Current Status of Development and Regulatory Approval of Cardiac Devices

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Abstract

Medical devices are rapidly advancing and changing the medical field. Progress has been demonstrated in many fields such as minimally invasive surgical techniques for valve replacement and 3D cardiac mapping of arrhythmias. These medical device advances allow physicians to help more patients quicker and more efficiently. The field of cardiac device development can be considered as relatively new, beginning in the early 1950s, and today new technologies in this field are presented at ever increasing rates. Many times, these advances come from an unmet clinical need. In some ways, physicians are unable to treat (or are at best ineffectively treating) certain types of patients in this aging society. Motivated by these needs, medical device designers—scientists, physicians, patients, or simply individuals with good ideas—choose to undergo the rigorous, yet rewarding, path of medical device development.

The development path follows a certain route from device conception, intellectual property generation, and testing to regulatory approval. Since cardiac medical devices are created to help patients, they must also undergo stringent testing for durability, biocompatibility, and manufacturability. To complete these assessments, both animal and clinical testing can be utilized, especially with regard to valve replacement devices. Once an adequate amount of data pertaining to the safety and efficacy of the device has been collected, it will then be sent to a regulatory body to gain approval to market the device.

Keywords

Cardiac device design • Cardiac device development • Device ideation • Risk mitigation • Intellectual property • Device testing • Regulatory approval

Abbreviations

DFM	Design for manufacturability
FDA	Food and Drug Administration
FMEA	Failure mode and effect analysis
HDE	Humanitarian device exemption
IDE	Investigational device exemption
IFU	Instructions for use
IP	Intellectual property
USPTO	United States Patent and Trademark Office
VOC	Voice of customer

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42.1 Introduction

All it takes is a napkin drawing or a rough shape crafted with clay. Such humble beginnings can spark an idea or revolution for the way that cardiac care is administered. Ideas can blossom into intricate high-tech medical devices that push

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the envelope of design and advance the field of medicine. These are exciting opportunities, yet the journey of creating a medical device can be daunting. However, for those who are successful in developing such devices, there can be great rewards. This is the reason for so many entrepreneurs entering the medical device space!

When you consider what it takes to fully create, develop, manufacture, and market a cardiac device, there are many points to discuss. First and foremost, the device needs to serve an unmet need (whether or not it is apparent). Within the cardiac space, this can range from the inability to measure a particular pressure to finding a way to successfully repair or replace failing myocardium. Any cardiac device must be technically feasible, and it requires that issues of design, quality, manufacturability, regulation, cost, and reimbursement must be considered during the design process. In many cases, the earlier these areas are considered in the design space, the more effectively the device can be brought to market. Even if a device is the best idea in the world and can cure a disease, if you cannot successfully make it or if no one can afford to buy it, then the product is doomed to fail.

42.2 Anatomy of a Cardiac Device

For a product to be viable, there are some key characteristics that must be incorporated or considered in the design. These characteristics demonstrate that the device has been tested and manufactured correctly, and they also take into consideration the risks inherent to the device. This next section will discuss the different design considerations that need to be developed while creating a medical device. These will drive toward a device that functions the way it is required and will do as little harm to the patient as possible. These topics on design characteristics can be used in other areas of medical product design, but, for the sake of brevity, this chapter will focus on cardiac devices.

42.2.1 Functionality

Consumers—including physicians, patients, and buyers—all have certain expectations of a cardiac device. When a physician uses a device, he/she expects that it will function in the manner in which it is intended. This may seem elementary, but the idea that the device must always work as specified is integral to the design, and the first device must work the same as the one thousandth device. To be successful, a new product must elicit *functionality* above and beyond the currently available solutions and techniques. The functionality of a given cardiac device ideally also encompasses an ability to perform the desired tasks without compromising any other biological process. For example, an atrial septal occluder device should not impede the function of the tricuspid or mitral valve, nor should it increase the potential risks of embolism and stroke which it is trying to mitigate. These specifications are often outlined by regulatory committees such as the International Organization for Standardization (ISO).

For therapeutic devices deployed in the left atrium, the functionality of the device also encompasses the delivery of such therapies. For instance, left atrial cardiac ablation requires a transseptal puncture to be performed before the device can be inserted into the left atrium. The delivery path is such that it must create a hole in the interatrial septum and thus provide an access point to get to the left atrium. If the hole is misplaced, or if during the puncture the needle is advanced too far, it can cause unwanted complications of either cardiac tamponade or aortic perforation. Neither one of these situations is desired and, as such, must be considered while thinking about the left atrial ablation therapy (see Sect. 42.3.4 on risk mitigation). To ignore this portion of the procedure may result in unforeseen issues with the procedure which may or may not have been caused by the delivery of the device. In many cases, the delivery of a device has a larger impact on the ability to perform the procedure. For some mitral valve repair procedures, the location of the puncture in the atrial septum is paramount to having a quick and successful procedure [1]. In summary, the device being developed must be thought of as a *device delivery procedure* and include everything involved with its successful use. This approach takes into consideration the system as a whole instead of a single part; the system must be considered as a whole; otherwise, issues may occur due to the unforeseen interactions between parts of the procedure.

Another aspect of functionality is related to unforeseen uses or the *off-label* use of devices by physicians. An off-label use of a device is one where the manufacturer of the device has clearly specified the use conditions in which such a device can be utilized, yet the physician has elected to use it in another fashion or in a patient in which the device is not intended to be used. An interesting thing to note is that the physicians have a fair bit of freedom to use the cardiac device however they see fit. Since they are ultimately responsible for the well-being of the patient, if they believe that a cardiac catheter would better serve the patient in a manner other than what is listed or suggested by the company in their instructions for use (IFU), they can and may decide to use the device however they choose. In other words, in most cases, they will use the devices as intended, but may also use them outside of the bounds of the IFU if they believe it is in the best interest of the patient.

Nevertheless, an off-label use of devices puts medical device companies in a peculiar position. On the one hand, the company likely enjoys the benefits of their product helping more people than was originally intended, as well as possibly

higher sales. On the other hand, the action of using the device in such an off-label fashion cannot be condoned, marketed, or suggested by the company without potential repercussions for promoting the device to be used in such a way that has not been tested or cleared through regulatory channels.

42.2.2 Biocompatibility

In 1987, Williams described how the biocompatibility of a material can be qualitatively evaluated to assess its relative performance when implanted. He said that biocompatibility can be defined as the ability of a material to perform with an appropriate host response under specified conditions [2]. The succinctness of the term *biocompatibility* can be misleading when applying the principle to cardiac devices. Often within a single medical device, there may be a multitude of different materials that are utilized. For example, the WATCHMAN™ left atrial appendage (LAA) closure device (Boston Scientific, Marlborough, MA, USA) is made of a collapsible nitinol structure with a polyethylene terephthalate (PET) mesh covering which is permanently implanted into the patient, whereas the delivery system is made of another polymer that will be in contact with the patient for <24 h. This means that the delivery system must not elicit acute immune responses within the patient including (but not limited to) allergic reactions. The WATCHMAN does not need to be biologically inert, but it must not cause an undue biological response from either the PET or the nitinol. The purpose of the device is to block the LAA to mitigate the formation of a blood clot within the LAA, followed by the subsequent release of emboli into the bloodstream. Thus, the requirement for the device is that it will effectively section off the LAA and endothelialize, thereby creating a biologic barrier between the left atrium and the LAA. Although this is a biological response due to a foreign object in the heart, it can still be deemed biocompatible since it will elicit this appropriate response from its host and will not be detrimental to overall function (Table 42.1).

The mechanisms related to how the host or patient may respond to different components of a cardiac device must be extensively evaluated to ensure that appropriate materials are selected for the final device design. This evaluation can be complicated by the fact that it is hard to replicate the range of human immune responses that may exist in vitro. To address this, all cardiac devices must also undergo rigorous animal testing, although it is important to note that animal testing can sometimes provide misleading results on species-specific bioreactivity. An example of this can be seen in the design and development of the Braunwald–Cutter heart valve ball and cage prostheses (Fig. 42.1), whereby cloth-covered cage struts were designed to encourage endothelialization and subsequently decrease any chance of thrombolytic events [3].

Table 42.1 Potential patient–device interactions causing clinical complications [2]

• Adverse local tissue interactions:
– Inflammation – Toxicity – Carcinogenic response – Calcification – Embolization or lymphatic spread of material fragments
• Induced device migrations: encapsulation or foreign body response
• Inappropriate or altered healing responses
• Associated infections
• Thrombosis
– Thrombotic occlusion – Thromboembolism

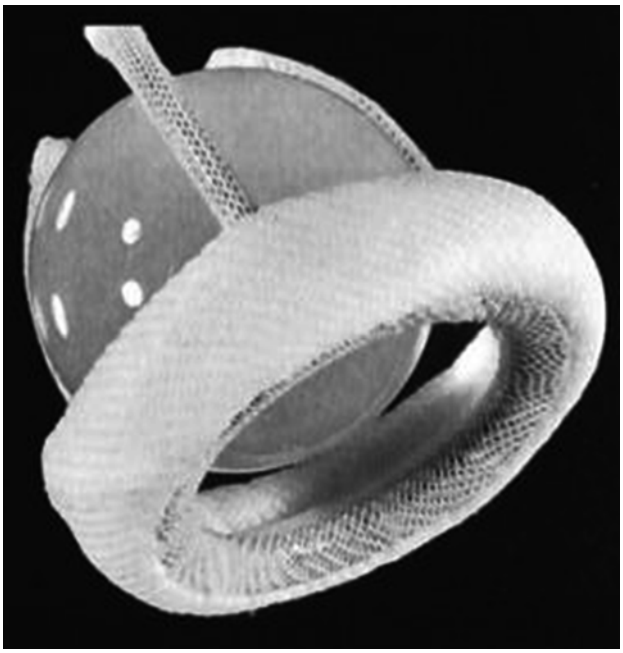

Fig. 42.1 Braunwald–Cutter valve

Extensive testing in the mitral position of pigs, sheep, and calves showed promising results; thus, the device was approved for human clinical trials. However, the device did not elicit the same host responses when implanted in humans; rather, it resulted in aggravated wear on the cloth cage struts and, more critically, the formation of debris embolization.

It should also be emphasized that host responses are not limited to immune reactions. For example, implanted tissue heart valves remain susceptible to accelerated prosthesis leaflet calcification. More specifically, it has been reported that this type of calcification is initiated by reactions between the extracellular fluid and the leaflet membranes, creating calcium phosphate mineral deposits [4]. As a result, much research is ongoing to enhance leaflet materials and minimize bioreactivity, including calcification inhibitors on the

valves that limit mineral deposition on the implanted materials. Furthermore, the materials used in a device can display unexpected interactions with the host, as evidenced by the earliest versions of the Starr–Edwards caged-ball mechanical heart valve. The valve design used a silicone ball that was found to absorb lipids from the blood and thus swell [4]. In addition to resultant poor valve function, this also caused the silicone balls to become brittle; in turn, this increased the possibility of ball fracture and consequent embolization of small fragments into the arteries downstream of the valve position.

42.2.3 Durability

Along with the biocompatibility, a device must be *durable* enough to withstand the mechanical loads placed upon it. These forces can be exerted upon the device by implantation, cardiac motion, or external events such as getting hit in the chest or falling on the ground (specifically for implantable devices). Potential situations like these must be considered when designing the device, to ensure it has the robustness needed to withstand such environments as well as an active lifestyle.

Major factors that any design engineer must take into consideration are the repetitive movements and strains that will be placed on a device within a patient's body. If you were to imagine the environment in which a coronary stent is placed, the arteries will have a cyclic pressure placed on them which, in turn, will flex and relax the stent with each heartbeat. This requires the stent's material to either: (1) oscillate with the artery while being durable enough to withstand flexing for the lifetime of the stent or (2) provide enough opposing force to the artery that it does not move during these times of increased pressure.

Cardiac pacing and defibrillation leads are also exposed to repetitive mechanical stresses that can cause faults or failures in their integrity. Two individual incidents were observed within defibrillation leads from two separate companies—St. Jude Medical (St. Paul, MN, USA) and Medtronic, Inc. (Minneapolis, MN, USA)—that were competing to get a small defibrillation lead on the market. The two companies produced small-diameter leads, the Riata (St. Jude Medical) and Sprint Fidelis (Medtronic, Inc.), that gained FDA approval and were then appropriately implanted clinically [5]. Before the release of these smaller leads, >8F defibrillation leads were the standard of care, but in 2002, St. Jude Medical released their 7.6F Riata defibrillation lead. In response, Medtronic, Inc., released their 6.7F Sprint Fidelis in 2004, shortly followed by the 6.3F Riata ST by St. Jude Medical. The perception was that a smaller lead would decrease the blockage caused within the venous system at the level of the subclavian vein. However, it was found that these systems were unable to perform at adequate levels of durability within the body [5]. Both companies ended up having issues where their leads broke or eroded to the point where the conductor wires could penetrate and cause misreading of the cardiac signals and potentially lead to excessive shocks being delivered to the patient (or even worse, no shocks were delivered when they were needed).

In 2007, Medtronic, Inc., sent a letter to physicians informing them that they had seen failures in the field both at the distal portions of these leads and at points near the anchoring sleeve tie-down. Further, they reported that the distal failures were significantly affected by the bending of the lead body due to tortuous anatomy in the veins. The failures at the tie-down location were potentially caused by the way physicians implanted and secured the leads within the body. Each of these failure modes suggested that the way in which the lead was implanted could make a significant impact on the longevity of these devices and their potential for failure. Ultimately in late 2007, Medtronic, Inc. issued a voluntary market suspension that the FDA formally considered to be a recall. During this time, St. Jude Medical was also seeing similar issues with their leads. They reported that portions of their leads were being eroded to the point where the wires were being externalized in both styles of the Riata leads. It was also reported that the primary reason for this externalization was due to abrasion of the lead insulation with either the anatomy (e.g., tricuspid valve) or the internal components of the lead (e.g., the pacing/sensing wires). In one study, they found that a common defect was due to the internal abrasion of either the pace/sense coils or the shocking coils against the silicone insulation. This would be in response to the repetitive motion of the lead and the ability for the internal components to move relative to the external insulation. This caused what they deemed to be an inside-out abrasion, where these wires were wearing away at the insulation and become externalized and readily visible under fluoroscopy [6]. Due to these failures, St. Jude Medical ended up removing the Riata family of leads from the market in 2010 and recalling them in 2011. Since these recalls, the defibrillator lead market has stayed at >8F, due to the perception that smaller leads could be associated with potential failures in patients.

Both of these cases are prime examples for why device durability testing is essential for the development of robust cardiac devices. Notice that it is not always a matter of how the device will react within the body (which seemed to be the case for the Riata leads), but also how the devices are implanted that may lead to potential failure modes. Ultimately, if a cardiac device is not tested properly in *relevant use* conditions, certain factors can be overlooked and may ultimately end up negatively impacting patients.

42.2.4 Design for Manufacture

The ability to put together a device, or *manufacturability*, is something that should not be overlooked during the design processes. By incorporating early feedback about manufacturing the product, the risks of not being able to build the device efficiently enough or to produce adequate quantities to fulfill demand will be greatly reduced. Failure in either case could cause the product to be stifled, no matter how successful or clinically helpful it is. As such, design for manufacturability (DFM) has become a common practice in the cardiac device industry, a practice that emphasizes how a successful design should ensure the highest-quality products while decreasing manufacturing costs. This is accomplished by making manufacturing cost estimates to proactively guide and prioritize cost reduction efforts involved with design. Consequently, DFM should have significant effects on product lead times, development costs, and ultimate product quality. As such, DFM specifically requires input from a multidisciplinary team, including manufacturing engineers, cost accountants, and production personnel, in addition to the design engineers [7]. Yet, when applying these principles to cardiac device design, it is imperative to understand that the quality of care impacted by the device must not be compromised by the need for a more cost-effective manufacturing process. One needs to consider that production costs can be controlled by using existing technologies and established manufacturing techniques. There are many methods for ensuring that the requirements for manufacturing are being taken into consideration, and there are several numerical methods of design and testing (also known as *in silico testing*) that can be used to streamline the design for the manufacturing process.

42.3 Development Process

There are often two types of development referred to by designers—iterative and disruptive. Those that fall into the *iterative* category are devices that generally are perceived as logical next steps in the development chain. For example, this would include the addition of a third and fourth electrode to a left-sided lead that would give the physician more vectors to choose from when programming a pacemaker, as discussed in Chap. 30. The ideas and devices that are considered to be *disruptive* are those that medical industry professionals would consider as *game changers*. These are devices like transcatheter-delivered cardiac valves. The option prior to these transcatheter valves was open-heart surgery, which often involved placing the patient on cardiac bypass and fully stopping the heart; this procedure limited the population of patients who could receive the treatment to those that were able to physically undergo an invasive surgery and required weeklong recovery periods in the hospital. In other words, these devices have effectively provided a means to treat more of the patient populations which were underserved by prior medical management.

Although there may be a valid unmet clinical need, oftentimes there are points along the product development pathway that may ultimately put a halt to a device or therapy. This can be as simple as the product not working as intended or a business decision to not pursue a particular therapy because it does not align with their internal objectives. This, along with other reasons, is generally why larger companies will often focus their efforts on incremental improvement of devices as opposed to disruptive technologies. The incremental improvements are much more predictable and lower risk, since the market is already known and the needs often come directly from their voice of customer (VOC). Disruptive technology offers a greater amount of risk and, conversely, often a higher reward. This volatility of the device can be a deterrent for larger, publicly held companies that rely on stability, but it provides an opportunity for smaller companies willing to take the risk.

Whether it is an iterative or disruptive technology, the development process generally follows a similar pathway (also utilized in nonmedical device development), with the hope of producing a marketable product. Often, a problem is identified within the field, and to better understand the clinical needs, the designers must empathize with those experiencing the problem. This can be the physician, patient, payers, or any other stakeholders. While studying and understanding these situations, the designers gain invaluable insights as to the root cause(s) of the clinical problem or need, as well as what confounding factors are present. Then, by defining which portion of the issue they are trying to address, designers can begin to hone in on a potential solution. In turn, this will spark ideas and a multitude of solutions (partial or complete) will be generated. These solutions (as you will see in Sect. 42.3.3) will be prototyped and selected based on technical and market feasibility. Promising options will then be tested for usability and functionality; if an acceptable option is produced, the design will be frozen to move on to preclinical animal testing and eventual clinical testing (Fig. 42.2) (see Chap. 43). The generalized overarching progression of how cardiac devices develop from concept to market will be presented in the following sections.

42.3.1 Six-Phase Approach to Device Development

There are many ways that device development can be approached, but often they follow a similar pattern: (1) generate an idea, (2) prove it to be feasible, (3) test the idea, (4) market the idea, (5) and make sure that it does not cause unfavorable

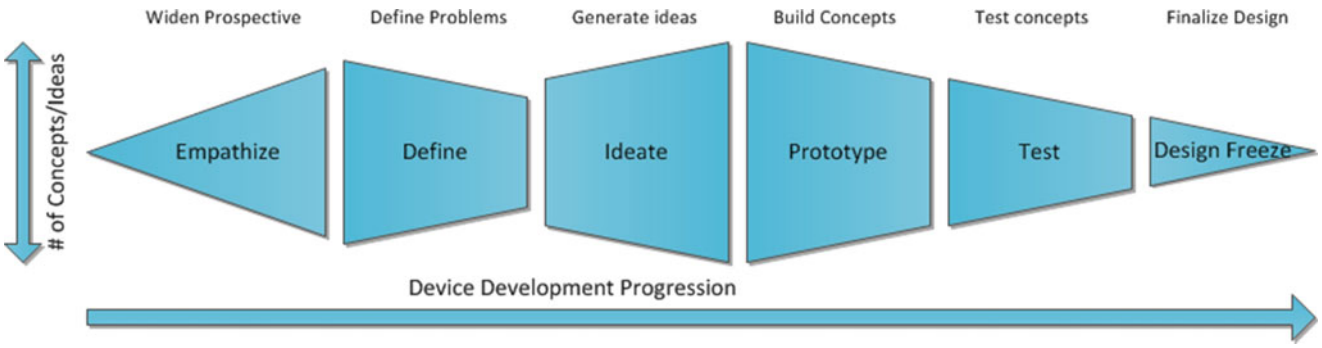

Fig. 42.2 Flowchart of the design thinking process

issues in the field. This is obviously oversimplifying things, and each of these steps requires a vast amount of work to "get it right." Despite the simplification, all of these steps are essential to fully develop and market a cardiac device. This section will describe a more commonly used phase–gate system that breaks up the process into six phases of development, as shown in Fig. 42.3. Importantly, throughout each of these phases, a number of different elements need to be checked and rechecked in order to create a successful device.

As the development process advances along the phases, the subsequent tasks are generally associated with higher costs. For instance, the first phase of the development process is *device conception*, in which a clay model or a sketch of the product may be the only thing required, along with asking some key stakeholders whether or not the idea is worth the time and effort. This requires very little monetary investment. The next phases require creating animations and prototypes and testing of these advanced concept devices; these phases will incur greater costs. Prior to market release, at a minimum, preclinical and even some clinical testing will be necessary, which may require the investment of millions of dollars and multiple years of study before finally being able to market and realize profit from the device.

Phase 0 is the *planning phase* during which much of the groundwork is completed, including developing prototype devices, creating a product platform, assessing market opportunities (determining if it will be worth pursuing financially), and identifying product constraints associated with intellectual property (see Sect. 42.3.2). The decision to move on to the next phase often requires insights related to perceived market value versus return on investment, an evaluation that is required to bring any device to the market.

Phase 1 is considered the *concept development phase*. This is when the development/refinement process, as well as benchtop testing, of the device begins. For example, feasibility studies are performed to determine whether the product is technically possible to manufacture and create, as well as to estimate the potential market size. Ultimately, the market

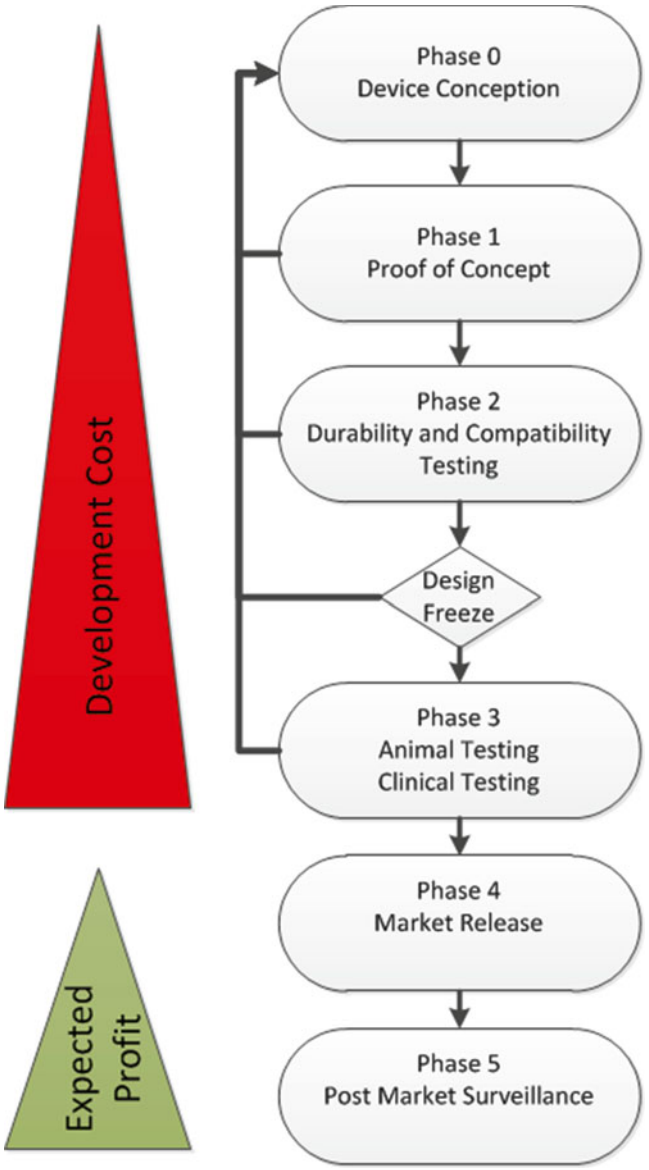

Fig. 42.3 Flowchart of the device development process. The six phases of device design are shown, as well as the associated cost and profit factors related to marketing a medical device

size will determine the profitability of the device. It should be noted that there remains a special need for pediatric-sized cardiac devices, partly because they are often considered nonprofitable to manufacture at small volumes and are thus generally developed as a humanitarian effort.

Phase 2 (*durability and compatibility testing*) occurs after the device design meets the previous criteria from Phase 1. This is where further benchtop tests are performed for both accelerated failure and required function of the devices. In vitro work or acute animal studies can also be initiated to assess potential biocompatibility. The end of Phase 2 generally involves a design freeze where nothing can be changed on the device without going back to Phase 1 or 0. At this point in time, the design engineers, in partnership with the entire development team, must determine the most optimal design and cease all design work and begin the preclinical and clinical testing.

Phase 3 (*animal and clinical testing*), which is initiated after the design freeze, assures that testing will provide an accurate assessment of the device function within a living organism. Testing often includes chronic implantation in appropriate animal models, which is then followed by regulatory approvals before the onset of clinical trials in humans. Yet, even subsequent to a success clinical trial, final approval for market release of the product is sought.

Phase 4 is initiated when the product is actually *market released*. Usually, this is the phase of the overall process where the company expects to see a return on investment. Yet profitability is contingent on successful clinical trials, approval of the device for market release by the regulatory body of the country, and the ability of the company to commercialize and market the device, as well as receive payment (reimbursement) for sales.

Phase 5 is considered to be the *post-market assessment*. Even though a product is fully marketed and approved by a regulatory agency, the company is still required to perform follow-up studies to ensure that the device does not cause any unforeseen issues with patients over time. This acts as a safeguard to the patients that are being served by the device. In some cases, even though stringent testing in animal and human trials has been performed, there may be unexpected issues with the longevity of the device or unanticipated failures. This also provides the company with additional information for future improvement of the device. Assessment that can be performed in this phase includes postmortem studies, where the company may receive the explanted device and then analyze its status/condition.

42.3.2 Intellectual Property

Before finalizing any design, one aspect that must be taken into consideration is the intellectual property (IP) associated with the device idea. Generally, IP refers to a work or invention to which one has rights. This is often associated with patents, copyrights, trademarks, or trade secrets. In all of these cases, there are specific actions that need to take place to protect the creator of the idea, so they can utilize their ideas without others unduly copying or inappropriately using their works or inventions.

Ultimately, a major part of the product design process is to maintain ownership or licensing agreements of IP relative to the technologies being developed. A *trademark* is a name or symbol that is associated with a product or brand in which a company (and only that company) has full rights to use that name or symbol. This prevents others from using the name and associated marketing as a means of promoting their products or services. Similarly, a *copyright* may be granted for any written and/or graphical materials to an individual or group of individuals to protect their work and reduce the risk of plagiarization [8]. Another method to protect an idea or product is to keep it a *trade secret*. Simply put, this is the act of not divulging any information regarding how a product is made, operates, or performs (e.g., a device running on proprietary software or novel circuitry) while banking on the notion that no one can reverse engineer the product and thus replicate it. Yet it should be noted that anyone successful in reverse engineering a product may then duplicate the product or procedure (even without knowing the trade secret) with no legal consequences [8].

Within the medical device arena, a primary way of protecting IP is to file and obtain a device *patent* with broad claims. A patent is a legal document that explicitly describes how a device works or how a procedure is completed, providing enough information that anyone within the field could duplicate the device or process. In the USA, patents provide legal protection for 20 years, thus guaranteeing exclusive marketing rights during that period. However, upon expiration, the device can be copied by competitors without legal recourse [8]. With the long life span of patents, there is often little concern of the patent expiring due to the speed at which devices are developed or improved, as newly created and updated products will likely hold new patent protection. For this reason, it is vital for any product developer to have a solid understanding of how to read patents in order to avoid patent infringement upon the development and release of their own device. Typically, patents are classified according to device type and use and will first provide the filing number(s), inventor(s), and the date filed. Next, a description of the device/process is presented, generally involving sketches and other images of IP. The most pertinent information is contained within the claims section, which specifically describes what part of the IP is novel and hence what is officially patented and protected by the law. The claims section is generally the portion that legal teams will address when reviewing a patent case.

To obtain a patent, the United States Patent and Trademark Office (USPTO) requires that the idea must be novel, useful, and nonobvious. As such, the idea must fall into one of the categories of a process, machine, article of manufacture, composition of matter, or improvement of any of the previous items [9]. The USA has recently changed to a first-to-file patent system, which is similar to the current European patent procedure. Previously, the USPTO granted ownership of a patent to individuals who were the first to invent. This would mean that documentation was vitally important with dates and signatures referencing the date of the initial invention of the idea. While this method has its merits, the USA decided to move to a first-to-file system which means the patent is awarded to the individual or group of individuals who were the first to file a patent on that particular process, machine, and/or patentable idea.

In general, in order to determine if an idea is patentable, one must first search existing patents to see if it has already been invented. In many cases, finding and utilizing patent information can benefit medical device designers. According to the European Patent Office, there are a number of reasons and ways to use patents to your benefit including to "find out what currently exists and build on it," "keep track of who's doing what," and/or "avoid infringing on other people's patent rights" [10]. To find pertinent patents relative to the cardiac device you hope to develop, there are many online databases that can be searched for specific information. A few examples of such databases include the European publication server [11], FreePatentsOnline [12], and Google [13].

42.3.3 Device Ideation

While a "new" medical device is still in the early conceptualization phase, it is important to fully investigate the potential landscape of the design space. This is often referred to as *brainstorming* and is an easy way to obtain a multitude of device options to solve the underlying problem(s). A good approach to a brainstorming session is to understand that any idea is a good idea, which is similar to the idea employed in acting/improvisation comedy of "yes, and…." This statement is seemingly insignificant, but it emphasizes the idea that you need to build upon the ideas of others. If one actor says that they are just coming home from the circus, their counterpart must go along with the premise that it is where they came from and add upon the story. If the counterpart were to say "no, that is not what you did," they effectively stopped all progression in the scene and added nothing of value. In the same way, during a brainstorming session, even though an idea suggested by a colleague may be completely impossible, it is important to run with the idea instead of shooting it down outright. For example, even though it is currently impossible to physically levitate the patient during open-heart surgery, the notion that you could gain access to both the front and the back of the patient without flipping them may spark an idea of how to support patient management during a procedure. In that sense, it is important to maintain these "off-the-wall" ideas because often they can lead to alternative solutions to the problem that was not previously considered.

Once the ideas are compiled, then a session to down-select to the best options or routes is required. Often for a smaller project, 4–10 options may be initially considered, and prototyping can begin on each of them. Generally during this time, the resources are limited, so "quick and dirty" prototypes are often the way to go. The purpose is not to obtain fully working prototypes that portray all of the intended features, but to create rough models (i.e., out of clay or cardboard) that may help one to understand a proposed feature. In many ways, the act of prototyping over the past decade has seen some huge changes. Often when someone says prototyping, a common conception is an engineer sitting in his garage and building a model of a device. However, in recent years, this has transformed to that same engineer, although still likely to work in his garage, creating a CAD model of possible designs and sending it to a 3D printer to have the part(s) actualized from the computer. Due to technologies such as 3D design software and 3D printers, prototyping offers even more possibilities for generating ideas. Note that the New Product Design and Business Development course at the University of Minnesota has required, for several years, that all design teams utilize 3D technology to create at least one of their prototypes.

Whether designers decide to 3D print or build their initial prototypes, they can begin to down-select from these concepts and refine their ideas, to understand the best path forward for their design space. One of the primary purposes of Phase 0 is to develop *proof of concept* and to confirm that the idea can be constructed and eventually manufactured into a viable product.

After proof of concept has been attained and market potential assessed, the design team should select a handful of devices from their initial mock-ups that will be fully prototyped and can be shown to customers for feedback. This is generally a part of Phase 1, where feedback is obtained by collecting the VOC from a large sample size of potential users with varied backgrounds and clinical experiences. The VOC can be obtained through direct questioning, observation, and/or discussions (or use of a prototype) with the customer. The "customers" that will be addressed may consist of many different groups of individuals, including: (1) those who will use the device, (2) those who may be on the receiving end of the device, (3) those who would purchase or pay for the device (reimbursement, insurance companies), and (4) those who could potentially profit from the successful device (investors). These groups of individuals will often

aid in the design process and hopefully improve the overall design of the product, to fully meet the expectations of all the primary customers. For instance, a user may want the device to be easy and intuitive to use, while the payer's focus is on expense and potential benefit to the patient in order to ultimately reduce healthcare costs (e.g., including a reduction in the number of required future procedures). Those who expect to profit from the product (e.g., a company's chief financial officer) may demand that the costs of product development are minimized. Hence, all of these design criteria and concerns must be proactively considered and addressed by the design team, if their desire is to create a product that satisfies the majority of their potential customers.

42.3.4 Risk Mitigation

An important fact to remember is that there are no cardiac devices without risks. These risks may be simple, such as an implantable device recording for longer than required for each time segment, in turn causing the battery to deplete faster and require more frequent replacement. The risks can be as significant as a turbine in a ventricular assist device being stressed to the point where it fractures and sends fragments into the bloodstream. Obviously, neither of these situations is favorable, but, at the same time, one is certainly more acceptable than the other based on the risk that it poses to the patient.

In addition to brainstorming, it follows that all of the potential device defects and failures need to be tracked and accounted. Note that early on in the development process, one needs to consider the risks and benefits of employing any new procedure that utilizes a newly developed device (Fig. 42.4). In order to complete the risk analysis on a device, one typically employs a failure mode and effect analysis (FMEA), generally defined as a procedure in product development and operations management for identifying potential failure modes within a system, including classification of the severity and likelihood of failure. It is considered that any successful FMEA activity helps the research and development team to identify potential failure modes based on past experiences with similar products or processes. This, in turn, enables the team to eliminate such failures with minimum effort and resource expenditure, thereby reducing development time and cost. Complete FMEA on a new prosthetic valve typically creates a 150-page spreadsheet of potential problems, including everything from leaflet material breakdown to misalignment of the prosthesis within a heart. Each identified failure mode must be assessed for how likely it will happen and how severe the impact on the patient could potentially be. If one particular failure mode could feasibly occur in 1 out of every 100,000 patients and have minimal impact on the patient's health, it will not create a drastic design change. However, if within the same occurrence rate a patient may potentially die from the resulting complications, such a failure mode would need to be addressed.

42.3.5 Device Testing

When a cardiac device design moves from Phase 0 into Phase 1 of the design process, a series of testing regimens are initiated to ensure that the device meets the standards set forth by various international governing organizations. These testing methodologies are not only required for the successful market release of a new cardiac device, but they also provide insights into the design and development of the device and/or subsequent devices. For example, the testing results

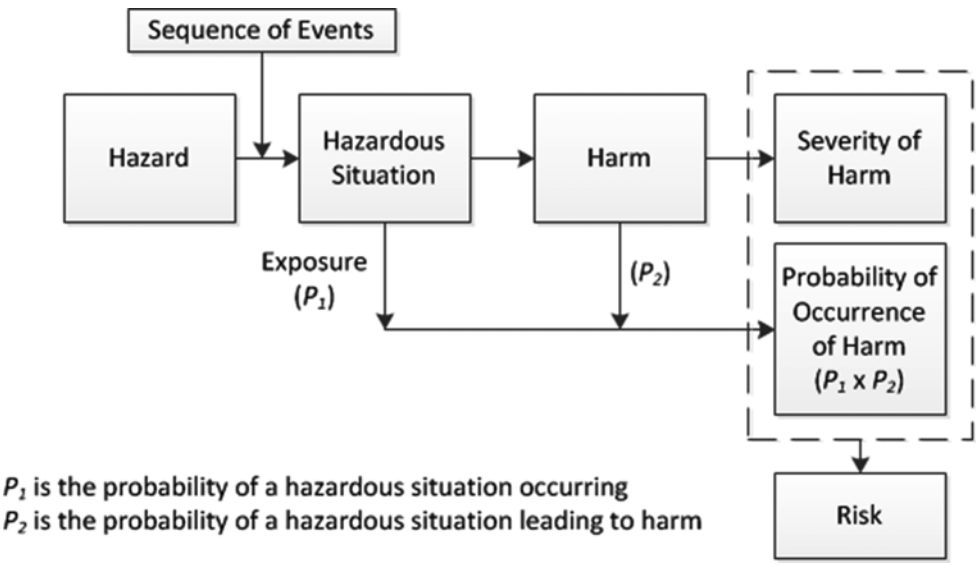

Fig. 42.4 Example flowchart for performing risk estimations

from a cardiac ablation catheter can elicit information to the design team on which portions of anatomy need to be ablated to treat the underlying arrhythmia more effectively. Based on this information, an anatomically shaped catheter like the Arctic Front Advance cryoballoon (Medtronic, Inc.) can be developed to address circumferential ablation needs for the pulmonary vein ostia.

Cardiac device testing can take many forms and often starts with basic static benchtop testing without the use of native biological tissues. In place of biological tissues, surrogate materials can be used as tissue analogues such as silicone, nylon, sponge, or foam [8]. For example, mock silicone substrates approximating the anatomy of a human left atrium and pulmonary veins can be created to investigate the ability for ablation catheters to reach key arrhythmogenic locations within the left atrial anatomy. This is not only a more repeatable procedure due to a decrease in substrate variability, but it is also more cost-effective than obtaining live tissue or live animals to perform such initial basic testing. However, these techniques may not provide necessary insights into specific tissue interactions and/or biocompatibility, which are primary concerns when developing catheters that must be placed and manipulated within a human body.

In the case of cardiac pacemakers and defibrillators, all current therapies involve devices, delivery systems, and monitoring tools that are inserted into the body and exposed to a harsh biological environment. Some of these products (e.g., delivery systems and introducer sheaths) will only be in contact for a short period of time, yet the pacemaker and the cardiac lead may remain in the patient for the rest of his/her life. Note that specific concerns regarding biocompatibility are discussed at length in Sect. 42.2.2 of this chapter. In general, the potential for device rejection can be assessed with in vitro immunological responses to the device; a strong immunological response would be indicative of a possible problem relative to biocompatibility and thus a possible device rejection. However, today most pacemakers and leads are constructed from well-studied materials with known levels of biocompatibility as well as several years of clinical experience. As such, adverse reaction testing is predominantly assessed during chronic animal studies if new materials are used, and adequate data on the materials cannot be leveraged during regulatory submissions to agencies like the FDA.

Another important factor to consider when designing medical devices is the combined effect that temperature and pressure may have on the device. For instance, the polymers and metal wires inside a deflectable delivery sheath will have altered properties after being subjected to human body temperatures while being submerged in a fluid (blood) for prolonged periods of time. In some cases, these altered properties can be advantageous depending on how the device is designed. The informed engineer may choose to design the device, a percutaneous delivery system, for example, to be stiff when entering into the vein/artery, thus allowing for easier placement, and then become more malleable inside the body, as the temperature increases, so as not to cause internal damage to the vasculature.

It is important to consider that before embarking upon the expensive animal testing protocols, which are required to prove the efficacy of a potential replacement valve technology, there is exceptional value in testing the device in reanimated beating heart models. Described at length in Chap. 41, such an approach allows researchers to employ an isolated, living heart as a model to visualize what occurs inside the heart during device deployment and/or how the device may interact with the myocardium throughout all the phases of the cardiac cycle. Additionally, the reanimation of human donor hearts, deemed not viable for transplant, allows for the visualization of specific valve interaction with the varied endocardial anatomy of human hearts, both healthy hearts and those with indications of heart valve disease.

Once in vitro testing techniques have been properly utilized and the device design has been locked in, the development process moves into Phase 3, whereupon the device must be proven safe in appropriate preclinical testing. Generally, this requires extensive testing on animal models (acute and/or chronic) before it can progress into a human clinical trial. With this, a well-written preclinical testing protocol defines that in order to predict the safety and performance of clinical use, a sufficient number of animals of the same species must be used (preferably the same gender and age). In addition, the animals should have both experimental and control valves implanted in them in each position, as indicated by the IFU. The number of animals to be studied may be best determined based upon the risk analysis of the device and the required statistical significance of the experimental design. The duration of the experiment is typically specified in accordance to the parameter(s) under investigation, and each animal must undergo a macroscopic and microscopic postmortem examination. Once the preclinical animal testing is performed using good laboratory practices, a third-party observer (outside auditor) typically will produce a report summarizing all data collected and making a recommendation regarding the clinical safety and performance of the device.

42.3.6 Clinical Testing and Regulatory Approval

Once a cardiac device has been proven safe and efficacious during rigorous animal testing, device developers will then embark upon human clinical trials before it can be properly market released. Current regulatory processes in the USA and European Union differ significantly in the requirements

and guidelines laid out for clinical testing and market approval. However, both regulatory committees share the same fundamental principles and apply frameworks designed to ensure the safe and effective release of medical devices into the market. This section will briefly highlight features of both approval processes, and additional details about the clinical trial process can be found in Chap. 43.

From a legal standpoint, human clinical testing of an unapproved cardiac device in the USA that poses a significant risk to the patient population cannot be initiated without preapproval from the Food and Drug Administration (FDA) in the form of an investigational device exemption (IDE). The IDE is designed to provide the FDA with relevant data on device design and preclinical testing, as well as the intended study protocol. A device company must also apply for an IDE if they wish to expand the indication of an existing device. These clinical investigations may begin at an approved site 30 days after the FDA receives the IDE application, assuming that in-house Institutional Review Board approval has already been obtained and that the FDA has not notified the sponsor that the investigation may not begin [14].

To date, FDA approval is contingent on various factors and based upon the intentions of the device; the rigor associated with the approval process increases with the classification of the device. These device classifications are briefly defined as:

- Class I devices which pose the lowest risk to the patient and include noninvasive devices such as surgical bandages and tongue depressors. These devices are placed under the general rules applied to all medical devices and nothing more. Controls include prohibitions against adulteration and misbranding, requirements on establishing registration and device listing, adverse event reporting, and good manufacturing practices [15].
- Class II devices, such as cardiac catheters, are deemed to pose a high enough risk that regulation through the general controls alone is not sufficient. The majority of class II devices require a premarket notification in the form of a 510(k), to provide data demonstrating that the described device is "of substantial equivalence" to an existing product with regard to its safety and effectiveness. Although a 510(k) can be substantiated through preclinical testing, approximately 10 % of applications include clinical data [14].
- Class III devices which are used to support and sustain human life and would also present a high risk of injury or fatality if the device fails (i.e., implanted cardiac valves). Almost all class III devices require premarket approval by the FDA before they can be legally marketed, thus requiring clinical data demonstrating that the devices are safe and effective in the target population [14]. As such, all types of cardiac replacement valves fall exclusively into this category. Since the valve aids in sustaining human life and device failure could be fatal, the valve must be tested to ensure that it meets the testing required for class III devices.

Another approach for device regulatory approval is the humanitarian device exemption (HDE). This is a regulatory pathway for the accelerated market release of class III devices, an exemption which is intended for devices that address diseases or conditions that affect fewer than 4000 patients a year in the USA. Nevertheless, approval of an HDE requires the sponsor to prove that the device is safe and effective and that all possible risks associated with it are outweighed by the foreseen benefits. Typically, such approval requires smaller clinical trials in fewer institutions, allowing smaller companies to develop class III devices beyond preclinical investigations.

The idiosyncrasies of clinical trial requirements, development, and completion are described in Chap. 43. In summary, gaining market approval in either the USA or the European Union can be a lengthy, expensive, and time-consuming endeavor. Before embarking on the development of a cardiac device, an understanding of these pathways and the intricacies of each regulatory body will help the designer complete the process in the most timely and cost-effective manner possible. To date, the differences between the US and the European Union regulatory bodies result in a large portion of pilot clinical trials and early device testing occurring outside of the USA. Thus, the typical cardiac device is introduced into general clinical practice in the USA 1–3 years after its market release in the European Union [14]. For more details on the design and execution of clinical trials for cardiac devices, the reader is referred to Chap. 43.

42.4 Summary

The key principles for designing any medical device generally hold true for all cardiac devices. A generalize path is to (1) critically define the clinical problem; (2) sketch concepts, develop animations, and build prototype; (3) test the concepts and perform benchtop testing; (4) conduct preclinical studies; (5) initiate clinical trials as needed; and ultimately (6) obtain regulatory approval prior to full market launch of the device. Throughout this process, there are a multitude of factors that need to be considered and taken into account when determining the requirements of the device. These factors include its planned function, biocompatibility, manufacturability, and marketability, to name a few. Although difficult to manage at times, these considerations will be vital for creating a successful product. Any development process for a medical/cardiac device requires a great deal of

upfront effort to ensure that the product will thrive. In today's world, this process relative to cardiac devices can take many years, even up to a decade before a device receives approval to be used in a patient and/or before any real profit may be realized. As such, the cardiac device industry can be a very difficult environment for a start-up, yet it can be exceedingly rewarding not only financially but also due to the fact that the product can directly and indirectly affect millions.

When you consider the breadth and depth of the cardiac medical device field, it is encouraging to observe how it continues to rapidly develop and expand the industry and, in turn, provide innovative and revolutionary clinical technologies. Although many therapies are conceived from a need within the operating room or cardiac catheterization laboratory, their design and development will lead to future novel procedures and techniques that continue to improve treatment for patients with various pathologies. There is little doubt that these innovative improvements will continue to extend and enhance the overall quality of life for millions of patients worldwide.

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