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Strategic Planning and Costs of FDA Regulation

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Summary

- The regulatory burden for medical device innovation varies based on the specific Food and Drug Administration (FDA) pathway required, and early strategic planning for this regulatory burden is critical.
- The regulatory strategy and milestones must be integrated with other key components of the innovation process and informed by an understanding of and/or direct communication with all the stakeholders involved, including the customer, engineering/manufacturing team, research and development team, safety/regulatory bodies, the potential payers, and investors.
- While it is almost never too early to initiate contact with the FDA, inquiries through 513(g) petitions or pre-submission meetings should be focused on specific questions and goals to make the most of these engagements.
- Regulatory assessments and consultation with experts require upfront costs, but saving time and money in the long term by designing an efficient regulatory strategy can be the difference between success and failure for the academic entrepreneur.
- Fundraising (private and public) must be considered in the regulatory strategy, as approximately 90% of fundraising is based on claims tied to regulatory milestones.

Strategic Planning and Costs of FDA Regulation

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Topic Relevance by Timeline

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- While it is almost never too early to initiate contact with the FDA, inquiries through 513(g) petitions or pre-submission meetings should be focused on specific questions and goals to make the most of these engagements.
- Regulatory assessments and consultation with experts require upfront costs, but saving time and money in the long term by designing an efficient regulatory strategy can be the difference between success and failure for the academic entrepreneur.
- Fundraising (private and public) must be considered in the regulatory strategy, as approximately 90% of fundraising is based on claims tied to regulatory milestones.

Introduction

Regulatory strategy is a critical component of the medical device innovation process, and early development of an effective regulatory plan can be the difference between success and failure for

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the academic entrepreneur. The regulatory burden, including time, clinical evidence, and costs, varies based on the required FDA regulatory pathway, which itself is mainly determined by the medical device class and the novelty of the device. In addition, the regulatory strategy should align with reimbursement and regulatory claims needed for commercial success. A well thought-out regulatory strategy allows for the creation of a realistic roadmap for medical device development, and this strategy works best when integrated with the other core components of the innovation process, including research and development, engineering, sales, reimbursement, and marketing strategies. While the regulatory strategy establishes a foundation for these other core components, the other components also inform the regulatory strategy, and success often depends on consideration of this interaction at an early point in the innovation process.

Consider the Stakeholders

Successful medical devices must speak to all involved stakeholders. This simple concept is critically important when considering medical device development and assessing the feasibility of device technology. Stakeholders in medical device innovation include the customer, marketing specialists, the engineering and manufacturing team, safety/regulatory bodies, the payer, and investors. Each stakeholder has unique goals and considerations. An academic entrepreneur must, therefore, look at the product through the perspective of each party and be able to tell a different facet of the story to each group of stakeholders. For instance, the customers need to understand the benefit of the device and why they should be interested in it from a healthcare standpoint, while the engineering and manufacturing team needs to consider the claims for regulatory approval, such that the device technology meets FDA requirements. For the payer, the academic entrepreneur will have to speak to why the device is necessary—does the device decrease morbidity or save healthcare costs? Innovators will want to know the key innovation of the device, how the innovation is protected (i.e., intellectual property, especially patents), and the exit strategy.

The successful academic entrepreneur must be able to tell these different stories and consider the entire life cycle of the device innovation process, from premarket to post-market. While the focus of this chapter will be on navigating the FDA regulatory pathways, the complexity of having multiple stakeholders becomes compounded when the market strategy involves a global approach rather than a domestic one. In these situations, the academic entrepreneur will need to consider each country's stakeholders and unique laws, regulatory processes, and healthcare systems in order to successfully launch a medical device in each desired country.

Building a Team

While it is possible to gain expertise in any domain of the medical device development process, becoming a true expert in all facets of the process is likely impossible. For this reason, the academic entrepreneur must build an experienced team around them with members from each domain

who understand the process (see the chapter "Building a Successful Startup Team"). This core team must be an integrated, flexible, collaborative team that covers core strategic functions (i.e., clinical, regulatory, legal, research and development, reimbursement, engineering, sales, and marketing) (Goldenberg and Gravagna). Communication across the team is critical to success, and also important for potential investors. Projects where engineers work together with the regulatory team are more successful than those in which engineers design devices or products independently of regulatory concerns. This team will also serve to improve the chances of fundraising success, as the quality of the team is a core component of a good investor's decision-making process.

For an academic entrepreneur, an early key to success is to identify groups and/or centers at their academic institution that specialize in innovation (see the chapter "Resources at Academic Entrepreneurship Centers"). The past two decades have seen a rise in the focus on entrepreneurship at academic medical institutions across the U.S., as these centers are uniquely positioned with access to biomedical research, technology, and potential users of innovation (patients and physicians) (Toner and Tompkins). While the terminology may differ across academic research institutions, these offices often have engineers and staff with technology transfer and regulatory expertise (i.e., centers or offices for innovation or entrepreneurship) (see the chapter "Working with the University Technology Transfer Office"). Furthermore, engaging with these offices or centers is free for the academic entrepreneur and can save valuable time and money.

Another option is to hire, or in some cases partner with, a private commercialization organization, such as a contract research organization or innovation center. The academic entrepreneur must recognize that these organizations and companies offer a range of services, from focused consulting services (i.e., prototype development) to one-stop-shop integrated programs that combine multiple domains. Some companies have incubator or accelerator programs that take advantage of a collaborative environment to facilitate interactions between the technical and business sides of device development (see the chapter "Accelerators and Incubators"). Once again, identifying these potential partners and contacting them early in the process is extremely important. The costs for hiring these organizations depend on the services required and the level of detail needed.

Regulatory Considerations

The regulatory strategy for device innovation is based on device classification and the required pathway as determined by the FDA (see the chapter on "FDA Device Regulation: 510(k), PMA"). Determining the appropriate pathway early is essential to establishing a rough estimate of the amount of time and money that will be required to bring the product to the market. Early and frequent contact with a regulatory expert consultant is crucial for the successful navigation of a new medical device through the FDA regulatory process.

First and foremost, the academic entrepreneur must consider if the device is under FDA regulation, as some devices may be outside of the FDA's jurisdiction and therefore do not need FDA clearance. Realizing this early can safe unnecessary time and money. To facilitate the academic entrepreneur in making this determination, the FDA has important information on its website—a searchable database of devices and classes, as well as a formal inquiry process called the 513(g) petition (Center for Devices and Radiological Health, *Procedures for Section 513(g) Requests for Information - Guidance*; Center for Devices and Radiological Health, "Is The Product A Medical Device?"). Through this petition, the academic entrepreneur can ask the FDA to consider a product and make a formal determination as to whether that product is a medical device or not, based on the FDA's definition; additionally, the FDA will often provide a device classification and regulatory requirements for products deemed to be medical devices. Thus an academic entrepreneur can utilize this process to determine the least burdensome regulatory pathway for a proposed device. The current standard fee for each 513(g) petition is $4,349, and the FDA is required to respond within 60 days of receipt of the formal written request (Center for Devices and Radiological Health, "Medical Device User Fee Amendments (MDUFA) User Fees").

Once the academic entrepreneur has determined that a product is a medical device, the next step is to assess the potential FDA regulatory pathway. Identifying the correct pathway early is critical to set milestones, plan necessary preclinical and clinical trials, estimate cost requirements, determine fundraising goals, and create a realistic timeline for all stakeholders for when the product may reach the market. As mentioned above, the FDA website allows searching for similar products, which can be used as a foundation for the potential regulatory pathway. Findings similar devices or predicates offers valuable guidance to the academic entrepreneur by helping to establish a route to market and identifying standard and special controls and requirements.

The FDA also allows and encourages early contact from academic entrepreneurs and innovators through the use of pre-submission meetings, also called "Q-sub" or "pre-sub" (Center for Devices and Radiological Health, "Feedback and Meetings for Device Submissions: The Q-Submission Program"). These meetings, which are described in the chapter on FDA regulation, can be requested prior to submitting an application to the FDA and range from informational sessions to discussions of specifics in regards to application preparation or protocol development for studies. While the FDA will never give an official approval of the regulatory plan or device itself in a Q-sub meeting, obtaining early feedback from the FDA can allow for necessary changes or modifications to the regulatory strategy and provide long-term savings in cost and time.

FDA Application Costs

First established in 2002, medical device user fees are required for all pre-market application submissions, as well as when companies register their facility or list their devices with the FDA. The fees are standardized by application type and by fiscal year as part of the "Medical Device User Fee Amendments" (MDUFA) published on the FDA website (Center for Devices and Radiological

Health, "Medical Device User Fee Amendments (MDUFA) User Fees"). Additionally, there are two separate fees for each application type: standard and small business. To qualify as a small business, a company must have an approved small business determination (SBD) from the FDA and gross receipts or sales of less than $30 million. Small businesses are also eligible to have their first premarket approval (PMA) application fee waived. For FY2019, the standard fee for 510(k) submissions is $10,953, while the fee for small businesses is $2,738 (Center for Devices and Radiological Health, "Medical Device User Fee Amendments (MDUFA) User Fees"). For the de novo 510(k), these user fees are $96,644 and $24,161 for standard applicants and small businesses, respectively (Center for Devices and Radiological Health, "Medical Device User Fee Amendments (MDUFA) User Fees"). The PMA application is the most expensive and costs $322,147 for a standard application or $80,537 for a small business (Center for Devices and Radiological Health, "Medical Device User Fee Amendments (MDUFA) User Fees"). As discussed in the previous section, these application fees are strictly the costs paid to the FDA with each submission and do not take into account the cost of device development and research studies. Another important point to remember is that pre-submission or Q-sub applications and requests are free. Note that any 510(k) or PMA application for a device intended solely for pediatric use is exempt from user fees. However, if one wants to change the intended use of a device from pediatric to adult, this requires a new 510(k) or PMA application and is subject to user fees.

Strategies for Each Specific FDA Regulatory Pathway

When the appropriate FDA regulatory pathway is determined, the next step is to plan an effective and integrated strategy to fulfill the regulatory requirements. For instance, applications for a 510(k) submission are often thousands of pages or more, while the PMA applications are often tens of thousands of pages. Additionally, PMA applications cost more and often require lengthy clinical trials, which may not be needed for a 510(k). The costs include not only those of the application itself but also the costs of the appropriate bench studies, preclinical studies, and clinical trials, if necessary (see the chapter "FDA Device Regulation: 510(k), PMA"). According to a survey of over 200 medical technology companies conducted by Makower et al., every additional month (i.e., for FDA inefficiencies or unforeseen delays) spent attempting to work through the 510(k) or PMA process costs a company/academic entrepreneur more than $520,000 and $740,000, respectively (Makower et al.). Therefore, the commercialization plan for a device must incorporate an understanding of the regulatory component, and the academic entrepreneur must consider the specifics for each pathway, including estimates of the time and costs involved.

Investigational Device Exemption

For new devices that present more than a nonsignificant risk, an Investigational Device Exemption (IDE) is required before the device can be used in clinical studies to collect safety and efficacy data, which will later be used in support of a 510(k) or premarket approval (PMA) application. The academic entrepreneur will be required to present the IDE number to the academic research institution's internal review board (IRB) for protocol approval before the device can be studied

clinically. One important point about the IDE is that it is not required for nonsignificant risk devices as they do not pose significant risks to human subjects. Nonsignificant risk devices still require IRB approval prior to starting a clinical trial, and the investigators must comply with an abbreviated set of IDE requirements, including proper labeling, obtaining informed consent, and safety monitoring. The FDA has published a guide to distinguishing between significant and nonsignificant risk devices, which can be reviewed freely on the FDA website (Office of the Commissioner).

The application for an IDE includes a description of the device and all previous testing, including preclinical or clinical (if available) and bench data, and the FDA will respond with an IDE number upon receipt. As per the FDA, the IDE application is considered approved 30 days after its receipt if the investigator receives no email or correspondence stating that the application was disapproved. These applications can be from a few hundred pages up to several thousand pages, including a detailed protocol and plan for biostatistical analysis. Overall, the costs from beginning the application to obtaining an IDE can range from tens of thousands of dollars to even millions, but the average is ~$40,000.

510(k)

Devices that go through the 510(k) pathway must be at least as safe and effective as an approved device (i.e., a predicate). The new device must be substantially equivalent to the predicate, and the predicate device must also have gone through the 510(k) process. The academic entrepreneur must remember that selecting predicates and identifying intended uses for the new device are critical points in the regulatory process. A device that is cleared with a 510(k) can only be marketed based on the intended use, and claims are often limited by the uses of the substantially equivalent predicate device. Therefore, a regulatory strategy that includes broad descriptions of the device and intended use are preferable compared to a very narrow 510(k) application, in terms of the marketability and commercialization of the device. The 510(k) pathway is frequently used by many companies, but, by definition of the pathway, it is challenging to differentiate the product from others.

A 510(k) application can also be used when changing the indication for use of a previously cleared device (i.e., expanding a previously cleared intravenous device for intra-arterial use) and when proposing a significant modification to a previously cleared device. These additional uses are important to consider, as in some cases an academic entrepreneur may be able to do a series of 510(k)s for a few million each, instead of a lengthy PMA that may cost over $100 million.

While the application processing fee to the FDA is relatively cheap (see the section above on application costs), the survey by Makower et al. revealed that the mean cost to bring a 510(k) product from concept to clearance was $31 million, with 77% of that money spent on FDA-related activities (Makower et al.). The same survey found that the mean time from first filing to clearance

for a 510(k) application was 10 months, while the time from first communication with the FDA to clearance was 31 months (Makower et al.).

PMA

PMA applications are required for almost all class III devices and for those devices without an existing predicate. This regulatory pathway is more likely to require animal and clinical data, although these data are becoming increasingly required for 510(k) devices as well. Given the lengthy and costly process of the PMA pathway, it is essential to manage the associated risks through monitoring study outcomes and proactively discussing test failures or data issues with the FDA. Manufacturing and quality systems must also be audited prior to PMA clearance. This is important to consider when identifying manufacturing and commercialization partners, as organizations with product experience but not necessarily medical device experience may not have the appropriate quality systems and controls in place as required by the FDA.

The Makower et al. survey found that the mean cost from concept to approval for a PMA product was $94 million, again with over 75% of the money spent on steps related to the FDA regulatory process (Makower et al.). Mean time from first communication with the FDA to PMA approval was 54 months. Interestingly, the same survey found that time from first communication to obtaining the Conformité Européenne ("European conformity," or CE) mark from the European Union's regulatory body for PMA-type products was only 11 months. While this faster approval by the CE may be enticing to the academic entrepreneur in terms of regulatory strategy, they must remember that even with the CE mark there is no guarantee the device will be accepted widely by physicians in different EU countries or that the device will be reimbursed by each EU country (Van Norman). These tradeoffs could potentially lead to increased time and costs compared to going through the longer FDA process with its benefits of marketing and obtaining reimbursement in a more consistent manner in a single country.

Fundraising and Regulatory Milestone Planning

A well-developed regulatory strategy must also consider fundraising and the cost requirements at each step. To develop an appropriate set of regulatory milestones for a potential device, the academic entrepreneur can refer to the FDA website for the required data for 510(k) or PMA applications. For 510(k) devices these milestones often include: 1) prototyping and design, 2) preclinical studies including bench, wet-lab, and animal (if needed) results, 3) submitting 510(k) application, 4) application approval, and 5) post-market studies (Figure 1). For PMA products the milestones include the addition of more robust clinical studies: 1) prototyping and design, 2) preclinical studies including bench, wet-lab, and animal (if needed) results, 3) obtaining IDE and performing first-in-humans study, 4) pivotal clinical trial (often randomized controlled trial), 5) submitting PMA application, 6) application approval, and 7) post-market studies (Figure 2).

Figure 1. Timeline of Regulatory Milestones for 510(k).

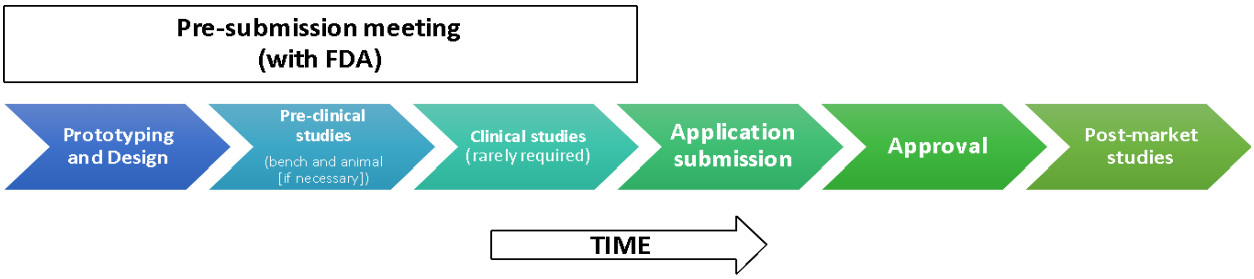
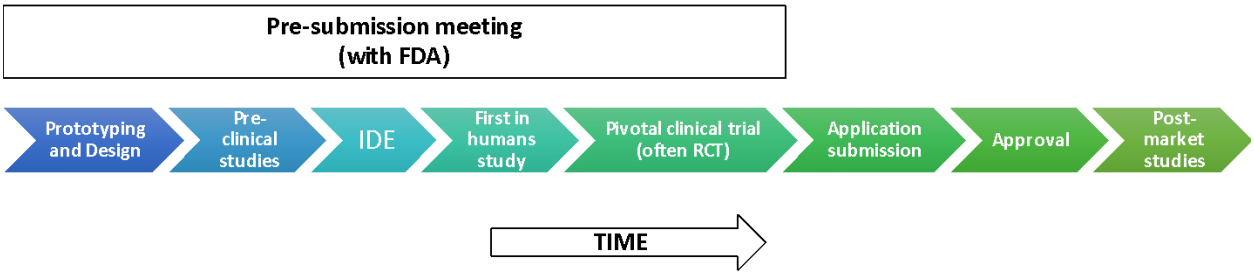


Figure 2. Timeline of Regulatory Milestones for PMA.



Tying regulatory milestones to fundraising series can help the academic entrepreneur plan an appropriate timeline and understand the points at which an infusion of money will be necessary to reach the next stage. Furthermore, unexpected or negative results from an early step or failure to achieve a milestone can prevent overspending funds on a device that may never make it to market. Importantly, approximately 90% of fundraising is based on claims tied to regulatory milestones. When approaching potential investors (i.e., government departments, private foundations, venture capitalists (VC), or angel investors) it is always better to ask for $5 million once than for $1 million five times, since each request can potentially lead to more dilution of equity (see the chapters "Seeking Venture Capital Investments" and "Angel Investors").

The academic entrepreneur must also remember that government funding is often slower (up to 18 months from submitting an application to receiving funds), but private funders, such as VCs, expect a return on their investment, want quicker turnarounds, and hate surprises, especially unexpected regulatory burdens or hurdles. Therefore, early FDA engagement so the academic entrepreneur can estimate the total cost to market at the beginning is crucial for VCs. Investors want to know that there is an appropriate regulatory strategy in which the pathway is defined and relatively smooth from prototype to market.

In today's medical device innovation landscape, early VC investment rarely exists, and instead many entrepreneurs and companies are searching for angel investing for prototyping and initial

preclinical and feasibility studies. After this initial round of funding, the next round requires pursuing regulatory clearance through additional studies and development of the core team. After regulatory approval, another funding round is often required for commercialization and for building sales and manufacturing teams.

Consulting with Regulatory Experts

The importance of early and frequent contact with regulatory experts cannot be overstated. Regulatory consultation can come in several forms, from large experienced consulting companies to independent consultants. The same consulting company may even work on competing technologies in the same space and would thus be experienced with navigating the regulatory landscape. An independent regulatory consultant will only be able to answer a certain percentage of questions (i.e., ~60%) and will therefore have to research some questions at a cost to the academic entrepreneur. Consequently, one benefit of working with larger consulting companies is the variety of internal consultants with expertise in many specific topics, which allows these companies to be more efficient, and they may end up costing less over time. In addition, independent consultants are at times willing to take equity shares as payment, while a larger company will not, as this can create conflicts of interest that limit the company's ability to work with competing technologies. Prior to discussing device innovation or intellectual property with any consultant, the academic entrepreneur should contact their academic institution's office of technology transfer to ensure the appropriate confidential disclosure agreement (CDA) or nondisclosure agreement (NDA) is generated and signed by both parties.

Consulting costs may come in the form of hourly fees, ad hoc agreements (i.e., maximum budget set or not-to-exceed values), or pay-for-service contracts. As a general rule of thumb, brief discussions where nothing is in writing are free. If discussions are more complex and written deliverables are expected, then it is reasonable for a consultant to bill for services. In general, consultation costs for a full regulatory assessment for both the U.S. and the European Union range from $2,000 to $8,000, with an increase of ~$2,000–$4,000 for each additional geographic area or new country (see Table 1 for estimates of regulatory assessment costs).

Conclusion

Early in the process of medical device innovation, the academic entrepreneur must consider the regulatory pathway to get a product from the prototype stage to the market. Developing a realistic regulatory strategy should be done in a way that integrates other critical strategic components of the innovation process, including clinical, legal, research and development, reimbursement, engineering, sales, and marketing domains. All of these components are based on the marketing claims in the regulatory application. By setting regulatory milestones that estimate the time and cost for each step, the academic entrepreneur and their team can understand the timeline for fundraising and necessary money infusion from the start. Different strategies may be possible for a specific

device, and the FDA encourages early and frequent contact, which can be essential for avoiding unexpected setbacks in the approval process. While the academic entrepreneur may think it possible to do it alone, early consultation with regulatory experts, despite the initial upfront cost, can save significant time and money in the long run.

Table 1. Regulatory Assessment Cost Estimates.

Regulatory Component	Ballpark Cost Range:
Full Regulatory Assessment	
• For US and EU combined, including clinical requirements	$2,500 - $8,000
• Each additional geographic area/country	$2,000 - $4,000
• Literature Search (Basic)	$7000 - $10,000
Functional and Efficacy Assessment	
• Large model study	$5,000 - $10,000/model
• Small model study	$1,000 - $3,000/model
Quality Systems Implementation and Biocompatibility Testing	
• Virtual manufacturing (contract out all manufacturing)	$30,000 - $60,000
• Full manufacturing	$50,000 - $100,000
• Biocompatibility testing	$150,000 - $200,000
Regulatory Meetings and Submissions	
• Pre-IDE submission and meeting	$14,000 - $20,000
• IDE submission	$15,000 - $30,000
• 510(k) submission without clinical data	$17,000 - $22,000*
• 510(k) submission with clinical data	$22,000 - $26,000*
• PMA submission	$70,000 - $100,000*

* = Plus FDA submission fee, which changes annually on October 1st.

Resources

1. Biodesign: The Process of Innovating Medical Technologies
    a. In the book *Biodesign: The Process of Innovating Medical Technologies*, written by Paul Yock, Stefanos Zenios, and Josh Makower, the chapter "5.4 Regulatory Strategy" presents an excellent overview of regulatory pathways in the U.S. and worldwide, especially in the European Union, Canada, China, India, and Japan.
    b. Book available on Amazon: https://www.amazon.com/Biodesign-Process-Innovating-Medical-Technologies/dp/110708735X/ref=sr_1_1?s=books&ie=UTF8&qid=1517864373&sr=1-1&keywords=Biodesign%3A+The+Process+of+Innovating+Medical+Technologies.
    c. Book's accompanying website: http://ebiodesign.org/.
2. Pre-submissions and Meetings with FDA Staff
    a. The presentation "Pre-submissions and Meetings with FDA Staff" by the U.S. Food and Drug Administration is an extremely helpful guide on the pre-submission or Q-sub process—the types of meetings and how and when to request them. It also includes a list of best practices for meeting with the FDA at the end of the powerpoint.
    b. Presentation available here:https://www.fda.gov/downloads/Training/CDRHLearn/UCM387291.pdf.
3. Product Classification Database
    a. The *Product Classification Database* hosted by the U.S. Food and Drug Administration and the Department of Health and Human Services is an important resource to utilize early during device ideation or development. It allows users to identify the classifications of current devices on the market to use as a guide for the likely classification of their new device.
    b. Database available here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm.

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