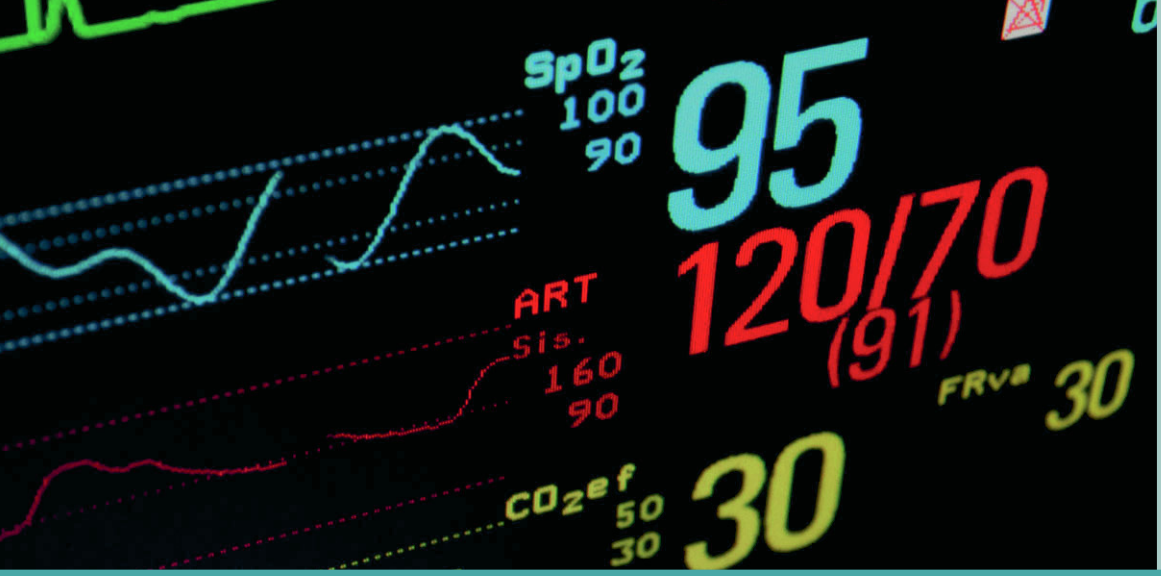

5.4 Regulatory Strategy

INTRODUCTION

The team spent 28 months and more than $45 million on the clinical trial. The PMA submission totaled over 10,000 pages and required three detailed responses to questions from the FDA. The panel meeting was a rollercoaster, with several experts voicing significant initial concern about the safety profile of the device. Now the official letter has finally arrived from CDRH and the team is savoring one short sentence: "You may begin commercial distribution of the device."

Developing an effective, strategic approach to regulation is of critical importance in the biodesign innovation process, not only because this is the gateway to clinical use of the product, but because of the considerable time, cost, and effort associated with this work stream. A sound and thoughtful strategic regulatory plan is tightly coupled with the competitive positioning of a new technology, and it informs the sales and marketing approach, clinical strategy, quality processes, and risk management policies that the innovator puts into place. The regulatory strategy establishes the foundation and sets the constraints within which these interrelated issues must be managed.

While 4.2 Regulatory Basics provides foundational information about the requirements and tactical implications of current regulatory requirements, this chapter addresses the strategic aspects of regulation as part of the broader biodesign innovation process.

See ebiodesign.org for featured videos on regulatory strategy.

OBJECTIVES

- Understand the strategic risks and opportunities associated with the PMA and 510(k) pathways in the US.
- Explore strategic and tactical issues in dealing with the FDA.
- Consider alternative regulatory approaches outside the US, as well as ways of integrating these strategies with FDA approval.
- Recognize common regulatory mistakes and learn how to avoid them through the creation and implementation of a strong regulatory strategy.

REGULATORY STRATEGY FUNDAMENTALS

When innovators set out to develop a regulatory strategy that includes the US as a target market, there are a few key considerations that should guide this effort. First, although it is possible to help inform the thinking of the Food and Drug Administration (**FDA**) about the regulatory pathway for a **medtech** innovation, ultimately the decisions will be made by the center, division, and branch based on the experience and orientation of the specific group charged with reviewing the submission.

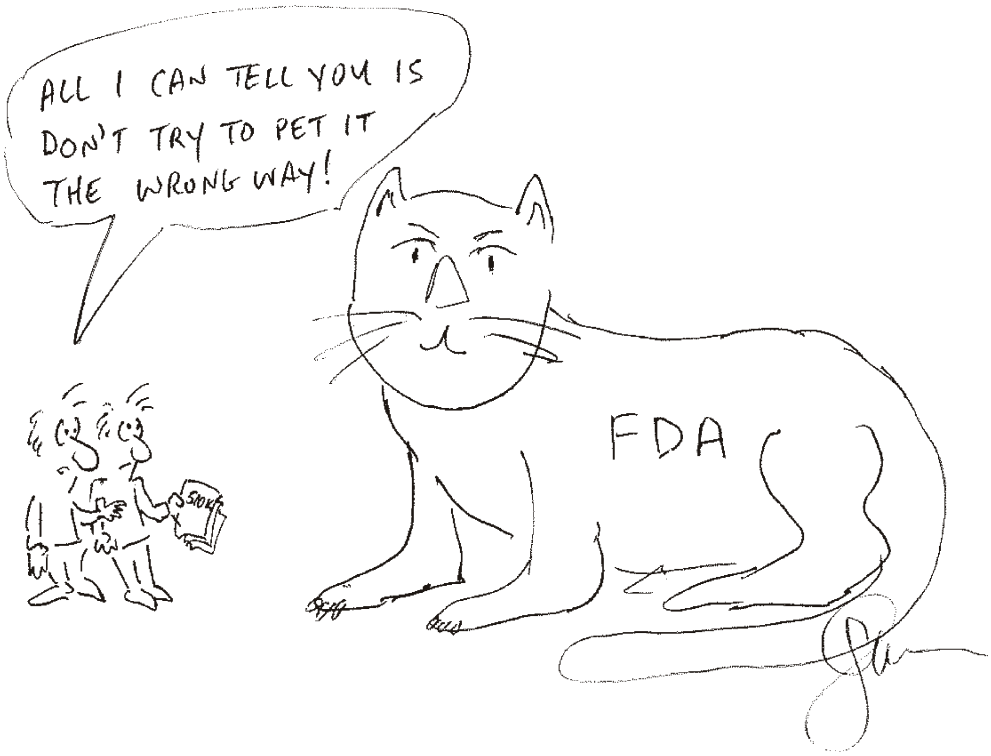

FIGURE 5.4.1
Approaching the FDA can be daunting, especially for first-time innovators. A well thought-out strategy, the right consultant, and effective communication are key elements to success.[1]

As described in 4.2 Regulatory Basics, the overall culture of the FDA is strongly rooted in its primary mission of protecting public health. How this mission is interpreted when making a decision on a particular submission depends on the context of current events (and can be heavily influenced by recent problems with devices or drugs). In general, regulatory processes for devices are becoming more rigorous and the level of evidence required is moving closer to that for drugs (though the size, complexity, duration, and expense of device trials still tends to be lower). There is significant risk to innovators and companies working within this constantly changing context (see Figure 5.4.1) – but this risk can by mitigated, at least in part, by understanding the dynamics in the regulatory environment. At the same time, the FDA is showing an increased willingness to accelerate the regulatory process for truly innovative technologies – and a willingness to work with companies to explore ways of reducing the time and expense in getting new products to patients in general.

A second important "big picture" issue is that FDA clearance or approval, although an important milestone for the company, by itself is essentially worthless if there is not a way for the company to get paid for the new technology. As described more fully in 5.6 Reimbursement Strategy, the Centers for Medicare and Medicaid Services (**CMS**) is responsible for determining whether or not a device will be reimbursed by the US government. This, in turn, can influence the practice of hundreds of private insurers. Therefore, unless the device is intended to be paid for by individual consumers, developing a **reimbursement** strategy must proceed in concert with crafting a regulatory strategy.

Is the device regulated?

One important question to clarify at the start is whether or not the innovation should be regulated as a medical device. In some cases, it is possible to develop claims for the uses of a product that take it outside of an FDA pathway. One example is exercise equipment, where the boundaries regarding whether or not these are medical devices are not completely clear. If a product can be developed and sold as a consumer product and not a medical device it can be advantageous to take a route that bypasses FDA clearance or approval. However, innovators must be careful about how they promote the

product so as to not place it under FDA's jurisdiction. For instance, an exercise treadmill could be advertised as a way of increasing the pulse rate, but not as a technology that reduces the incidence of heart disease. In some cases, it may be feasible to market a product directly for consumer use while developing a related product that will be regarded by the FDA as a medical device. An innovator can petition the FDA to obtain a formal determination of whether or not a product is a medical device under the FDA definition (this is known as a 513(g) petition). If, in response to a 513(g) petition, the FDA determines that the product is a device, the agency will generally provide information on the device classification and applicable regulatory requirements.

The tactical question of whether or not to engage the FDA comes up frequently in the case of mobile wellness and other **mHealth** technologies (for example, monitoring devices for ambulation and heart rate). Similar to the treadmill example, there can be a gray zone regarding the degree to which medical claims are being asserted for the technology. The final guidance for mobile medical applications, published in 2013, helps clarify for innovators whether or not their technologies will face oversight from the agency.[2] At its core, the guidance states that if a mobile technology or application 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) using patient-specific information, it is a medical device and will be subject to regulation.[3] Given the rapidly growing number of mobile apps being developed, the FDA will rely on "enforcement discretion" to pursue companies that overextend their marketing claims (see 4.2 Regulatory Basics for more information on the regulation of mobile medical apps).

Innovators and companies are encouraged to think carefully about whether or not to pursue regulation and seek professional advice about an appropriate course of action. Examples like the action against genetic testing start-up 23andMe increasingly underscore the potential risks of deciding to bypass regulation. In late 2013, the FDA issued a warning letter to the company expressing concern that 23andMe did not have adequate scientific evidence demonstrating that its health-related genetic tests provide accurate results. Moreover, they raised the issue that the unsubstantiated genetic information provided by the Personal Geromic Survey (PGS) could cause consumers to make unnecessary or potentially dangerous health-related decisions, consistent with the 23andMe marketing claims that many of its test results offer a "first step in prevention" that enables **users** to "take steps toward mitigating serious diseases."[4] As one article explained, "By definition, these claims classify the PGS as a medical device under the federal Food, Drug & Cosmetic Act, and as such it is subject to FDA regulation including the requirement for FDA approval or clearance prior to marketing. However, 23andMe has never been granted such approval."[5] In response, the company agreed to stop marketing its health-related genetic tests in order to pursue **510(k)** clearance.

Which center and division/branch to target?

If it is determined that a product is a device and will be regulated by the FDA, innovators must make an initial determination of which class of product – device, drug, or biologic – is most appropriate, as well as which center – the Center for Devices & Radiological Health (**CDRH**), Center for Drug Evaluation & Research (**CDER**), or Center for Biologics Evaluation & Research (**CBER**) – should evaluate the technology. Most often for medical devices, this is a straightforward decision (see chapter 4.2 for FDA's definition of devices) and CDRH is the appropriate center to perform the evaluation. One practical point is that CDRH tends to be somewhat easier for innovators to deal with than the other centers and, if clinical data are required to demonstrate safety and effectiveness, the requirements and number of **subjects** can be substantially less. If a technology is intermediate with respect to classification, innovators are often advised to push for regulation by CDRH.

Increasingly, devices are being integrated with drugs or biologics and this has led to the creation of the Office of Combination Products (**OCP**). OCP's charter is to make decisions about whether or not a new technology constitutes a combination product and, if so, which centers regulate it (and which one takes the lead). The most well-known example of a combination product is the drug-eluting stent, in which a basic metal lattice

device used to hold open an artery was modified with a coating or surface that releases a drug to inhibit the restenosis (tissue re-growth) that occurred with bare metal stents. In this case, the OCP determined that the mechanical effect of opening the artery was the primary mechanism of action and that the drug effect on restenosis was secondary to the mechanical aspect in achieving its intended use. As a result, CDRH took the primary regulatory role, with substantial input from CDER.

All things being equal, the approval pathway for a combination product will be clearer (and the review will be more likely to be based at CDRH) if the drug or biologic that is added to the device is already cleared through its respective center (and the sponsor can argue that it is secondary to the device aspect of the product). However, because combination product submissions are so complex, strategies to address them must be developed on a case-by-case basis. Even if the combined product is evaluated by CDRH, it will likely have a consultation review by CDER or CBER and, in any event, will need to meet requirements for the drug or biologic.

Once a technology is directed to CDRH, there may be latitude in some cases regarding which division or branch reviews the submission. The various divisions and branches tend to have somewhat different standards of evidence (type and length of trial, number of subjects, etc.), based on their traditions and experience. For example, the first company to seek approval for vessel anastomotic devices (devices to attach blood vessels together without requiring a surgeon to suture by hand) was reviewed by the General Surgery Group. Once the devices reached the marketplace, there were some unanticipated cardiovascular complications. As a result, the market leader – along with a number of other companies that had begun the regulatory process in the interim – were shifted to the Cardiovascular Division, with new sets of standards that were much more difficult to meet. In practice, it is unusual for the innovator or company to have much latitude in choosing a division, but it is worth understanding the implications of dealing with one division versus another. Expert regulatory consultants track these dynamics closely and can be extremely valuable as advisors in navigating this process.

Strategies related to IDEs

As described in 4.2 Regulatory Basics, an investigational device exemption (**IDE**) is required before any trials are initiated with US patients. For a device or study with **significant risk**, the innovator must submit an IDE to the FDA prior to initiating the clinical investigation. The FDA will review the protocol and other accompanying information and must grant IDE approval in order for the study to commence. For a device or study that the company considers to pose a non-significant risk to patients, the company is not required to submit an IDE to the FDA as long as the hospital institutional review boards (**IRBs**) approve the study protocol and informed consent documents. In this case, the study can proceed (for example, to generate data for a 510(k) submission). It is important to note, however, that the FDA must be notified if any IRB rejects the study because it poses a significant risk, even if several others have approved it.

It is also worth emphasizing that pursing a non-significant risk study with the expectation of using the data to support a marketing submission without prior discussion with the FDA can be problematic. In this situation, the innovators have no direct perspective on what the FDA will consider to be suitable data to support the ultimate claims, once the study is presented to the agency. For this reason, it is generally advisable to request a pre-submission meeting for an IDE with the reviewing branch for either a non-significant or a significant risk device. The purpose of the meeting is to ensure that the company and FDA are in general agreement prior to executing a clinical study. These meetings are also useful for companies intending to launch **pilot** human studies outside the US. In these meetings, the company, often accompanied by the lead **clinical investigator**(s), presents data to a team of reviewers at CDRH. The company will explain or demonstrate the device and outline the preclinical and clinical development plans. In the pre-submission package, the company also must pose specific questions to the FDA. The agency group members review existing **bench** and animal data, and they make informal, non-binding suggestions regarding the need for additional preclinical data, as well as comment on the suitability of the study design to support the proposed intended use and product claims. The FDA will

generally have a statistician in the group, so it is advisable to provide a detailed statistical analysis plan for the study (and bring a statistician along from the company side to answer questions and explain the rationale for the statistical methods chosen). Depending on the complexity of the device and study, it may be useful to request two meetings to occur at different stages in the planning process.

Each meeting will generally last an hour and typically requires scheduling at least four to six weeks in advance. The FDA has specific recommendations for the content of the pre-submission meeting package available on its website.[6] It is critically important that the team making the presentation outlines a study plan with sufficient detail in order to solicit meaningful agency feedback on its proposal and to address the specific questions posed. An open-ended approach to the FDA, asking for guidance in helping to design a study, is not a good idea and will likely result in a more complicated and expensive study than the company wants to undertake (and often can hurt the company's credibility with the agency).

Keep in mind that the FDA is not obliged to "approve" any aspects of the study design at this meeting and has the right to change its advice as the study matures or as new information becomes available. Nonetheless, it is extremely important for the company to formulate questions for the agency that will provide as specific and useful guidance as possible. For example, a company might ask, "Does the FDA agree that 100 patients is a sufficient study cohort for this trial to demonstrate a 20 percent improvement in the clinical endpoint specified?" or "Are nine months of follow-up data sufficient to adequately demonstrate safety and effectiveness or durability of effect?" A designated member of the company team should take detailed notes of the meeting and send a summary to the group leader from the FDA. There is no requirement for the FDA to record notes, although some agency teams will keep minutes. However, the FDA will send responses to the specific questions submitted as part of the pre-submission package.

510(k) versus PMA

The appropriate regulatory pathway within CDRH – 510(k) versus premarket approval (**PMA**) – is generally determined by the risk classification of the device. As emphasized in 4.2 Regulatory Basics, it is unusual that an innovator or company has the opportunity to exercise significant influence over the pathway chosen. However, it is worthwhile to have a clear understanding of the high-level advantages and disadvantages of a 510(k) versus a PMA, as summarized in Table 5.4.1 and in the discussion of the two pathways below.

Strategies for 510(k) clearance

Clearance under a 510(k) relies upon the concept of substantial equivalence to a predicate device, where a predicate device is defined as a device cleared before 1976, a device already cleared by the FDA through the 510(k) process, or a 510(k) exempt device. Substantial equivalence means that the new device is at least as safe and effective as the predicate device or devices. Importantly, according to the FDA, substantial equivalence does not mean the new and predicate devices must be identical. In fact, the predicates used in successful 510(k) applications sometimes appear not to have close similarities to the new device. But, from the standpoint of the agency, they do provide relevant comparisons. FDA's criteria for substantial equivalence are outlined in chapter 4.2.

Strategically, selecting predicate devices and specifying the intended uses for the new device requires a sophisticated understanding of substantial equivalence – and, in practice, requires input from a regulatory specialist. 510(k) clearance limits the use of a device to a finite set of clearly defined indications (which will ultimately be described in the package insert once the product is sold). For expeditious 510(k) clearance, the indications for the new device must be described in language that is the same as that used to obtain clearance for the chosen predicate device(s). There can be no "creative license" in the language about indications. The only way that new language surrounding indications will be acceptable to the FDA is if data are provided to back up any modifications, while still proving substantial equivalence in terms of the technological characteristics and intended use of the device. For these reasons, companies must think carefully about the predicate devices they choose and the clinical uses they

Table 5.4.1 The advantages and disadvantages of a 510(k) versus a PMA pathway have important strategic implications.

Pathway	Pros	Cons
510(k) Substantial equivalence (**SE**) to predicate device(s)	• Quicker route to market • Less expensive submission • Easier to modify the device post-clearance • Clinical data needed only 10–15 percent of the time • Fewer post-surveillance requirements • No facility pre-inspection required • No panel meeting required	• Competitors can more easily follow company to market (claiming substantial equivalence, with the new device as the predicate) • May limit company's ability to market the device as desired (since it must follow the indications of its predicates)
PMA Reasonable assurance of safety and effectiveness established by valid scientific evidence (**clinical trials**)	• Harder and more expensive for competitors to follow (as they are also subject to PMA requirements) • Can be used to allow a company to market a device for a new or different indication than existing devices • Potentially exempt from product liability cases	• Safety and efficacy must be proven • Longer, more complex application/approval process • Expensive submission and approval process • Requires clinical data (often **randomized**, **controlled**) • May require panel review • Requires a pre-approval facility inspection (PAI) • Difficult to make post-approval device modifications • May require post-marketing studies as a condition of approval

intend to promote. Otherwise, they may find themselves in a situation where regulatory clearance of the new device has been achieved, but the new device cannot be marketed to the target clinical population with the desired claims.

It is worth noting that regulatory practice is akin to case law in that the interpretation of substantial equivalence changes according to the accumulated experience of the FDA and the regulatory professionals with whom the agency works. Understandably, the FDA reacts to public and Congressional concerns. For example, the association of silicone breast implants with autoimmune conditions in the 1990s brought into suspicion many devices containing silicone elastomer when, in fact, it was liquid silicone that was thought to be the risk factor (note that these concerns were never scientifically proven). Clearance of devices containing silicone – of any type – was stalled for a time while the FDA reacted to the events generated by these fears.

A company pursuing a 510(k) strategy must consider its desired speed to market in the context of the indications for which it intends to market its device. If speed to market is particularly important, a company may choose the simplest predicate device(s) and indications for use to clear the device quickly, and then pursue additional indications following initial clearance. This may take less time overall than testing the limits of predicate bundling and undergoing multiple rounds of questioning with an FDA reviewer. One example of this was the 510(k)

Table 5.4.2 A company has different alternatives in the way that it approaches the 510(k) regulatory pathway, depending on its strategic priorities.

510(k) strategy	Pros	Cons
Quickest: Use one established predicate device, if it provides the indications for use that are needed to sell to the initial target market	Facilitates the fastest clearance with fewest question rounds (90 days or less)	May not provide the desired indications for use to sell to the target market
Moderate Risk: Bundle two or more predicate devices to add desired indications	Increases the possible market to which the device can be sold	May be subject to further rounds of questions or additional testing which will increase review time
Riskiest: Push the limits of what is a **Class II** device by using predicate device(s) that have tenuous substantial equivalence arguments	May enable a company to avoid a PMA	Definitely will be subject to increased FDA questioning, additional data, and possible determination that the device is not substantially equivalent to anything currently on the market Caution: Split predicates are not allowed, that is, one predicate for the intended use and another for the technology under a different intended use

strategy pursued by Intuitive Surgical (see case example in 5.1 IP Strategy), which developed a robotic technology to enhance a surgeon's capabilities. As a first step, Intuitive Surgical approached the FDA with the concept of using its device as a surgical assistant to hold tools while the surgeon operated. This required mostly bench data for the 510(k) clearance. In order to obtain clearance for the purpose of actually performing the surgery, the FDA required a randomized, controlled trial. However, the company was able to use the initial 510(k) clearance for the surgical assistant as a predicate for itself in obtaining a second 510(k) clearance for performing the surgery. In the meantime, the initial 510(k) clearance provided the company the opportunity to familiarize surgeons with the technology and gain initial revenues from sales of the robot system and equipment for the more limited use.[7]

The amount of time and risk a company is willing to bear in terms of generating all desired indications in one submission (versus pursuing additional indications following initial market release of the product) is an important issue that requires careful thought early in the regulatory process. Rapid product release enables a company to accumulate early experience with the device and directly understand which alternative clinical applications are worthy of further study. On the other hand, if the device will be a direct competitor to a product already on the market, the company may benefit from taking more time to gain clearance for additional indications or to gather data that substantiate the benefits of its device.

If a company receives regulatory clearance under a straightforward 510(k) based on substantial equivalence to a competing device, it may be difficult for the company to differentiate its new device from the predicate for marketing purposes. When a device is cleared for use under a 510(k), the company is not allowed to make claims above and beyond those of the substantially equivalent device or beyond what was allowed in the 510(k) clearance. Common 510(k) regulatory strategies are summarized in Table 5.4.2.

It is useful to be as broad as possible in describing the features of a device for a 510(k) submission. For instance, if a company makes a type of catheter that comes in a variety of diameters, it should be sure to

include a range of sizes in its 510(k) submission that incorporates all diameters of the existing device, as well as those diameters that may be developed in the future. Thus a guide catheter of the same design can be submitted in 5, 6, 8, and 9 French sizes,[8] even if the original released product is only 6 Fr (though the original submission performance data must bracket all of the sizes for which clearance is sought).

Clinical data in 510(k) submissions

Currently, the inclusion of clinical data is only required in approximately 10–15 percent of all 510(k) submissions. In some cases, the FDA issues specific requirements or expectations for clinical data in a guidance document. There are other situations in which submitting clinical data is strategically important. If there are measurable differences between the new device and the predicate device(s), clinical data can be used to demonstrate the safety and effectiveness of the new device. Clinical data can also be submitted to the FDA in order to support the expansion of the device's intended use (over and beyond what is indicated by the predicate device(s)).

There is an ongoing trend for the FDA to require clinical data more often for 510(k) clearance and to require higher levels of clinical proof in the study designs. Clinical data can come in a variety of forms. It is not uncommon for companies to submit small human registry-type trials to satisfy the data requirement. In general, in the 510(k) setting clinical data are used to validate bench data and to establish *safety* rather than effectiveness. Trials should be designed to be as small and as simple as possible. Rarely (if ever) are randomized clinical trials required for the 510(k) pathway, and rarely do studies have to be large (20 to 100 subjects is commonly considered adequate). Often, the necessary clinical data can be collected outside the US and the studies, therefore, are exempt from the formal requirements of an IDE. However, they are still subject to international ethical standards and informed consent, and may require approval by the country's competent authority (the regulatory body charged with overseeing clinical research in that country) (see 4.2 Regulatory Basics and 5.3 Clinical Strategy for more information).

Meeting with the FDA

For a 510(k) submission that does not require clinical data, it is generally not necessary to have any "pre-meeting" with the agency to discuss the application. If the technology and predicate device(s) are reasonably straightforward, a request for such a meeting could demonstrate to the FDA that a company does not possess the expertise necessary to understand their obligations and comply with them (which could be a liability in terms of how the company is perceived by the FDA). However, a 510(k) pre-meeting might be appropriate under circumstances in which: (1) the company knows of problems with the predicate device it plans to use; (2) the company is concerned that the agency might have new questions of safety or effectiveness based on the technology employed; or (3) the company is aware of a competitor using the same predicate device(s), technology, or materials and there has been difficulty with its submission. Similarly, a meeting with the FDA may be appropriate when an innovator or company wants to confirm the appropriate pathway before investing significant time or effort in the development process. As mentioned above, when there is a substantial clinical trial involved, it is wise to meet with the FDA to review the adequacy of the trial design.

Strategies for premarket approval (PMA)

The ratio of PMA to 510(k) submissions ranges roughly from 1:50 to 1:100, reflecting the fact that the time, cost, and risk involved in the PMA pathway is significantly higher than for 510(k) clearance. However, there are some clear advantages to the PMA pathway. An approved PMA is essentially a private license granting the owner permission to market the device.[9] In effect, this is a kind of "regulatory patent." The PMA provides a barrier to entry such that competitors who desire the same type of device and same indications are required to undergo the longer, more costly PMA process as well. In early 2008, the US Supreme Court added further weight to the importance of PMAs in one of its landmark medical device preemption decisions in Riegel versus Medtronic, in which the high court stated that medical device manufacturers could not be sued

for complications if the device used was approved by a PMA or PMA supplement.[10] This ruling was generally viewed as a shield for industry from a legal perspective, as it prevents litigants from pursuing tort action on a state-by-state basis in most cases. Companies can still be sued for negligence, however, and the full implications of this decision are subject to further interpretation and clarification.

While it is not common for a company to pursue a PMA if a 510(k) can be justified, a company may decide to pursue a PMA in an attempt to get approval for indications that are beyond the scope of those cleared for predicate 510(k) devices. This would usually only be undertaken by large companies with significant resources and an aggressive desire to erect competitive barriers. If successful, the **first mover** can block followers who simply do not have the resources to conduct the necessary clinical trials and overcome the other hurdles arising from the new bar set by the first PMA. It is also worth mentioning that Medicare and other insurance plans are increasingly requiring evidence from randomized clinical trials that are similar to the scale and complexity of PMA trials to support reimbursement decisions. If the company is obliged to conduct large trials for purposes of reimbursement, the added benefit of PMA approval may come at a relatively small cost. It is also clear that in recent years both the FDA and the Department of Justice are being more aggressive in pursuing medtech companies that promote devices for "**off-label**" uses – that is, uses beyond those explicitly cleared or approved by the FDA (more information about off-label usage is provided below). A PMA approval provides a clear go-ahead for marketing the device for the indications that have been studied.

PMA approval is required for **Class III** (high-risk) devices, even those that are similar to competitors in the field (e.g., stents and pacemakers). Seeking regulatory approval under the PMA pathway as a follow-on device can have both upsides and downsides. For a technology that has a long history of established clinical safety and efficacy (for example, femoral closure devices pioneered by AngioSeal and Perclose), undertaking a PMA for a similar device leaves little guesswork. The study design and endpoints are well established, and the FDA is familiar with the technology. The PMA process, therefore, is still rigorous, but is significantly de-risked due to the many lessons and shortcuts that can be leveraged as a direct result of the predecessor's experience.

On the other hand, the FDA can impose acquired learning onto the PMA process. This happened with abdominal aortic aneurysm stent grafts (synthetic conduits placed within an aortic bulge to reduce the risk of rupture). The FDA approved two technologies (Medtronic's Aneuryx and Guidant's Ancure) based upon early, promising results. As these two technologies enjoyed wide commercial use and market share, more was learned about performance issues and design problems. Followers in this area, therefore, were hit with significantly increased requirements over and above those faced by the original applicants.

In order to obtain PMA approval, a company is required to validate every indication it seeks with clinical research data. Often, there is temptation to pursue as many indications as possible with the initial submission. However, it is essential to consider how this will complicate clinical trial design. Initial clinical trial design should focus on the simplest, most achievable endpoints possible to maximize the study's chance of success (see 5.3 Clinical Strategy).

A strategy employed by many companies is to target the most important indications for use to capture the initial market, and then add indications following initial approval through a mechanism known as a PMA supplement. A PMA supplement is required by the FDA following PMA approval before a company makes any changes affecting the safety or effectiveness of the device. These changes may include new indications for use of the device, changes in labeling, changes in sterilization procedures or packaging, changes in the performance, technology, or design specifications, changes in operation or layout of the device; and use of a different facility to manufacture or process the device.[11] Approval of a PMA supplement can require anywhere from 30 to 180 days of review time and, in

some instances, might require another advisory panel meeting.

The strategy of obtaining PMA approval for core indications first (followed by subsequent PMA supplements) allows the company to earn initial revenue to support the development and testing required for the additional indications. Every year, many more PMA supplements are received and approved by the FDA than PMA applications.

Meeting with the FDA

From a strategic perspective, the PMA process should be highly collaborative, with numerous interactions occurring between the FDA and representatives of the company. One of the most important opportunities for collaboration occurs early in the evaluation and submission process.[12] A meeting with the appropriate FDA branch should occur before significant time and expense is put into device development. While these meetings are optional, they are strongly recommended because they help establish a relationship with the FDA and allow the agency to unofficially buy in to the selection of safety and effectiveness measures in advance of the submission. Companies may request a formal **determination meeting** before the PMA application process is initiated, in which the FDA is obliged to give an official response to the study that is proposed. However, a determination meeting usually does not turn out to be productive for the company (i.e., the agency does not endorse the study). For this reason, it is generally recommended for companies to work within the context of the more informal meetings.

PMA post-approval requirements

Increasingly, the FDA is interested in collecting data on the impact of new technology *after* PMA approval, as the technology is disseminated into more widespread practice. The high-profile issue of stent thrombosis (clotting) following implantation of drug-eluting coronary stents added impetus to this trend. The FDA approved the first two drug-eluting stents based on data that the restenosis rates were lower than with the conventional bare metal stents. Following PMA approval, the stents were deployed in millions of patients, and clinicians began to see a problem with some stents abruptly clotting off completely – a serious event that can occur years after the procedure. This complication was not detected in the PMA trials and led the FDA to require post-market surveillance for the two companies with approved products, as well as mandating larger and longer trials for the approval of new drug-eluting stent products from other companies.

Post-approval requirements, which may include continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use, are an increasingly common part of the PMA landscape. Evaluation and reporting may be achieved through any of the following measures: a post-market study or registry to track outcomes; reporting on the continuing risks and benefits associated with the use of the device; maintaining records that will enable the company and FDA to trace patients if such information is necessary to protect the public health; inclusion of identification codes on the device or its labeling or, in the case of an implant, on cards given to patients in order to protect the public health; submission of published and unpublished reports of data from any clinical investigations or non-clinical laboratory studies involving the device or related devices; and submission of annual post-approval reports.[13] Another post-approval reporting mechanism under development is the unique device identifier (UDI) system, which will require device manufacturers to assign a distinct number to most medical devices distributed in the U.S so they can be tracked through a publicly available database. The intent of the program is to reduce medical errors, facilitate more accurate reporting of adverse events, and provide an improved understanding of any underlying problems with devices. Class III devices are required to comply with the new system first, with staggered deadlines for Class II and **Class I** devices following soon after.[14]

The Emphasys example, which is a continuation of the case study in 5.3 Clinical Strategy, demonstrates some of the many challenges of devising and executing a regulatory strategy.

FROM THE FIELD EMPHASYS MEDICAL

Navigating complex clinical and regulatory challenges on the path to market – part 2

When the Emphasys team made its PMA submission to the FDA for its novel endobronchial valve for treating patients with severe emphysema (see 5.3 Clinical Strategy for the first part of the Emphasys story), the company anticipated that it again would be working with the Plastics and Reconstructive Surgery branch of the Center for Devices and Radiologic Health (CDRH). This branch had cleared tracheobronchial stents, one of the few device interventions available in the pulmonary arena. Emphasys had negotiated with the Plastics and Reconstructive Surgery group on its IDE application and the parameters of its **pivotal trial** for the device (as shown in Figure 5.4.2). However, recalled Emphasys CEO John McCutcheon, "A week later we found out our submission had been transferred to the Anesthesiology and Respiratory Therapy Device branch of CDRH."[15] Although this seemed to be a more logical place to evaluate pulmonary devices, the branch had no experience with the Emphasys study or the history leading up to the company's PMA submission. "We had to start all over with developing the trust we had gradually built up," McCutcheon noted. The only reviewer that followed Emphasys to the new branch was the consultant who had disagreed with the team about the control group for the pivotal trial.

Based on the lack of treatment options available to emphysema patients, the FDA granted the Emphasys device expedited review status. Yet, said Hanson Gifford, a partner with The Foundry, which had incubated the device, "Our submission spent a year at the FDA. Their statisticians got into every detail and said, 'No, you're doing the statistics wrong.' We went back and forth and back and forth." The main source of disagreement had to do with how Emphasys imputed outcomes data for roughly 20 percent of patients in the study for which the company did not have complete follow-up data. To resolve its standoff with the FDA,

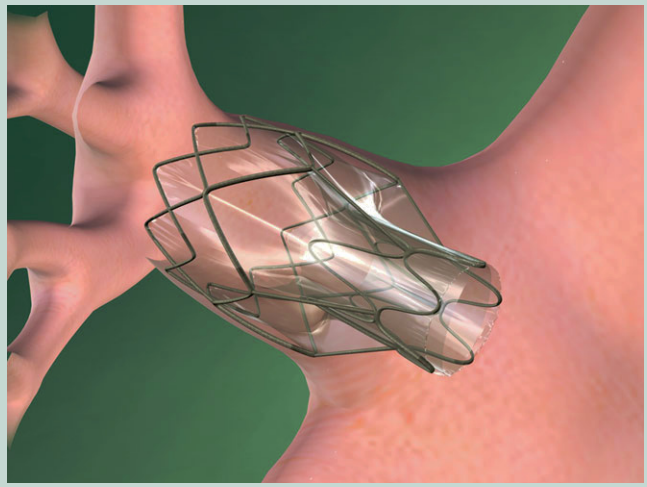

FIGURE 5.4.2
The Emphasys device (courtesy of Emphasys Medical).

the Emphasys team finally hired a leading "imputation guru" in the field to work through the data one more time. "That's when the FDA statistician said, 'Okay, you're right. No matter how you did the imputation, it really is statistically significant,'" Gifford stated. Having reached an agreement on the statistics, the FDA scheduled an advisory panel meeting to review the company's PMA submission.[16]

In parallel, a confluence of events in the external environment created increased public scrutiny of the FDA and device manufacturers alike. First, the withdrawal of the arthritis medication Vioxx from the market[17] and the **recall** of the Guidant defibrillator heightened public concerns about the safety of FDA-approved drugs and devices. Subsequently, in response to criticism that drug and device makers were asserting undue influence over the approval process through panel members, the FDA passed new conflict of interest rules regarding advisory panel participation. Adding more fuel to the fire, a group of CDRH scientists and physicians sent a letter to the then chairman of the House Committee on Energy and Commerce alleging that managers at the device center "knowingly corrupted the scientific review process and approved or cleared medical device applications in gross

violation" of the law and agency regulations.[18] These claims led to a House Committee investigation into the matter, which was underway at the time the Emphasys device went to panel. Meanwhile, *The New York Times* launched an article series called "The Evidence Gap," with the purpose of examining how the FDA each year allows "thousands of medical devices onto the market with only cursory review and with no clear evidence of improved clinical outcomes."[19] Unfortunately, as some observers pointed out, the FDA rarely received credit for doing its job well and approving good therapies. Instead, it was only blamed for any problems that occurred with drugs and devices after they were approved. This trend persisted even though it was impossible for the agency (or a company) to foresee all potential problems at the time of approval, no matter how exhaustive the clinical research.

Against this backdrop, the FDA convened the Anesthesiology and Respiratory Therapy Devices Panel to discuss, make recommendations, and vote on a premarket approval application for the Emphasys medical valve system. In addition to the chairman, the panel included 13 voting members, a consumer representative, an industry representative, and an executive secretary. Among the voting members, only three had backgrounds in pulmonology and worked directly with emphysema patients, three were trained in anesthesiology, three in cardiothoracic surgery, two in statistics, one in pediatrics, and one in device research and development.

Prior to the panel meeting, participants were provided with briefing materials prepared independently by Emphasys (referred to as the "sponsor" of the PMA application) and FDA. In the meeting itself, both the sponsor and the FDA were asked to make a presentation to the panel, followed by question and answer sessions. Next, there was a panel discussion, during which the sponsor responded to additional questions from the panelists. Deliberations followed, with the panel considering pre-specified questions about the PMA application put forth by the FDA. Afterwards, the agency and the sponsor were given the opportunity to make summary remarks and the consumer and industry representatives had the opportunity to make comments. Finally, the panel voted on which of three possible recommendations to put forth to the FDA's Office of Device Evaluation (ODE) and the branch in charge of the PMA regarding the submission: (1) approvable, (2) approvable with conditions, or (3) not approvable. Once a recommendation had been made, each panel member was asked to explain his/her vote. After the meeting, the ODE would consider the recommendation, along with input from the branch, and then render a final decision.

During the meeting, the Emphasys team asserted that the company met its co-**primary endpoints** in a statistically significant way, even when considering only completed cases (without including any imputed data or patients who had inclusion/exclusion protocol violations). Furthermore, by using a **core laboratory** to gain additional insights, the team had identified two clinical subgroups that had experienced even greater improvements in the lung function tests than the general patient population in the trial. These algorithms could be used during future patient screening to facilitate patient selection and treatment targeting. In terms of safety, while there were more complications in the treatment group, the difference was not statistically significant and diminished with time. The team also presented data that the devices could be safely removed when deemed necessary.

In response, the FDA raised four primary issues that it believed affected the estimation of the treatment effect. These included: (1) the lack of blinding in the study, opening the door to the possibility of a placebo effect; (2) the fact that Emphasys had extended the follow-up window without explicit FDA approval; (3) the issue that data were missing for more than 20 percent of patients; and (4) that there were violations in the **inclusion** and **exclusion criteria** for the trial. In addition, the FDA argued that while Emphasys had met the endpoints in a statistically significant way, those outcomes were not necessarily clinically significant. According to the FDA, "The study was designed to show a pre-specified clinical difference between the . . . treatment and control arms of 15 percent for co-primary endpoints, FEV_1 and 6MWT as

recommended by the General and Plastic Surgery Devices Panel …. The 15 percent clinically significant response for an individual was used along with pilot study results to power the trial."[20] So, argued the agency, "An analysis of the co-primary effectiveness endpoints showed statistically significant differences at 6 months. However, at no point in time did either of the endpoints reach clinical significance." Emphasys disputed that the 15 percent threshold had been formally established as a clinical significance requirement for each of the co-primary endpoints in the study. "The FDA went back to our study protocol and pulled our powering number, which had 15 percent in it, and then tried to say, 'We agreed that this is the threshold.' But that just wasn't the case," said McCutcheon. While this difference of opinion was not resolved in the meeting, the panelists spent a significant amount of time discussing the matter. Regarding the subgroup analysis based on the findings from the core lab, the FDA contested the results, stating that the software used by the lab for its analysis had not been validated by the agency.

After a lengthy discussion surrounding these and other issues, the panel arrived at a "not approvable" recommendation by an 11:2 vote. Significantly, the two dissenting members of the panel were those with the most direct experience with emphysema. In statements after the vote, both of these physicians underscored the limited options available to emphysema patients, the fact that the company was well on its way to finding the most appropriate use of the technology, and that the improvement conveyed by the therapy outweighed the limited safety concerns.

The ODE stood by the panel recommendation, requiring Emphasys to do a confirmatory study prior to any possible approval. Faced with this difficult situation, the company evaluated a wide variety of strategic options, including raising additional funds to support another trial. But most of Emphasys' backers had been investors for as much as five to eight years and were not in a position to commit more capital. Speaking as one of these investors, Mike Carusi of Advanced Technology Ventures remembered, "We did the math for putting in another $50 million and concluded that the return on investment was not going to be there. Plus, the investors were tired. People didn't have budget and the economy had started to get bad. Nobody was going to write those checks – and certainly not for a company with this kind of FDA risk." Another option was to market the device more aggressively in Europe, where it had been approved more than five years earlier based on the results from the Emphasys pilot studies. Ultimately, however, the company was forced to sell its assets at auction to a competitor called Pulmonx.

Reflecting on the Emphasys experience, The Foundry partner Hank Plain said, "In the current environment, fewer and fewer projects like this will be financeable, which I think is really unfortunate for patients and for innovation. The levels of uncertainty, the financing risk, the clinical risk, the FDA risk, all of those hurdles have gotten too high." As Gifford added, "Speaking for The Foundry, as we look at new things, unless they are just clearly going to have a dramatic benefit on huge patient populations, we're unlikely to consider any PMA products."

As for the Emphasys technology, it remained uncertain when it would reach emphysema patients in the US. At the time of the acquisition, the initial strategy of Pulmonx and founder Rodney Perkins was to concentrate on marketing the device in Europe. As Perkins explained, "We didn't want to go back to the FDA too early because if you don't have a period of separation you're just carrying the same baggage." Importantly, the company intended to market the device with its Chartis assessment tools, which could be used to help pulmonologists detect the leaks (collateral ventilation) in the lung airways that could cause the valve to be less effective. Pulmonx would carefully design a European study, selling the approved valves into the trial sites, and then would decide when to go back to the FDA. However, Perkins emphasized, "One of the points to consider is that we didn't have to be in the US to be successful as the market outside the US is larger."

Over the next several years, Pulmonx established a sizable field office in Switzerland and completed close to 8,000 cases with more than 120 hospitals across

Europe. Based on the strength of the results, the Pulmonx team determined that the time was right to once again to pursue FDA approval. "We want to get back to the US because we know we have a good treatment," Perkins said. In 2013, Pulmonx applied for and was granted an IDE by the FDA to initiate a US pivotal trial to support a new premarket submission for the valve.[21]

Strategies regarding off-label device use

One of the more subtle areas of regulatory strategy deals with devices that are used outside of the cleared or approved FDA indications (so-called off-label use). Recall that the FDA does not have jurisdiction to regulate the practice of medicine. Physicians may use a device in any fashion they see fit, provided this use is in the best interests of the patient and is broadly within the **standard of care**. In practice, this means that many devices are used outside of the indications for which they are cleared or approved by the FDA. A classic example is the biliary stent, which was approved to prop open the bile tracts in the intestine. For years, the large majority of biliary stents were, in fact, used by cardiologists to treat blockages in the coronary arteries, despite the fact that these stents were not approved for this indication (coronary stents were approved in Europe several years earlier than in the US, convincing U.S cardiologists that this practice was within a reasonable standard of care).

When companies ultimately sought approval for coronary stents from the FDA, they designed trials strategically with an eye toward proving that the stents were superior to the existing technique of balloon angioplasty. Among other things, this meant targeting vessel sizes that were likely to yield favorable results (smaller coronary arteries, it turns out, have a higher incidence of renarrowing after stenting than vessels greater than 3 mm in diameter). Once the stents were approved for vessels of the optimal size range, however, cardiologists began using the stents widely in the smaller vessels.

Although companies often are tempted by the off-label potential for their devices, a blatant strategy based on this approach is not advisable. The FDA understands this issue well and is on the look-out for companies promoting off-label uses of their products. As a cautionary tale, the 10 or more companies making biliary stents were effectively censured by the FDA for not being more forthcoming about the dominant use of their products.

Integrating US, European, and other regulatory strategies

Innovators can often achieve important advantages by integrating regulatory strategies across geographic areas. In some cases, regulatory processes may be optimized by leveraging clinical data and regulatory approvals obtained in one market to the shorten time to regulatory approval, reimbursement, or market adoption in another. For example, many US medical device startups pursue **CE marking** of a device subject to a PMA pathway in advance of US approval (see the Edwards Lifesciences case in 4.2 Regulatory Basics). Conversely, companies may seek the clearance of a 510(k) device in the US before entering the EU market and then use the US clinical data to gain reimbursement abroad. Another common strategy is to use clinical data from a CE marking trial in lieu of a US pilot study to enable the company to start a US pivotal trial earlier. This data can also be used to obtain regulatory approval in other markets, such as Canada. More information about these integrated strategies is provided below.

Early CE marking of PMA devices

For the majority of devices on a PMA pathway in the US, CE marking still can be obtained more quickly than a PMA. This may be helpful to companies for several reasons: (1) it can provide a valuable revenue stream while the product is working its way through FDA approval in the US; (2) it provides the company with early user feedback on device performance and adoption; and (3) it provides early clinical data that may be used in subsequent FDA submissions.

The reason why CE marking of Class III devices is faster than premarket approval is directly related to the

differences in the clinical data requirements between the US and EU regulatory pathways. The FDA requires that Class III devices demonstrate reasonable safety and effectiveness, which is typically achieved through prospective randomized controlled trials involving hundreds of patients (see 5.3 Clinical Strategy). In contrast, CE marking traditionally only requires that devices demonstrate safety and performance. Usually, compliance with the EU requirements, even for Class III devices, can be demonstrated with much simpler trials. For instance, the GuardWire® from Percusurge, Inc., which enables debris created during endovascular interventions to be captured to prevent it from embolizing, was awarded CE marking on the basis of a 22 patient single-arm study[22] demonstrating safety and performance (i.e., that debris was aspirated during the interventional procedure). In the US, however, the FDA required an 800 patient multi-center randomized trial[23] for effectiveness (i.e., that compared the device to the standard care to demonstrate a reduction in complications).

Deferring EU market entry of 510(k) devices

Early European approval of a device that is headed for 510(k) clearance in the US rarely provides the same value to a company seeking to penetrate the US market as it does for a PMA device, unless the 510(k) device requires clinical data. 510(k) clearances that do not require clinical trials can usually be obtained much more quickly than premarket approvals, allowing a company to begin providing the device to US physicians and building this market. Furthermore, clinical data generated in the US (before or after 510(k) clearance) may subsequently be used to build markets in other geographies. This strategy was successfully used, for example, by Kyphon® for its interventional device to perform kyphoplasty for the treatment of vertebral body compression fractures.

Using EU clinical data for US and other regulatory approvals

Pre- and post-CE marking trials may be used for US and/or other regulatory approvals, provided that certain aspects of clinical trial design and conduct conform to necessary requirements. These include compliance with all relevant local regulations and any applicable Good Clinical Practices (e.g., set forth by the ICH[24]). All such requirements should be designed into the trial from the outset to ensure that the clinical data will be acceptable by the authorities outside of the EU.

It is important to be aware that the FDA looks critically at data obtained from foreign studies in terms of its applicability to the US patient population. If medical therapy or practice differs significantly from that in the US, or if there are expected or unexplained differences between the patient populations within and outside the US, the data can be deemed not applicable. For example, in coronary interventions, a certain class of blood thinners or anticoagulants (IIb/IIIa inhibitors) is not used as commonly in the EU as in the US. Therefore, trials involving devices for coronary interventions must be carefully designed to ensure that data acquired overseas will be accepted by the FDA if the sponsor is expecting it to be used to support a US approval. Note that the FDA reserves the right to audit foreign clinical sites to confirm whether or not the data are valid for the purposes of obtaining an approval to market a device in the US. The agency has a specialized Bioresearch Monitoring (BIMO) Program for this purpose.

Efforts toward the increasing harmonization of regulatory standards have created a dynamic and complex environment that demands a regulatory consultant with strong international experience. The EU is still the largest market outside the US for most medical devices and is the best understood region in terms of regulatory approvals. Japan is a market that reimburses well but has been notoriously slow to approve new devices, often expecting the company to repeat clinical studies in Japan (the government is working to streamline the approval process). Young companies are becoming increasingly familiar with regulatory agencies in Australia and South America (especially Argentina and Brazil) since "**first-in-human**" studies are often conducted in these countries. As described in chapter 4.2, regulations in other large markets (e.g., China, India) are evolving. When considering overseas regulatory approval as a means of conducting earlier clinical trials, be cautious about the credibility and applicability of the data to ensure a wise investment.

Online Resources

Visit www.ebiodesign.org/5.4 for more content, including:

- Activities and links for "Getting Started"
  - Validate device classification and regulatory pathway
  - Develop a regulatory strategy
  - Modify and monitor regulatory strategy
- Videos on regulatory strategy
- An appendix on common regulatory pitfalls

CREDITS

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NOTES

1 Cartoons created by Josh Makower, unless otherwise cited.

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7 From in-class remarks made by Howard Holstein as part of Stanford's Program in Biodesign, Winter 2008. Reprinted with permission.

8 The French catheter scale is used to measure the outside diameter of a cylindrical medical instrument. 1 French (Fr) is equivalent to approximately 0.33 mm.

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14 "Unique Device Identification," U.S. Food and Drug Administration, http://www.fda.gov/medicaldevices/deviceregulationandguidance/uniquedeviceidentification/default.htm (December 4, 2013).

15 All quotations are from interviews conducted by the authors, unless otherwise cited. Reprinted with permission.

16 All PMA applications are reviewed by a special panel, a group of 5 to 15 physicians, statisticians, and other experts (all non-FDA employees) who serve a 3-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, the panel convenes to hear presentations from the company sponsor, its expert consultants, and from the FDA team. The panel votes to recommend whether the technology should be approved, approved with conditions, or

disapproved. The recommendation is non-binding, but generally carries great weight in the approval process. 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 (ODE).

17 In September 2004, drug maker Merck withdrew its arthritis medication Vioxx from the market in the face of new data that showed its sustained use doubled a patient's risk of heart attacks and strokes. In the investigation, which followed, the FDA faced allegations in the press that its relationship with drug companies was "too cozy" and was interfering with public safety.

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24 ICH stands for the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. This project brings together experts and regulatory authorities from Europe, Japan, and the United States to discuss scientific and technical aspects of product registration.