4.2 Regulatory Basics

INTRODUCTION

Without regulatory approval or clearance by the FDA (or the equivalent agency abroad), even the most innovative and important breakthrough in medical technology will never reach patients. The issues involved in determining the safety and effectiveness of a new technology are often complex – and the data on which decisions are made are never perfect. Innovators can lose patience with a process that seems vague, arbitrary, and interminable, while FDA reviewers can lose sleep over the prospect of approving a device that may someday do unexpected harm to patients.

Because of the critically important role that regulatory issues play in the ultimate success of a new technology, understanding the regulatory landscape early in the biodesign innovation process is essential. In practice, innovators almost always employ an expert to write and manage their regulatory submissions. However, given the extent to which regulatory requirements affect product design, development, and commercialization, innovators must have at least a general understanding of regulatory requirements, options, and nomenclature in order to provide effective leadership in the biodesign innovation process.

This chapter provides an overview of regulatory terminology and a primer on basic regulatory pathways. A second chapter, 5.4 Regulatory Strategy, describes the more nuanced implications of regulatory requirements and how they can become a source of competitive advantage (or disadvantage) to an innovator or company.

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OBJECTIVES

- Understand the basic goals of the FDA and how the agency is organized.
- Learn about the US medical device classification system and how it relates to the two main regulatory pathways for medical devices: 510(k) and PMA.
- Develop a basic understanding of requirements for regulatory approval outside the US.
- Appreciate how to use regulatory risks as a screen for prioritizing concepts.

REGULATORY FUNDAMENTALS

The US Food and Drug Administration (**FDA**) is a regulatory, scientific, and public health agency with a vast jurisdiction, overseeing products that account for roughly 25 percent of all consumer spending in the US.[1] Products under FDA jurisdiction include most foods (other than meat and poultry), human and animal drugs, therapeutic agents of biological origin, radiation-emitting

products, cosmetics, animal feed and, of course, medical devices.[2] The FDA is the lead regulatory agency in the world, although other important device markets either have or are developing robust regulatory systems (regulatory approaches in countries outside the US are addressed later in this chapter).

FDA background

The modern era of the FDA began in 1906 with the passage of the Federal Food and Drugs Act, which created the regulatory authority for the agency. This law was replaced in 1938 by the Food, Drug & Cosmetic Act, which focused primarily on drug safety.[3] Remarkably, devices were essentially not regulated until the Medical Device Amendments Act of 1976. The device amendments were stimulated, in part, by a therapeutic disaster in which thousands of women were injured by the Dalkon Shield intrauterine device.[4] The new law provided for three classes of medical devices based on risk, each requiring a different level of regulatory scrutiny (see below for details).

At the most basic level, the FDA's goal is to protect the public health by assuring the *safety* and *effectiveness* of the products under its supervision.[5] A strong focus on safety is at the core of the FDA's mission and culture. In most cases, the laws that have shaped the regulatory authority of the agency have come in response to high-profile incidents involving unintended, harmful effects of drugs or devices. Even though the FDA's mission also refers to the goal of "advancing the public health by helping to speed innovation," the mandate to protect the public health takes precedence. It is important for innovators to understand this priority and how it influences the reviewers who make key decisions about new technologies. These reviewers are government employees who share a deeply held motivation to serve the public by spotting problems before they get to patients. It follows that there is less incentive to approve submissions quickly than there is to be as certain as possible about the safety of the device.

To understand what the FDA means by effectiveness, innovators should realize that the end result of a successful FDA submission is that the agency clears or approves the marketing and sale of a device for certain, specific clinical indications. For example, a pacemaker might be approved to treat symptomatic bradyarrhythmias (slow heart rates causing dizziness and other symptoms). The exact language FDA approves for the use of the device is reviewed in great detail by the agency and results in a statement of "indications for use" (**IFU**) that is included in the product packaging and advertising. To judge effectiveness, the FDA must decide that the device functions as specified by the IFU. Exactly what kind of evidence is required by the FDA to prove effectiveness depends on the risk associated with the device. While a device with minimal risk will be exempt from any type of FDA premarket clearance (no evidence is required), a device that treats a life-threatening condition will typically require a large-scale, **controlled clinical trial** for approval. It is important to understand that the criteria for clearing or approving a device are not fixed, but evolve with time in response to a number of factors, including new clinical science and accumulating experience in the marketplace with medical technologies. As mentioned, the general tenor of regulation can be strongly influenced by major safety failures that attract media and public attention. For instance, issues with pacemaker leads[6] and metal-on-metal hip implants[7] are two relatively recent examples of incidents that have contributed to a climate of particular caution and scrutiny at the agency. Because device regulation was implemented relatively recently (compared to other areas under the FDA's authority), and because of the complexity of medical devices, the agency's practices and policies continue to evolve as it tries to keep up.

There are two broad and important areas over which the FDA does not exert regulatory control. First, *cost-effectiveness has no part in the FDA's assessment of new technologies*. Data about cost are not part of any submission and there is no mandate for the FDA to be involved in the determination of prices or **reimbursement**.[8] In the federal government, reimbursement levels for medical technologies are determined by the Centers for Medicare and Medicaid Services (**CMS**) – see 4.3 Reimbursement Basics. CMS generally awaits FDA approval before making a positive reimbursement decision, but this is not an absolute requirement. Second, *the FDA does not regulate or otherwise monitor the practice of individual physicians*. Once a device is cleared or approved for sale

in the US, physicians can use it as they see fit.[9] If something goes wrong, a physician may be sued for malpractice if the device has been used in a manner that is not in accordance with the clinical **standard of care** in the medical community. However, the FDA has no jurisdiction in the matter. The agency only has jurisdiction over the device manufacturers and how those companies promote and sell their products.

The FDA is headquartered in Silver Spring, Maryland, in the White Oak Federal Center. The agency has nearly 11,000 permanent employees with approximately 4,000 of them working for Center for Devices and Radiological Health (**CDRH**), the main unit overseeing medical devices.[10] In 1980, the FDA became part of the Department of Health and Human Services. The agency is periodically reauthorized by Congress and is subject to Congressional oversight which, in practice, is distributed across a large number of committees. The proposed FDA operating budget for fiscal year 2013 was approximately $4.5 billion.[11] The FDA commissioner is nominated by the President and confirmed by the US Senate. For the most part, however, the FDA has relatively few political appointees compared to other government agencies, so it is less subject to internal staff changes with turnover in political administrations.

FDA's Center for Devices and Radiological Health

The FDA is organized into several centers according to types of products they regulate. As noted, CDRH provides oversight for devices and also regulates radiation emitting products (including X-ray and ultrasound instrumentation). The Center for Drug Evaluation and Research (**CDER**) regulates pharmaceuticals, while the Center for Biologics Evaluation and Research (**CBER**) oversees biologics (e.g., vaccines, blood products and biotechnology-derived products). Within CDRH, the Office of Device Evaluation (ODE) is the entity responsible for review and approval of most devices, while primarily in vitro diagnostic technologies fall under the Office of In Vitro Diagnostics and Radiological Health (OIR). The Office of Combination Products was established in 2002 to help triage submissions and manage drug-device, drug-biologic, and device-biologic therapies.

The FDA defines a medical device as:[12]

> *An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.*

The key to decoding this complicated description is to understand that chemical action and metabolic change are hallmarks of drugs and biologics. Therefore this definition says, in effect, that if the product is not a drug or biologic, it *is* a device. Of course, there are therapies that fall in the gray zone of this definition (e.g., drug-eluting stents). If there is ambiguity about whether or not a new product will gain access to the market via a drug or biological application or device application, the company can file a request for designation (RFD) and propose a recommendation.[13] However, the FDA will ultimately make the determination. The Office of Combination Products is now making the assignments in most of these ambiguous situations.

Device classification

Once it is clear that a new product is properly characterized as a medical device, the next major consideration is to determine its risk profile based on the current three-tier safety classification system (see Table 4.2.1). **Class I** devices are those with the lowest risk, while **Class III** includes those with the greatest risk.[14] This categorization serves as the basis for determining the regulatory pathway that the device must take before being cleared or approved for human use (the "premarket" stage), as described in more detail below.

Innovators developing devices are initially required to make a "best-guess" selection of the appropriate

Table 4.2.1 Device classification has direct implications on the number and complexity of the requirements imposed by the FDA.

Class	Examples	Description	FDA requirements
I	Bandages, tongue depressors, bedpans, examination gloves, hand-held surgical instruments	Class I devices present minimal potential harm to the person they are being used on and are typically simple in design.	With Class I devices, most are exempt from premarket clearance. There is no need for **clinical trials** or proof of safety and/or efficacy since adequate predicate experience exists with similar devices. However, they must meet the following "general controls": • Registration of the establishment with the FDA. • Medical device listing. • General FDA labeling requirements. • Compliance with quality system regulation (**QSR**), with the exception of design controls, unless specifically called out in the regulation.
II	X-ray machines, powered wheelchairs, surgical needles, infusion pumps, suture materials	**Class II** devices are often non-invasive, but tend to be more complicated in design than Class I devices and, therefore, must demonstrate that they will perform as expected and will not cause injury or harm to their **users**.	Class II devices are generally cleared to market via the **510(k)** process, unless exempt by regulation. They must meet all Class I requirements, in addition to the "special controls" which may include: • Special labeling requirements. • Mandatory performance standards. • Design controls. • Post-market surveillance.
III	Replacement heart valves, silicone breast implants, implanted cerebellar stimulators, implantable pacemakers	Class III devices are high-risk devices. These are typically implantable, therapeutic, or life-sustaining devices, or high-risk devices for which a predicate does not exist.	Class III devices must generally be approved by the **PMA** regulatory pathway, although a small number are still eligible for 510(k) clearance. (FDA has begun the process of requiring PMAs for all of these.) Class III devices must meet all Class I and II requirements, in addition to stringent regulatory approval requirements that necessitate valid scientific evidence to demonstrate their safety and effectiveness, before they can be used in humans.

classification of their device in consultation with their expert regulatory consultants. The FDA offers device classification panels and codes that can be referenced to help with this determination.[15] The classification will be reviewed by the branch of CRDH that evaluates the technology. Roughly half of all medical devices fall within Class I, 40–45 percent in Class II, and 5–10 percent in Class III.[16] If the technology does not fit into one of the existing device regulation intended uses (published in the Code of Federal Regulation (CFR) database) or if the technology is so novel that it raises new questions of safety or effectiveness such that the innovator cannot judge the likely classification, then informal or formal discussions can be pursued with the FDA to clarify the classification. Be advised, this can significantly impact the time and cost of device development.

Through CDRH, the FDA regulates more than 100,000 medical devices ranging from simple thermometers, tongue depressors, and heating pads to pacemakers and kidney dialysis machines. These devices are organized into 1,700 different categories of technology which are managed within ODE. Currently there are seven divisions with a total of 33 branches that are based on medical specialties (see Table 4.2.2).[17] Note that ODE frequently reorganizes its structure as part of efforts to improve the review process.

Each of these branches has separate teams of reviewers who are experts in that area. The primary reviewer will typically have at least an undergraduate degree in engineering or one of the biomedical sciences. Reviewers work on a dozen or more submissions at a time. As mentioned, in vitro diagnostic devices are evaluated under a separate Office of In Vitro Diagnostic and Radiological Health, which has five divisions (Chemistry and Toxicology Devices, Immunology and Hematology Devices, Microbiology Devices, Radiological Health, and Mammography Quality Standards).

Innovators can choose which branch to target for their device submission based on the intended use (although the FDA will ultimately determine which branch reviews the device). The process for making the initial selection of a branch is described in more detail in the Getting Started section of this chapter, but basically involves either searching the FDA's classification database or browsing the regulations for device precedents to determine where other similar devices have been assigned. Using these tools, innovators are able to determine an appropriate classification by finding the description that best matches their own device. For instance, if a team created a new type of steerable colonoscope, members could go to the classification database and do a search on "colonoscope." Alternatively, they could access the device classification panels, choose Gastroenterology Devices, select Diagnostic Devices, and then review the description for Endoscope and Accessories.

Regulatory pathways

There are three major pathways for medical device regulation by CDRH, which are based on the three-level risk classification (although, unfortunately, there is not a one-to-one correspondence between the classification and the pathway). Which pathway the device takes is extremely important to the innovator and any company developing the technology because the effort, time, and cost associated with these different alternatives vary significantly (see Table 4.2.3). Note that the regulatory pathways for pharmaceuticals and biologics, which are overseen by CDER and CBER, respectively, are different than the ones described here (see the websites of those centers for further information).

Relatively speaking, only a few medical devices are required to receive premarket approval (PMA). For example, in fiscal year 2012 the ODE received over 4,000 510(k) submissions, but only 33 original PMA applications or panel track PMA supplements.[18]

Exempt devices

Roughly three-quarters of Class I devices are exempt, meaning that they do not require FDA clearance to be marketed.[19] Examples of exempt Class I devices include elastic bandages, tongue depressors, bedpans, and surgical gloves (see Table 4.2.1). A much smaller number of Class II devices are exempt (less than 10 percent), based on the agency's determination that they represent a minor safety risk. No Class III devices qualify for exemption. In addition to devices that pose little or no risk to patients, there are some other special circumstances under which an exempt classification is given, such as

Table 4.2.2 The ODE is currently organized into seven major divisions with 33 branches that are based on medical specialties (compiled from the US Food and Drug Administration's CDRH Management Directory by Organization).

Office of Device Evaluation (ODE)	
Division	**Branch**
Division of Neurological and Physical Medicine Devices	• Neurostimulation Devices • Neurodiagnostic and Neurosurgical Devices • Physical Medicine Devices
Division of Orthopedic Devices	• Joint Fixation Devices Branch One • Joint Fixation Devices Branch Two • Restorative and Repair Devices • Anterior Spine Devices • Posterior Spine Devices
Division of Surgical Devices	• General Surgery Devices Branch One • General Surgery Devices Branch Two • Plastics and Reconstructive Surgery Devices One • Plastics and Reconstructive Surgery Devices Branch Two
Division of Cardiovascular Devices	• Cardiac Diagnostics Devices • Cardiac Electrophysiology Devices • Circulatory Support Devices • Interventional Cardiology Devices • Implantable Electrophysiology Devices • Peripheral Interventional Devices • Structural Heart Device Branch • Vascular Surgery Devices
Division of Opthalmic and ENT Devices	• Contact Lenses and Retinal Devices • Diagnostic and Surgical Devices • Intraocular and Corneal Implants • Ear, Nose, and Throat Devices
Division of Reproductive, Gastro- Renal and Urological Devices	• Obstetrics/Gynecology Devices • Urology and Lithotripsy Devices • Renal Devices • Gastroenterology Devices
Division of Anesthesiology, General Hospital, Infection Control and Dental Devices	• Anesthesiology Devices • General Hospital Devices • Respiratory Devices • Infection Control Devices • Dental Devices

Table 4.2.3 The three regulatory pathways for medical devices vary in their requirements based on the level of risk associated with the device (compiled by authors from the FDA website).

Pathway	Description
Device exemption	These are devices for which the risk is so low that they are exempt from regulatory clearance. Most Class I devices take this pathway.
510(k)	This is the largest category of medical device applications, in which clearance is based on a device being similar (or substantially equivalent) to existing, predicate devices in clinical use. Some Class I devices and most Class II devices take this pathway.
Premarket approval (PMA)	This is the most stringent pathway, used for devices that are significantly different from existing technologies and/or represent the highest risk to patients. The vast majority of Class III devices take the PMA pathway, although a few still remain eligible for 510(k) clearance (these will ultimately be eliminated).

finished devices that are not sold in the US or custom devices (one-off devices made for a specific patient or application).[20]

Even if a device is determined to be exempt, it still must comply with a minimum set of FDA requirements called "general controls" that also apply to the other two regulatory pathways. These requirements oblige the company to register their facility or establishment with the FDA, fill out a form listing the device and its classification, comply with general FDA labeling and packaging requirements, and adhere to the FDA's Quality Systems Regulation (QSR) – a set of guidelines for safe design and manufacturing (see 5.5 Quality Management). However, exempt devices are not subject to the Design Control Regulations of the QSR unless specifically noted in the regulations. A limited number of Class I exempt devices are also exempt from other QSR requirements.

The 510(k) pathway

The 510(k) review process applies to devices of moderate risk where there is some similarity to an existing technology already in use. This is the pathway required for most Class II devices. A device that passes FDA scrutiny by 510(k) is said to be *cleared* and to have achieved *premarket notification* (in contrast, a Class III device that follows the PMA pathway is *approved* by the FDA). The company making a submission for either a 510(k) or a PMA is referred to as the *sponsor* of that submission.

The "510(k)" nomenclature refers to the section of the 1976 Medical Device Amendments (MDAA) to the Federal Food, Drug & Cosmetic Act that describes this pathway. In creating a new system for medical device approval, the MDAA took into account the fact that there were a number of existing, moderate-risk devices that were already widely and safely in use. These devices were essentially grandfathered by the act and are now described as *pre-amendment devices*. The MDAA also enacted a mechanism for clearing new devices based on similarities to these existing pre-amendment devices that had been "road tested" prior to 1976. A further provision allows for new devices to be cleared based on comparison with other devices that have received 510(k) clearance subsequent to 1976. In any of these cases, the preexisting device to which the new device is compared is called the *predicate device* (see Figure 4.2.1).

To support the 510(k) pathway, the innovator must demonstrate how the device is *substantially equivalent* to the predicate(s) to allow the FDA to compare the new device to these existing devices. In essence, in order for a new device to be found substantially equivalent to a predicate device, it must: (1) have the same indication for use; (2) have technological characteristics that are similar to the existing device; and (3) not raise any new questions of safety and effectiveness in those areas where there are differences with the predicate device.[21] Specifically, this means that the device must be comparable to the predicate device in terms of its intended use,

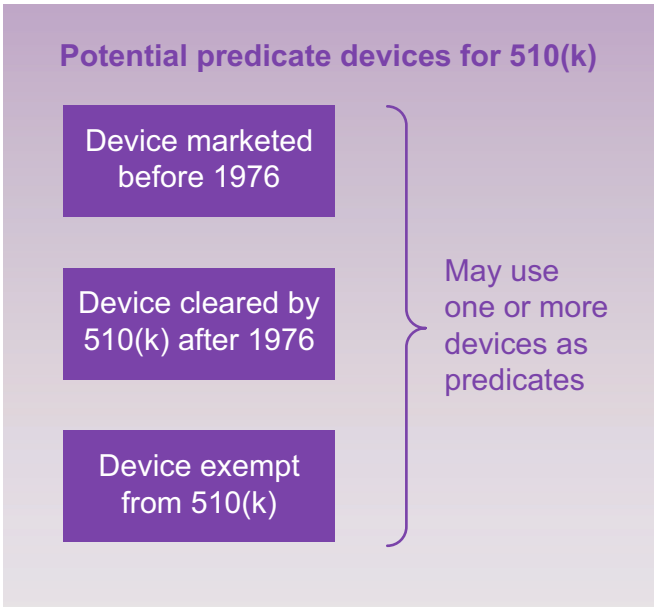

FIGURE 4.2.1
510(k) clearance can be obtained based on either a pre-amendment predicate device, a post-amendment device that has already been cleared via the 510(k) pathway, or a 510(k) exempt device.

design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.[22] Substantial equivalence does not mean that the new and existing devices are identical. However, it does require that the new device provides a relevant comparison (a concept that is ultimately decided by the FDA) and is at least as safe and effective as the predicate device.

Another important aspect of the 510(k) pathway is that a sponsor may choose *more than one predicate device* to make the argument of substantial equivalence. However, the FDA will not allow "split predicates," that is, a situation in which a sponsor is attempting to split the 510(k) decision-making process by demonstrating that a new device has the same intended use as one marketed device and the same technological characteristics as a second, different type of marketed device.

Substantial equivalence for 510(k) clearance usually can be demonstrated on the basis of bench and animal testing. However, although the FDA only requires clinical data for approximately 10 percent of annual 510(k) submissions,[23] that figure is gradually increasing. The FDA will advise innovators and companies whether clinical data collection is necessary. If required, the clinical studies to gather such data are typically much smaller, faster, and less expensive than the trials required for the PMA pathway (see 5.3 Clinical Strategy).

In recent history, the FDA's application of the 510(k) process has been under scrutiny from the media and Congress. An Institute of Medicine (IOM) report criticized the FDA's application of the 510(k) process as overly liberal, allowing too many products to be cleared via this pathway with minimal clinical testing as opposed to the more rigorous PMA pathway.[24] This, along with continued media attention, has led to continued debate surrounding devices cleared via the 510(k) pathway. There is a general trend for more extensive data requirements for 510(k)s, which in some cases may approach the type of filing more typically required for a PMA.

De novo 510(k) clearance In 1997, a new category of 510(k) clearance was introduced called the de novo pathway. This alternative was further modified in 2013 by Congress in the FDA Safety and Innovation Act (FDASIA). The de novo pathway is intended for devices that do not have the major risks of a Class III device, but for which no predicates exist – or for products that raise different questions of safety and effectiveness than those for a legally marketed predicate. The de novo 510(k) generally requires a higher level of proof of efficacy than a standard 510(k), but less evidence than for a PMA. One example of a de novo 510(k) clearance is the Given Imaging Pillcam™ endoscopic capsule. This capsule contains a tiny video camera that transmits images from inside the intestines as the capsule works its way through the gastrointestinal tract. The company provided convincing data to the FDA that the capsule provided acceptable images to aid in diagnostic evaluation, as an adjunct to standard endoscopy procedures. The FDA did not regard the device as sufficiently similar to any existing predicate to support 510(k) clearance, but was willing to grant the de novo 510(k) because of the favorable safety profile of the capsule and the demonstration of effectiveness in imaging. This pathway historically has been used mostly for in vitro diagnostic devices. However, it may prove to

be a useful tool as more complex devices are developed that do not rise to the level of high risk but for which no predicate exists or which raise different questions of safety and effectiveness versus a legally marketed predicate.

Two other categories of 510(k) clearance are worth a brief mention. A company can pursue a special 510(k) when it has modified its own device and is seeking clearance for this modification. An abbreviated 510(k) can be used when the company is able to certify compliance with an FDA recognized special standard – a published document that lists explicit requirements regarding the characteristics or performance of the device. In this case, the company submits a declaration that the device is in conformance with these standards and does not need to submit the detailed test reports required for a traditional 510(k).

Mechanics of 510(k) submissions In almost all circumstances an innovator will use an expert regulatory consultant to prepare a 510(k) submission. The necessary documentation can be many hundreds of pages long (or more), and the approach to choosing predicates and arguing substantial equivalence requires experience.

While there is no standard 510(k) application, the requirements for a 510(k) submission are relatively well defined.[25] The heart of the submission is a section in which the new device is compared to the predicate(s). This requires a detailed and scientific comparison that includes device performance characteristics, data from bench testing and, in some cases, the results of animal and clinical tests. A second important section is the indications for use – a list of the clinical indications for which clearance is sought. The submission also includes a copy of all draft printed material and labeling to be distributed with the device or provided to patients. The sponsor may also submit sample advertising and educational materials. If biocompatibility or shelf-life/stability data are required, these results are also provided. Finally, the submission includes a 510(k) summary or 510(k) statement, which is a public statement that will be posted on the FDA website if the device is cleared.

Numerous device-specific guidance documents are available via the FDA's guidance document database. These guidance documents contain detailed information regarding the FDA's current expectations in order to determine substantial equivalence for the new device,[26] as well as the format to be used,[27] and how to be sure that nothing is overlooked.[28]

510(k) review process and timeline As noted, each 510(k) submission received by the FDA is assigned to one of the agency's primary divisions for review. Not all divisions have the same approach to doing business or working through the review/approval process and there may be benefit in trying to direct the submission to a particular group.

The FDA is required to review a traditional 510(k) submission within 90 days of its receipt. This does not necessarily mean that the FDA must issue a decision within 90 days, but it is obligated to provide feedback within that period. If the FDA cannot make the determination based on the information that has been submitted, the sponsor will receive a request for additional information. There may be multiple such requests and, each time the FDA requests information, the clock may be stopped until the manufacturer submits the requested information. Ultimately, the FDA issues either a substantially equivalent (**SE**) determination or a not substantially equivalent determination (**NSE**). The notification of substantial equivalence comes in the form of a letter from the FDA stating that the device can be marketed in the US. An NSE decision puts the company "back to the drawing board" and is a major liability not only for that device but for the company in general, since it can take a significant amount of time to either file a PMA or rework the 510(k) in order to allow it to be cleared (e.g., change the intended use, collect additional data, etc.).

Although the statutory review timetable for 510(k) clearance is 90 days and there are target review timelines issued by Congress, the actual time for review of a 510(k) can be unpredictable. For the most part, a straightforward clearance can be obtained in several months. Some 510(k)s can drag on for more than a year, based on the complexity of the analysis and number of requests for additional information. The process can also be slowed by substandard preparation of the submission on the part of the sponsor or poor communication between the

sponsor and the reviewer. The FDA now conducts an initial review upon receipt of the submission to ensure that all the required information is present before beginning the 510(k) review process.

The PMA pathway

The PMA pathway is required for devices that represent the highest risk to patients and/or are significantly different from existing technologies in use within a field. There are also certain strategic reasons for an innovator or company to pursue a PMA versus a 510(k); these are reviewed in chapter 5.4. A PMA is based on a determination by the FDA that sufficient, valid scientific evidence exists to assure that a device is safe and effective for its intended use(s) before it is made commercially available. Approval of a PMA device is made based on the merits of that device alone, regardless of any similar Class III devices that may exist. The large majority of PMA applications are submitted for Class III devices. Although there are certain Class III pre-amendment devices that can still be cleared by the 510(k) pathway, the FDA is working to complete classification actions for these remaining devices.[29]

Pursuing a PMA is considerably more complicated than pursuing a 510(k), primarily because the sponsor needs to provide valid scientific evidence to support safety and effectiveness and this often means clinical data from a **pivotal study**. Such studies are typically large, multicenter, **randomized clinical trials** and often represent the single largest expense – and the biggest risk – in the entire biodesign innovation process (see 5.3 Clinical Strategy). As a rough rule of thumb, these studies involve hundreds of patients and cost millions of dollars – or tens of millions. In turn, PMA submissions often reach thousands of pages in length (see Figure 4.2.2).

If a device is life-sustaining, it will require PMA submission whether or not there are similar devices that are already approved. For example, coronary stents are a type of Class III device. Even though other coronary stents exist in the market, all new stents must follow the PMA pathway. A device that was previously classified as Class III and entered the market via premarket approval *cannot* be used as a predicate device for 510(k) regulatory clearance.

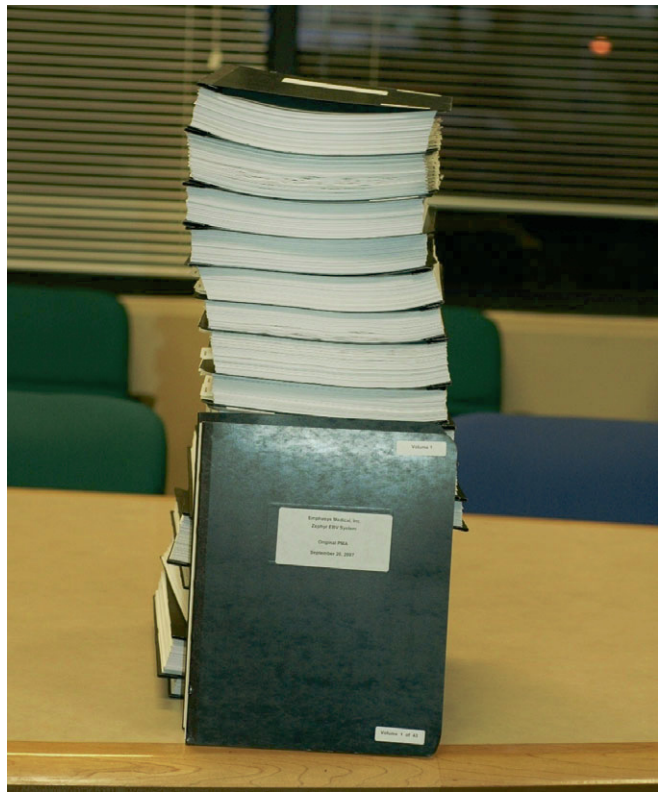

FIGURE 4.2.2
Informally, the length of a PMA submission is often measured in feet rather than by pages (by Joan Lyons, courtesy of Emphasys Medical).

Mechanics of PMA submissions The PMA submission begins with a summary of the safety and effectiveness data. The core of the submission is the clinical study report, which includes the study design and protocol, patient enrollment and exclusion data, **primary** and **secondary endpoints** of the study, data from all patients entered into the trial, and detailed statistical analysis of the results. There are also major sections on technical data, which include biocompatibility and non-clinical (animal or biological) testing, as well as non-clinical laboratory testing that encompasses bench-top testing results and data on stress and fatigue, shelf-life, sterilization, software validation and verification, and other relevant non-clinical tests to support the safety or effectiveness of the device. The proposed labels and IFU are included in the submission. The sponsor may also provide a physician training plan. There is a section on the manufacturing of the device and compliance with

QSR for the FDA to use in preparation of a preapproval facility inspection. There is also a section that outlines a negotiated agreement of additional studies that will be required following approval of the device (called post-market surveillance or post-approval studies). Regulations and guidance documents clearly outline the FDA's expectations and requirements for the contents and format for a PMA submission.[30] Guidance documents for similar products across divisions or for other devices within the division can be helpful to understanding the FDA's current thinking or expectations for a given device.

PMA applications are reviewed by a special advisory panel, a group of 5 to 15 physicians, statisticians and other experts (all non-FDA employees) who serve a three-year term. In addition to the core experts, the panel can add topic experts on a case-by-case basis and also has nonvoting industry and consumer members. After the PMA is submitted and has undergone FDA review, the panel convenes to hear presentations from the company sponsor, its expert consultants, and from an FDA review team. The panel votes to answer questions related to the safety and effectiveness of the device. The recommendations are non-binding, but generally carry great weight with the FDA in making its determination whether to approve or disapprove a new device. The final decision is based on the analysis of the CDRH branch team, subject to the approval of the director of the Office of Device Evaluation.

There are two different types of PMA routes.[31] The traditional PMA is an all-in-one submission that is typically used when the clinical testing has already been completed or when the bench/non-clinical testing or other information will not be completed ahead of the clinical study. The modular PMA is increasingly being used by sponsors in the US. With this approach, the complete contents of a PMA are broken down into well-delineated components (or modules) and each component is submitted to the FDA as soon as the sponsor has finished it, compiling a complete PMA over time. The FDA reviews each module separately, as it is received, allowing companies to gain timely feedback during the review process. This approach may lead to a quicker approval, though this is not guaranteed. The caveat is that the clinical module must be the last one submitted.

The **product development protocol (PDP)** method is an alternative to the PMA process, and is essentially a contract between the sponsor and FDA that describes the agreed-upon details of design and development activities, the outputs of these activities, and acceptance criteria for these outputs. Ideal candidates for the PDP process are those devices for which the technology is well established in the industry. Note that although the PDP mechanism has existed for years, it has not been widely used, and the FDA is currently exploring ways to make the process more efficient and more attractive to sponsors.[32]

PMA review process and timeline The formal FDA review period for PMA submissions is 180 days. As with 510(k) applications, the FDA will approve, deny, or request additional information from the company upon review of its application. There are usually at least two cycles of requests and responses before a decision is made. If the sponsor submits new information on its own initiative or at the request of the FDA, the agency can extend the review period up to 180 days. Final approval comes in the form of a letter from the FDA and represents, in effect, a private license granted to the applicant for marketing a particular medical device (see online Appendix 4.2.1 for a sample). There is no reliable approval time for PMA submissions, but it is by no means unusual for it to take a year or longer.

Investigational device exemptions

In order to begin human testing in advance of regulatory clearance or approval, official permission must be granted to the innovator, either by the FDA, the supervising institutions where studies will be conducted, or both. For a device that is low risk, the innovators can apply for approval of a study to the Institutional Review Board (IRB) of one or more hospitals (see 5.3 Clinical Strategy for more information about IRBs). If the IRB(s) agree that the study involves a non-significant risk, there is no requirement for the FDA or other agency to review the study before patient enrollment commences. However, if even one of the IRBs does not approve the

study, the study may not proceed at *any* hospital without FDA involvement.

For significant risk devices that are headed for a 510(k) or PMA submission, clearance to begin clinical testing must be granted by the FDA via an Investigational Device Exemption (**IDE**). No patients in the US can be enrolled in one of these studies before an IDE is approved by the FDA. Unlike the submissions required for 510(k)s and PMAs, the IDE application process is manageable enough that the innovators who are interested in testing the device may make a submission without using an expert regulatory consultant (although a review by an expert is advisable).[33] Importantly, an IDE does not allow a company to market the device; it is a legal exemption to ship the device for investigation under well-defined and carefully controlled circumstances. Companies can charge for investigational devices under an IDE.

To obtain IDE approval by the FDA, sufficient data must be presented to demonstrate that the product is safe for human clinical use; this may require mechanical, electrical, animal, biocompatibility, or other supportive testing. In addition, the patient consent form (also called the **informed consent** form) to be used in the study must be approved by the FDA. IRB approval is also required for all centers in which testing will be performed. Sponsors have the opportunity to meet with the FDA in an informal pre-submission meeting, during which the **clinical protocol** and any preclinical studies can be reviewed. Strategies for approaching these and other FDA meetings are described in chapter 5.4 Regulatory Strategy. Following submission of an IDE application, the FDA has 30 days to respond. The application is approved, disapproved, or conditionally approved. If the response is a conditional approval, the sponsor has 45 days to respond to the FDA with the revised device and/or clinical trial proposal.

Humanitarian device exemptions

The FDA recognizes that certain devices have a limited application in terms of numbers of patients affected, but still are important medically. For these devices, termed Humanitarian Use Devices (HUDs), there is a special approval pathway, the Humanitarian Device Exemption (**HDE**). The agency defines a HUD as a device that would be used in 4,000 or fewer patients in the US per year. The first step in pursuing a HDE is for the sponsor to apply for a HUD designation for its device from the Office of Orphan Products Development. The sponsor then must have IRB approval before submitting an application for an HDE. Because clinical data for these devices are so difficult to obtain, the HDE pathway does not require the same type or size of trials as for a PMA (in general safety must be assured, but effectiveness requires a lower standard of proof than for a typical PMA). The sponsor must also make a convincing argument that it cannot develop the product except by using the HDE pathway and that no existing device can be used as effectively for the same clinical purpose.

The review period for an HDE is 75 days. An example of a device receiving HDE approval is the Amplatzer® PFO occluder for the treatment of patent foramen ovale (PFO). This condition results from the incomplete closure of the septal wall between the right and left atria (upper chambers) of the heart, a problem that allows blood to partially bypass the natural filtration process provided by the lungs. The new technology was originally developed to target the small group of patients who suffer from strokes related to PFO. However, other exploratory data suggested that PFO closure could potentially help relieve migraine headaches. If confirmed, this would, of course, affect a significantly larger patient population. In the face of this type of new opportunity, the Amplatzer device would not be eligible to address the broader market unless the company obtains approval for a PMA with supportive data for the broader use. **Off-label** promotion by the sponsor of an HDE-approved product for broader use can lead to withdrawal of the HDE.[34]

Costs of FDA submissions

The Medical Device User Fee and Modernization Act (**MDUFMA**), enacted in 2002, established user fees in the medical device industry. Pharmaceuticals and biologic applicants had been paying user fees for some time, but medical devices were historically reviewed "for free." MDUFMA was created to generate resources to help the FDA address increasing review times and to facilitate quicker access to market for medical device

applicants. User fees for establishment registration and for covered submissions are published for each fiscal year.

In general, the fees for a 510(k) submission are modest when the time and expertise required by the FDA for review of these applications is taken into account. For fiscal year 2013, the standard application fee was $4,049 and the small business fee (for companies with less than $100 million in sales) was $2,024. PMA applications are considerably more expensive ($220,050 for a standard application; $55,013 for small businesses).[35] There is no PMA fee for the first PMA submitted by companies with gross receipts or sales less than $30 million.

One upside of the fee schedule is that the law now requires increased measurement and accountability of the FDA in terms of its performance and review times. Effectively, this creates a more businesslike model in which there is an agreement between the applicant and FDA to complete a regulatory review. Importantly, however, it does not hold the FDA to specific timelines associated with applications. The FDA is not obligated to clear a 510(k) in 90 days or approve a PMA in 180 days. Yet, Congress measures the FDA's performance against these goals and the agency's continued funding depends on its performance, thereby creating an incentive for the agency to complete timely reviews and approvals. To date, FDA performance seems to have improved as a result of these changes.[36]

A note on FDA regulation of mobile health technologies

With increasing mobile phone usage, a larger number of health-related services are being delivered by mobile devices, a trend known as digital health or mobile health (**mHealth**). In 2013, the FDA issued guidance for the regulation of mobile medical applications (apps) in the US, which developers of these technologies can use to help determine whether or not they will face oversight from the agency.[37] The intended use of the app is central to making this determination, with the FDA focusing its attention on those mobile technologies that are intended to: (1) be used as an accessory to a regulated medical device, or (2) transform a mobile platform into a regulated device. The guidance further clarifies that, "In general, if a mobile app is intended for use in performing a medical function (i.e., for diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease), it is a medical device, regardless of the platform on which it is run."[38]

The guidance outlines three different categories of apps that correspond to FDA's view toward regulating them, as shown in Figure 4.2.3. The category at the base of the pyramid includes technologies that do not meet the FDA definition of a medical device and, therefore will not be regulated (e.g., medical references for physicians or patients, educational apps for medical training, or apps meant to facilitate medical office functions such as scheduling or tracking insurance claims data). In the middle are apps that meet the definition of a medical device, but pose limited risk to patients (e.g., technologies that coach patients or provide them with health-related prompts and reminders). For these apps, the FDA will exercise discretion regarding the need for regulatory oversight. Stated another way, the agency will investigate potential issues on a case-by-case basis, and it reserves the right to enforce the need for regulation after a product is already in the market. At the top of the pyramid are apps that are considered medical devices and have a significant risk of harming patients if they malfunction. Technologies in this category will be classified using the same risk-based scheme that applies to traditional medical devices (Class I, II, or III) and regulated according to the same requirements.[39] Key examples include:[40]

- *Mobile apps that are an extension of one or more medical devices* by connecting to such device(s) for purposes of controlling the device(s) or displaying, storing, analyzing, or transmitting patient-specific medical device data (e.g., remote display of data from bedside monitors, display of previously stored ECG waveforms). These apps are subject to the regulations governing the devices to which the apps serve as extensions.
- *Mobile apps that transform the mobile platform into a regulated medical device* by using attachments, display screens, or sensors or by including functionalities similar to those of currently regulated

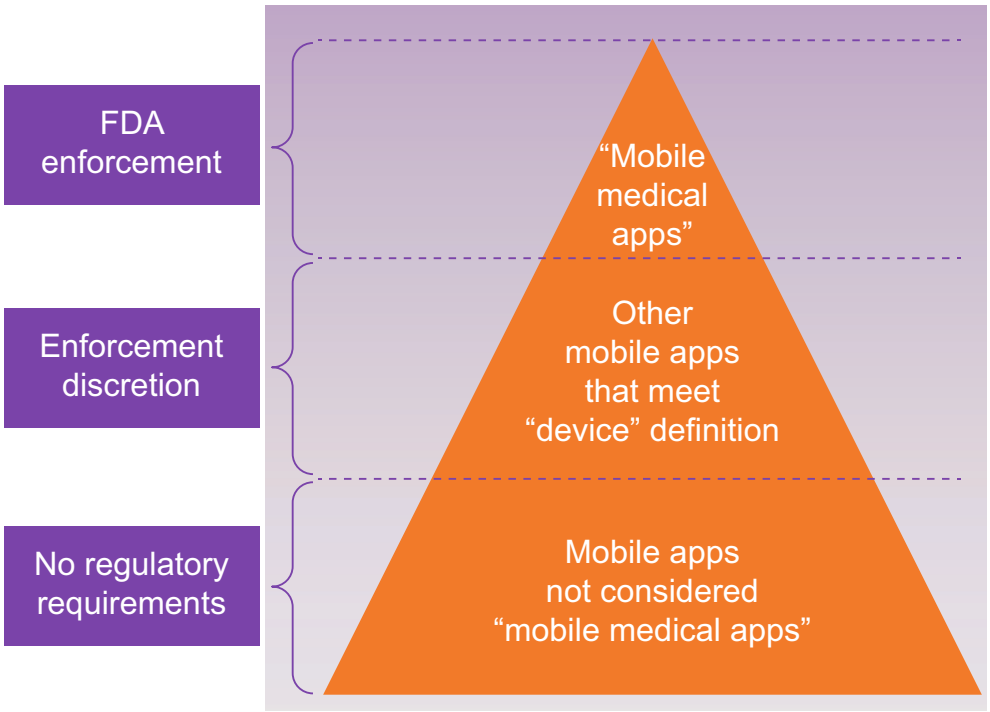

FIGURE 4.2.3
FDA oversight of mobile medical applications (www.fda.gov).

medical devices (e.g., a mobile app that uses a mobile platform for medical device functions, such as attachment of a blood glucose strip reader to a mobile platform to function as a glucose meter; or attachment of electrocardiograph (ECG) electrodes to a mobile platform to measure, store, and display ECG signals). These apps are required to comply with the device classification associated with the transformed platform.

- *Mobile apps that become a regulated medical device (software) by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations* (e.g., apps that use patient-specific parameters and calculate dosage or create a dosage plan for radiation therapy; computer aided detection (CAD) software; image processing software; and radiation therapy treatment planning software). These types of mobile medical apps are similar to or perform the same function as those types of software devices that have been previously cleared or approved. The FDA recommends that the manufacturers of these technologies contact the agency regarding applicable regulatory requirements.

Importantly, the FDA excludes from regulation the hardware on which the mobile medical applications run, as well as the sources (e.g., online app stores) that distribute them.

Summarizing the philosophy underlying the guidance, Geetha Rao, Vice President of Corporate Development at Triple Ring Technologies, Inc., said, "Given the proliferation of mobile medical apps, there's just no way the FDA can exhaustively review everything. So the agency is taking a risk-based approach."[41] The challenge, she continued, is for innovators to interpret the FDA's view of risk. According to Jafar Shenasa, Senior Director of Regulatory Affairs at Proteus Digital Health, one of the most relevant flags is if the app provides patient-specific information. "If the outgoing data from the mobile app becomes patient specific, and that information can potentially lead to clinical decisions, then it's highly likely to be regulated," he stated. "If a technology creates the potential for a patient to bypass the clinician or doctor that is another flag that could lead to an oversight case." The agency will also be on the look-out for companies promoting their apps for use in performing any function of a medical device without having fulfilled appropriate regulatory requirements.

A company called Biosense Technologies was the subject of the FDA's first enforcement action in this space, related to its uChek Urine Analyzer. The company promoted the uChek mobile app to people with diabetes who want to check the amount of glucose in their urine. These individuals download the uChek app to their mobile device. Then, after a "mid-stream collection" of a small amount of urine, they dip an over-the-counter urine test strip into the sample. After a few minutes, the strip changes color to reflect the presence of relevant compounds in the urine, and the patients photograph it with their device's camera. The app assesses the colors and provides the results via email for patients to review and even chart over time.[42]

After uChek had been in the market for some time, the FDA issued the company a letter, with the following message at its core:[43]

> *Please note that though the types of urinalysis dipsticks you reference for use with your application are cleared, they are only cleared when interpreted by direct visual reading. Since your app allows a mobile phone to analyze the dipsticks, the phone and device as a whole functions as an automated strip reader. When these dipsticks are read by an automated strip reader, the dipsticks require new clearance as part of the test system. Therefore, any company intending to promote their device for use in analyzing, reading, and/or interpreting these dipsticks need to obtain clearance for the entire urinalysis test system (i.e., the strip reader and the test strips, as used together).*

After significant back and forth with the agency, Biosense Technologies pulled its original device from the market and made "uChek Lite" available, which did not measure blood or glucose in urine. In parallel, the company began preparing a 510(k) application to pursue regulatory clearance for the next generation of the complete uChek system.[44]

Of course, gaining regulatory clearance from the FDA can be resource intensive. However, it offers certain benefits above and beyond the ability to market the full capabilities of a mobile medical app. The regulatory strategy pursued by AirStrip Technologies, one of the first app providers to receive FDA clearance, illustrates a few of the advantages. Airstrip's technology allows physicians to monitor mothers and their babies remotely during delivery and make clinical decisions that affect the childbirth experience. According to the company, its efforts to secure FDA clearance gave it the confidence it needed to market the app as a clinical tool and not a simple mobile app. Moreover, executives reported that seeking FDA clearance helped AirStrip develop a better product because of the quality standards required by the agency.[45] As a competitive strategy, FDA clearance also puts a stake in the ground for the rest of the market. In effect, it forces all potentially similar apps to follow suit, giving a company that is first to market a head start. Specifically, if the quality bar is set high and includes a thorough clinical validation, it will be more difficult for competitors to easily market a "**me-too**" solution. Also, if the company wants to test the app in a clinical setting – even if only to establish usability – an approval by an IRB will most likely be required, and having 510(k) clearance will simplify this process. Finally, FDA clearance can open the door to reimbursement since it is often a prerequisite to be considered for **coverage**.

To gain a better understanding of how to develop a mobile medical app that will withstand FDA scrutiny, it is invaluable for innovators to engage a regulatory expert well versed in the mobile medical arena as part of their strategic planning process. Rao also recommended investigating the standards being developed by a joint working group of **ISO** (the International Organization for Standardization) and the International Electrotechnical Commission (IEC).[46] In the US, the American National Standards Institute (ANSI) has initiated a joint working group, AAMI-UL 2800, to address interoperability among medical devices in clinical use situations.[47] The FDA itself is unlikely to develop detailed standards for mobile technologies, but will consult the output of these working groups as a reference for decisions about which new mobile technologies to regulate, as the agency currently does with ISO and IEC standards on medical device quality and **risk management**.

Regulatory approval outside the US

Innovators and companies seeking regulatory approval outside the US should conduct in-depth research to understand the unique regulatory requirements they will face. Working with a seasoned regulatory expert with experience in each target country is also advisable.

Traditionally, the most significant medical device markets outside the US have been in Europe, Canada, Australia, and Japan (based on their size and revenue potential). Regulatory requirements in these countries are generally well understood and have converged through the efforts of a Global Harmonization Task Force, which has now been replaced by the International Medical Device Regulators Forum (IMDRF).[48] However, many developing countries are becoming increasingly important medtech markets, particularly Brazil, Russia, India, and China. The regulatory policies of these nations are also converging towards the regulatory model defined by the IMDRF. The most significant difference between the US and the rest of the world is FDA's requirement for proof of efficacy for medical devices, whereas in most other countries the objective is to demonstrate appropriate performance, with an emphasis on safety.

Europe

Medical devices are regulated in the European Union (EU) by three European Commission (EC) directives.[49] The main directive, which covers the vast majority of medical devices from surgical gloves to life-sustaining implantable devices such as heart valves, is the Medical Devices Directive (**MDD**). Further directives cover active implantable medical devices (the **AIMDD**) and in vitro diagnostic medical devices (the **IVMDD**). These three EC directives have been transposed into the national laws of each EU member state, resulting in a legislative framework comprising literally dozens of medical device laws. The MDD and AIMDD will be replaced, sometime after 2015, by a single European Regulation. Unlike Directives, a Regulation is directly applicable without the need for transposition into national laws.

Regulatory approval in the EU is signified by a "CE" mark of conformity. "CE" is not an official acronym, but may have originated in the terms Communauté Européenne or Conformité Européenne, meaning European community or conformity.

The medical device directives are known as "new approach" directives; that is, their purpose is to ensure the free movement of goods and services. Based on these directives, medical devices bearing the **CE marking** can circulate freely and be sold and marketed according to approved indications throughout 31 European countries. The underlying principle of the new approach is that each of the medical device directives contains a list of "essential requirements" that must be met by any product falling within its scope. In the MDD, the list of essential requirements can be broken down into two groups: (1) a set of general requirements for safety and performance that apply to all devices; and (2) a list of specific technical requirements with regard to design and manufacturing that may or may not apply, depending on the nature of the device. For example, the technical requirement for electrical safety will not apply to a urinary catheter. Compliance with the technical requirements is generally demonstrated by using the relevant harmonized European standard. Most European standards are now identical to ISO standards. A harmonized standard is one that has been verified by the EC to be sufficient to carry the presumption of conformity with essential requirements.

Under the MDD, there are four classes of devices that generally correspond to the US device categories, as shown in Table 4.2.4.[50]

In Europe, a clinical evaluation is needed to demonstrate compliance with the Essential Requirements of the Medical Device Directives (90/385 or 93/42). A clinical evaluation may be a written review and summary of published literature which demonstrate that similar devices meet the Essential Requirements. However, data from clinical trials may be required for Class IIa, IIb, and III devices, depending on clinical claims and risk management outcomes. Data from clinical investigations are generally required for Class III, active implantable and implantable medical devices. The key difference between CE marking and FDA clearance or approval is that the CE standard is based on safety and *performance*, which in practice is generally less rigorous than the safety and *effectiveness* standard applied by the FDA (where the

Table 4.2.4 The four device classes in the EU generally correspond to the three classes defined by the FDA in the US.

EU class	Description	US equivalent
Class I	Devices that present a relatively low risk to the patient and, except for sterile products or measuring devices, can be self-certified by the manufacturer. Typically, they do not enter the human body.	Class I
Class IIa	Devices that present a medium risk to patients and may be subject to quality system assessment. Generally, they are invasive to the human body, but only via natural body orifices. This category may also include therapeutic diagnostics and devices for wound management.	Class II
Class IIb	Devices that present a medium risk to patients and may be subject to quality system assessment, as well as third-party product and system certification. They are usually either partially or totally implantable and may modify the biological or chemical composition of body fluids.	Class II
Class III	Devices that present a high risk to patients and require design/clinical trial reviews, product certification, and quality system assessment conducted by a European Notified Body. In most cases, they affect the functioning of vital organs and/or life-supporting systems.	Class III

data must demonstrate that the device is effective in the indications for use). This difference is a major reason why many companies developing devices in the US pursue CE marking first, before entering an FDA pathway (refer to 5.4 Regulatory Strategy). In order for clinical trials to be carried out in the EU, the studies must comply with EN ISO 14155 "Clinical Investigations of Medical Devices for Human Subjects – Good Clinical Practice" and the national laws in the member states where the trials will be conducted. This involves obtaining ethics committee approval (comparable to an IRB in the US) and making necessary notifications to the relevant Competent Authorities. In some countries, approval must also be obtained from the Competent Authority.

A key aspect of medical device regulation in the EU is that the responsibility for ensuring that devices meet the essential requirements lies with the manufacturer. For low-risk devices (Class I), such as tongue depressors or colostomy bags, the manufacturer is allowed to self-declare conformity with the essential requirements. For medium- to high-risk devices (Class IIa, IIb, III) or for devices supplied sterile or with a measuring function, the manufacturer must call on a third party (a **Notified Body**) to assess conformity. To some degree, the manufacturer may choose among methods for "conformity assessment" of the device and/or manufacturing system. The end result is a certificate of conformity that enables the manufacturer to apply the CE marking to the product.

Another major aspect of the CE marking process is that, contrary to the US, the "conformity assessment" for medical devices in Europe is not conducted by a central regulatory authority. The CE marking system relies heavily on third parties known as Notified Bodies to implement regulatory control over medical devices. Notified Bodies are independent commercial organizations that are designated, monitored, and audited by the relevant member states via the national "Competent Authorities." The Competent Authority, which reports to the minister of health within the member state, is empowered to act on behalf of the member state government to apply and uphold the requirements of the EC directives. Currently, there are more than 70 active Notified Bodies within Europe, although this number is likely to be significantly reduced in the wake of stricter control by Competent Authorities. A company is free to choose any Notified Body designated to cover the particular class of device under review. After approval, post-market surveillance functions are the responsibility of the member states via their Competent Authority.

The medical devices directives (MDD and AIMDD) were amended in 2007. This amendment significantly increased the requirements for clinical data in the EU in

the preapproval and post-market phases, emphasizing the importance of clinical risk/benefit assessment. For more information, see the European Commission's guidance to the Medical Device Directives.[51]

Canada

In Canada, medical devices are regulated by Health Canada's Therapeutic Products Directorate and are subject to the Medical Devices Regulations under the country's Food and Drugs Act. Before they can be sold in Canada, all medical devices must be classified and most must be licensed. Health Canada has enacted four device classes (I, II, III, or IV), which vary based on the level of risk associated with their use. Classification is based on 16 rules or factors, including the degree of invasiveness and whether the device is active or non-active.[52]

As in the US and EU, Class I devices present the lowest potential risk and do not require a medical device license (MDL). Class II devices involve moderate risk and require the manufacturer to submit an MDL application, quality system certification, and a declaration of conformity to Health Canada.[53] Class III and IV devices involve substantial risk and for, this reason, are subject to more in-depth regulatory scrutiny before licensing. Manufacturers of these devices must submit the same information as Class II manufacturers; however, they must also prepare a premarket review document. Among other information, this document must include a summary of safety and effectiveness studies, a risk assessment, and information on labeling and instructions for use. For Class IV devices, a complete package of clinical trial data must also be made available. In some cases, data will be accepted from trials conducted in other device markets.[54] More detailed information about completing an application to secure an MDL are provided in the guidance document on this topic[55] and also on the Health Canada website the most up-to-date resource on device regulation in Canada.[56] Review times vary from less than a month for Class II devices to up to six months for Class III and IV devices.[57]

Australia

Formal processes for regulating medical devices and medicines in Australia were enacted in 1989 under the Therapeutic Goods Act.[58] The Therapeutic Goods Administration (TGA) is the entity responsible for administering the Act. The Office of Devices Authorization (ODA) oversees premarket regulation of medical devices and the Office of Product Review (OPR) manages post-market regulation. The Australian Register of Therapeutic Goods (ARTG) is the central point of control for the legal supply of devices and other therapeutic goods in the country. Most devices have to be entered in the register before they can be made commercially available. Limited exceptions to this requirement (e.g., devices undergoing experimental use) are outlined in the Australian Regulatory Guidelines for Medical Devices (ARGMD).[59]

Australia maintains five device classes that correspond to their level of risk – I, IIa, IIb, III, and active implantable medical devices (AIMDs). Class I devices (except those that are sterile or have a measuring function) do not require assessment by the TGA before they are included on the ARTG. All other classes of device must undergo premarket regulation procedures. This includes: (1) the manufacturer applying appropriate conformity assessment procedures; (2) the manufacturer making an Australian Declaration of Conformity – a legal declaration that all the required evidence exists and that the device complies with Australian regulatory requirements; (3) the Australian sponsor submitting the manufacturer's conformity assessment evidence to the TGA; (4) the TGA evaluating the available evidence for high-risk devices; and (5) the device being included on the ARTG.[60] If the manufacturer of a medical device resides outside of the country, it must work with a sponsor that is a resident or incorporated body conducting business in Australia to apply to complete step 3 listed above.[61]

Because the Australia regulatory system is modeled after the system used in the EU, devices that have been granted a CE mark from a European Notified Body can more easily substantiate conformity according to TGA requirements.[62] More about the Australian regulatory system can be found on the TGA website[63] or in the ARGMD.[64]

On a related topic, the Australian government has actively sought to develop a strong clinical research

industry in the country. Companies from around the world come to Australia to conduct **first-in-human** testing and **pilot studies** to capitalize on the country's well-developed healthcare system. Australia's clinicians have a reputation for being highly skilled and interested in trialing new medical device technologies, and the data generated through these studies is generally well regarded internationally. Additionally, conducting clinical trials in Australia is considered to be relatively cost effective.[65] More information is available on the Australian Clinical Trials website.[66]

Japan

Japan's regulatory authority is the Ministry of Health, Labor, and Welfare (MHLW), which oversees the regulation of medical devices through its technical arm, the Pharmaceutical and Medical Device Agency (**PMDA**). Medical devices are regulated under the Pharmaceutical Affairs Law (PAL), with the regulatory pathway determined by device classification. General medical devices (Class I) require a premarket submission (*todokede*), but do not undergo assessment by PDMA. Some Class II devices – referred to as specified controlled medical devices – can undergo premarket certification (*ninsho*) by working with an independent Registered Certification Body (similar to European CE marking through a Notified Body). Higher risk Class II devices as well as Class III and Class IV technologies (referred to as controlled and highly controlled medical devices, respectively) require premarket approval (*shonin*) through the PMDA. Once a device is certified or approved, the MHLW decides on the reimbursement of the technology and its price based on the documents submitted as part of the regulatory process and advisory panel opinions.

All companies intending to manufacture and/or distribute medical devices in Japan must first seek a business license (*kyoka*) that certifies them as a Marketing Authorization Holder (MAH) before pursuing a regulatory pathway.[67] There are three categories of MAH: Category 1 can distributed all classes of devices; Category 2 can distribute Class I and II devices; and Category 3 can distribute only Class I devices. Overseas manufacturers can appoint an MAH (often a local distributor) or a designated MAH (called a D-MAH, which is an independent entity) to manage the device registration process and all interactions with the PMDA.[68]

In late 2013, PAL reforms were passed to strengthen safety measures for devices and medical equipment, as well as to more closely link regulatory oversight to device characteristics.[69] One of the primary changes is to allow Japan's third-party Registered Certification Bodies to review a greater number of devices, including some considered controlled and highly controlled, to speed the approval process and make innovative technologies available in a more efficient manner. Additionally, the reforms will require stand-alone software used for diagnostic to undergo premarket submission, certification, or approval depending on its risk profile.[70] (This requirement may be broadened to include software used for treatment purposes, as well.)

The lack of forms available in English and the country's complex registration process can make Japan a more challenging and time-consuming market for device manufacturers to enter than Europe, Canada, and Australia. For this reason, the advice and guidance of a regulatory consultant is particularly important for companies seeking to do business in the country. It is also helpful to seek consultation from PMDA. The MAH and/or manufacture can schedule a meeting with representatives from PMDA during the early stages of device development to discuss specific regulatory requirements and an appropriate approval strategy. PMDA will also provide guidance on the clinical data necessary to support a submission and the preparation of essential documents. Note that through these consultations, companies can also discover if they may be able to take advantage of special regulatory pathways for particularly innovative devices or those that address important diseases. Although regulatory approval for devices in Japan has typically lagged the United States, the international Harmonization by Doing (HBD) task force was launched in late 2003 to move Japan and the US toward greater synchronization in terms of their pre-submission requirements and timing.[71]

The BRIC countries

The large and developing markets of Brazil, Russia, India, and China are becoming increasingly important medical device markets.

Brazil The Brazilian National Health Surveillance Agency (ANVISA) is an independent agency that works in cooperation with the country's Ministry of Health under a management contract. ANVISA has responsibility for the regulation of all medical products and pharmaceuticals. A 2001 resolution pertaining to medical devices outlines the specific documents necessary in order to register devices and equipment with ANVISA before making them commercially available.[72] In contrast to the EU Notified Body system, ANVISA performs its own registration and inspection functions.[73] Only companies based in Brazil can apply for ANVISA registration, so those without a local headquarters or subsidiary must contract with a hosting company or distributor. This representative becomes the only company authorized to sell or distribute the product in Brazil for a five-year period, so choosing the right partner is essential.[74]

In addition to registration, companies bringing medical devices to Brazil must comply with the Code of Consumer Protection and Defense. This code is meant to ensure consumers that equipment is safe and will be used correctly by requiring companies to provide sufficient documentation to demonstrate the safety of their products. As in other countries, medical devices covered by this code are classified into one of four risk-based categories (I–IV),[75] each with different safety requirements. Companies may be required to compile extensive documentation in a technical file, depending on the nature of the device. Defining the specific requirements for each unique device can be complicated,[76] and all documentation must be submitted in Brazilian Portuguese.

One important form of frequently required documentation is INMETRO certification, which applies to many electromedical devices as well as other non-electrical devices as required by ANVISA. Brazil's National Institute of Metrology, Standardization and Industrial Quality (INMETRO) is the body responsible for accrediting organizations to certify medical devices (and other products) for compliance with the Brazilian Conformity Assessment System (SBAC). To qualify for INMETRO certification, medical device manufacturers must have their products tested to SBAC-recognized standards by an INMETRO-accredited testing laboratory.[77]

Another unique requirement is the completion of an Economic Information Report (EIR), which ANVISA requires for some devices. The EIR includes price comparisons for other countries, patient or user information, information on comparable products, and device marketing materials.[78]

Some devices will also require certification by the National Telecommunication Agency (known as ANATEL) if they include a telecommunications component. ANATEL provides oversight of these products to ensure they meet minimum quality and security standards. Products seeking ANATEL certification must be tested by an authorized laboratory in Brazil.[79] Additionally, companies are required to have an import license for each shipment of medical devices into Brazil. These licenses are used to control imports into the country and are separate from the manufacturer's Ministry of Health registration and safety hurdles.[80]

Innovators are encouraged to work with local regulatory experts to help them understand the specific requirements for bringing a product to market in Brazil. Although the process for registration of medical products has been harmonized across the MERCOSUR countries (Argentina, Brazil, Paraguay, and Uruguay) in the past few years, it can still be lengthy, in some cases taking more than two years between filing for registration and final approval by the government.

Russia Two major government entities oversee the regulation of medical devices in Russia. The first is the Ministry of Health, which works to ensure the clinical safety and effectiveness of products through the process of issuing registration certificates. The second is the Federal Committee (government entity) for Healthcare Oversight (Roszdravnadzor) that reports to the Ministry of Health and focuses on registration of medical devices in the Russian Federation. Roszdravnadzor issues certificates of conformity based on established technical and safety standards.[81]

Before pursuing a certificate of conformity, a company must register its product with the Ministry of Health and have it added to the national register. Within three days of submitting an application, Roszdravnadzor appoints one of the two Expert Council Commissions that

scrutinizes product documentation, as well as the results of technical, safety, toxicology, hygienic, and clinical tests to make its registration recommendations. If the council determines that foreign products have analogs in Russia, it may deny registration of the foreign product. Once registered, the company can seek a conformity assessment by submitting a declaration-application to the authorized certification organization of its choice. The focus of a conformity assessment is on end-product testing.[82]

Roszdravnadzor maintains a website where it publishes the requirements for the registration of foreign-made medical technologies. However, the contents of the site are only available in Russian. Additionally, Roszdravnadzor officials prefer to conduct any consultations in person rather than by phone or email. For these reasons, it is imperative for companies to have an experienced local representative to assist with registration and other regulatory matters in the country.[83]

India Medical device regulation is relatively new in India, although the Central Drug Standard Control Organization (CDSCO) has regulated pharmaceuticals since 1940. In the absence of a comprehensive regulatory framework for new medical technologies, any form of medical device oversight has consisted of classifying certain devices as "drugs" and then applying drug laws to them under the purview of the country's Drug & Cosmetic Act (DCA).[84]

In 2014, the CDSCO regulated only 14 technologies referred to as notified medical devices. This list includes catheters, cardiac stents, drug-eluting stents, heart valves, intraocular lenses, orthopedic implants, internal prosthetic replacements, bone cements, disposable hypodermic syringes, perfusion sets, scalp vein sets, I.V. cannulae, and some in vitro diagnostics.[85] Medical technologies that do not appear on the notified medical devices list do not require registration or certification prior to their sale in India. Historically, they have been adopted based on the purchaser's evaluation of quality, with FDA- and CE-regulated products receiving preferential treatment. Imported medical devices on the notified devices list that have already obtained clearance or approval in the United States (by the FDA) or the European Union (by CE marking) are allowed on the Indian market without undergoing separate conformity assessment procedures.

Recently, a bill was introduced that seeks to amend the DCA and modify its name to the Drugs, Cosmetics & Medical Devices Act. The bill proposes a series of changes, including recognizing medical devices as independent from drugs. Under the new Act, a Centralized Drug Authority would replace the CDSCO and have a separate chapter for overseeing the regulation of all medical devices imported, manufactured, and/or sold within the country.[86] The new rules would provide for the more systematic regulation of medical devices in India and bring its requirements in line with those in other established countries.

The newly proposed legislation will create a Central Licensing Approval Authority (CLAA) under the new Centralized Drug Authority. CLAA will manage the licensing and classification of medical devices, based on the classification system shown in Table 4.2.5.[87] Once the medical devices are appropriately classified, assessed, and licensed, they will bear the Indian Conformity Assessment Certificate (ICAC) mark, authorizing their sales in India.[88]

In 2013, India passed a new policy meant to protect patients who participate in clinical research studies performed within the country. While the intent of the new rules has been lauded, companies and researchers have raised concerns about the burden the policy creates in terms of compensating patients for research injuries or death. Critics assert that the definition of what qualifies for compensation is too broad to be reasonable (for example, one condition attributable to research injury is the "failure of investigational product to provide intended therapeutic benefit").[89] The long-term effects of the policy remain to be seen, but some observers of the medtech and pharmaceutical industries anticipate that it will significantly reduce the number of trials conducted in India and, in turn, the availability of new treatments.[90]

China China passed its first set of laws for the regulation of medical devices in 2000.[91] Regulation is managed by the China Food and Drug Administration (**CFDA**) and

Table 4.2.5 The proposed classification systems for notified medical devices in India (www.icac.in).

Class	Risk level	Device examples	Procedures
A	Low risk	Thermometers, tongue depressors	Class A devices, the manufacturer is required to register with the CLAA.
B	Low–moderate risk	Hypodermic needles, suction equipment	For Class B devices, a Notified Body must assess and certify the manufacturing facility quality management system and the manufacturer is required to register with the CLAA.
C	Moderate–high risk	Lung ventilator, bone fixation plate	For Class C devices, certification by a Notified Body is required with regard to the design and manufacture of the device(s); the manufacturer is required to apply for a manufacturing license from CLAA.
D	High risk	Heart valves, implantable defibrillator	For Class D devices, certification by a Notified Body is required with regard to the design and manufacture of the devices; the manufacturer is required to apply for a manufacturing license from CLAA; the manufacturing facility will also be inspected jointly by CLAA and state licensing authority.

its local counterparts, which are the primary regulatory authorities that apply and enforce laws and regulations concerning medical devices. The CFDA oversees the complete lifecycle of medical device regulation, from clinical trials and marketing authorizations to manufacturing, distribution, and post-market surveillance. Other key regulators governing the medical device industry include the State Administration of Quality Supervision, Inspection, and Quarantine (AQSIQ), the Ministry of Human Resources and Social Security (MOHRSS), the National Development and Reform Commission (NDRC), the National Health and Family Planning Commission (NHFPC), and the State Administration of Industry and Commerce (SAIC).[92]

Medical devices are primarily governed by the Regulations on the Supervision and Administration of Medical Devices,[93] which were amended in 2014.[94] To sell a medical device in China, a company must register its product with the CFDA. Devices are organized into three product classes (I–III) based on their risk profile. The CFDA is primarily focused on regulating Class III products, delegating oversight of Class I and II devices to provincial government agencies.[95] A medical device is either registered as a locally manufactured device or an imported device manufactured outside China. The marketing authorization for a medical device is in essence a permit to manufacture or import a device, and is issued to the manufacturer on record. Importantly, devices to be imported must receive marketing approval in their country of origin before the manufacturer pursues their registration in China.[96]

In some cases, devices may also require approval by either the Ministry of Health or AQSIQ. AQSIQ conducts mandatory safety registration, certification, and inspection for certain devices. Once certified, devices are awarded a "China Compulsory Certification" (CCC) mark, which serves as evidence that the product can be imported, marketed, and used in China.[97]

FDA view of clinical trial data from outside the US

Many US companies perform their initial clinical studies and/or seek preliminary regulatory clearance in foreign locations, driven by the less cumbersome regulatory processes found in some other countries (e.g., those in South America). In some cases, regulatory bodies outside the US accept compilations of key literature and a written analysis of those papers to make a case that a device is expected to be safe and efficacious in lieu of expansive clinical data.

As a result, approval can be quicker, easier, and less expensive in other countries than it is in the US. The FDA does not prohibit this practice, but expects to see all patient data obtained from such studies. Many times, companies use these trials to support an IDE application in the US. In some cases, data from another geography may be sufficient to support a 510(k) submission although, depending on the disease state, the agency may have concern about potential differences in the response of American patients to the device. However, almost all PMA applications and the majority of 510(k) submissions that require patient data will require at least some studies to be performed in the US.

The Edwards LifeSciences story provides an example of how one company approached regulatory approval, as well as the collection of clinical data to support its submissions, for a ground-breaking product with global relevance.

FROM THE FIELD EDWARDS LIFESCIENCES LLC

Navigating global regulatory pathways for a novel device

Beginning in the late 1950s, Edwards Lifesciences established itself as a leader in design and manufacturing of prosthetic heart valves for surgery. Over time, however, the company began to appreciate the **need** for a non-surgical approach to treating aortic stenosis and began working on a solution that became known as Transaortic Valve Replacement (see the CoreValve story in chapter 4.1 for more information on aortic stenosis and TAVR). Progress was accelerated by the acquisition of a start-up company, Percutaneous Valve Technologies (PVT), which had developed and tested a unique valve consisting of tissue leaflets buttressed by a surrounding, expandable stent framework. The valve plus stent could be compressed at the tip of the delivery catheter, so that it could be inserted through a sheath into the femoral vein for delivery to the heart via an antegrade or retrograde approach. Because this technology was deployed without the use of a heart-lung machine and did not require sternotomy (opening of the chest cavity), it promised to be appropriate for patients contraindicated for standard valve replacement surgery and potentially for other patients for whom surgery was challenging.

With its new implant and delivery system, the company anticipated that the new valve (called SAPIEN, see Figure 4.2.4) would be a Class III device and would require clinical data for approval in almost all geographies. The challenge was that Edwards had no specific precedents to follow in terms of what specific studies would be needed to demonstrate the device's safety and efficacy to regulators. Scott Beggins, Edwards' Vice President of Regulatory Affairs, recalled the first steps of the company's approach: "We tried to accumulate knowledge related to the different elements

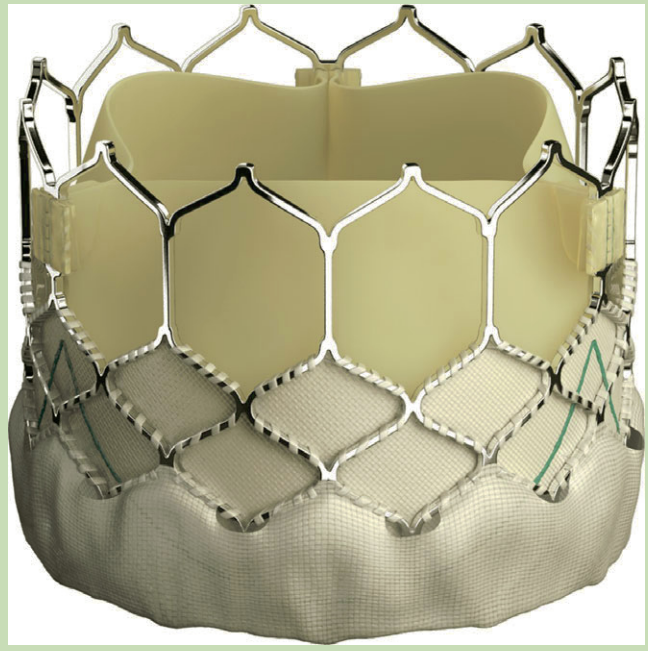

FIGURE 4.2.4
The SAPIEN transcatheter heart valve (courtesy of Edwards Lifesciences LLC).

of our device." For instance, he and his team looked at how similar delivery systems had been regulated and studied the guidance documents available for the existing surgical heart valves in the market. "We started mining through all kinds of documents to figure out which ones were potentially relevant to what we were trying to do," he continued. "And we used that information to help us approach regulatory bodies to open a dialogue on how they would expect us to challenge this type of a device from an engineering perspective." Through this approach, Edwards discovered that many well-established tests would be applicable to TAVR devices to validate their safety and durability.

From the outset, the company thought globally about its approach to bringing the device to market. "The US is such a large market opportunity, we always knew we would end up there," Beggins explained. "It was more an issue of timing. Would it be the first market we'd go after, or the second, or the third?" At the time of the TAVR project, he explained, "It was very difficult to get an IDE through the FDA to get a US trial up and running. It was much simpler, faster, and more consistent to initiate clinical trials outside of the US." Once bench testing had confirmed that the SAPIEN valve was safe to move into human trials, Edwards decided to launch parallel clinical trial processes in Europe and the US, with the expectation that the company would make faster progress in Europe and use that accumulated experience to helpguide its clinical and regulatory interactions with the FDA.

One early step in pursuing a CE mark in Europe is to choose a Notified Body to work with on making the company's regulatory submission. "At the time, Edwards had a few different Notified Bodies that we were working within our other business units," Beggins said, including the leader in performing conformity assessments for surgical heart valves. "But for this product, we wanted a Notified Body that had more experience with interventional cardiology products. The idea was to proactively identify an organization that would appreciate the characteristics of the device, and would not bring a lot of surgical valve preconceptions into the process," he recalled.

Next, the Edwards team began meeting with the Notified Body to discuss clinical data requirements to support its CE mark submission. One factor central to these interactions was agreeing on the target patient population for the preliminary submission. "We came in with a phased approach," Beggins stated, focused first on inoperable patients with severe symptomatic aortic stenosis (using transfemoral access). This was a population where trials could be relatively aggressive from a risk/benefit perspective, he emphasized, "Because there was no treatment alternative available to these patients and people were dying." Based on this grave situation, Edwards and the Notified Body agreed that the clinical hurdle should be manageable with the hope of providing this population with a treatment opportunity in a timely manner.

Edwards requested ethics committee approval to conduct trials in Europe and made necessary notifications to the relevant Competent Authorities. These trials were run at 2–5 sites, and the results were promising. Edwards initially planned to submit data from these preliminary EU studies, but ultimately supplemented this early experience with data from additional studies prior to making a CE mark submission. Although the early data showed potential for the therapy, it also demonstrated that there was room for improvement. Specifically, the company worked to strengthen its approach to patient selection and design of the delivery systems, as well as improvements to the procedure itself. Edwards then submitted a Class III design dossier to the Notified Body. In turn, the Notified Body took the company through a series of questions and answers. After a total review period of about a year, Edwards received a CE mark for the SAPIEN device.

"Post CE marking, we did a controlled rollout in Europe since this was a brand new therapy," Beggins remembered. "At the same time, we continued to pursue approval for transapical access [through the chest wall into the ventricle wall of the heart], as well as continuing studies for a broader population. The next generation of the device, the SAPIEN XT was also in development." Additionally, Edwards initiated regulatory efforts in parts of Asia, South America, and Eastern Europe.

Meanwhile in the US, Edwards was still in discussions with the FDA regarding requirements for pursuing the PMA pathway with the primary emphasis on clinical trial design. "We were in negotiations for many months with the FDA on trial requirements and getting the IDE protocol finalized," Beggins stated. "We were dealing with something new and novel to the FDA, with people who were used to dealing with surgical valves over the last 5, 10, 15, 20 years of their careers. It became a lengthy process and resulted in all of us becoming educated about the engineering dynamics associated with this technology. There was also some resetting of expectations on both sides about what type of testing is appropriate, what that should look like, what the durations and acceptance criteria should be, and so on. There was a lot of interaction on the test side and a huge amount of interaction on what it took to ultimately design the PARTNER trial," with the FDA taking a relatively conservative stance and requiring a full randomized controlled trial. This decision was likely directed by the current approval process for a new surgical valve, which is fairly prescriptive in terms of the engineering testing needed and requires a single arm clinical trial with defined criteria that is then compared to objective performance criteria (OPC).

In the end, Edwards conducted two randomized controlled trials in the US. The first would target a population of patients for whom surgical valve replacement was not an option, comparing TAVR with medical management, with approximately 350 patients at 22 sites and a one-year endpoint. The second trial would target high-risk surgical patients, comparing TAVR with traditional valve surgery, enrolling over 650 patients at 26 sites with a one-year endpoint.

"Once we started the trial and got the enrollment going, our progress was a little more seamless," Beggins commented. "The hard part was just how long it took to get the actual pivotal trial up and running in the US." Once the trial data had been collected, the PMA review process was also relatively uneventful. "We had some back-and-forth negotiations on what the clinical report would look like," he said. "And we had to go through the panel process, which added time to the overall process." The FDA approved SAPIEN in 2011 – a full four years after the device received its CE mark. By then, the valve was approved in more than 40 other countries.[98] Edwards began a controlled rollout of the product across the United States, limited mostly by the extensive physician training requirements associated with the new technology.

Admittedly, the much longer US regulatory process translated into additional time and expense for Edwards. However, Edwards learned a tremendous amount through these interactions. "FDA was very engaged throughout the process." Beggins stated. "Early EU data was also helpful in discussions with FDA. As the early procedural feedback was obtained in both the EU and the US, our engineering teams were able to iterate the delivery systems as well as incorporate new features into the next generation valve designs."

Looking ahead, Beggins explained that the regulatory landscape is undergoing something of a shift, which could potentially affect the way innovators decide to navigate global regulatory pathways. "From the European perspective, their risk appetite is decreasing. I think they're under some pressures to raise the bar for the safety and efficacy of certain products, and they're moving in that direction," he said. In parallel, the FDA is working to be more responsive, focused and supportive of innovation. "My sense right now is that it's easier to interact with the FDA today than it was when we started with SAPIEN. I think we now get better feedback from FDA and they're a better partner."

In terms of other lessons, Beggins stressed that initiating early discussions with regulatory bodies is essential, regardless of geography and especially if clinical data will be required to support a submission. "The early interactions are critical; you don't want to be guessing what they want," he said. Innovators used to worry, he noted, that these negotiations were relatively informal and non-binding, creating the risk that certain recommendations could change without warning. "But now they tend to be more definitive, the feedback more tangible, and the interactions more valuable to

innovators." With novel therapies, Beggins also pointed out that education is essential. "The more you can educate the regulatory bodies about your new therapy, the better the process will work. In some cases, regulatory approval requires a paradigm shift, and they won't support that in the absence of information."

As of early 2014, more than 50,000 patients had been treated with SAPIEN valves around the world.

A final note: using the regulatory pathway to screen and eliminate concepts

To recap, one important reason for gaining a basic understanding of regulatory issues at this stage in the biodesign innovation process is to clarify the risks associated with the **concepts** under consideration. Those with killer risks can be eliminated immediately (e.g., regulatory and related clinical requirements that are way out of alignment with the parameters of a team's strategic focus). For the others, innovators can use the data they gather about the regulatory pathway to help populate a risk scoring matrix (along with IP, reimbursement, and business model factors) as described as part of 4.6 Final Concept Selection.

As should be clear from reading this chapter, regulatory issues can be exceedingly complex: sorting out the final pathway for a new product requires a great deal of time and effort. However, for purposes of screening, some straightforward guidelines can help innovators prioritize which concepts look promising and which are potentially more problematic.

1. **Revisit the team's strategic focus** – Because the path to regulatory approval or clearance is such a major determinant of the time and expense of bringing a technology forward, the level of regulatory risk for different concepts can provide a highly effective screening criterion. The amount of risk a team is willing to take on should correspond directly to its strategic focus. If the team's goal is to create a breakthrough technology platform, it should not be wary of pursuing concepts that require a PMA approval in the US (or a comparable pathway in other geographies). Alternatively, if the team has a desire to bring a device to market relatively quickly and inexpensively, it should target concepts that can be likely can be cleared via the 510(k) pathway in the US (or an equivalent elsewhere).
2. **Look for a template** – If the team is working in an area where other products have previously achieved regulatory clearance or approval, it can be useful to filter concepts based on a template of how these products achieved regulatory success. In cases where a prior technology has gone through the FDA or another regulatory body reasonably quickly and the trial design is available through a journal publication or other means, the existence of this information can make it much easier for companies to understand what it will take to navigate the regulatory pathway. Of course, there is no guarantee that FDA or another agency will agree to the same testing criteria (regulators sometimes modify their requirements based on new clinical or scientific data, or even political pressure). But, in general, the clarity provided by a preceding product can be helpful for companies taking a fast follower approach. In some technology areas, the regulatory agency may have created guidance documents, which can make the regulatory pathway clearer than for a concept where no guidance exists (with the same caveat that the FDA can always change its approach). Based on this knowledge, if the template suggests a pathway that is attractive to the team, concepts that look like they could use this regulatory approach might be more attractive.

3. **Estimate the cost to clearance/approval** – As emphasized earlier, the main burden that regulatory requirements represent for a team or company is the time and cost required to get a product to market. Time and cost are directly driven by the size of the clinical trial, the type of data to be gathered, and the duration of follow-up required. In most cases, it should be possible to estimate what information the FDA or another regulatory agency is likely to request and, on this basis, perform a "back of the envelope" calculation of the time and expense needed to provide the data. The difference between a 510(k) that requires only bench data and one that will involve a two-year study with hundreds of patients may be tens of millions of dollars or more. These numbers provide a critically important measure for screening different concepts in order to find ones that are consistent with a level of funding that is realistic for the team. The key is to make sure that the benefits (in terms of improvement in clinical outcomes, economic impact, and potential financial return to the innovators, investors, or company) are sufficient to justify whatever level of effort is required to clear the anticipated regulatory hurdles.

Online Resources

Visit www.ebiodesign.org/4.2 for more content, including:

- Activities and links for "Getting Started"
  - Confirm the appropriate regulatory branch
  - Classify the device
  - Determine the regulatory pathway
  - Secure a regulatory consultant
- Videos on regulatory basics
- An appendix that shows a sample FDA premarket approval letter

CREDITS

The editors would like to acknowledge Janice Hogan and Nancy Isaac for their extensive editing of this material. Many thanks also go to Scott Beggins of Edwards Lifesciences and Ritu Kamal for their assistance with the case example, and to Geetha Rao of Triple Ring Technologies, Inc. and Jafar Shenasa of Proteus Digital Health for their guidance on the mHealth regulatory section. Further appreciation goes to Milena Adamian of Life Sciences Angels Network; Andrew Cleeland of The Foundry; Julie Delrue and Sarah Sorrel of MedPass International; Ajay Pitre of Pitre Ventures; and Katherine Wang of Ropes & Gray LLP; as well as Robson Capasso, Raj Doshi, Peggy McLaughlin, Jan B. Pietzsch, and Chris Shen for contributing to the information on international regulatory requirements. Darin Buxbaum, Trena Depel, and Asha Nayak deserve recognition for their early assistance with the chapter.

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