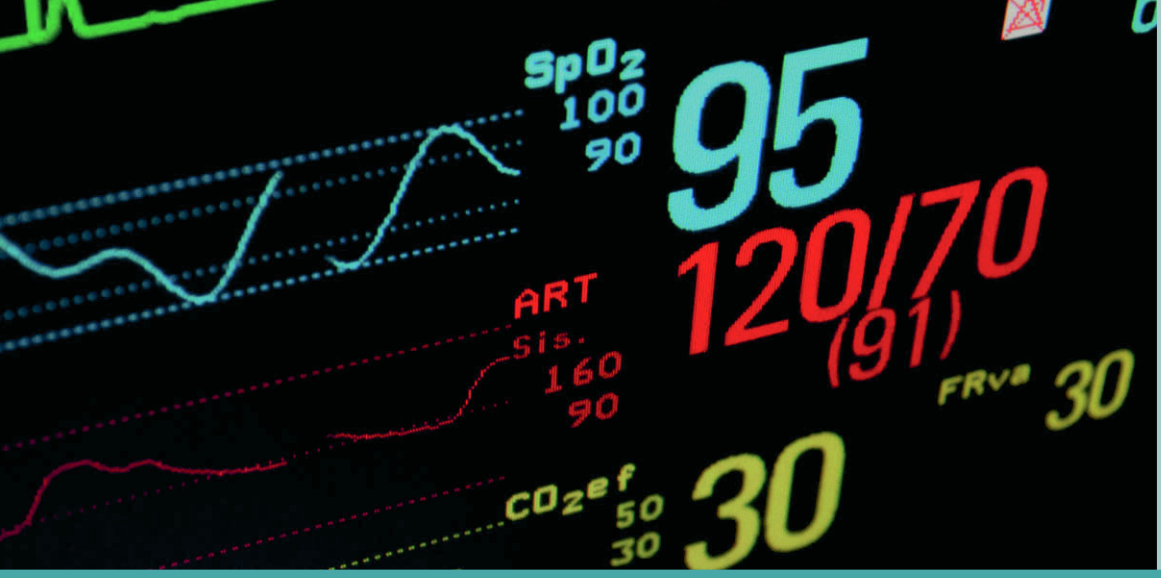


5.2 R&D Strategy

INTRODUCTION

Initial exploration and testing of the chosen concept has shown that it is technically feasible and can address user requirements. But now the solution has to be made real. Successive iterations must lead to a device that is safe, performs effectively in humans, and can be efficiently manufactured. Thousands of hours, scores of raw materials, and varied and expensive equipment will be dedicated to engineering and testing to incrementally reduce project risk and produce a final product. This is R&D.

OBJECTIVES

- Appreciate that R&D encompasses a wide range of iterative activities that work together to help innovators retire risk and create value.
- Understand the importance of defining strategic R&D milestones.
- Recognize how to identify and prioritize the key technical challenges associated with each milestone.
- Learn to outline the engineering activities, resources, and tests required to address these challenges as part of a high-level R&D plan.

In the medtech field, research and development (R&D) typically refers to the scientific and engineering work required to take a concept from an early-stage prototype to a user-ready final device. Whereas early prototyping focuses on proving the general feasibility of an idea, the goal of R&D is to develop a series of progressively advanced working iterations until all critical user requirements and core technical specifications have been met. Along the way, bench, tissue, and animal tests are employed to confirm that a product can be safely and effectively used in humans. The entire process can be lengthy and complicated, and it calls upon many different engineering disciplines and skills. But, taken as a whole, the two main outcomes of R&D are to reduce project risk, typically technical, business, or pre-clinical in nature, and in the process, lead to the creation of significant value. As such, it is essential to have a cohesive strategy for approaching R&D.

An R&D strategy defines key milestones that need to be achieved to demonstrate development progress, identifies and prioritizes the technical challenges that must be addressed to achieve each milestone, and calls out the engineering activities, resources, and testing necessary to validate the solutions to these challenges. At its core, an effective R&D strategy, and the tactical R&D plan that supports it, seeks to resolve the greatest risks associated with developing an innovation as early as possible, with the most efficient commitment of capital, time, and effort. Ultimately, the articulation of a sound R&D strategy with clear milestones (and an understanding of how to tactically achieve them) may be one of the most critical factors enabling the successful development of an innovation.

Importantly, this chapter focuses on providing innovators with an overview of key considerations and a recommended approach for developing an R&D strategy, which includes a high-level R&D plan. Innovators without an engineering background should seek more tactical information about R&D from the additional resources listed in the Getting Started section. Additionally, while the discussion is primarily focused on more traditional medical devices, many of the concepts and approaches integral to R&D strategy apply equally well to a wide range of medical innovations, from software to more complex projects.

See ebiodesign.org for featured videos on R&D strategy.

R&D STRATEGY FUNDAMENTALS

R&D is sometimes referred to as "engineering" in the **medtech** field, since the design and development of medical technologies is heavily dependent on activities related to one or more engineering disciplines. In the context of the biodesign innovation process, R&D typically includes all engineering and testing activities, beginning as early as **concept** exploration and final concept selection (see chapters 4.5 and 4.6) and then continuing to the point when a product is ready to be released into production. The type of testing used to support R&D varies from project to project, but innovators can draw from all of the types outlined in the biodesign testing continuum (see Figure 5.2.1).

The primary distinction between the development and testing described in 4.5 Concept Exploration and Testing and the activities outlined in this chapter is that now innovators are working on a single concept rather than building and testing models to help them choose a final solution idea to take forward. Typically, after selecting a final concept, innovators may perform additional simple testing (e.g., **user**, **bench**, simulated use, or tissue tests) and then transition to more advanced testing methods (e.g., animal and human studies) as R&D progresses and critical project **risks** are retired. However, R&D is a highly iterative activity that sometimes requires innovators to move backwards in the testing continuum. For example, if innovators have made a long-term implant that fails due to an unforeseen degradation of a material while chronically implanted in an animal, they would need to make important technical modifications. Once these changes had been made, they would then need to revisit bench and tissue tests before resuming animal studies.

Overall, a company's ability to transform an initial concept to a "proof-of-concept" **prototype** into a final product, with many other iterations in between, is central to its viability. However, there are many other reasons why a strategic approach to R&D is important. From a practical, near-term perspective, an effective R&D strategy:

- Plays a role in determining how the original **need** is ultimately addressed.
- Provides an optimized engineering framework for developing a company's technology in order to address the most significant technical risks.
- Establishes an approach for incorporating **user experience** feedback and design input in order to create products aligned for real-world use, thereby reducing **clinical trial** and commercialization risk.
- Helps manage a primary driver of cost early in the company's life in terms of how personnel and other resources are used and managed.
- Lays the foundation (i.e., processes and culture) that helps the company continue innovating to develop new products and product iterations.
- Can lead to important insights related to the firm's intellectual property (IP) position.

In the longer term, a strategic approach to R&D can also help a company:

- Continually increase product differentiation and help mitigate market risk.

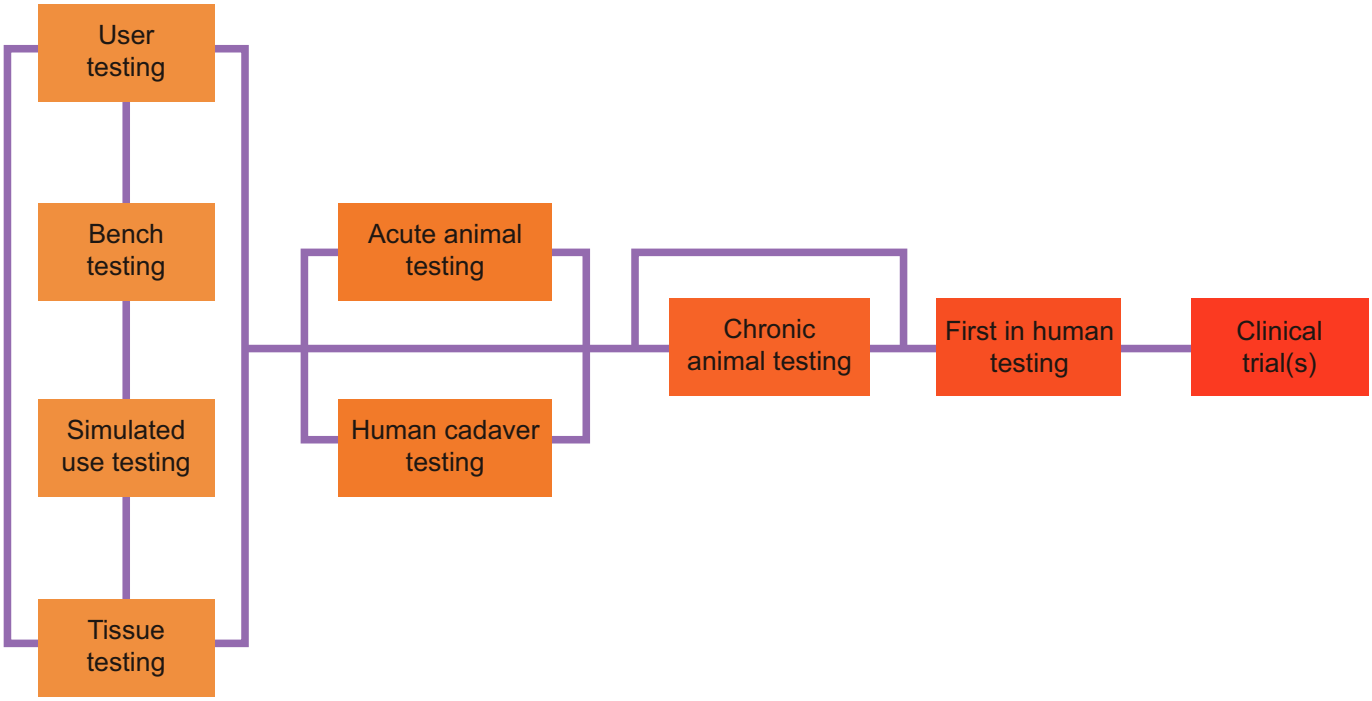


FIGURE 5.2.1
The biodesign testing continuum applies to R&D as well as concept testing and exploration (chapter 4.5), where it was originally introduced. It also extends into human clinical trials (chapter 5.3).

- Drive growth through new product innovation.
- Create a product development pipeline, which can make the company more attractive to investors and/or prospective acquirers.

As these benefits demonstrate, R&D is inextricably linked to other important aspects of the business and must be pursued keeping these other functions in mind. Additionally, the R&D strategy must be built with a clear focus on the clinical need and how it can best be solved from the perspective of the target audience, not just from a technical point of view. As Guy Lebeau, a physician and businessman who became company group chairman of Cordis Corporation, explained:[1]

> *One big issue is the lack of connection that can arise between the clinical need and the pure engineering desire. And that means you have to tell your engineers, "Be sure you're in contact with people who are using the tool every day."*

The linkage between R&D strategy and planning

An R&D strategy can be thought of as a company's overall approach to addressing the key engineering challenges anticipated in the development of the final product. Usually, the innovators already have a general idea of what the final concept should do and how it will solve key **user requirements** and satisfy important technical specifications based on the work performed as part of concept exploration and final concept selection (see chapters 4.5 and 4.6). An R&D strategy picks up from this point by articulating how the team or company will actually develop the product, in particular by considering the obstacles that it will need to overcome and how long that is expected to take. Accordingly, an R&D strategy can be developed by focusing on three key activities:

1. Defining high-level R&D milestones.
2. Using these milestones to identify and prioritize anticipated technical challenges.

3. Creating an early R&D plan that identifies the engineering work, testing methods, resources, and time required to solve these challenges.

The creation of an initial R&D plan can be considered part of R&D strategy since understanding high-level issues related to engineering personnel, resources, and timelines is important to determining when certain milestones can be achieved. More detailed information about R&D planning building on the information in this chapter can be found in 6.1 Operating Plan and Financial Model. The specifics of an R&D plan are usually articulated as part of an integrated approach that accounts for all of the personnel and resources required to take a final solution into commercialization. Some of the resources listed in the Getting Started section of chapter 6.1 may also be helpful when developing a more detailed, tactical R&D plan.

Quality (and the implementation of a quality system) is another facet of development that is closely linked to R&D strategy and planning. Quality management systems (**QMS**) play a key role in informing the engineering methods that address the development and manufacturing requirements necessary to receive regulatory approval for a new medtech innovation. Specifically, quality systems lay out processes for properly capturing user requirements and technical specifications. They also detail key testing and validation methods, which are important considerations when thinking about the timeline for engineering R&D work. Finally, quality systems require that detailed risk analyses that articulate potential failures and hazards of a device and how to mitigate them are performed. Risk analysis exercises and their results are a crucial input into R&D in order to ensure that the final product is safe and will pass regulatory scrutiny. However, because R&D strategies vary significantly from innovation to innovation and are usually relatively high level, the requirements governing the implementation of a quality system, which tend to be more consistent across companies and encompass many more aspects than those just related to R&D, are discussed separately in 5.5 Quality Management.

Defining high-level R&D milestones

As outlined above, the first step in creating an R&D strategy is to define essential R&D milestones. Such milestones usually embody significant events in the R&D process and correspond to the retirement of key risks. Many such risks relate to regulatory and clinical requirements that must be addressed on the way to market and, thus, planning to address them is crucial. Importantly, the emphasis innovators place on certain milestones and how they sequence them can be affected by the regulatory pathway for the product. For example, if a device will require a **510(k)** pathway in the US, innovators might choose milestones and anticipate risks based on what is known about the predicate. In contrast, when working on a **PMA** device in the US or a **Class III** device in the EU, for which there might not be precedents to follow, innovators will likely need to achieve additional milestones to retire additional risks.

Accomplishing key R&D milestones is one way that companies can demonstrate value in the eyes of their investors and potential end users. Certain R&D milestones also represent well-accepted **valuation** points to investors. For example, a start-up making an invasive or therapeutic device, is viewed as more credible among clinicians and more attractive to investors after it demonstrates the feasibility of a device on the bench, and then again once it develops a prototype that is effective in animal tests or a pre-production model that is safe and efficacious in early human studies. For other types of projects, particularly related to software or mobile health applications, gathering extensive feedback from many users about the interface and their experience can be valuable. While some of these steps may have been done during concept exploration and testing, additional, iterative work in these areas is often needed to successfully retire risk and achieve a value-creation milestone. By thinking about milestones early, innovators can also use R&D to their strategic advantage by sequencing and timing these types of milestones to correspond with other important events in the company's evolution (e.g., financings, or the formation of clinical advisory boards).

The specific R&D milestones chosen by a company as part of its R&D strategy can vary, but for many medical technologies they may resemble those shown in Table 5.2.1. In the company's overall operating plan, these R&D milestones may be "rolled up" into a smaller number (see chapter 6.1). Regardless, innovators should

Table 5.2.1 Key R&D milestones are typically chosen to demonstrate the retirement of risks.

Important R&D milestones
Proof-of-concept that addresses the scientific and technical feasibility of the concept
First working prototype that performs effectively in a bench model
First prototype that performs effectively in tissue testing
First prototype that performs effectively in live animals
First prototype that results in long-term safety in live animals
First prototype that performs safely and effectively in humans
Pre-production device that demonstrates manufacturing feasibility
Production device that supports scalable manufacturing

recognize their serial, progressive nature – no single milestone can be achieved until those before it have been successfully addressed. That said, sometimes learning related to a later milestone may produce results that require innovators to revisit earlier R&D activities to make changes (recall the example of the long-term implant that fails during chronic animal studies due to an unforeseen degradation of a material and then must be modified and retested on the bench and in tissue tests before animals studies can resume). Furthermore, although milestones such as proof-of-concept and working prototype may already have been achieved as part of concept exploration and testing (before much thought may have been given to an R&D strategy), they are still important R&D milestones to note as having been accomplished, though additional refinement along these paths may still be needed. Given the iterative nature of R&D, it is important to understand that the process of achieving these milestones is likely to take multiple, successive attempts on a development pathway that is not necessarily linear.

To help illustrate how innovators define an R&D strategy, the Working Example introduced in 4.5 Concept Exploration and Testing will be continued in this chapter. This example involved injecting the left atrial appendage (LAA) with a material that can be delivered in liquid form, which then changes to a solid-like consistency to eliminate the space where thrombi can form via a percutaneous approach as a way to solve the need for *a way to prevent strokes in patients with atrial fibrillation caused by LAA thrombus*.

Assuming that the innovators pursuing this need have already used some crude works-like prototypes and bench tests to show that the concept is likely feasible, the next most important strategic milestones to achieve might be to: (1) show acute effectiveness of the material in a live animal; (2) show long-term safety of the material in an animal; (3) show effectiveness using a percutaneous method of delivery in an animal; and then (4) show safety and effectiveness in a human.

Importantly, the milestones chosen and the way they are sequenced reveal information about the project and the innovators leading it. For instance, this particular sequence of milestones would seem to indicate the innovators' belief that demonstrating effectiveness and long-term safety in live tissue is of higher importance from a risk standpoint than developing a percutaneous solution. This is why it is addressed earlier in the development path. As it relates to R&D planning, this sequence further indicates that resources and personnel aligned with developing the percutaneous component of the solution will likely be needed only after or perhaps in parallel with understanding long-term tissue compatibility as part of the R&D effort.

Identifying and prioritizing technical challenges

After selecting relevant R&D milestones, innovators can next consider the key technical challenges that need to be addressed to achieve them. They must think about all of the important engineering issues that they will likely encounter and then prioritize them. Typically, those challenges that involve the greatest uncertainty should be addressed sooner rather than later, so that a minimal amount of time is wasted if a particular challenge cannot be overcome.

Table 5.2.2 Key technical challenges associated with the LAA example.

#	Technical challenge
1	Creating a prototype that can deliver the material to the LAA in less than 1 hour (timeframe based on a user requirement by physicians who would use the device). (Note: The solution to this particular challenge does not necessarily have to be percutaneous, as that requirement is associated with a subsequent milestone.)
2	Ensuring that the substance from which the delivery prototype is made does not react with the material being delivered.
3	Finding a material that can remain in a liquid form for delivery into a living animal.
4	Finding a material that, once released, can reliably and predictably become solid when required within the conditions of a living body (e.g., blood flow, body temperature, clotting factors).
5	Finding a material that will not migrate from the place where it is released or finding a method to prevent migration.

Technical challenges obviously vary greatly by project. Each may have a different focus, depending on the milestone they are associated with in the overall development path. However, identifying engineering challenges is similar to thinking about the functional blocks of a concept during concept exploration and testing (see chapter 4.5). Often, the challenges that need to be solved break down along the lines of different engineering disciplines (e.g., mechanical engineering, materials science, electrical engineering). In this way, technical challenges represent the critical questions that the functional blocks of a prototype seek to address.

Using the LAA example, and focusing on the milestone of showing effectiveness in an animal, the innovators might come up with a short list of key technical challenges, as shown in Table 5.2.2. With these technical challenges identified, the innovator can think about how to prioritize them. From the above list, it is clear that there are three important challenges related to the material intended to fill the LAA, one related to a delivery mechanism, and one related to the interaction of the two. To prioritize them, the innovators can think about which challenges have been solved before and which have not. For example, many innovators working on other projects have accessed the LAA of an animal. In contrast, it is unclear whether anyone has ever found a material that meets the challenges outlined in items 3–5. For this reason, the innovators might sequence the work as follows: 4, 3, 5, 2, 1. This order makes finding a material that reacts in a specific manner with living tissue – which is likely the greatest challenge with the most inherent uncertainty – their top priority.

As this example demonstrates, innovators often need to speculate which technical challenges will be the most difficult to address. In doing so, they must not forget to draw from foundational knowledge in the various engineering disciplines that exists and, more importantly, leverage the expertise of other engineers. While some of this knowledge would likely have come to bear during early concept exploration related to the feasibility of certain elements of a final concept, it is nonetheless important to tap into this knowledge when considering all of the technical challenges together. Depending on the innovators' backgrounds and level of experience, they may have difficulty making the determination about which technical challenges will actually be the most important (or difficult) to address. For instance, with the LAA concept, an innovator with a strong mechanical engineering background might have a clear understanding of the challenges associated with developing a percutaneous delivery system, but may not be able to predict with great accuracy the challenges involved in finding a material to deliver to the LAA. The best way to address gaps in one's knowledge base and avoid the effect of personal **biases** is to involve individuals from all of the engineering disciplines that play a part in developing the total solution. These individuals can help innovators understand the degree of engineering complexity and uncertainty associated with each challenge. which is critical in the prioritization process. However, even with input from a comprehensive and capable team,

unanticipated technical challenges will almost always arise in any R&D effort. By considering known and anticipated challenges at the outset, having plans in place to address them, and staying on the look-out for unexpected problems, the innovators will be in the best possible position to overcome whatever challenges arise.

As innovators and companies start developing an R&D strategy, they must carefully consider how to customize the milestones and testing strategies they choose for their specific project. The importance of thinking critically about these assumptions and testing the most important ones is illustrated by the ArthroCare story.

A second story about Oculeve provides a look at the specific R&D milestones and testing requirements for a product that requires a more rigorous regulatory pathway.

FROM THE FIELD ARTHROCARE CORPORATION

Tailoring an R&D strategy

Hira Thapliyal and Phil Eggers, the founders of ArthroCare Corporation, originally came up with a novel way to use an electrical current directed to electrodes in contact with coronary artery plaques, often the underlying cause of arterial narrowing and occlusions, to "melt" the plaques away. However, "This was before the field of coronary interventions had exploded with the introduction of stents," Thapliyal recalled.[2] Accordingly, he and Eggers had difficulty raising funding for the idea. To help them understand if there were other needs that would benefit from their solution, they began seeking advice from experienced colleagues in the medtech field. Among others, they talked with Bob Garvey, "a marketing guy who had spent part of his career in arthroscopy." When Garvey heard about their experience with treating occlusions, he suggested that they look at various orthopedic applications since there were still important unmet needs related to tissue removal. At the time, the tools used to perform arthroscopy, a minimally invasive orthopedic procedure involving a small endoscope and tools inserted via small incisions in a joint to examine and treat various joint conditions, were still relatively crude. Taking this advice, the two men spent some time understanding the need for *a better way to remove joint tissue* and tried their device in a chicken meniscus, which he likened to "the gasket between the bones of a joint." "It worked very well," Thapliyal said. "It eliminated the tissues, which just melted away."

Based on the results of these early tests using a prototype of the device, Thapliyal, Eggers, Garvey, and another colleague from Thapliyal's past, Tony Manlove, were able to raise some funding to develop the arthroscopic application. As part of this effort, they realized that they would have to lay out an R&D strategy that would make sense to investors and give the project the best chance to achieve regulatory clearance in the shortest time frame. Thapliyal and his colleagues made a series of new assumptions regarding the sequence of events that needed to occur. "The recipe is the same for all medical devices. Bench-top, some live animals, cadaver types, and then maybe on to humans. But it has to be looked at from the context of the regulatory framework. If you have a PMA device, you structure it differently than a 510(k). If it's a 510(k), then you need to understand more about the 510(k) requirements. Some are straightforward **substantial equivalence**. Many require live animal data. But you don't want to be second-guessed there. By the time you have filed your regulatory submission, you have put in a lot of resources, time, money, and sweat. You don't want to get caught without the right data. Review all your early assumptions."

The team sought advice from various sources and used that information to decide on the best course of action. They first determined that they would likely be able to file a 510(k) based on substantial equivalence to the current electrosurgical cautery tool used in arthroscopy. Their regulatory advisor told them to "keep it a ho-hum 510(k). Don't make a big deal of it. Electrosurgery tools are

already in the market. You want to be in the market. So just show, with some live animal data, that your device performs equivalently to what's already available." With this regulatory approach in mind, they next sought to understand which R&D milestones would be most important and how to prioritize them based on the technical challenges they anticipated.

They had already achieved an early technical feasibility milestone through their work in chicken menisci. For their next milestone, they had two options. They could either seek to show efficacy in live tissue through live animal testing or perform cadaver studies to show feasibility with human anatomy. For many devices, especially ones using combinations of electrical and mechanical components, animal studies are done earlier in the R&D path in order to optimize the electrical engineering functionality in live tissue. Once this is achieved, and the risk associated with using the device in live tissue is eliminated, the technology can then be refined for use in human anatomy. However, in Thapliyal's case, he and his team felt confident about the electrical components of their solution and felt strongly that effective arthroscopy was anatomy-dependent. Therefore, they decided to focus on the mechanical components of their device and optimize them for human anatomy using cadavers before performing animal tests.

To accomplish this, they teamed up with a physician they knew from San Diego, Dr. James Tasto, who helped them to work on cadaver samples. "We linked up with him and he said, 'Sure, you can come to where I'm working in the evenings, after hours, and test some menisci with your tool.'" Several months of testing and design iterations on cadavers allowed them to validate the feasibility of using the technology in human anatomy and to optimize the design. "We used the cadaver data to make sure that what we did was correctly sized and designed for human use," Thapliyal said. For example, it was essential to understand the correct angles to build into their probe to make it compatible with human joints.

The next challenge was to find an appropriate animal model. The model needed to provide similarities to human anatomy and needed to be a widely available resource. Thapliyal recalled, "We settled on a goat model. Goat models were well published by that time and they had important similarities to humans. The size of the joint was a little smaller, but the anatomy and presentation of the meniscus was similar. Plus, goats were available and we could do a lot of them."

Over the course of a few months, the team performed experiments on about a dozen goats, with the objective of generating in vivo data to support regulatory clearance. "We didn't have to do a chronic study; we just had to acutely show that we can remove tissue in a way that was equivalent to what was currently on the market. Our tests were all statistically designed to show non-inferiority. We were not targeting that our tissue damage would be lower, but we were amazed that we saw virtually no tissue damage."

Based on the results of the goat tests, regulatory clearance was granted for the company's arthroscopy device. (See Figure 5.2.2 for a summary of the high-level R&D milestones leading up to regulatory clearance.) Once in the market, the technology caught on relatively quickly because it operated at a lower temperature and was more precise than traditional surgical tools so that damage to healthy tissue surrounding the target area could be minimized.

In terms of its ongoing R&D strategy, the team committed 80 percent of its time, resources, and engineering staff to development opportunities in arthroscopy and 20 percent on exploring new areas. Over time, ArthroCare expanded into the fields of spine and ENT. According to Thapliyal, "What we found is that we have a platform. It's not just arthroscopy. We believed it would be useful in other areas and we wanted to explore the limits of our technology." However,

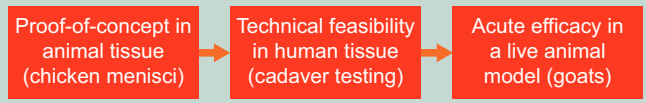


FIGURE 5.2.2
Arthrocare's early R&D milestones, which led to regulatory clearance for its device.

he offered a word of caution to innovators as they manage their R&D strategies: "Guard against projects that can take away from the focus of your company. If they become too strong, do something about it to protect the core business."

Reflecting on his experiences, Thapliyal suggested that innovators should "take a lot of advice." Moreover, he said, "Don't be seduced by the elegance of your assumptions. You have to go back and review them and test them from time to time." This philosophy allowed Thapliyal to effectively recast his focus when he ran into difficulties, and to also keep a complex technical development effort on track through the achievement of important company milestones.

FROM THE FIELD OCULEVE

Defining an R&D strategy to retire key risks

Seeking a way to treat dry eye disease (DED) that would be more effective than the prescription eye drops that are the current **standard of care**, Michael Ackermann and his Stanford Biodesign team developed the idea of using neurostimulation to activate the lacrimal gland, which produces natural tears, in order to increase its tear production. Earlier in the biodesign innovation process, they developed a series of "looks-like" prototypes to explore the idea of an intra-orbital implantable device with physicians. They also created a "works-like" model to test the technical viability of the idea. After multiple refinements, the team used the works-like prototype to confirm the basic **mechanism of action** through a progression of bench and animal tests (see chapter 4.5 for more about its experience with concept exploration and testing).

To chart a course forward, Ackermann defined a series of strategic R&D milestones for the team (see Figure 5.2.3). These milestones were intended to sequentially retire the most significant risks in the project and help the team make steady progress toward the market. "Establishing milestones requires innovators to identify what the value creators are," said Ackermann. "You have to ask yourself, what do you need to prove to yourselves, to your potential investors, and to the public?" He added, "Oftentimes, those things aren't exclusively R&D related, but they require R&D to achieve."

For Oculeve, an early strategic R&D milestone was to confirm that the mechanism of action worked in the team's population of interest. As Ackermann explained, "We needed human clinical data to prove that the concept of stimulating the lacrimal nerve would produce tears in patients with dry eye disease." From a technical perspective, the company already had a works-like prototype (based on a commercially available, 510(k) cleared neurostimulation device) that would allow it to test the concept in the clinic. However, Ackermann and colleagues faced a significant challenge in terms of planning and executing an acute, **first-in-human**, **off-label** study. "We were low on cash and under some financial pressure to meet this milestone quickly," recalled Ackermann. "We had a venture firm interested in providing seed financing, but the partners wanted to see human clinical data before they would commit to coming on board."

Although Oculeve would have liked to conduct its first-in-human study at Stanford, where the team was familiar

R&D Milestones	Critical Technical Challenges	Study Type	Risks to be Retired Based on Results
First works-like prototype that performs safely and effectively in humans	• Confirming that neurostimulation of lacrimal tissue in humans will create tears	First-in-Human Acute Safety & Efficacy Study	Mechanism of action works in humans with DED
First works-like/looks-like model that performs safely and effectively in humans	• Building custom neurostimulation electronics • Embodying all required functionality into a form factor that can be implanted into the ocular orbit • Ensuring hermeticity, biocompatibility, and reliability of the implant • Developing a basic insertion device and technique • Validating the ability to communicate with implant from remote energizer outside the body	Chronic Safety & Efficacy Studies	Mechanism of action can be given a functional form and works in humans with DED over a sustained period of time
Pre-production system that performs safely and effectively in humans	• Optimizing functionality of system for use on a larger scale • Finalizing implant design • Confirming that the implant can be manufactured at a reasonable cost	Pilot Trials	Identify optimal trial design for pivotal trial to collect data for US regulatory submission
Market-ready system that performs safely and effectively in humans	• Optimizing functionality of system for use on a commercial scale • Validating human factors and usability of the insertion device and energizer • Confirming large-scale manufacturability of all system components	Pivotal Trial	Collect data for US regulatory submission

FIGURE 5.2.3
The major milestones that served as the basis for Oculeve's R&D strategy (courtesy of Oculeve).

with the quality of the research and the clinic, "The realities of early stage clinical work made that impossible," Ackermann stated. "It's not realistic for a small company without much money to do a study in the US, especially if it requires an IDE [Investigational Device Exemption] from the **FDA**." He noted that this process is not only arduous and time-consuming, but prohibitively expensive. "Fortunately," he said, "there are plenty of high quality, early-stage clinical study sites outside of the United States."

The team's mentors, Daniel Palanker, Associate Professor in the Department of Ophthalmology, Stanford School of Medicine, and Mark Blumenkranz, worked with one such site in Mexico. "Daniel and Mark had experience with a highly regarded clinical facility in Mexico City, as well as an investigator there who had an excellent reputation and had run sophisticated trials before," Ackermann said. Importantly, the facility had a fairly streamlined process for getting ethics committee approvals and addressing other important requirements, making it possible for the team to launch a ten-person, first-in-human study in just a few months. "Using our works-like prototype, we were able to get up and running pretty quickly to get real clinical data on patients with dry eye disease," he stated.

The study confirmed the general concept that electrical stimulation would produce lacrimation. "By placing needles adjacent to the lacrimal gland, we were able to stimulate tear production acutely in an office setting, proving that the concept did work in human patients," Ackermann reported. Based on these data, he was able to secure several hundred thousand dollars in venture backed-seed funding. With these funds in hand, Ackermann recruited Jim Loudin, a postdoctoral physicist, electrical engineer, and bioengineer, who "had been building electronics for small microstimulators as a hobby and research project," to lead the next phase of electrical engineering work. Together, Loudin, Ackermann, Palanker, and Blumenkranz officially co-founded Oculeve. The seed funding also allowed the two men to hire a deeply experienced mechanical engineer, Janusz Kuzma, to build the housing for Loudin's electronics. "Janusz helped pioneer multi-channel cochlear implants in the 1980s," Ackermann explained. "We actually pulled him out of retirement to spearhead our mechanical efforts." He added, "So we had this great combination of young, smart, hardworking people, and people with lots of experience and gray hair."

With this team in place, Oculeve turned its attention to another major R&D milestone: developing a "works-like/looks-like" model that would perform safely and effectively in humans over time. To achieve this particular milestone, the team had multiple technical challenges to overcome, including "packaging all of these 'smarts' into a tiny device that could fit into the ocular orbit and addressing issues related to developing an implant such as maintaining hermeticity, reliability, and **biocompatibility**," recalled Ackermann. Oculeve also needed to show that it could adequately power and communicate with the device from outside the body. With a long list of related specifications to address, Loudin and Kuzma progressed quickly through 30–50 iterations before deciding on the model they would use in the chronic clinical study. After approximately 15 months of development and testing, Oculeve was satisfied that its solution was safe for a chronic safety and efficiency study.

The team's next R&D milestone was to develop a pre-production system that performs safely and effectively in humans in a series of **pilot trials**. One important goal of the pilot trials would be to help Oculeve prepare for its subsequent milestone: a **pivotal trial** to support the company's regulatory submission to the FDA. The idea was to conduct two or three different pilot studies to help Oculeve decide on an optimal design for the pivotal trial. According to Ackermann, "Despite its significant regulatory hurdles, the US is still the biggest, most viable market for a device like ours. So we're preparing to go through the premarket approval [PMA] process, and we're doing everything we can to be confident in the outcome of our pivotal trial."

The key technical challenges to address in advance of the pilot studies involved advancing the development of all three components of the Oculeve system: (1) the intraorbital implant, which delivers small electrical pulses that activate the gland and restore tears to the eye; (2) an insertion instrument to place the implant; and (3) an energizer that serves as an external "remote control," for powering and communicating with the implant (see Figure 5.2.4).

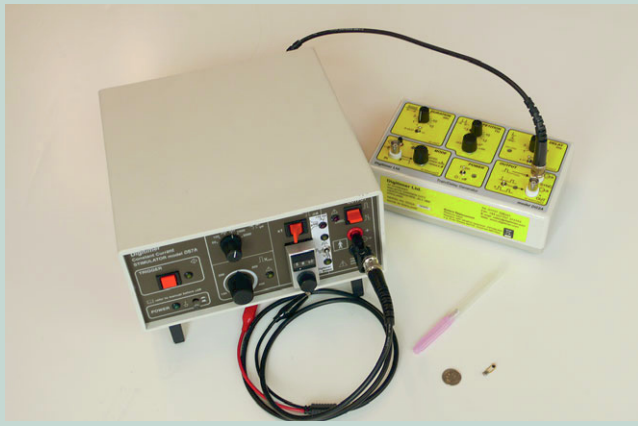


FIGURE 5.2.4
The Oculeve System, including the implant, insertion device, and energizer (courtesy of Oculeve).

In this round of R&D, the team devoted special time and resources to the implant. First, the engineers tried to lock in the design of the implant. As Ackermann described, they could continue to iterate the design of the insertion device and energizer because the testing requirements and cycle time associated with these elements of the systems were much lower. But each time they made significant changes to the implant, they had to complete lengthy and expensive animal tests, biocompatibility tests, and so on before they were able to try the device in humans. "So concerns that might seem down-the-road, like cost of goods and manufacturability, were actually important from the beginning," he said. "The other two components are much less critical and risky. We could afford to put off their productization until we're sure the implant works really well."

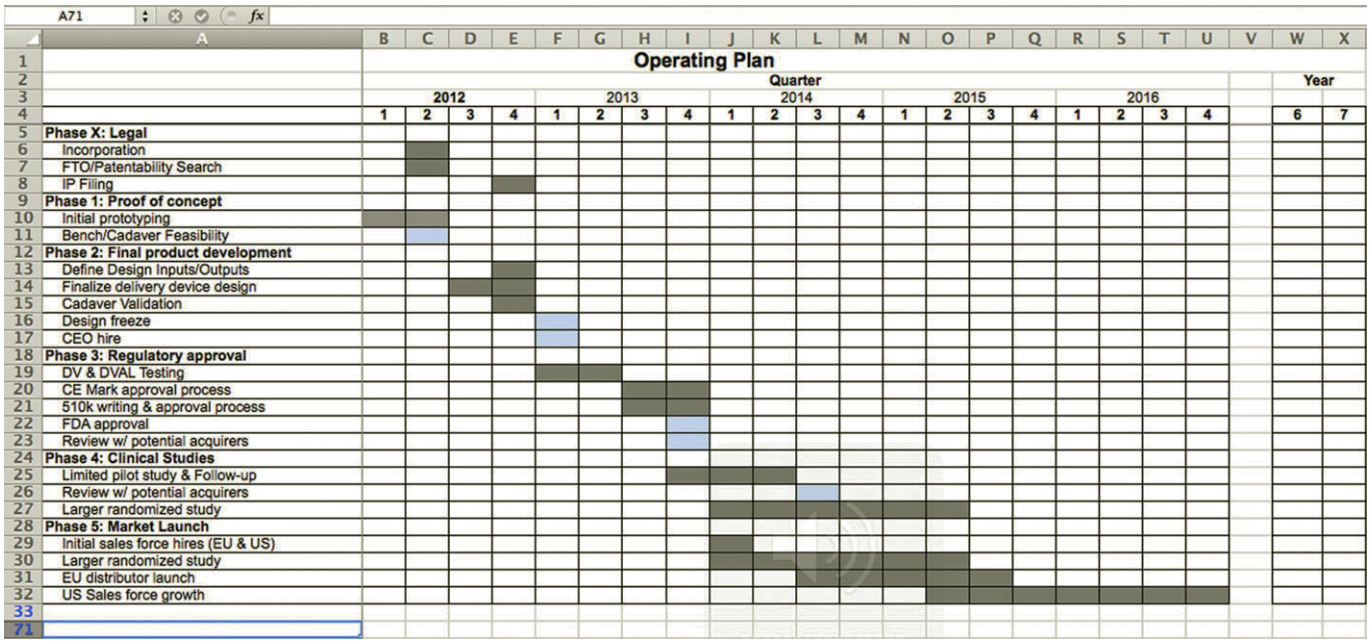
However, they did initiate productization of the implantable device, under **design controls**, focusing on long-term manufacturability and ensuring that it could be produced at a price that decision makers and other **stakeholders** would find compelling. Commenting on this transition, Ackermann observed, "I think that bringing in a heavy quality system should be delayed until you're confident that you have good working device. There's a little bit of push-pull in the beginning. You need enough of the quality elements in place so that you are comfortable doing clinical work with the prototype. But not so much that it prohibitively slows down your R&D efforts and your ability to iterate quickly. Once you're really confident that things are working on a clinical level, and on various business and commercial levels as well, then it's time to go in and start developing a formal product."

When asked for advice about building an R&D strategy, Ackermann encouraged other innovators to keep the "big picture" squarely in mind. "Although it is tempting as an engineer to be overly focused on building the actual device, it's more important to pull up and concentrate on proving value," he said. "You have to view your R&D strategy as a means to an end, rather than an end in itself."

Developing an initial R&D plan

With specific R&D milestones and related technical challenges identified and prioritized, innovators can next develop an initial R&D plan. As part of an R&D strategy, this initial plan should be kept at a relatively high level. However, to construct a high-level plan, innovators still must begin with a detailed list of engineering activities required to achieve each milestone, making sure to thoroughly consider the technical challenges and testing that will be required to achieve them. With this understanding, they can then layer in R&D personnel and engineering resources, such as equipment and facilities, which will then help determine overall R&D timelines. Many innovators capture their R&D plans in a Gantt chart, which is a project management tool that displays activities sequenced over time (see Figure 5.2.5). More detailed Gantt charts also can be used to capture interdependencies between activities (see Figure 5.2.8) and the resources/staff they require.[3]

More specific details, such as costs, will be reserved for inclusion in the company's integrated operating and staffing plan (see chapter 6.1). Costs are not directly addressed in this chapter because they differ so significantly from project to project, as well as across geographic areas. For instance, developing a mobile health application will likely be dramatically less expensive than creating a traditional medtech device. And developing a complex system that relies on multiple engineering disciplines will probably be far more costly than engineering a simple mechanical solution. The best way for innovators to gain a benchmark for R&D-related expenses is to network with other innovators working on projects that roughly resemble their own projects.



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IP Filing																								
Phase 1: Proof of concept																								
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Bench/Cadaver Feasibility																								
Phase 2: Final product development																								
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Phase 3: Regulatory approval																								
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Limited pilot study & Follow-up																								
Review w/ potential acquirers																								
Larger randomized study																								
Phase 5: Market Launch																								
Initial sales force hires (EU & US)																								
Larger randomized study																								
EU distributor launch																								
US Sales force growth																								

FIGURE 5.2.5

This relatively high-level Gantt chart, which might be presented to investors or at a board meeting, can be used to communicate important milestones across the company (courtesy of Ciel Medical).

High-level discussions about these issues are necessary as part of the R&D strategy process to allow innovators make more accurate forecasts of when R&D milestones can realistically be met. As noted, once the timing of key milestones is determined, innovators can strategically position R&D as a contributor to other important development milestones, such as funding and regulatory clearance.

R&D activities

The first step in creating an R&D plan is to define the scope of work required to resolve the technical challenges related to each major R&D milestone. This should include listing all of the steps involved in building any required models and then testing them through the most appropriate method(s) in the biodesign testing continuum (revisit Figure 5.2.1). To do so, company or team leaders will need to work closely with the engineers to ensure that the key activities are captured in the plan. Most teams start by making their R&D milestones the major headings in their Gantt chart. Then, under each one, they list the critical technical challenges that have been identified. Next, they outline the work steps required to understand and address each technical challenge. Finally, they add the testing-related activities that will confirm that the technical challenges have been overcome and the milestone has been met.

One important factor to remember is that development and testing is highly iterative. This can sometimes make it difficult for innovators to anticipate all activities that should be included in the R&D plan. While there is no "right" answer, innovators are usually advised to build in multiple rounds of development and testing when addressing a complex technical challenge.

Innovators may also struggle with the right level of detail to include in an initial R&D plan. Again, each team must use its own judgment but it can be helpful to keep in mind that all key activities, as well as the tasks that represent discreet pieces of work that need to be accomplished, should be listed so that specific personnel and resources can be assigned to these activities and tasks. What is typically not included in an R&D plan is how these activities and tasks are

performed. This is usually left to individual engineers and/or engineering subteams to determine once the overall plan has been defined.

In addition to being important milestones themselves, completing certain tests is often integral to demonstrating that critical certain technical challenges have been overcome. Accordingly, to create a reasonably accurate R&D plan, the testing activities that will be undertaken need to be thought about carefully, as multiple rounds may be needed. This work can be resource intensive. For instance, when a company has moved into animal studies, each iterative round of testing to achieve a milestone can be costly in terms of time, personnel, and other resource requirements.

Considering the LAA example provides some insight into how to think about technical challenges, how to forecast activities in the initial R&D plan, and how different testing methods may have different impacts on the use of time and resources. It also demonstrates how playing out potential testing outcomes can elucidate important issues relevant to subsequent R&D activities and milestones.

An important early technical challenge in the LAA example is the identification of material that can occlude a simulated LAA using a prototype in a bench-top test. To perform this test, an LAA-like pouch could be created simply by suspending a plastic bag in a chamber filled with moving and heated blood. By attempting to deliver the material into the plastic pouch, the innovator could then determine if it solidified to achieve the occlusion. If it did not solidify, a new plastic bag could be swapped with the old one and testing could be performed again, once a new prototype (e.g., using different material) that addresses a limitation of the failed prototype is created. The failure may have been due to the material, the delivery mechanism, or the artificial set-up. Even though iterative prototyping and bench testing at this stage can be performed relatively quickly, innovators may want to think about allocating a small buffer of time for multiple iterations given the number of failure modes that are possible.

If the material did solidify, in addition to meeting the technical challenge, an innovator might gain an appreciation of the timeline to solidification. While perhaps not initially anticipated, understanding what this finding means could impact other parts of the plan. If it took many hours, for example, this might be problematic if an important user requirement is that the material solidifies in one hour or less. Hence, in the next round, the innovator might need to make repeated modifications until this important design requirement is met. Once a prototype that works adequately is created, additional experiments would be needed to further optimize the solution, especially with respect to integrating it with other components of the solution. Bench and simulated use testing could allow various technical challenges to be tested in parallel or with one variable altered each time. While the innovators would need to scope this activity to take into account how many series of tests might be needed, at this pre-animal stage multiple iterations are unlikely to require significant additional resources or cost.

Taking the example one step further, if achieving effectiveness in a tissue model is an important subsequent milestone, a similar set-up could be created using a cow's heart instead of a plastic bag. While this might be somewhat more complicated, based on the availability and cost of hearts, this type of testing can be performed iteratively and relatively quickly. The basic point is that to achieve milestones that do not involve live animal testing, the testing methods do not have to be time-consuming or expensive, but budgeting some time and resources for iterative rounds of prototyping and testing is important.

In contrast, live animal testing, which is typically another important R&D milestone, takes more time to prepare and plan for, is far more costly, and must be performed in approved facilities. When working with live animals, it is important to keep in mind that the need for multiple rounds of prototype iteration can have a significant impact on the R&D timeline because of ethical and other requirements associated with these tests (see 5.3 Clinical Strategy). If chronic studies are needed that involve many animals, important controls, and specific follow-up protocols to investigate long-term safety and effectiveness, the time and expense to conduct them will be even greater. As such, chronic live animal tests should typically be used only when necessary and be performed as few times as possible to achieve the desired results.

To progress to milestones related to live human testing, a final prototype must demonstrate its safety and effectiveness in animal studies (if animal testing is required) and meet quality requirements (see 5.5 Quality Management). It also will require the transfer of a design to manufacturing. Many innovators make the mistake of thinking about design for manufacturability late in R&D planning. However, to maximize results while controlling time and costs, innovators should consider this factor when developing their initial R&D strategy and plan. Engineers with experience designing products for high-volume production can add tremendous value from the relatively early stages of the R&D life cycle. For one, they can help ensure that the right materials are used so the technology is safe in humans but also compatible with large-scale manufacturing techniques. Additionally, they can help eliminate unnecessary design constraints and process inefficiencies that add time, cost, and complexity when it comes to manufacturing. Further, these engineers can ensure that key components are sourced from vendors and suppliers who are reliable and can scale to handle larger volumes. Finally, they can assist a company in accelerating its time to market by anticipating critical production requirements and initiating long lead-time activities early enough in the R&D plan so they do not become bottlenecks later as development and testing progresses.

The story about 3rd Stone Design and the DoseRight syringe clip illustrates some of the issues related to the transition from prototyping and initial R&D to design for high-volume production. Additional references on manufacturing can be found in the online Getting Started section.

FROM THE FIELD — DOSERIGHT® SYRINGE CLIP

The importance of design for manufacturability

According to Robert Miros, CEO of 3rd Stone Design, a design, strategy, and development consultancy, issues related to design for manufacturing are common among teams of aspiring innovators, especially university-based teams and early stage start-ups. Often, since the focus of these innovators is on early-stage design, concept generation, prototype development, and preliminary bench and field testing, the importance of considering manufacturing and industrial engineering issues early in the process is lost. As a result, while many early engineering teams can successfully develop and produce small numbers of prototypes for testing under controlled circumstances to overcome important technical challenges, they sometimes lack the expertise to design for mass production and create products that perform as intended when implemented outside an R&D environment. "They [university-teams] are coming from a largely theoretical training, so the basics of manufacturing are often not top of mind – that is, to get a factory set up, to have the right sort of drawings and quality documents and inspection criteria," Miros commented.

3rd Stone Design worked with one team of undergraduate students from the Rice 360° Beyond Traditional Borders (BTB) program to help address such challenges. The team had successfully designed and tested what the members dubbed the DoseRight syringe clip to enhance the dosing accuracy of liquid, antiretroviral medications in resource-limited settings. The product was a simple plastic clip that could be inserted into the top portion of a standard oral syringe to control the amount of medication that could be drawn into the syringe. Produced in varying lengths to correspond to different dosing volumes, the clips could be quickly and easily affixed to a standard syringe to ensure dosing accuracy regardless of caregiver literacy or visual acuity (see Figure 5.2.6). Based on field tests that demonstrated that the clips increased dosing accuracy, the team lined up its first customer and a sizable order: the Clinton Health Access Initiative (CHAI) requested 200,000 clips to be distributed in Swaziland,

FIGURE 5.2.6
The DoseRight syringe clip (courtesy of 3rd Stone Design).

Africa via the Ministry of Health. However, the students had fabricated their plastic prototypes in-house, using a 3D printer. Although this approach enabled them to complete a proof-of-concept, it was not cost-effective for high-volume production. “Even if they could have made 200,000, which they really couldn’t have with that technology, it probably would have cost them a dollar apiece,” said Miros. With CHAI eager to procure the clips as quickly as possible at a much lower price, BTB asked Miros for help. 3rd Stone Design **licensed** the technology from Rice and took the project forward.

The primary challenge was figuring out how to transfer the process to manufacturing at scale. Injection molding offers a lower-cost alternative to 3D printing that would produce high-quality results. With this process, heated polymers are forced into a multi-part mold that was essentially a negative form of the desired part. The mold is opened after cooling and the finished part is ejected. Given its simple design, molding the part would be relatively easy. However, the DoseRight clips needed to be produced in 10 different lengths in order to provide dosing volumes from 0.5 mL to 5.0 mL in half mL graduations. Normally, this would require the creation of 10 different molds. The 3rd Stone Design team estimated that 10 hard tooling molds (made of hardened steel with multiple cavities for large-quantity production) would cost $200,000–$300,000 – far too much for a product in start-up mode. Tooling costs had to be held to a fraction of that in order to keep the capital investment reasonable and to produce the clips at a cost that global healthcare customers could afford to pay while maintaining the quality of the finished clips.

Miros and team solved the problem by designing a limited mold set based on multiple inserts of varying size that enabled them to produce high-quality parts at a reasonable cost. While this solution did not bring the cost down to a few pennies per clip (which was the ultimate goal), it was a good start. As the first customer for the DoseRight clips, CHAI understood that it would have to pay slightly more for the product initially, with subsequent costs likely to decrease as production volume rose. “The customer had been coached, a little bit, on what the initial pricing would be, and we were able to hit that price and still have some profit in it; not a lot.”

Using the limited mold set, 3rd Stone cost-effectively manufactured all 10 lengths of the DoseRight clips out of polypropylene in a quality-controlled environment, with all parts bagged and labeled in a manner appropriate for medical disposables. In partnership with CHAI, Swaziland’s Ministry of Health began distributing more than 200,000 dosing clips as part of its Prevention of Mother to Child Transmission of HIV/AIDs program. 3rd Stone subsequently went on to pursue additional orders in developing countries, working with large NGOs and local ministries of health that were running, or planning, countrywide vaccination programs.

When asked for advice to help other innovators, Miros recommended that teams develop strong competencies in design for manufacturing, either by adding experienced individuals to the group or by contracting with a seasoned partner. Especially for early-stage start-ups, personnel with a background in manufacturing processes should be brought in well before most technical challenges have been overcome and customers are being lined up. If they are a part of the design process and R&D planning effort, they can help influence important choices made by the R&D team, potentially prevent significant rework, and ensure a more efficient transfer of the product to manufacturing.

R&D personnel

Once the activities in an R&D plan have been outlined, innovators can next consider what R&D personnel are necessary to complete those activities. Thinking about the skills sets and number of engineers needed is critical because it has a direct impact on when R&D milestones can be achieved. Furthermore, R&D staffing costs can be the highest R&D budget expense and, thus, will affect financing events.

To determine what types of engineering and technical resources a company will need, innovators should assess each milestone and associated activities individually, in terms of the relevant engineering skills required to address the specific engineering work. Then, the R&D plan should be evaluated as whole, paying particular attention to the interactions between key aspects of the solution and any unique engineering skills needed to address them.

Assessing the difficulties involved in particular activities can be a challenge in itself, particularly for innovators working outside their area of expertise. However, developing reasonable estimates is important since it directly drives the number (and skill levels) of engineers required to get an activity completed in a reasonable amount of time. The best approach to overcoming this hurdle is to query others with varied backgrounds to get a rough idea of the time and effort needed to address a challenge, assuming that knowledgeable resources are found. As a rule of thumb, the length of time spent on engineering depends heavily on the complexity of the innovation being developed. Even with a clear plan, achieving certain milestones will simply take longer for a complicated solution.

During concept exploration, innovators may have been able to develop working models that demonstrated a concept's basic feasibility with little more than hard work, book research, and some guidance and/or coaching from those with relevant expertise. However, the transition from early-stage prototyping to R&D usually necessitates much deeper knowledge and expertise in each of the relevant functional blocks or engineering disciplines. Unless the company intends to outsource the development of its innovation, it must hire a team of appropriately skilled engineers and map out how that team will grow over time as it works to achieve successive milestones.

To address the technical challenges in Table 5.2.2 for the LAA example, the innovators would recognize the need for both mechanical engineering and materials science expertise. Based on how these challenges are prioritized, they would also surmise that getting a materials science expert on board first would be advantageous to retire the risk of finding a material with the desired properties before thinking about the mechanical aspects of the solution. Later, a mechanical engineering resource could be brought in to address the development of a delivery system. A third resource, perhaps an expert in how the material and delivery system interact, could be added next, at the appropriate point in time. In a resource-constrained environment, it would not be practical to hire the latter two resources until enough is known about the core material used in the solution, since this will affect the design of the delivery mechanism and the substance from which it is made. Understanding these types of sequential interactions allows the innovators to more effectively manage R&D staffing within prevalent resource and time constraints.

Other projects may lend themselves more readily to parallel development efforts. For example, recall the ACS case example in 4.6 Final Concept Selection, in which parallel development efforts focused on a balloon catheter, a guidewire for catheter navigation, and a guiding catheter are described. In this scenario, the company made a strategic decision to run multiple engineering work streams rather than working in sequence. In some types of project, and where time and money allow, this alternative is available to the team.

The key point is that, in a start-up with scarce resources, it may be possible for a company to stagger its approach to hiring based on the R&D strategy and product development pathway. However, this decision should still be predicated on ensuring that the greatest technical challenges and those with the longest development time are addressed early in the process so that adjustments in the development pathway can be made as soon as possible.

Another reason to think about staffing as part of the R&D plan is that hiring itself poses an element of risk. For

example, if a highly skilled electrical engineer with many years of experience in a given field will be needed in three months to help solve a key technical challenge, actually finding and hiring the right resource may be unrealistic in the given time frame, especially if the demand for such engineers is high and availability is low. Understanding this may help an innovator re-sequence key technical challenges more realistically. This, in turn, may affect the timing of certain strategic milestones, causing further impact on other factors, such as company funding. Furthermore, while having more people on the R&D team does not necessarily lead to faster resolution of critical issues, planning for adequate staff eliminates at least one constraint that can interfere with a company's R&D progress.

Importantly, when hiring R&D personnel, companies face a trade-off. They can spend more money to attract and hire engineers with deep, often specialized experience. Or, they can pay less to add bright but relatively inexperienced staff members to the team. Inexperienced engineers might be easier to find and hire, but they typically introduce more risk from a development standpoint (in terms of needing more time to solve a technical challenge). On the other hand, while experienced engineers can represent less risk from the standpoint of knowledge, they are more expensive and harder to find. That said, it is usually necessary to have at least one experienced manager with product development expertise to oversee the R&D process and ensure that product development is launched in the right direction (e.g., in the role of vice president or director of R&D). Beyond that, a company should consider the type of work it must accomplish in order to achieve its goals, as well as the likelihood of hiring experienced engineers in a reasonable time frame. With complex technologies in treatment areas that are relatively unexplored, it usually makes sense to hire experienced engineers, even if that means the company can bring on fewer people and needs more time to hire. In contrast, when working on incremental technologies in areas where speed to market may be an important driver, a somewhat greater number of less experienced individuals can more effectively swarm the development challenge. As a general rule, however, start-up companies almost always benefit from hiring the best people they can – particularly in assembling a core team of experienced engineers to ensure that product development is launched in the right direction.

Another approach that can help a company carefully manage its investment in R&D personnel is to use consultants to assist with certain tasks. Hiring engineers on a contract basis can aid the company in several ways. First, it can be an effective mechanism for gaining access to expensive, specialized expertise required to address a specific engineering challenge, but not required on an ongoing basis. For example, in the LAA scenario described above, an expert materials consultant could help guide the materials scientist(s) working at the company to more quickly find an appropriate material, but may not be required once this effort has been completed. In some cases, seeking such expertise on a contract basis is more feasible than trying to hire a full-time employee because many engineers with critical, yet highly specific skills often gravitate to consulting simply due to the nature of their knowledge base (i.e., their value-added skills are not required for long-term projects). Second, hiring consultants can allow the company to respond to temporary or short-term peaks in the engineering workload without having to hire (and then lay off) dedicated resources. For instance, as the LAA delivery system moves toward regulatory submission, there may be multiple, short-term tests that can be accomplished simultaneously. Hiring contract labor may be beneficial to execute the tests without distracting in-house engineers from their other priorities. Finally, consultants can help bring a fresh perspective to the resolution of challenging problems.

According to Hira Thapliyal of ArthroCare, the company used contract manufacturers to develop and produce its prototypes for its animal studies. "Seek out known entities with expertise in a specific area," he said. "In the early stages, you can get a lot of work done very quickly when you outsource. You just need to have a smart group of people inside the organization who can communicate and convey to your vendors what you need." However, as part of its plan, the team knew it would eventually have to bring development in-house. By the time of ArthroCare's FDA filing, Thapliyal recalled, "We had a director of R&D, a couple of

engineers, and some quality assurance people. We had started bringing disposable device development in-house because we knew we had to have control of it since this would allow us to iterate more quickly."

When using consultants, just be aware that they may work differently from in-house staff and require different incentives. Occasionally, consultants may not exercise the same sense of urgency as dedicated, full-time employees in performing their tasks. They also may not be knowledgeable about all of the intricacies of the development process that would allow them to move at a fast or consistent pace. Moreover, issues related to confidentiality and IP must be adequately addressed before any contract work is initiated. Finally, consider the fact that when consultants finish their assignments, much of the working knowledge that has been accumulated through their involvement leaves the company with them. At a minimum, the company should orchestrate a proactive knowledge transfer and ensure the completion of relevant documentation prior to their departure.

Engineering resources

In addition to R&D personnel, a company will be required to make an investment in facilities, equipment, and other resources to support R&D (see Figure 5.2.7). While there is less risk associated with the acquisition and utilization of these resources from a timeline perspective (i.e., most of these other resources are readily available), some thought must be given to this from a strategic development standpoint so that the resources obtained match the availability of R&D personnel and both are fully and efficiently utilized. This is particularly important given that decisions related to engineering resources can have significant financial implications.

In the LAA example, if the company decides to develop a delivery system via an in-house engineering effort, it will need to purchase enough equipment to support this activity. However, if finding a mechanical engineer with skills in developing percutaneous systems takes too much time, the development work could instead be contracted to an outside firm. Such a move would obviate the need to purchase the equipment required to develop this portion of its device. In another scenario, the company might be able to hire an engineer, but decide to not purchase any equipment and have the engineer work with an outside vendor that possesses the machines and equipment to develop the product. All of these choices have an impact on the timeline to develop the delivery system. They also directly affect issues related to resources, which must be taken into account when developing the overall operating plan. Finally, the ultimate decision can affect the level of funding required (as different investments are needed to equip and maintain an engineering shop versus contract with an outside firm).

When the need for specialized equipment, parts, materials, or processes is anticipated in the development of a product, lead-time issues often have to be considered. If a company requires hard-to-get items, this may affect the hiring of personnel, the sequence of addressing challenges, and the time required for milestones to be achieved. For example, creating a certain electronic circuit may require many circuit board revisions to reach a final board design. Outsourcing the fabrication of each of its prototype board designs with every revision may necessitate a substantial lead time of weeks to months for each of the boards to be fabricated. By understanding and anticipating such needs, a company can determine whether a different development pathway is more efficient (e.g., outsourcing design as well as fabrication to the same board house).

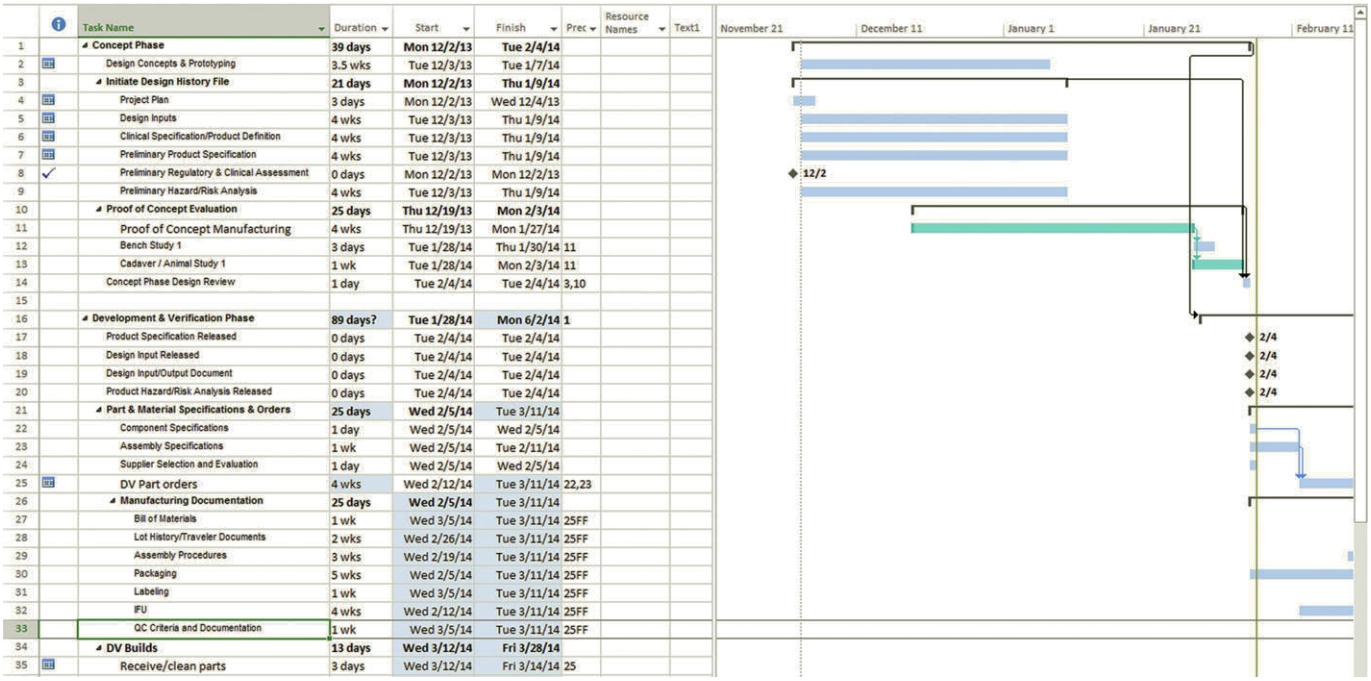
Other resource issues to take into account include laboratory space, as well as the specific lab equipment that will be required. These questions are largely driven by the type of engineering work being performed, along with what functions might be outsourced by the company. For example, a company with a mechanical engineering-based device that it plans to develop in-house might need a basic machine shop that includes a mill, lathe, drill, and/or grinder, as well as common hand tools and assorted supplies from a hardware store (nuts, bolts, springs, tubing, etc.). More specialized equipment and test fixtures may also be required based on the specific type of device being developed. For instance, if the engineering team intends to use computer-aided design (CAD) programs (e.g., SolidWorks, SolidEdge), appropriate computer equipment will also be needed. As the cost of 3D printers continues to decrease, this

FIGURE 5.2.7

Clockwise from top left: the team at ExploraMed working on a new concept in the R&D lab (ExploraMed); engineers at Element Science, performing two different types of device tests (Element Science, Inc.); and two views of R&D space and equipment (Singapore-Stanford Biodesign).

equipment is becoming more common in engineering shops as well.

Materials science engineers often require significantly different equipment from that of mechanical engineers. For example, a wet lab for extensive tissue testing will likely be needed (e.g., sinks, burners, precise scales and measuring equipment, ovens, fume hoods and exhaust, refrigeration), as well as space for analyzing, mixing, and



	Task Name	Duration	Start	Finish	Prec	Resource Names	Text1
1	Concept Phase	39 days	Mon 12/2/13	Tue 2/4/14			
2	Design Concepts & Prototyping	3.5 wks	Tue 12/3/13	Tue 1/7/14			
3	Initiate Design History File	21 days	Mon 12/2/13	Thu 1/9/14			
4	Project Plan	3 days	Mon 12/2/13	Wed 12/4/13			
5	Design Inputs	4 wks	Tue 12/3/13	Thu 1/9/14			
6	Clinical Specification/Product Definition	4 wks	Tue 12/3/13	Thu 1/9/14			
7	Preliminary Product Specification	4 wks	Tue 12/3/13	Thu 1/9/14			
8	Preliminary Regulatory & Clinical Assessment	0 days	Mon 12/2/13	Mon 12/2/13			
9	Preliminary Hazard/Risk Analysis	4 wks	Tue 12/3/13	Thu 1/9/14			
10	Proof of Concept Evaluation	25 days	Thu 12/19/13	Mon 2/3/14			
11	Proof of Concept Manufacturing	4 wks	Thu 12/19/13	Mon 1/27/14			
12	Bench Study 1	3 days	Tue 1/28/14	Thu 1/30/14	11		
13	Cadaver / Animal Study 1	1 wk	Tue 1/28/14	Mon 2/3/14	11		
14	Concept Phase Design Review	1 day	Tue 2/4/14	Tue 2/4/14	3,10		
15							
16	Development & Verification Phase	89 days?	Tue 1/28/14	Mon 6/2/14	1		
17	Product Specification Released	0 days	Tue 2/4/14	Tue 2/4/14			
18	Design Input Released	0 days	Tue 2/4/14	Tue 2/4/14			
19	Design Input/Output Document	0 days	Tue 2/4/14	Tue 2/4/14			
20	Product Hazard/Risk Analysis Released	0 days	Tue 2/4/14	Tue 2/4/14			
21	Part & Material Specifications & Orders	25 days	Wed 2/5/14	Tue 3/11/14			
22	Component Specifications	1 day	Wed 2/5/14	Wed 2/5/14			
23	Assembly Specifications	1 wk	Wed 2/5/14	Tue 2/11/14			
24	Supplier Selection and Evaluation	1 day	Wed 2/5/14	Wed 2/5/14			
25	DV Part orders	4 wks	Wed 2/12/14	Tue 3/11/14	22,23		
26	Manufacturing Documentation	25 days	Wed 2/5/14	Tue 3/11/14			
27	Bill of Materials	1 wk	Wed 3/5/14	Tue 3/11/14	25FF		
28	Lot History/Traveler Documents	2 wks	Wed 2/26/14	Tue 3/11/14	25FF		
29	Assembly Procedures	3 wks	Wed 2/19/14	Tue 3/11/14	25FF		
30	Packaging	5 wks	Wed 2/5/14	Tue 3/11/14	25FF		
31	Labeling	1 wk	Wed 3/5/14	Tue 3/11/14	25FF		
32	IFU	4 wks	Wed 2/12/14	Tue 3/11/14	25FF		
33	QC Criteria and Documentation	1 wk	Wed 3/5/14	Tue 3/11/14	25FF		
34	DV Builds	13 days	Wed 3/12/14	Fri 3/28/14			
35	Receive/clean parts	3 days	Wed 3/12/14	Fri 3/14/14	25		

FIGURE 5.2.8

This Gantt chart shows a more detailed engineering project plan with durations assigned to key activities and critical interdependencies noted between work streams which can help innovators understand how long the entire R & D process may take (courtesy of Ciel Medical).

testing chemical reagents, polymers, and other compounds. Raw materials and tissue samples can be moderately expensive, especially for certain polymers.

For electrical engineering and computer science-based projects, more advanced computer equipment and different software programs (MatLab, LabView) are needed, but fewer machine tools must be purchased. Additionally, no raw materials are typically needed.

R&D timelines

As described, estimating R&D timelines is an important part of R&D planning because time is a significant driver of both value and risk given its obvious connection to the consumption of capital and resources.

The key inputs to determining a realistic timeline are the necessary R&D activities and tests that must be performed to prove the effectiveness and/or safety of a design, the type of R&D personnel that are needed, and the number and type of engineering resources required. Proper documentation of user requirements, technical designs, experimental reports, and verification/validation testing (which are all aspects of the quality system – see chapter 5.5), will also affect R&D timelines. Understanding the trade-offs between different scenarios can help innovators articulate a realistic timeline that still takes into account the effort required to address key technical challenges and retire risks. This information also allows the innovator to answer the important strategic question: "How long will R&D take?" (see Figure 5.2.8).

Seasoned innovators and engineers will be able to estimate the time associated with many activities in the R&D plan based primarily on past experience. However, if the R&D plan includes unfamiliar work steps or the innovators are relatively inexperienced, the best way to come up with appropriate timelines is to network with consultants or other innovators working on similar projects.

While R&D timelines vary dramatically across projects, some engineers believe that it generally takes less time to

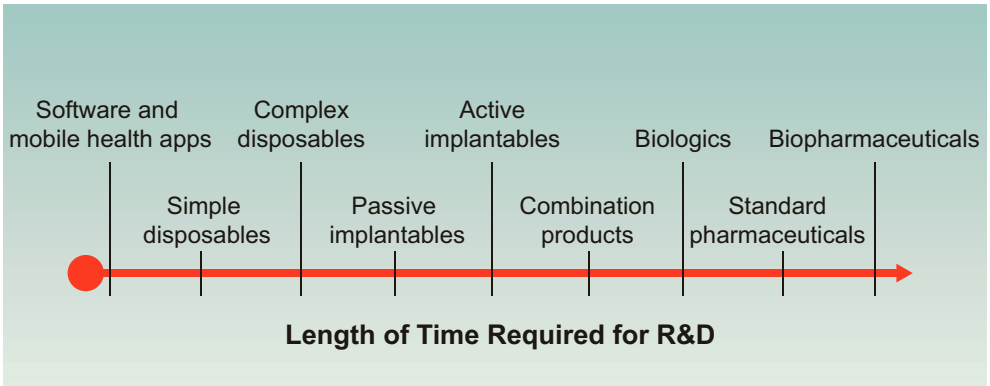


FIGURE 5.2.9
A simplified view of the relative R&D time spent on different types of projects. As combined business models that include products, services, software, and other offerings become more common, innovators can expect to spend increasing time on R&D, as well as testing and integration activities.

achieve key R&D milestones for mechanical devices and solutions that are primarily software based or mobile health applications. In contrast, devices that depend on materials science and/or electrical engineering fundamentals are often more time-consuming (see Figure 5.2.9). For instance, it might take innovators as little as a year to develop a mechanical device that is ready for controlled animal testing. On the other end of the scale, five or more years may be needed to reach that milestone for a high-complexity or combination product, such as a drug-eluting stent. These variations are primarily driven by the greater number of unknowns that are introduced when chemistry, biotechnology, and other scientific disciplines become part of the medical device R&D process.

While creating an R&D plan often may seem to be an isolated exercise done primarily by an engineering team, it must be integrated into the context of the broader organization. R&D plans, as part of R&D strategies, that do not consider the interplay between achieving technical milestones and the larger clinical, regulatory, and marketing needs of the company often lead to misalignment of timelines, create significant inefficiencies and, ultimately, require more time and resources to move ahead and this may affect funding requirements. The case example focused on NeoTract demonstrates how one company, which prioritized a user-focused approach to developing its product, was able to merge this organizational priority with the rigorous R&D milestones they identified as most important.

FROM THE FIELD NEOTRACT, INC.

Developing and deploying a user-focused approach to R&D

According to Ted Lamson, co-founder and CTO of NeoTract, Inc., a start-up based in Pleasanton, California, there are 4.2 million men in the United States on medication for benign prostate hyperplasia (BPH) and its accompanying urological symptoms. However, each year 1.3 million of these patients stop taking their medication, with only about 250,000 of them seeking surgical intervention to address the disease. The rest, though still suffering, remain untreated. “We sought to find out through a needs assessment why there is such a huge discrepancy,” said Lamson, describing NeoTract’s focus when the company was founded in 2005. “We spent our time trying to tease out what it is about the current interventional option that is scary or doesn’t fit the risk/benefit profile that these patients are looking for.” Over time, the team conceptualized a less invasive, office-based procedure that could be performed relatively quickly and easily, and required only a local anesthetic. To realize this solution would require the development of an implant and the instruments to deliver it.

However, when NeoTract began developing an approach to R&D, it set aside some of its more elaborate designs and defined a first strategic milestone focused solely on proving the fundamental technical concept in the clinic with a strong focus on the end user – the patient. "To develop the complete, more elegant solution would have taken quite a bit of time and money," recalled Lamson. "But we recognized before making this investment that we really hadn't answered the one question that would make it all worthwhile, which is will patients respond well to our approach? So rather than spending time building the perfect device that could potentially do the wrong thing, we asked ourselves what's the quickest way we can answer this question. It turned out that this was to figure out a more invasive, bare bones way to see if the concept would achieve the result we were after and then bring that forward into an operating room setting. We were going for a clinical proof of concept that would deliver results that were better than the surgery that was currently available, but was not necessarily all the way to our end goal."

The NeoTract team developed a somewhat crude set of surgical instruments to deliver the implant and a procedure performed under general anesthesia that more closely resembled the current surgical treatment (see Figure 5.2.10). "Of course," said Lamson, "It was still a lot of work. We had to build everything within the guidelines of a quality system. But the intense design work and engineering to build the more elegant solution could be put on hold." The company also had to act ethically, developing a reversible procedure so that the patients receiving it could still undergo conventional therapy if there were any adverse effects. But in the end, the user feedback was encouraging. "We did ten patients with that device – only then did we confirm that they responded really positively to our idea," Lamson explained. "At that point, we knew we had the right approach, and we were ready to start the program to develop the real device."

"We probably spent about six months on this first milestone, which ultimately delayed the final product," he continued. "But this early clinical experience [and direct user input] gave us the confidence that this was worth doing. More times than not, I've seen projects develop a very elegant and well-engineered device and procedure only to find that there's a critical flaw once they get into the clinic. When that happens late in the engineering process, it's harder to abandon the project. Or, even worse, you've got so much momentum that you just keep trying to tweak the solution when really there's more of a critical flaw in it and you should really just change course. If I had one piece of advice that served us well, it is that a team needs to identify the single biggest risk in the program and emphasize taking that on first."

FIGURE 5.2.10
Lamson testing a device in an animal study (courtesy of NeoTract).

Another benefit of NeoTract's user-oriented approach, including its rapid R&D work, early clinical experience, and collection of user input, was linked to the fact that the device was focused on improving **quality of life** for sufferers of BPH. "Your ability to eliminate pain and discomfort is not something that you can get from an animal experiment," he said. "These cases allowed us to figure out if what we want to do is feasible and helps patients, but also if it's going to be something patients want or if they're going to say, 'This doesn't feel good. I don't want it,'" Lamson noted.

Although the patient was the primary target of the user-oriented approach, NeoTract also paid close attention to

physician feedback. “By getting into the clinic early, we learned a lot about aspects of the therapy that we might have designed incorrectly,” Lamson said. “For example, at one point, we had the surgeon performing the procedure holding a sterilized force gauge to measure forces on the instruments. By doing that, we found out what force works and could make that a key requirement.” The team also spent considerable time assessing the physician’s user experience and then analyzing the data it had collected in the clinic and translating the information into important design requirements and technical specifications to guide the R&D effort.

NeoTract’s next strategic R&D milestone was to develop a device and a procedure that more completely addressed all of the team’s goals and then get those into the clinic. To accomplish this, Lamson focused on identifying the key technical challenges that needed to be overcome along the way and then set up checkpoints or sub-milestones to make sure the project was tracking to them. “When you have a broad project where people are doing different subassemblies and it’s supposed to all come together at the end, you realize that the end is often too far away to make sure everything works. A lot of times we break up the development work into functional elements. But before we get too far down the road on developing a certain configuration, we try to identify the key things we can test in some simple mode to know that we have the right basic design. This approach can keep you from going too far down the wrong path.” When an engineer reached a key checkpoint, the entire R&D team would get together to review the work, ask questions, and help identify any fatal flaws. “Often,” said Lamson, “the people who aren’t working on that element have most valuable insights about what may present a problem.”

Another approach that Lamson advocated to help his team members keep the physician squarely in mind during R&D was for them to become “amateur surgeons.” “To the extent that you can actually do your procedure and operate your device [in animals or cadavers], it helps you understand what a clinician worries about and doesn’t worry about.” Lamson and team performed approximately 80–90 percent of their own pre-clinical procedures, enabling them to capture key learnings. That said, “I always bring in at least one clinician to do early experiments, teach us about his or her concerns, and help mark out the procedure,” he noted. Then, experts are involved periodically throughout the development process to “make sure we’re not being biased in what we’re seeing and to help give us a fresh look at our work,” he added.

When asked about common pitfalls in the R&D process, Lamson reiterated the importance of “being disciplined in assessing your key unknowns and in being sure you are addressing them.” Get into the clinic as soon as possible, he said, and “be clever about answering your key clinical issues.” He also underscored the need to “build a bed of testing and quality that applies to everything as it moves forward.” He continued, “It’s always a delicate balance to assess how well your previous testing applies to the next generation device – what can you take from it, and what you have to re-do. It requires a fairly constant and continuous conversation because enough improvement is going on that we’re always weighing whether it creates the need for additional testing, or different testing, or that sort of thing.”

Finally, Lamson offered, “I truly believe one of the key strategies to pursue when doing a start-up is to constantly seek expert advice. Ask yourself what you critically need to know and who you can ask. People will generally share information and you usually don’t have to disclose much to get your answer. You can say, ‘I’m building something that looks like this, this is what I think the team looks like, and here’s our proposed development approach.’ If you have the rapport with the person, they’ll generally challenge you on a few things and give you important information to think about,” which can be used to refine and improve the R&D strategy.

In late 2013, NeoTract achieved a major milestone, based on its R&D efforts and thorough clinical testing, when the FDA cleared the UroLift system for the US

market through the de novo 510(k) pathway.[4] Shortly thereafter, the company announced that both the US Centers for Medicare and Medicaid Services (**CMS**) and the UK's National Institute for Health and Care Excellence (**NICE**) issued coding and support for the device's routine use by American and British doctors.[5,6] The UroLift system was then awarded a Category 1 **CPT** (Current Procedure Terminology) code by the American Medical Association (**AMA**).[7]

Online Resources

Visit www.ebiodesign.org/5.2 for more content, including:

- Activities and links for "Getting Started"
  - Determine strategic R&D milestones
  - Identify and prioritize key technical challenges
  - Develop an initial R&D plan
- Videos on R&D strategy

CREDITS

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NOTES

1 From remarks made by Guy Lebeau as part of the "From the Innovator's Workbench" speaker series hosted by Stanford's Program in Biodesign, April 5, 2005, http://biodesign.stanford.edu/bdn/networking/pastinnovators.jsp. Reprinted with permission.

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

3 "What Is a Gantt Chart?," Gantt.com, http://www.gantt.com/ (January 30, 2014).

4 "NeoTract, Inc. Receives U.S. FDA De Novo Approval for the UroLift® Prostate Implant," NeoTract press release, September 16, 2013, http://www.prnewswire.com/news-releases/neotract-inc-receives-us-fda-de-novo-approval-for-the-urolift-prostate-implant-223893231.html (March 31, 2014).

5 "NICE Gives Go Ahead to NeoTract's Groundbreaking UroLift Prostate Implant That Can Preserve Sexual Function While Offering Urinary Symptom Relief for Millions of Men Affected by Enlarged Prostates," NeoTract press release, January 29, 2014, http://www.prnewswire.com/news-releases/nice-gives-go-ahead-to-neotracts-groundbreaking-urolift-prostate-implant-that-can-preserve-sexual-function-while-offering-urinary-symptom-relief-for-millions-of-men-affected-by-enlarged-prostates-242576791.html (February 4, 2014).

6 "NeoTract's UroLift® Implant Procedure for Men with Enlarged Prostate Receives Medicare and Medicaid Outpatient Billing Codes for Reimbursement," NeoTract press release, March 13, 2014, http://www.prnewswire.com/news-releases/neotracts-urolift-implant-procedure-for-men-with-enlarged-prostate-receives-medicare-and-medicaid-outpatient-billing-codes-for-reimbursement-250045231.html (March 31, 2014).

7 "CPT® Editorial Summary of Panel Actions," American Medical Association, February 2014, http://www.ama-assn.org/resources/doc/cpt/summary-of-panel-actions-feb2014.pdf (March 31, 2014).