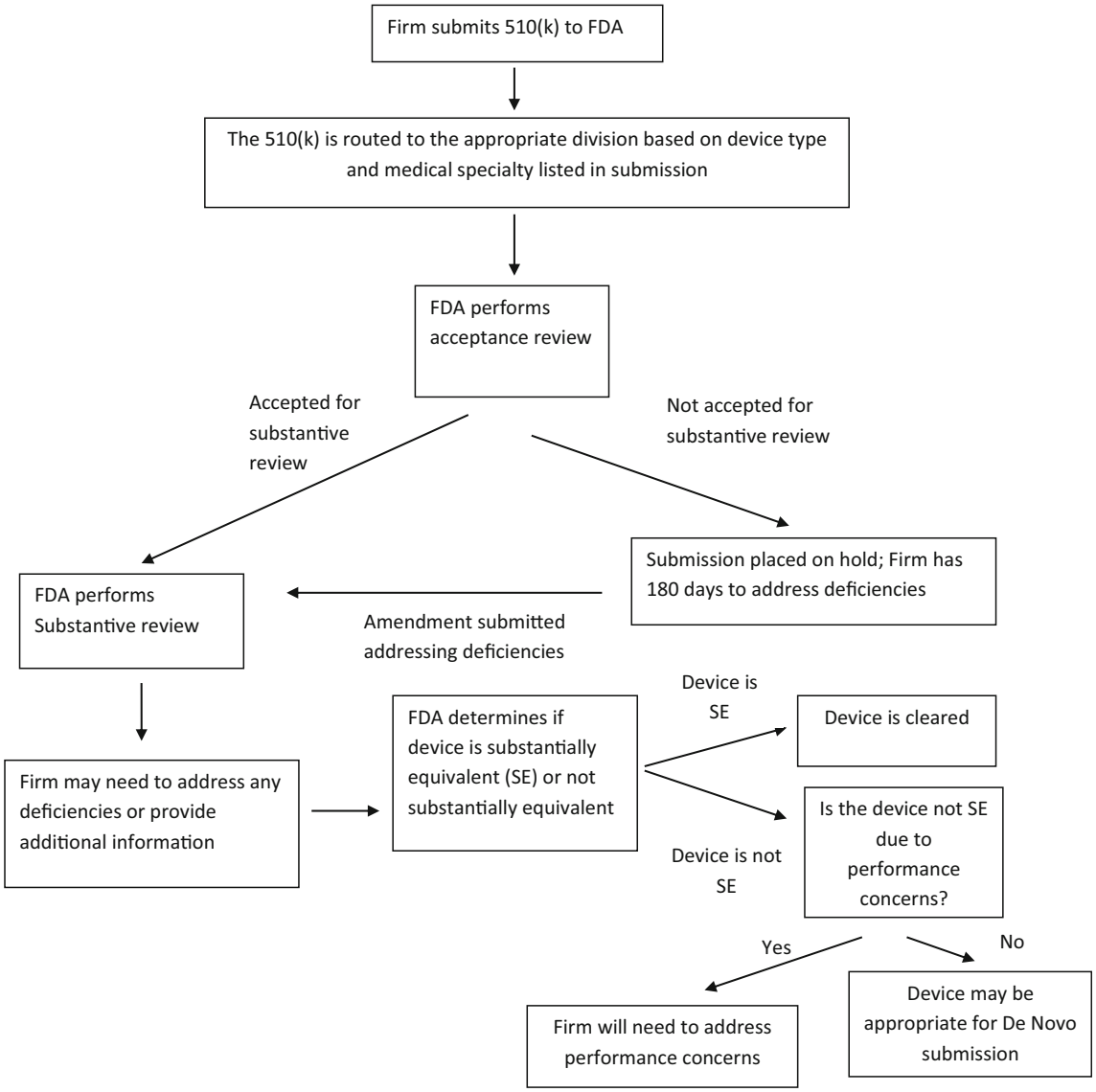

Fig. 3 510(k) pathway

implantable cardiac monitors, transcutaneous pacemakers, and steerable diagnostic catheters. While less common with the 510(k) pathway compared with the PMA pathway, animal or clinical data can be deemed necessary to support 510(k) clearance but the FD&C Act mandates that all requests for additional data be least burdensome [27, 28]. There have been criticisms of the 510(k) process over the years out of concern that it is not rigorous enough and some have even suggested that many of the devices recalled between 2005 and 2010 were due to their clearance under 510(k) [29, 30]. For example, many of these recalls involved automatic external defibrillators (AEDs). Some of the other devices included equipment such as insulin pumps, infusion devices, and mechanical ventilators. Over the past several years, FDA has reviewed current class III devices to determine if a PMA is still required to provide a reasonable assurance of safety and effectiveness or whether reclassification to a lower class would be appropriate. This has resulted in some devices, such as pacing system analyzers (PSAs), being reclassified to Class II because special controls and 510(k) notification provide a reasonable assurance of safety and effectiveness, and has also resulted in some devices such as AEDs now being regulated via PMA rather than 510(k) due to the greater control offered by this pathway [31, 32]. The 510(k) process, which is typically faster and cheaper than the PMA process, continues to evolve as medical technology evolves but is an important regulatory pathway for devices with an appropriate predicate.

3.3 The *De Novo* classification regulatory pathway

New devices that do not have a valid predicate and therefore cannot be considered substantially equivalent to another legally marketed device, have traditionally been automatically placed into Class III. However, novel devices that are lower

risk, based on their functionality and risk profile, and could be classified into Class I or II may use the *De Novo* classification process to get to market. A recent example is the software-only ECG mobile medical app which is used with the Apple Watch. This ECG app can record and display a single lead I electrocardiogram and determine the presence of atrial fibrillation. FDA concluded that it could be classified as Class II with certain mitigation measures in place [33]. FDA recently released a guidance document detailing the *De Novo* classification process [34]. If the device meets criteria, the *De Novo* request can be granted and the device will be classified based on the risk and regulatory controls necessary to mitigate those risks. Once a device is granted *De Novo* classification as a Class I or II device, it can serve as a predicate for future similar devices [35].

3.4 The twenty-first Century Cures Act

The twenty-first Century Cures Act is a legislation that was signed into law in December 2016 that is aimed at providing funding and a regulatory framework for encouraging biomedical research at the NIH level and for facilitating research and modern trial design at the FDA [36]. Regarding medical devices, among other provisions, the Act charges the FDA with pursuing a least burdensome approach and prioritizing the reviews of breakthrough medical devices [37]. A device may be considered a breakthrough device if it is truly a disruptive technology and no alternative therapy exists, or it is superior to currently available alternatives [38].

Some experts have expressed concern that twenty-first Century Cures overly emphasizes speed rather than valid scientific evidence when reviewing devices by favoring real world evidence such as claims data and registry data rather than randomized controlled trial data which are time consuming and costly [39]. However, the bar requiring the demonstration of a reasonable assurance of safety and effectiveness has not been altered. FDA will receive 500 million dollars over 9 years to make improvements, modernize, and importantly, to staff adequately. FDA has already begun implementing twenty-first Century Cures provisions. For example, FDA has started to work with various tools such as computer modeling and simulations to enhance product design and device evaluation. Additionally, the Cures Act facilitates marketing devices indicated for the treatment of rare disorders by allowing more devices to qualify for a humanitarian device exemption (HDE) for small patient populations (less than 8000 patients per year affected in the USA) [40, 41]. The twenty-first Century Cures Act will likely impact future PMA and 510(k) submissions, as well as HDE applications, by creating an overarching environment within the FDA where innovation and efficiency will be enhanced while striving to maintain the focus on protecting public health. This delicate balance of getting new technology to patients quickly while maintaining a sufficiently high bar for safety and effectiveness will likely impact devices in the electrophysiology arena given it is a very "high-tech" field with constant device enhancements and breakthroughs.

4 Regulation of medical devices outside the USA

While reviewing the US regulatory process, it is helpful to compare it with the systems utilized in two other key geographies, representing the next largest global markets for medical devices after the USA: the European Union (EU) and Japan.

4.1 European Union

Unlike the FDA where the standard for approval is a demonstration of a reasonable assurance of safety and effectiveness, CE marking is based on a determination that the device performs as intended and that there is a lack of evidence of serious safety-related issues. Since the passage of the Medical Device Directive (MDD) in 1993 and continuing with the Medical Device Regulation (MDR) legislation in 2017, the premarket requirements for medical devices in EU member countries have been aligned [42]. Manufacturers are required to meet the requirements specified in the MDD in order to be granted a Conformité Européenne (CE) marking and therefore approval to market their device across all EU member states. The EU device classification is similar to the US system in that it is risk based (with four categories) and that this classification determines the regulatory pathway for the device.

Each EU member state has its own governmental body called a competent authority (CA) that oversees medical device regulation and safety. For Class I (lowest risk) devices, manufacturers can market their devices after certifying to the CA that their device conforms to essential safety and performance requirements. The higher risk devices such as pacemakers and defibrillators undergo a more intensive premarket review process by independent companies known as Notified Bodies (NB). These entities are non-governmental, for-profit, private companies that are designated by the CA of their country to review certain types of devices. They charge the device manufacturers a fee for their device review. If the NB agrees that the device conforms to the relevant essential principles and performance standards, it can issue the CE marking. The level of evidence typically necessary to support this decision can vary based on the device classification, with higher risk devices more often requiring clinical data. Prior to initiating any premarket clinical study, the CA must grant approval [43]. As part of the premarket review, the NB can mandate that companies perform specific postmarket studies as a condition of CE marking. The governmental CAs, however, are solely responsible for the postmarket surveillance.

4.2 Japan

Since 2004, the Japanese regulatory process has been overseen by two governmental groups [44]. The Ministry of Health, Labor and Welfare (MHLW) is responsible for the creation, implementation, and enforcement of regulatory policy and for providing the final decisions on regulatory actions such as device approvals and withdrawals. A separate administrative agency, the Pharmaceuticals and Medical Devices Agency (PMDA) conducts the actual technical review of regulatory submissions and postmarket safety information. Like the EU, Japan uses a four-category risk-based classification system, with marketing approval for lower risk devices based either on the manufacturer's self-certification (Class I) or certification by an independent registered third-party organization (Class II and some Class III), with such review predicated heavily on the use of performance standards and criteria established by MHLW. For higher risk devices, companies must submit directly to PMDA. As part of PMDA review, the manufacturer must satisfy any relevant device-specific guidelines in place for these products and demonstrate sufficient safety and effectiveness.

The need to provide clinical data to support Japanese approval is comparable with that in the U.S. and perhaps more common than current EU practices. As with the USA and EU, premarket clinical studies intended to support a future marketing application require governmental approval. In Japan, the MHLW is responsible for granting approval. Postmarket surveillance can be an important condition of marketing approval, although protocol-driven postapproval studies are less common than in the USA (see Table 1.

4.3 Comparison and trends

Compared to FDA approval, CE marking has long been seen as a faster, less expensive pathway to market, due in no small part to less reliance on clinical data, particularly from randomized, controlled trials [45]. However, this attitude may be changing. Due to high-profile instances of device failures in recent years, such as silicone breast implants and metal hip joints, the EU decided to implement a new regulatory review system and the European Parliament and the Council of the European Union passed the Medical Device Regulation (MDR) legislation in 2017 [46]. Scheduled to go into effect in 2020, these new regulations include more oversight of the NB, which is aimed at reducing the variability in the interpretation of the directives among the various NBs across the EU, and closer scrutiny of the premarket evidence by a group of experts at the EU level. Additional changes introduced by the MDR include reclassification of certain device types into higher risk categories, establishment of more stringent safety and performance criteria, more frequent need for clinical data, and greater EU oversight of NBs and involvement in the review of high-risk devices [47]. Taken together, the impact of these changes may narrow or perhaps eliminate the perceived gap between the EU and USA device approval process and lessen the difference between geographies when manufacturers seek a device's initial marketing approval.

In contrast to the EU, the Japanese market is often seen as having a higher bar to entry than that of the USA, due to the perception of more conservative review attitudes and clinical data expectations [48]. In response and in a similar fashion as the FDA, the Japanese government has implemented several new initiatives intended to facilitate access to promising devices. These include establishing a priority regulatory pathway for breakthrough medical devices, promoting the use of clinical registries and increased reliance on postmarket data [49–51]. In addition, in recent years MHLW and PMDA have demonstrated a greater willingness to accept clinical data collected outside Japan to support regulatory approval. This is particularly true for cardiovascular devices. Recent approvals for some novel devices, such as peripheral and coronary drug-eluting stents, and a trending reduction in review times for complex products can be attributed in part to these efforts [52].

Table 1 Contrasting the different regulatory agencies across the U.S., the EU and Japan

	USA	European Union (EU)	Japan
Classification of devices	Classes I, II, III	Classes I, II, III, IV	Classes I, II, III, IV
Premarket review	FDA (federal governmental agency)	Notified bodies (private, for-profit entities)	PMDA (federal governmental organization)
Postapproval study requirement	Fairly common for class III devices	Postmarket registries of novel high-risk devices fairly common	Greater reliance on post market surveillance than on protocol-driven post approval studies
Postmarket surveillance	FDA (federal governmental agency)	Competent Authority (national governmental agency in each individual EU country)	PMDA (federal governmental organization)
Performance requirement for highest risk devices (class III and IV devices)	Demonstration of a reasonable assurance of safety and effectiveness	Device performs as intended without serious safety issues	Demonstration of safety and effectiveness

Truthfully, all three geographies are similarly striving to find the optimal balance between pre- and postmarket data to protect and promote the public health of their citizens. In addition, the growing cooperation between the USA, EU, Japan, and other key authorities as part of the International Medical Device Regulators Forum (IMDRF) is contributing to the harmonization of premarket and postmarket regulatory approaches [53]. The IMDRF is a voluntary group of regulators from several countries to discuss and facilitate convergence of medical device regulation. They meet every 6 months to review various regulatory topics such as cybersecurity, the use of and international device standards and terminology [54]. There has also been an increase in dialog between CDRH and the equivalent EU and Japanese governmental agencies on specific pre- and postmarket device-related issues to gain insight into whether similar concerns or safety signals are present outside of the USA. Given the improved cross-border communication, the electrophysiology community may see greater convergence in regulatory review practices and approaches to clinical evaluation across these jurisdictions in the coming years.

5 Summary

The US FDA regulatory process for Class II, Class III, and *de novo* devices, which includes many EP devices, encompasses the premarket review which can include relevant software testing, bench testing, animal testing, and clinical data depending on the device type and intended use as well as postmarket surveillance. Given that the electrophysiology device arena is rapidly advancing with developments of new technologies and improving those technologies, the EP clinical community is a vital contributor to FDA's regulatory framework by being involved in IDE and postapproval studies and sharing their expertise with FDA.

Medical device regulation and clinical evaluation in the U.S. are comparable in some ways with the regulatory systems employed in the European Union and Japan. All three geographies use a risk-based device classification scheme and require regulatory review and approval prior to clinical study initiation and general marketing. However, the methods used for classification and review differ in significant ways. Although reliance on premarket versus postmarket data varies among these three different regulatory systems, they may become more similar in the coming years as each regulatory authority considers how to strike the right balance between premarket evidence and postmarket surveillance, and as wider global harmonization efforts increase. The future of the regulatory process worldwide will slowly continue to evolve, hopefully with its own life cycle learning from prior regulations to maintain safety while enhancing the efficiency of the premarket evaluation and the detection of postmarket safety signals.

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Compliance with ethical standards

The authors are employees of the Food and Drug Administration.

Conflict of interest The authors have no other conflicts of interest.
The authors have no conflicts of interest besides what is stated above (employed by FDA).

Ethical approval There was no Ethics Committee or IRB approval for this manuscript. There was no research involving humans or animals.

Informed consent None.

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