Innovation under Regulatory Uncertainty: Evidence from Medical Technology

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Abstract

This paper explores how the regulatory approval process affects innovation incentives in medical technologies. While prior studies of medical innovation under regulation have found an early mover regulatory advantage for drugs, I find the opposite to be true for medical devices. Using detailed data on over three decades of high-risk medical device approval times in the United States, I show pioneer entrants spend approximately 34 percent (7.2 months) longer in the approval process than the first follow-on innovator. Back-of-the-envelope calculations suggest that the opportunity cost of capital of a delay of this length is upwards of 7 percent of the total cost of bringing a new high-risk device to market. I consider how different types of regulatory uncertainty affect approval times and find that a product's technological novelty is largely unrelated to time spent under review. In contrast, uncertainty about application content and format appears to play a large role: when objective guidelines for evaluation are published, approval times quicken for subsequent entrants. Finally, I consider how the regulatory process affects firms' market entry strategies and find that financially constrained firms are less likely to enter new device markets as pioneers.

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1 Introduction

When does regulation help or hinder pioneer innovators? On the one hand, first mover advantages in commercializing new technologies arise when firms can capture substantial market share, for example through exclusive patenting. On the other hand, early innovators may pay large fixed costs in order to establish regulatory precedents and in doing so, allow subsequent entrants to free ride. Thus, the effect of novelty on pioneer innovators' market entry incentives is ambiguous.

Industry regulation, in turn, is often associated with delayed or reduced firm entry; all else equal, extended time between a new invention and its commercialization will reduce incentives to innovate. For example Roin et. al. (2013) find evidence of this phenomenon in cancer research and development (R&D). Reductions in firms' innovation incentives will, in turn, have a downstream effect on their strategies for entering new markets. This paper explores one determinant of these market entry choices by considering the costs of being a first mover innovator in the context of new medical product regulation in the United States.

In the United States, all medical technologies are regulated by a single agency, the U.S. Food and Drug Administration (FDA). The FDA regulates two trillion dollars worth of products every year, including 80 percent of the U.S. food supply, cosmetics, animal products, and, importantly for this study, all ethical drugs and medical devices (Babiarz and Pisano, 2008). The FDA also regulates several emerging classes of medical products such as biologic drugs ("biologics"), nanomedicines, tissue engineered products, and the use and applications of cellular and gene therapies.

Previous studies of medical innovation under FDA regulation have focused almost entirely on the pharmaceutical drug industry (Goldman and Lakdawalla, 2012), where early mover regulatory advantages have been documented. For example, Carpenter et. al. (2010) find a small but statistically significant relationship between entry order into a drug market and approval times for new drugs: going from being first to second to enter a given market is associated with a regulatory approval process that is just over a week longer (approximately a 1.2 percent increase in the length of the approval process). Relatedly, Dranove and Meltzer

(1994) show that more important chemical drugs are developed and approved more rapidly. However, newer classes of medical technology – in particular, medical devices – are characterized by a much larger degree of product heterogeneity and significant *ex ante* regulatory uncertainty, changing the context of new product regulation.

I begin by comparing the dynamics of the well-established regulatory approval process for new chemical drugs to the less studied and more uncertain regulatory approval process for new medical devices, a category including products as wide-ranging as pacemakers, coronary stents, and silicone breast implants. I find that, in contrast to the early entrant advantages observed in drug regulation, first entrants in medical device markets experience a strong disadvantage in the regulatory approval process. Using data spanning three decades of regulatory approvals (1977-2007), I show that pioneer entrants in new device product categories spend 34 percent (7.2 months) longer in the approval process than the first follow-on innovator in that category. This represents 16 to 21 percent of the total period of *de facto* market exclusivity a pioneer device innovator can expect to experience. Given the concentration of earnings in the earliest years a device is on the market, back-of-the-envelope calculations suggest that the opportunity cost of a delay of this length is upward of 7 percent of expected lifetime product revenues.

I then ask how different types of regulatory uncertainty are related to approval times in the medical device setting. I first consider *technological* uncertainty – uncertainty on the part of the regulator that involves a lack of technological or scientific understanding of a specific type of product and how it is used for a given function in the human body. Technological uncertainty arises most clearly in the evaluation of very novel medical devices, where the regulator needs to understand the scientific mechanisms through which a device works and the data required to be convinced of such a product's safety and effectiveness.

Consider for example the first time that the FDA was asked to evaluate an implantable cardioverter defibrillator (ICD[1]) for approval. The first ICD was approved by the

[1]An ICD is a small device that is surgically placed in the chest or abdomen, which is used to treat irregular heartbeats called arrhythmias. An ICD uses electrical pulses to help control life-threatening arrhythmias – in particular, those that can cause sudden cardiac arrest and subsequent death (http://www.nhlbi.nih.gov/health/health-topics/topics/icd)

FDA in 1984 and at that time, the technological uncertainty faced by regulators was centered around understanding precisely how the device interacts with the heart and the surrounding tissues with which it is in contact. Research and development on ICDs continued over subsequent years and to date, over two dozen later-generation ICDs have been approved by the FDA. Some of these ICDs were classified under the same product code as the originally approved device, but starting in 1997, some approved ICDs were given a new product code due to modifications in the design of the device (for example, one group of ICDs that has emerged since 1997 involves two electrodes which are inserted into the heart, rather than just one). While these later products were somewhat different than earlier models, the FDA had already established a good understanding of how ICDs function as well as an understanding of how to assess the technology involved in these devices in clinical trials by the time that later-generation ICDs began applying for regulatory approval.

Exploiting the fact that some products with the same technical function are given a new nominal classification as a result of design changes, I ask how much of the longer regulatory approval times for first entrants can be explained by technological novelty vs. (nominal) categorical novelty. I find that once I control for the designation of being in a "new product code," knowing whether or not a device was technologically novel does not provide any additional explanatory power in understanding regulatory approval times. This suggests that the regulator's familiarity or lack of familiarity with the primary technology used in a new medical device is not the primary determinant of the length of the regulatory approval process. For example, the first ICDs to be regulated in later-established ICD product codes still experienced a regulatory delay associated with being the "first entrant," despite the fact that the regulator was already familiar with the technology used in these devices.

If technological novelty is not the primary driver of longer regulatory approval times for first mover innovators, than what else might be at play? The results suggest that there is something particular about the administrative designation of being in a new product code that is of importance – that for some reason the categorical change associated with a new

product code *itself* is predictive of longer regulatory approval times. With this in mind, I next consider the role of a different type of uncertainty: uncertainty about the content and format of a new medical device application for regulatory approval.

Content and format uncertainty occurs in the absence of clear guidelines for the protocol for evaluating a new product, leading to uncertainty on the part of the regulator as to how to assess the results of clinical studies and other (e.g. biocompatibility and engineering) tests and uncertainty on the part of the innovator firm as to what data to present in a regulatory approval application. This type of uncertainty almost certainly co-occurs with technological uncertainty for new products, and without the establishment of clear evaluation standards, it can persist well into a product's development lifecycle. Content and format uncertainty is easiest to think of in a scenario in which a product and its functionality are known to the regulator, but evaluation criteria are not formally articulated or established. This can be seen in the case of drug eluting stents[2] (DESs), which were first submitted to the FDA for approval in 2002. It was not until 2008, however – after five different DESs had submitted applications for regulatory approval and four had already been cleared – that the FDA published a formal guidance document, detailing what criteria it would use to evaluate all DESs moving forward.

I consider the release of FDA guidance on DESs and eight other unique medical devices. In each case, objective regulatory guidance was introduced for a group of already-established products (i.e. multiple approvals had already occurred). I find that on average, approval times for subsequent entrants fall by approximately 40 percent (6.1 months) after application content and evaluation procedures are made explicit through formal guidance. In contrast to technological uncertainty, uncertainty about content and format of new product applications appears to play a large role in explaining regulatory approval times for first movers, and overall.

[2]Catheter-based procedures are frequently used to treat blockages in the arteries of the heart (coronary arteries). Often a stent is used to prevent restentosis (renarrowing) of the diseased artery. Stents are small metal tubes that are inserted and expanded into the artery wall and used to keep the previously narrowed artery segment open. Drug eluting stents (DESs) are medication-coated stents that reduce the chance of renarrowing of the blood vessel (Maisel and Lasky, 2007)

This finding has implications for other emerging categories of medical technology including biologics, tissue engineered products, and the applications of cellular and gene therapies – all settings in which there is a large degree of uncertainty about the content and format of new product applications and as a corollary, around how to evaluate new products. This uncertainty is the result of both a short regulatory history and dearth of established regulatory criteria. For these new product categories, regulatory approval times for a given product are similarly likely to be substantially protracted (relative to what is administratively possible) until a time when objective product evaluation criteria are formalized and made available to innovators.

After showing the impact of uncertainty on review times, I consider how the implicit costs of the regulatory approval process affect firms' strategies for entry into new medical device markets (product categories). I consider firm behavior under regulatory uncertainty, given the likely additional costs of gaining regulatory approval in new product codes. I evaluate the behavior of all cardiovascular device firms in the data and find that financially constrained (smaller) firms are less likely to enter new device markets as pioneers: on average, the fraction of financially constrained firms among pioneer entrants into new device markets is between 25 and 52 percent lower[3] than among follow-on entrants.

The rest of the paper proceeds as follows: the next section describes the markets for drugs and medical devices and the institutions that regulate their entry. Section 3 lays out a model of regulatory delay and subsequent firm choice given large anticipated costs for pioneer innovators. Section 4 describes the data on new drug and device approvals used in the empirical analyses in Sections 5 and 6. Section 7 concludes.

[3]depending on the definition used; see Section 6 and Table 10 for detailed descriptions.

2 Background: Markets and Regulatory Frameworks

2.1 Medical Products: Definitions and Markets

This paper considers two large categories of medical products: chemical drugs and medical devices. Chemical drugs are defined by the FDA[4] as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body." Examples of drugs include familiar ingestible or injectable products such as antibiotics and oral contraceptives. A medical device is defined by the FDA[5] as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease" and "which is not dependent upon being metabolized for the achievement of any of its principal intended purposes." Examples of medical devices range from stethoscopes to breast implants, to prosthetic limbs and pacemakers.

U.S. drug and device markets are large: at an annual $320b and $140b respectively, these markets make up a meaningful share of the $2.7 trillion that is spent annually on health care in the United States[6]. Drug spending is higher – however, devices and other emerging medical technologies make up a growing share of national health expenditures: while spending on prescription drugs grew at an annual rate of approximately 3.3% over the five years leading up to 2012, spending on medical devices grew at a rate of 6.0% (versus 4.5% overall health expenditure growth over the same period). In addition to representing large medical product markets in the United States, drugs and devices offer substantial research opportunities: detailed approval data are available across product classes and over the entire history of the FDA's regulation of these products.

Other emerging categories of medical technology also comprise an increasing share of health spending. One prominent example is that of biologics, a group of large, com-

[4]FD&C Act, sec. 201(g)(1)

[5]http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice

[6]Source: *National Health Expenditures*, 2012

plex and heterogeneous proteins derived from living organisms, which are often the primary component of vaccines and cancer therapies. Because they are more complex and derived from living cells, biologic drugs are regulated separately from chemical drugs. Although biologics do not appear in the analysis below, they resemble devices in their heterogeneity and shorter regulatory history and are poised to increase in both economic importance and regulatory submissions over the coming years. In 2010, seven of the top 20 drugs in the US were biologics (Lancet, 2012).[7]

Drugs are a relatively homogeneous category of products with a century-long history of regulation. By comparison, medical devices and other non-drug medical products are far more heterogeneous and have a shorter regulatory history. As such, for devices and other newer categories of medical technology, it is more difficult to define detailed regulatory procedures and standards for new products *ex ante*. Given the greater degree of resulting regulatory uncertainty for innovators in the medical device industry, I explore what types of incentives have been created by the regulatory system in place.

2.2 Medical Product Regulation in the United States: The FDA

In the United States, all medical technologies are regulated by a single agency, the U.S. Food and Drug Administration (FDA). The FDA is an agency of the Department of Health and Human Services and is responsible for the oversight of two trillion dollars worth of products every year, including all over-the-counter and prescription drugs and medical devices (Babiarz and Pisano, 2008; Hamburg and Sharfstien, 2009). The FDA also regulates all other new and emerging classes of medical products. The precursor to the modern FDA was established through the Pure Food and Drug Act, which was signed by President Theodore Roosevelt in 1906. It was not until seven decades later, however, that the FDAs regulatory

[7]Another example of an emerging medical technology is that of nanomedicine – a term used to define the application of nanotechnology in medicine. Nanomedicine involves the use of particles in the size range of 100 nanometres (nm) or less and includes liposomes, polymer conjugates, protein/antibody conjugates, block polymer micelles, cross-linked (nano)gels, bioactive synthetic polymers/vesicles, nanoparticles and nano-sized drug crystals. Nanomedicines are mainly anticancer, anti-infective or immunomodulator drugs. The global nanomedicines market was valued at $72.8 billion in 2011 and is expected to reach $130.9 billion in 2016 (Generics and Biosimilars Initiative, 2013).

scope grew to include medical devices, which came under FDA regulation in 1976.

The FDA is organized into centers, each of which is tasked with the oversight of a different type of product. The two centers most relevant to the analysis below are the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH), which regulate chemical drugs and medical devices, respectively[8]. Within the CDER, the Office of Drug Evaluation is responsible for the approval of new drugs and within the CDRH, the Office of Device Evaluation is responsible for the review and approval of medical devices. Other categories of products are also reviewed by specialty centers within the FDA (e.g. biologics and human cells, tissues, and cellular- and tissue-based products are reviewed by the FDA's Center for Biologics Evaluation and Research, CBER).

2.3 The FDA and the Regulation of Drugs

The foundation of the FDA's modern statutory authority to regulate medical products is the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), which requires that new drugs be tested for safety and that those tests be submitted to the government for marking approval (Babiarz and Pisano, 2008; FDA, 2013). The FDCA "endowed the FDA with sole authority to reject the ex ante marketability of any new pharmaceutical product" (Carpenter, 2010) and resulted in the establishment of the new drug application process (NDA), the "vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S."[9] The goals of the NDA are to provide sufficient information on drug safety and effectiveness for proposed uses, to determine whether the contents of proposed labeling are appropriate, and to evaluate whether manufacturing methods used are adequate.

The NDA is organized into technical sections,[10] which are evaluated by specialized review teams of experts (Monahan and Babiarz, 2008). The components of the NDA are specific and well-defined for all types of drugs. For example, for the information required

[8]The CDRH also regulates radiation-emitting products such as X-ray and ultrasound machines

[9]http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA

[10]Requirements are outlined in FDCA and Title 21 of the US Code of Federal Regulations part 314

about the drug's manufacturing scheme, the applicant firm must describe the synthesis of the active ingredient, including details on all starting materials, solvents, reagents, intermediate substances and their compilations and analytical controls (Monahan and Babiarz, 2008). The results of randomized, typically placebo-controlled clinical trials[11] are also an important component of any NDA. During the FDA's in-depth review of the NDA, the drug's "sponsor" (i.e. the firm filing for regulatory approval) may also be required to submit additional information supporting the drug application (Babiarz and Pisano, 2008). The average approval time for a new drug in this study is 23.5 months, although the average for a drug that is first in its disease group is shorter, at 19.3 months. Figures 1 and 2 provide additional information on the chronology and requirements of the NDA process.

2.4 The FDA and the Regulation of Medical Devices

The FDCA of 1938 did not impose any pre-approval requirements on medical devices, which instead were regulated at the state level at the discretion of each state's legislature for nearly four subsequent decades. It wasn't until 1976, after a series of well-publicized medical device failures, that Congress passed the Medical Device Amendments Act (MDA), which gave the FDA primary authority to regulate devices sold in the United States (Sall, 2008; Kramer et. al., 2012; Munsey 1995).

Devices are wide-ranging in their cost, invasiveness, function, and risk: they include products ranging from tongue depressors and stethoscopes (which the FDA classifies as "low-risk" devices) to hearing aids ("moderate-risk" devices) to pacemakers and prosthetic heart valves ("high-risk" devices). The MDA delineates these three risk groups and lays out the

[11] Typically three phases of clinical trials are required in order for the FDA to be assured of a drug's safety and effectiveness (although sometimes approval decisions are made early based on demonstrated need for a drug and very promising results in phase II trials). Phase I trials are typically very small (N=20 to 80) and are primarily for determining drug safety and establishing side effects. Assuming that Phase I trials don't reveal unacceptable levels of harm, Phase II trials are conducted in a greater number of healthy subjects (as many as a few hundred, with the exception of drugs for diseases like cancer) and the focus is on establishing a product's effectiveness. Phase III trials begin following evidence of effectiveness in Phase II and are usually very large studies (N= hundreds to 3000). Phase III studies are designed to have sufficient statistical power to confirm a product's safety and effectiveness in different populations and different dosages (FDA, 2012; http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm)

rules for regulating each differently. This paper focuses only on approval regulation of "high-risk" (Class III) devices which "support or sustain human life" and are of the highest risk (FDA, 2002).[12] Unlike moderate and low risk devices, high-risk devices are are subject to a rigorous regulatory process that is similar to that imposed on new drugs (Zuckerman et. al. 2011; Goldman and Lakdawalla, 2012), requiring detailed product information and evidence of safety and effectiveness from clinical trials. While high risk devices represent only about one percent of the devices that the FDA regulates each year (Redberg and Dhruva, 2011), they represent an out-sized fraction of medical device spending: In 2008, spending on the six highest-cost implanted devices alone was about $13 billion (Meier, 2009), or approximately 10 percent of total U.S. medical device spending.

The regulatory approval process for high-risk devices is called "premarket approval" (PMA) and is necessary when a medical device developer wants to market a new high-risk device. Importantly, once the first device in a product code is approved through the PMA process, all subsequent devices in that product code must go through the PMA process.[13] The average approval time for a new device is 18.1 months, although the average for a device that is first within a product code is longer, at 22.5 months. Figures 1 and 2 provide additional information on the chronology and requirements of the PMA process and Figure 2 highlights similarities and differences between the requirements for the NDA and PMA.

Much like the NDA, the PMA is a complex document filed by the manufacturer that contains information about the product and results of clinical trials. As is the case for drugs, Section 515 of the FDCA requires that a PMA provide scientific evidence of safety and effectiveness, typically in the form of data from a pivotal study.[14] However, as the next

[12]http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm2007514.htm

[13]The 510(k) process, which allows devices to be cleared for marketing on the basis of being "sufficiently similar" to other already-cleared devices was originally intended for use with medium-risk devices only. In recent years, some high-risk devices have also managed to gain clearance through this process, but these are not devices that have a history or precedent of PMA approval within the product code. The 510(k) process has been criticized for being used too freely and the Institute of Medicine has convened a committee to look at its use (Garber, 2010). This is certainly an important area for further research, however this paper focuses only on those device product codes that are explicitly designated for the PMA-track approval process.

[14]The clinical study report includes the study design and protocol, patient enrollment and exclusion data, primary and secondary endpoints of the study, data from all patients entered into the trial, and detailed

section explains, the types of trials that can constitute a pivotal study for a new high-risk medical device are highly heterogeneous and to a large extent, open to interpretation – an important difference between the regulatory approval processes for drugs vs. devices.

2.5 Drugs vs. Medical Devices: Regulatory Differences

Importantly – and unlike drug trials – clinical trials for medical devices may take many different and often more flexible forms. In new drug studies, three phases of randomized controlled trials are the norm. In device trials, however, clinical evidence can come from a variety of sources: trials may take the form of well controlled investigations, partially controlled investigations, objective trials without matched controls, and other types of studies "from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use" (21 CFR 860.7(c)(2)).

This lack of specificity about the type and execution of clinical trials is largely the result of product and delivery-method heterogeneity across medical devices. Given these sources of heterogeneity, regulators have been unable to articulate general rules or guidelines for medical device clinical trials and subsequent regulatory evaluation that are both sufficiently broad so as to be relevant to devices ranging from pacemakers to silicone breast implants, while still being sufficiently specific to guide the clinical trials and the regulatory evaluation of all types of devices.

While drugs are almost always delivered in one of just a few conventional ways (administered orally, injected intravenously or intramuscularly, inhaled, or administered topically), the insertion and delivery method of a new high-risk medical device is often a novel process with few (if any) related prior clinical trials to use as a precedent or guide. Thus, both the planning and execution of device trials are substantially more uncertain than those for new chemical drugs. Devices can be used, implanted, or otherwise administered in hundreds of ways. Furthermore, how a device is used or the method by which an implantable

statistical analysis of the results. Technical data on biocompatibility, stress and fatigue, shelf life, and other relevant non-clinical tests are also submitted (Zenios et. al., 2010)

device is put into the human body is often not only unique, but also critical to the success or failure of a trial (Sall, 2008).

The large degree of heterogeneity across medical devices and in the processes required for their evaluation, combined with non-specific regulatory language about how clinical trials should proceed results in a much greater degree of uncertainty about the content and format requirements for new device approvals (vs. new drug approvals) because the regulator's expectations are typically not clearly known or defined *ex ante*.

Chatterji (2009) relays the anecdote of one extreme case of regulatory uncertainty: the company Acorn Cardiovascular "believed they were close to FDA approval in 2002 for their device that helps to shrink enlarged hearts, but the FDA instead recommended a much larger clinical trial that ended up taking three more years and costing the company $30 million." While this represents an extreme example of delay due to regulatory uncertainty, it is also true that in general, FDA decisions are rarely made immediately after a PMA submission. Indeed there are typically at least two cycles of requests and responses between the FDA and the applicant firm before a decision is made (Zenios et. al., 2010). This is because for most devices, the evaluation criteria that the FDA will use to assess a new product are not made explicit before the regulatory process begins. An important exception to this are cases where the FDA publishes regulatory guidance, a list of objective product evaluation criteria addressing application content and format that will be used to assess all devices of a certain type moving forward. The publication of such guidance is considered in detail in Section 5.3 of this paper.

Appendix A presents additional case studies of firms' experiences with regulatory uncertainty and delay. Case 1 in Appendix A presents the story of a heart failure monitoring system that has been under consideration at the FDA for three years. At the time of data collection for this paper, the device has already been through one large-scale controlled clinical trial and one follow-up study and at the time of the current draft draft, the device had just recently been approved for marking in the United States. Case 2 presents a typical occurrence for a new high-risk device: following the completion of a randomized,

double-blind, sham-controlled pivotal clinical trial that yielded statistically significant results supporting the device's safety and efficacy, the FDA returned to the manufacturer with follow-up questions related to device testing and clinical data.

In sum, although device manufacturers need to present clinical trial evidence to the FDA, the lack of regulatory specificity about what types of data to collect and present to regulators as well as the content and format of a new product application makes the regulatory process for devices far more uncertain than that of drugs. In the sections that follow, I explore how this uncertainty plays out in product approval times and firms' strategies for entering new markets.

2.6 A Note on Safety vs. Speed of Regulation

A long debate has engaged with the tradeoffs between regulatory speed and consumer safety. In a 2009 piece in the New England Journal of Medicine, FDA Commissioner Margaret Hamburg and Principal Deputy Commissioner Joshua Sharfstein discuss the balance that the FDA must strike between risks to consumers and speed of regulation: "as a public health agency, the FDA should always ask whether delays in approval or safety problems can be prevented" (Hamburg and Sharfstien, 2009).

This paper does not assess or weigh in on the balance between regulatory speed and consumer safety in current policies. Rather, I consider factors that may affect delays in new product regulation on the intensive margin – that is, given the regulatory system as experienced by medical product innovators in the United States – and as such, the length of development times experienced by firms. My conclusions concern only the context of the regulatory system in place, given a regulatory agency that aims to protect both consumer safety and its own reputation. These dual goals are reflected in the model discussed in the next section and described in detail in Appendix B.

3 A Model of Approval Regulation and Firm Strategy

In many industries, government approval or licensing is a prerequisite for market entry. Examples include nearly all parts of the energy, health care and transportation industries. This paper considers the experiences of medical technology firms in their interactions with the FDA.

3.1 Framework and Regulator Decision-Making

The first part of my empirical work builds on Carpenter et. al.'s (2010), model[15] of the FDA drug approval process. In this model, a farsighted regulator discounts the future pipeline of device approvals and decides how rapidly to approve a new device in light of this discounting. In such a setting, the regulator gets greater utility from quickly approving an earlier entrant into a given market than a later entrant. Appendix B presents details of this model of approval by a farsighted regulator.

In the model, the regulator can also respond to political factors. This feature is consistent with existing evidence on the political economy of the FDA's regulatory behavior. For example, studies show that the FDA responds to the demands of lobby groups representing (potential) drug consumers, such as cancer or AIDS organizations (Olson, 1995; Carpenter 2002; Carpenter et. al., 2010).

Individual firms may also exert pressure on the FDA[16], although recent work on pharmaceutical drug approvals has found limited evidence of firms' influence on regulatory approval times (Carpenter et. al., 2010). In the model and analyses that follow, I account for firm and disease-specific factors that may influence the duration of the regulatory approval process. For example, Acemoglu and Linn (2004) find that potential market size has a strong influence on the entry of non-generic drugs and new molecular entities while Carpenter (2004)

[15]This framework is also related to Carpetner (2004). In this model, "early entrants" into an exclusive market niche (disease) receive shorter expected approval times than later entrants, even when later entrants offer known quality improvements over earlier products.

[16]Other work – e.g. Thomas (1990) has found that FDA regulations have heterogeneous effects on firm productivity by firm size.

finds that firms submitting more new product applications may expect quicker and more likely approvals). In doing so, I deviate from Carpenter et. al. (2010) in defining a more general model of approval priorities for an uncertain regulator.

I begin with a simple, flexible model of regulatory approval times that includes known covariates, such as those factors identified above. Both firms and the regulator observe the relationship between regulatory approval times and application characteristics. Approval time (T) of product p, of entry order ϕ produced by firm f, in year t is then observed as:

$$T_{p_\phi ft} = f(\beta \mathbf{X}) \tag{1}$$

where **X**s include:

- Entry order within a product code (devices) or disease group (drugs)[17]
- Advisory panel (organized by medical specialty), product group, and firm fixed effects
- Year of review
- Applicant firm's cumulative regulatory experience
- Eligibility for expedited review (e.g. product is for a rare/orphan/terminal disease)

Because the regulator discounts the future pipeline of products, it would prefer to approve earlier products more quickly (see Appendix B). Thus, *ceteris paribus*, review times should be increasing in entry order. In other words, all else equal, earlier entrants should benefit from a shorter regulatory process (and later products should experience increasingly longer approval times) leading to "early mover advantages" in terms of approval speed in the regulatory approval process.

However, when there is regulatory uncertainty about how to evaluate a product, it will increase the time that a regulator spends on the approval decision. Further, because that uncertainty is likely to be inversely related to entry order (i.e. uncertainty is greater among the first products of a certain type to seek regulatory approval), the presence of regulatory uncertainty would be expected to affect approval times in the *opposite* direction of the early mover regulatory advantages described above. Indeed, if regulatory uncertainty

[17]These are described in detail in section 4; each represents a group of products that are good to excellent substitutes for one another.

is great enough, it could lead to *longer* regulatory approval times for earlier entrants, even given the regulator's preference for getting more novel products to market quickly.

To account for entry-order specific uncertainty, I modify Equation 1 in the next set of empirical modeling exercises. I relate review times to the set of determinants above as well as an uncertainty term:

$$T_{p_\phi ft} = f(\beta \mathbf{X}) + U_{p_\phi} \tag{2}$$

where

$$U_{p_\phi} = \begin{cases} D_\phi + \varepsilon & \text{if } \phi < \phi^* \\ 0, & \text{otherwise} \end{cases} \tag{3}$$

For simplicity, regulatory uncertainty, U_{p_ϕ}, can be thought of as generating a fixed delay during the regulatory approval process, on average D_ϕ, although a more general framework would model $U_{p_\phi} = g(\phi) + \epsilon$ where $g'(\phi) < 0$. That is, among some set of the earliest entrants, there exists significant regulatory uncertainty such that the new product in question experiences approval times that are D_ϕ longer, on average. As D_ϕ becomes larger, expected approval times will increase. Thus, even when the regulator *prefers* faster approval for earlier entrants, a large value of D_ϕ implies that approval times for the earliest entrants could be longer than those of subsequent entrants.

In the empirical section of this paper, I ask when there is evidence that $D_\phi > 0$ and for which values of ϕ this is the case. By knowing the values of ϕ (entry order), for which there are additional costs of regulatory approval, one can evaluate which set of entrants are disadvantaged (in the form of extended approval times) in the approval process. In Section 5, I first focus on estimating the additional regulatory approval times associated with early entrants – i.e. the cost of pioneer entry that is directly observable in this data. However, there are other additional costs likely to accrue to early innovators such as additional legal fees and shortened periods of market exclusivity; these are discussed later in the paper.

In addition, the empirical section of the paper addresses the fact that U_{p_ϕ} likely has several components. I am unable to identify all of them, but note that a factor that increases U_{p_ϕ} should, on average, also lead to longer and higher variance approval times. I consider

two such factors – technological uncertainty and uncertainty about application content and format – which I am able to analyze separately by taking advantage of two unique sources of variation in the regulatory approval data. I test the model above and the role of different types of regulatory uncertainty in Section 5.

3.2 Firm Strategy

Finally, I present a testable hypothesis about firm strategy that emerges from the model described above. Both firms and the regulator observe to-date regulatory approvals, approval times, and the entry order of all prior products. Firms know that greater uncertainty increases time spent on regulatory approval and decide which markets to enter, given anticipated costs and benefits. The first dimension on which a firm makes a decision is whether to enter a novel or existing market. All else equal, this decision will be influenced by the relative cost of novel vs. established product regulation.

Assume that each firm, F, has capital K_F. Firms expect an uncertainty-driven delay of length D_ϕ (as above) for innovating in a new market. For a firm, the implied cost of being a first mover is an increasing function of the length of the anticipated regulatory delay and a decreasing function of firm capital (as financially-constrained firms will have less capital allocated for R&D and/or higher costs of borrowing) such that $C_F = c(D, K_F)$. Now consider two firms: Firm A has a large stock of available capital (e.g. Firm A as a large, publicly listed company with a large R&D budget), while Firm B is financially constrained (e.g. Firm B is small and has a finite amount of venture capital to deploy and faces high costs of borrowing or additional fundraising) such that $K_A > K_B$. Then in a given product area, the relative cost of innovating in a new market is greater for Firm B than for Firm A (i.e., $C_B > C_A$) because the expected value of D is the same for both firms.

Assume a distribution of the value of pioneer entry into new markets, such that there is a range of potential profits, π, that can be captured by the first entrant. Then each firm decides whether the expected marginal value of being the first entrant is greater than the marginal cost of being the first mover: $\pi > c(D, K_F)$. Since the relative costs of new market

entry are greater for Firm B than for Firm A, Firm B will be willing to enter fewer new markets than Firm A. More generally, financially-constrained firms should be less inclined to enter new markets as pioneers when there are large costs (delays) associated with doing so.

Market Entry Hypothesis: In the presence of delays under regulatory uncertainty, financially constrained firms should be less likely to act as pioneer entrants than their financially less constrained peers.

4 Data

The first two sources of data I use are FDA databases: the New Drug Approval (NDA) database and the Premarket Approval (PMA) database. Later in my analyses, I also use information from a detailed firm-level dataset, which was collected by hand from financial databases and firm websites and includes financial, ownership, and acquisition data for all cardiovascular device firms represented in the PMA data.

The FDA's NDA database includes a comprehensive list of all new drug approvals in the FDA's regulatory history.[18] For comparability in my empirical analyses and in order to focus on contemporaneous regulatory periods for both drugs and devices, I limit the years of drug application data used to only those applications that were submitted after 1976 (when the FDA first began regulating medical devices) and through 2007. While later data are available for all products, I deliberately limit the years considered in the approval data to avoid any bias that would be created by using a sample in which only the fastest approvals in more recent years would be observed.

I consider a final sample of 693 unique drug approvals that are indicated for 187 disease groups. "Disease groups" are specific product categories that are based on the function and target of a drug. Within a disease group, products are likely to be very good to excellent clinical substitutes for one another – for example, anti-inflammatory agents, contraceptives,

[18] I am grateful to Daniel Carpenter for sharing the cleaned data from Carpenter, et. al. (2010) for this project. The raw data are available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm

and statins each represent specific disease groups. The data also include detailed information about the date of NDA submission, date of FDA decision, the submitting firm's identity, and an indicator for whether a product received "priority" or expedited review (e.g. a drug could be eligible for expedited review because it is used for a rare or late-stage/terminal disease). I observe approval times as elapsed days or months from the date of the NDA submission to FDA decision.[19] Summary statistics are presented in Table 1.

The data on high-risk device approvals come from the FDA's PMA database,[20] which includes an exhaustive record of all PMA approvals since the 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act. As with the NDA data, I include all submissions starting in calendar year 1977 and limit the data to include submissions through the year 2007.[21] The medical device approval data summarized in Table 1 include 847 unique device approvals in 249 product codes. Product codes are specific definitions based on design and function that "delineate [a device's] technology and indication,"[22] such as drug-eluding stents or silicone breast implants. As an analog to drug disease groups, device product codes are likely to be very good to excellent clinical substitutes for one another. A list of example device product code names as well as an example of a device product code definition from the FDA can be found in Appendix C. The PMA database also includes detailed information about the date of each application's submission, date of FDA decision, the submitting firm's identity, and an indicator for whether a product ever received "priority" or expedited review.

Table 1 highlights several similarities and important differences between the drug and device approval data. While average approval times in the sample are longer for drugs (22.5 months) than devices (18.1 months), the average approval times for the *first* product in

[19] One reader noted that it may be harder to recruit patients for clinical trials for non-first-in-class drugs, and that this could make the clinical trials last longer and extend commercialization lags for non-pioneers. While this may be true, it would represent an effect above and beyond what I observe in the FDA's data on approval times, which measure time between submission and an approval decision and not pre-NDA-submission phenomena such as the duration of clinical trials.

[20] The raw data are available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm

[21] For example: a device application that was submitted in 2007 and approved in 2010 would be included in the dataset. A device application submitted in 2011 and approved in 2012 would not because its submission occurred after the end of calendar year 2007.

[22] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments

a given category are shorter for drugs (19.3 months) than for devices (21.5 months). Drugs tend to have more entry per product category (13.6 products on average) than devices (6.4 products on average) and drugs are also far more likely to be eligible for "priority" (expedited) review (44 percent of drugs vs. 10 percent of devices).

I focus many analyses on understanding medical device approval times and for a subset of the exercises that follow, I focus only on high-risk cardiovascular devices, which are those reviewed by the Circulatory System Devices Panel. Table 2 shows the distribution of medical device approvals by specialty. Cardiovascular (circulatory system) devices make up by far the largest speciality area, comprising 241 out of the 847 applications in the data, or approximately 28.5 percent of the total device sample.

Finally, for the set of firms that produce the high-risk cardiovascular devices in the PMA database, I collect detailed firm-level financial and ownership data. These include data on firm size (as measured by annual revenues), firm ownership (public vs. private), and whether and when a firm was acquired by another company – as well as the identity of that company and the year of acquisition, if relevant. Financial data were collected from Google Finance, NASDAQ, NYSE Euronext, and from firm websites.

Throughout the paper, I observe data on new product approvals, not on innovation and other decisions prior to the regulatory approval process. This means that I do not observe those products that are abandoned before or during the Premarket Approval process, based on unpromising clinical results. As such, the approval time phenomena I observe and the effects that I calculate represent the *effects of regulation on the regulated*, and not the (deterrent) effect of regulation on those products that do not make it into (or through) the approval process.[23]

[23]While the fraction of PMAs that are rejected following the PMA process is negligible (zero in recent years), the fraction of devices that are granted investigational device exemptions and then never apply for approval through the PMA process is likely higher. This data is not currently available to the public. I have requested it through the FDA's Division of Freedom of Information and hope that future versions of this paper will be able to shed additional light on the existence and nature of selection that may be involved in understanding which devices (and which type of *firms'* devices) are most likely to make it to the stage of regulatory approval.

5 Empirical Estimation

I proceed with a series of estimates from the models above. I first compare drugs and devices using the model of regulatory approval times presented in Section 3. I then test the hypothesis about firm market entry strategies in detailed firm-level data.

5.1 Approval Times and Entry Order

The first part of this analysis is grounded in the literature on the determinants of FDA approval times for new drugs, notably Carpenter et. al. (2010) and others. I account for potential political and institutional factors that may affect approval times while estimating the relationship between product entry order and approval times for both drugs and devices. Carpenter et. al. (2010) define "entry order" as the order in which a drug within a given disease group submits an application for FDA approval. I extend this definition to its closest analog for medical devices: the order in which a medical device within a given product code submits an application for FDA approval.

I begin my analysis by replicating Carpenter et. al.'s (2010) results on the set of 693 new chemical drugs described above. Columns 1 and 3 of Table 3 show the results of both a parametric (log-normal) model and a semi-parametric (Cox proportional hazard) model.[24] As previously observed, I find evidence of a positive, statistically significant entry order gradient in approval times for new drugs that is persistent, robust to multiple statistical specifications, and tantamount to early mover advantage in the drug regulatory approval process. On average, a one unit increase in entry order is associated with approximately a 2 percent increase in regulatory approval times for new drugs within a disease group (e.g. among statins, oral contraceptives, etc.). The results are statistically significant at conventional levels and robust to the inclusion of firm and year fixed effects or a time trend, disease group fixed or random effects, and a time-varying indicator of a firm's "expertise" in navigating the regulatory process (for which I proxy using a firm-specific, time-varying

[24]The log-normal model can be interpreted as the percentage change in approval time associated with a one unit increase in entry order. The Cox proportional hazard model (Cox, 1972) reports the effect of a unit increase in entry order with respect to the hazard rate of exiting the approval process.

count of successfully approved NDAs at the time of a given new application).

I then conduct a parallel analysis for the approval times of new medical devices. In Columns 2 and 4 of Table 3, I repeat both the parametric (log-normal) and semi-parametric (Cox proportional hazard) analyses on the dataset of 847 new medical devices. In the medical device sample, I document a statistically significant relationship, which is oppositely signed compared to that estimated for drugs: on average, a one unit increase in entry order is associated with approximately a 1 percent *decrease* in regulatory approval times for new medical devices. That is, the later a product enters a given market, the shorter the average time to regulatory approval. These medical device approval models also present results that are statistically significant at conventional levels and robust to the inclusion of firm and year fixed effects or a time trend, product code fixed or random effects, and a time-varying indicator of a firm's "expertise" in navigating the regulatory process (for which I use a firm-specific, time-varying count of successfully approved PMAs at the time of a given new application as a proxy). F-tests comparing the drug versus device coefficients reject the equivalence of the relationships between entry order and approval times for these two categories of products at the 0.001 percent level in both sets of models.

Having found evidence of early mover regulatory advantages (on average) in drug approval times and early mover regulatory disadvantages (on average) for device approval times, I turn to understanding the drivers of these patterns. If the relationship seen in device approvals is a result of early entrant regulatory disadvantage, there are three empirical facts that should be observable in the data. First, if observed patterns are being driven by early entrants, one should expect to see stronger relationships in samples that include these entrants and should not expect to see the same patterns in samples that do not include early entrants. Second, it should be possible to identify those entrants for whom there are additional delays associated with entry order and third, to quantify their magnitude.

Table 4 tests the first case above. For reference, column 0 replicates the two sets of log-linear results in Table 3: on average, approval times are decreasing in entry order for devices and increasing in entry order for drugs. Subsequent columns of Table 4 then ask the

question: "what is the relationship between entry order and approval times when considering only entrants *beyond the Zth* product?" While the positive entry order gradient documented in the regulatory approval of new drugs is stable over the product development lifecycle of a category of drugs, this is not the case for devices: the negative entry order gradient disappears as soon as the first entrants are excluded from the sample. The device results in Table 4 thus suggest that delays accrue mostly to the first entrant in a device product code and that the inclusion of these early entrants drives overall averages in the data.

To unpack the entry order relationships further, the first column of Table 5 uses dummy variable indicators for a product being first, second, third, fourth, or greater than fifth in a product code (omitted category: entry order = 5), rather than a linear indicator of entry order. Column 2 estimates the same model as Column 1, but uses months as the independent variable. Column 3 compares only the first entrant to the first unambiguous follow-on entrant – that is, the first PMA submitted in a product code vs. the first PMA submitted *after* the first PMA had been approved – and finds that relative to the first follow-on entrant, a pioneer entrant spends approximately 34 percent longer in the regulatory approval process. Column 4 converts this result into months, indicating that a pioneer spends an average of 7.2 months (approximately 219 days) longer in the regulatory approval process than the first unambiguous follow-on entrant into the same product code. The results from Tables 4 and 5 also facilitate estimation of the value of ϕ^*: approval delays are only statistically significant for the first entrant into a product code, suggesting that the value of ϕ^* is close to 1.

With the brunt of the costs of delay borne by the first entrant, one might wonder about the financial implications of pioneer innovation. Consider the estimated value of D, the 7.2 month longer approval times estimated for pioneer entrants: how large is this? One benchmark is the length of delay relative to the length of the period of *de facto* market exclusivity that a pioneer can expect to have. In the full medical device sample, the first entrant into a product code has an average of 3.8 years as the sole product with regulatory approval before the second product is approved for market entry – that is, the pioneer can

expect an average of 3.8 years of *de facto* market exclusivity. For high-risk cardiovascular devices, this period is just 2.8 years. As a benchmark comparison then, the additional time a pioneer medical device can expect to spend in regulation is between 15.8 and 21.4 percent of the total period of time it can expect to spend alone on the market.

For medical devices, earnings are often concentrated in the first few years in which a product is marketed, making the role of approval times especially important in determining a device's profitability. According to the 2013 Annual Report from Medtronic (the world's largest medical device company) 38 percent of 2013 revenues were from products introduced in the last three years (Medtronic, 2013). While it is only a rough estimation of foregone revenue, it is illustrative to think about what a 7.2-month regulatory delay means in this context: 7.2 months represents 20 percent of three years. If, on average, a medical device makes 38 percent of its total profits over its first three years on the market, then a 7.2 month delay in getting to market could translate into a decrease of approximately 8 percent of lifetime revenues per new device.

A final way to think about the observed delay is in the context of the implied opportunity cost of capital. In medical product industries, the opportunity costs of capital are large. Assuming a typical discount rate used for the biotechnology industry of 11.5% (DiMasi and Grabowski, 2007), one can calculate the opportunity cost of a 7.2 month delay. Makower et. al. (2010) survey roughly 20% of firms in the medical device industry and find that the average cost of bringing a high-risk medical device to market is about $94 million. Assuming a discount rate of 11.5%, the results suggest that the opportunity cost of capital of the delay associated with being the first entrant in a product code is probably at least $6.7 million, or more generally, upwards of 7 percent of the total cost of device development.

5.2 Sources of Uncertainty Part 1: Is Technological Novelty Associated with Longer Approval Times?

Given evidence of longer regulatory approval times for the earliest innovators in a medical device product code, I next explore some potential explanations. Regulatory delay has

many possible components. One of the most obvious is technological uncertainty about the workings of a new product. Technological uncertainty broadly encompasses uncertainty on the part of the regulator due to a lack of scientific familiarity with or understanding of a specific type of product used for a given function.

When a product is very novel – i.e. the regulator has never seen anything that performs its function before – technological uncertainty is high. An example can be seen in the historical approvals of implantable cardioverter defibrillators (ICDs) described in Section 1. However, when the technological uncertainty around a certain type of device has been largely resolved – for example through multiple successful/completed assessments and approvals of that type of product – one would expect to see a decrease in that component of approval delay associated with technological uncertainty for subsequent product approvals.

I use the information embedded in FDA-defined, detailed device product names[25] to assess product "novelty" in a subsample of high-risk cardiovascular devices. I look within cardiovascular devices because this is by far the largest specialty area in the data, representing over 28% of all new device approvals and because this speciality includes the greatest number of unique product codes.

I identify eight "functional categories" of devices, each of which contains multiple unique device product codes, but all of which share a common cardiovascular function, making each category a natural setting for comparing highly related products. Examples include functional categories for stents, implantable cardioverter defibrillators (ICDs), and replacement heart valves. Each of these functional categories includes multiple products that have the same general function in the human body, but some variation in the materials from which they are made, their method of delivery, and/or the product design, resulting in administrative designations of multiple product codes within each functional category. Figure 3 provides a guide to functional category construction for the subsample. The eight functional categories analyzed and the number of products and product codes in each are

[25]The FDA has 16 independent panels for device classification. These panels are found in 21 CFR 862-892. For each of the devices classified by the FDA the CFR gives a general description including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice)

listed in Table 6.

To evaluate how technological uncertainty affects approval delays, I consider whether a prior device approval within the same functional category is associated with reduced approval times for subsequent new devices in that functional category. Devices in a functional category will, by definition, be highly similar to one another. Moreover, the prior approval of the first of a particular device (e.g. catheter) should lead to a technological understanding of that type of product among reviewers for subsequent products of that type. Thus I ask: *when a device is first in its product code, but its primary technological function and components are already known to the regulator, are regulatory times shorter?* In other words, I control for the designation of being first within a product code and then ask empirically how much additional explanatory power (if any) can be gleaned from knowing whether a device was technologically novel.

I identify the earliest entrant in each functional category of products and then look for subsequent entrants into that category. These subsequent entrants are the clear beneficiaries of reduced technological uncertainty because the first product utilizing that technology had already necessarily been approved. This is true regardless of entry order within the relevant device product code – which may or may not be different from entry order within the functional category.

Because this analysis is limited to a smaller sample of only cardiovascular devices, I first repeat the product-code-level analyses of Table 5 for the subset of cardiovascular devices alone. The results of this analysis are presented in Panel A of Table 7 and yield coefficients of a very similar magnitude and statistical significance to those seen in Table 5: being first within a product code is associated with a regulatory approval process that is 5.1 to 6.8 months longer. I next proceed with the analysis at the functional category level. I find little evidence of the importance of reduced technological uncertainty in explaining subsequent approval times (Panel B). The results suggest that on average, being first within a functional category is associated with a regulatory approval process that longer, but these results are not statistically significant at any conventional levels.[26]

[26]In models not presented, I also perform a "placebo test" in which I randomly assign each of the devices

In Panel C, I ask how much – if any – of the delay seen for a new entrant in a product code is reduced when a highly related product has already completed the regulatory approval process. Specifically, I control for the resolution of a large degree of technological uncertainty (at the functional category level) and then look at the residual relationship between product code entry order and approval delay. The statistically and economically non-significant coefficients on "First in Category" suggest a very limited role for technological uncertainty in explaining regulatory delays. However, in this specification, being first within a product code is associated with a regulatory approval process that is 5.3 to 7.2 months longer and these coefficients are statistically significant at the 1 percent level. Indeed, it seems that the delineation of a new product code *itself*, rather than the novelty of the technology involved in that product's primary function is the strongest predictor of longer regulatory approval times.

5.3 Sources of Uncertainty Part 2: Reduced Uncertainty about Application Content and Format through Publication of Objective Regulatory Criteria

This section addresses cases in which procedural uncertainty about new product application content and format is resolved through the publication of formal guidance documents. This type of uncertainty occurs in the absence of clear guidelines about the protocol for evaluating a new product, leading to uncertainty on the part of the regulator as to how to evaluate the results of clinical studies and other (e.g. biocompatibility and engineering) tests and uncertainty on the part of firms as to what information to submit to the regulator and in what format. An example of the resolution of procedural uncertainty can be seen in the publication of FDA guidance documents related to the regulation of drug eluting stents, which is described in Section 1.

The publication of formal FDA guidance about a specific product or class of prod-

to one of eight arbitrary dummy categories and then run the same set of regressions. As would be expected, a prior approval of another randomly selected and unrelated cardiovascular device does not help in predicting approval times for subsequent cardiovascular devices.

ucts[27] is the primary way in which protocols for evaluating a new medical device are formally established. In 1997, the FDA announced that it would formalize its *Good Guidance Practices* in order "to provide transparency and consistency in policy development" moving forward (FDA, 2007).[28] Examples include documents that describe the:

- *design, production, ...manufacturing, and testing of regulated products*
- *processing, content, and evaluation or approval of submissions*
- *inspection and enforcement policies*

In recent years, the FDA has released several pieces of guidance related to medical devices, which are available from the Office of Device Evaluation (ODE). Of the 162 pieces of guidance released since the approval of GGPs, the vast majority deal with Class II (moderate-risk) devices and several others relate to general evaluation practices, rather than focusing on specific technologies. I consider a set of high-risk device policy changes around the publication of four pieces of formal, product-specific guidance. These pieces of guidance directly outline objective evaluation criteria relating to the PMA process for nine specific product codes of high-risk (Class III) cardiovascular devices. These guidance documents and the dates of their publication are listed in Table 8.

In each of these cases, uncertainty around application content and format was largely resolved through the release of formal content and evaluation guidelines for new product applications and in each of these cases, average approval times subsequently decreased. In the analysis that follows, I define "post-guidance" applications as those that were submitted one month or more after the release of guidance for a given product code or set of products. This

[27]The history of FDA guidance dates back to the 1970s, when the FDA began to issue "guidelines" for clinical trials, a regulatory norm (less stringent than formal rule-making) that would lead to an important role of "guidance documents" in communicating structures of clinical experiment and drug development to the pharmaceutical industry moving forward (Carpenter, 2010). Guidance documents continue to shape the FDA's regulation of medical products to this day and their scope has expanded with that of the FDA to include medical devices and other products.

[28]Guidance documents are issued by the FDA, however their standardization in the 21st century has been governed by a formal congressional regulation: on September 19th, 2000, Congress approved regulation (21 CFR 10.115), which outlined the FDA's policies and procedures for developing, issuing, and using guidance documents. While the FDA had released various medical device guidance documents prior to 2000, they were not standardized and so their interpretability and significance were more limited.

ensures that all post-guidance applicants had the opportunity to incorporate information from the FDA guidance into their application prior to submission.

Table 8 shows that (without any controls), following the publication of regulatory guidance, an average decrease in regulatory approval times of 2.8 to 6.6 months was observed in affected product codes. Table 9 includes statistically appropriate control variables and estimates the covariate-adjusted average decrease in approval time associated with the publication of guidance. All models in Table 9 include product code fixed effects and controls for whether a product was granted "priority" (expedited) review, year of submission, and a count of the applicant firms total approved PMAs at the time of submission. The first column of Table 9 presents a covariate-adjusted pre-post analysis of approval times with respect to the publication of regulatory guidance for all applications in affected categories. Column 2 excludes the first two entrants in each group so as not to bias the results by including applications in the pre-guidance average that are known to have longer approval times.

Although these results are consistent with the conclusion that uncertainty about application content and format is an important driver of first mover disadvantage in the medical device regulatory process, one might be concerned about likely endogeneity in the FDA's decision to publish guidance for these particular devices. For example, it may be the case that more "popular" categories of medical devices were more likely to get regulatory guidance. To address potential selection, Column 3 presents results from a nearest neighbor matching analysis in which each device in a "treated" product code (i.e. one in which guidance was at some point published) is matched to two other "untreated" devices (other high-risk cardiovascular devices in product codes in which guidance was not published) based on *ex ante* observables about the application and relevant product code including entry order, submission year, total PMA submissions in the product code at the time of a given application, and average approval times in the product code. Both the average treatment effect (ATE) and average treatment effect on the treated (ATT) of the introduction of regulatory guidance are presented. Even the most conservative estimate (the ATE presented in Column 4), suggests that the resolution of procedural uncertainty through the publication

of formal guidance is associated with a 6.1 month (approximately 185 day) reduction in regulatory approval times. In this subsample, that represents a 41 percent reduction in average regulatory approval times.

The results above complement existing research on the determinants of entrepreneurial success in the device industry: Chatterji (2009) finds evidence that for venture capital funded companies, familiarity with protocols is more important then technical knowledge for predicting firm successes. My results in turn, suggest that uncertainty about the content and format of a new product application is more important then technological uncertainty about a product for predicting regulatory approval times.

6 Entrant Type and Strategy

The final empirical section of this paper considers the relationship between firm type and market entry strategies. The market entry hypothesis in Section 3.2, suggests that in the presence of delays under regulatory uncertainty, financially constrained firms should be less likely to enter new device markets as pioneers. Looking within the ownership and financial data assembled for all cardiovascular device firms in the data, I identify those firms that are most likely to be financially constrained. For this exercise, I define a financially constrained firm as one that a) is not publicly listed, b) does not have revenues of more than $500 million per year, and c) is not a subsidiary of firms of type a or b. This leaves a set of small, privately held firms, none of which are subsidiaries of larger companies.

Using the criteria above, Table 10 considers how the proportion of financially constrained firms varies with the application of the above definition. The most conservative definition ("Definition 1") looks only at those firms that were defined as "financially constrained" at least one year before an application was submitted. The next definition ("Definition 2") excludes those firms that were or became subsidiaries of established firms within a five year window of a given PMA submission (for example, Irvine biomedical's percutaneous cardiac ablation catheter was submitted to the FDA for approval in 2004, acquired by St. Jude in the same year, and received approval in 2005. This product would count as "finan-

cially constrained" under Definition 1, but not under Definition 2, which is broader). The third definition ("Definition 3") broadly classified "financially constrained" firms as those that never met criteria a, b, or c above – that is, they were never part of a more established (less financially constrained) company.

I find that financially constrained firms make up 6.9 to 17.2 percent of the sample among pioneer entrants but 14.3 to 23.0 percent of the sample among follow-on entrants. The difference between these two samples is statistically significant at the 10% level for Definitions 2 and 3 in two-sample t-tests of means with unequal variance. The difference between the two samples is not statistically significant based on Definition 1, likely a result of the small sample sizes used to calculate the averages, however the average differences between proportions of financially constrained firms among pioneers and follow-on entrants are consistent with the hypothesis's predictions in all three cases.

7 Discussion and Conclusion

I have considered how regulatory uncertainty is related to first mover advantages and disadvantages in the regulatory approval process for new chemical drugs and high-risk medical devices. The data on FDA drug approvals show that earlier entrants into drug markets experience a slight advantage over later entrants in the regulatory approval process. However, the data on FDA medical device approvals reveal large fixed costs of early entry into new device markets: pioneer entrants in new device product codes spend 34 percent longer in the approval process than the first follow-on innovator in that product code. I estimate that the magnitude of the additional approval time faced by pioneer innovators is approximately 7.2 months, a large delay relative to the 2.8 to 3.8 years of *de facto* market exclusivity that a pioneer innovator can expect. Back of the envelope calculations suggest that a delay of this length could translate to a loss of approximately 8 percent of expected lifetime product revenues and that the opportunity cost of capital of a delay of this length is upwards of 7 percent of the total cost of bringing a high-risk medical device to market. I find that financially constrained firms are less likely to act as pioneer innovators, a result that is consistent

with the prediction that firms with more capital should be better able and/or more willing to bear the additional regulatory costs associated with pioneer entry.

I analyze regulatory approval times under two sources of uncertainty by looking at settings in which either technological or procedural uncertainty are largely resolved. I find that large delays for the first entrant in an administrative product code persist even when a great degree of technological uncertainty has been resolved. In contrast, I find that the resolution of uncertainty about application content and format through the publication of formal regulatory guidance to clarify product evaluation criteria is associated with substantially reduced approval times thereafter. These results complement other research into the importance of understanding regulatory protocols in the medical device industry; for example, Chatterji (2009) finds that regulatory and procedural knowledge is more important then technical knowledge for predicting firm success.

This paper contributes to a broad literature about the relationship between regulatory uncertainty and innovation incentives – in particular, with respect to medical devices and other emerging categories of medical products, where methods for effectively incentivizing innovation remains poorly understood (Xu et. al., 2013). Generally speaking, incentives for engaging in R&D activity are negatively influenced by increases in the costs and risks of developing new products (Grabowski et. all, 1976). This study is therefore related to research on how R&D incentives affect the pipeline of innovation. Budish et. al. (2013) find evidence that private firms' incentives to innovate have meaningful impact on the level and composition of R&D investments. Moreover, they find that increases in R&D – in particular in cases where there may be underinvestment – have the potential to generate large improvements in patient health. This paper suggests that under regulatory uncertainty, the nature of the approval process for new medical products can create disincentives for pioneer entry by meaningfully increasing the length of the product development period for novel products. This, in turn, affects firms' strategies for entering new markets and could lead to under-development of new medical technologies, although a definitive statement about the extent to which this occurs in medical device innovation is beyond the scope of this paper.

The results also suggest that the regulation of medical technologies could potentially be made more efficient through the earlier resolution of uncertainty about new product application content and format whenever possible. This might be done, for example, through the earlier release of guidance documents about the content and format of new product applications and/or by encouraging firms to work with the FDA very early in the new product development process in order to help the FDA develop evaluation standards or formal guidelines for a new medical technology before a regulatory approval application is officially submitted.[29]

This study could be expanded in a number of ways. First, it would be interesting to know more about regulatory delays themselves: what happens over the period between PMA submission and the FDA's ultimate approval decision? Relatedly, how much of an observed delay is due to the FDA requesting additional information from device companies and what types of information are requested? And finally, are certain types of information requests (e.g. additional product manufacturing specifications) faster to execute and/or evaluate than others (e.g. additional biocompatibility tests)? The data that I use in this study do not allow me to satisfactorily answer these questions. In my conversations and interviews with medical device companies, it has frequently been expressed that the FDA's requesting of additional clinical or technical information is a major source of uncertainty for device firms entering a regulatory process in which the regulator's expectations are unknown *ex ante*. Unfortunately, no quantitative data that I know of are able to shed light on the relative frequency or size of these types of delays. As such, this would be a very fruitful area for future data collection and aggregation – both within and beyond the context of medical device regulation.

The results do not address the onerous process of regulatory reform. While it seems likely that earlier engagement and articulation of regulatory requirements on the part of the FDA could decrease regulatory approval times and minimize delays, the process for implementing any large changes to formal FDA regulatory policy is complex, time-consuming and institutionally entrenched. Yet, my findings suggest that there may be room for regulatory

[29]Interviews with regulatory consultants revealed that this is a strategy that they often recommend.

process efficiency improvements in the regulation of medical devices and other categories of products with a high degree of regulatory uncertainty, as delays are most prominent in cases where evaluation procedures are poorly defined and delays can be substantially reduced through clear articulation of the regulator's expectations for application content and format. FDA Commissioner Margaret Hamburg has noted that "these challenges are not the FDAs alone." Indeed, she argues that in order "to truly leverage advances in science and technology, there must be a collaboration of all relevant stakeholders, including government, academia, and industry. The FDA must work with its partners to promote innovation and creativity at various points throughout the development process" (Hamburg, 2010).

New medical technologies are poised to continue to grow in importance over the coming years and earlier engagement and clear communication between regulators and innovators may facilitate the acceleration of new products' regulatory approval. This study suggests that the goal of such communication should be to mitigate uncertainty about regulatory protocols as early as possible in the regulatory approval process. By minimizing content and format-related regulatory delays for entrants into new product markets, the FDA can also increase its overall efficiency and free up reviewer resources, potentially improving the efficiency of the of regulatory approval process not only for early entrants, but also for later ones as well.

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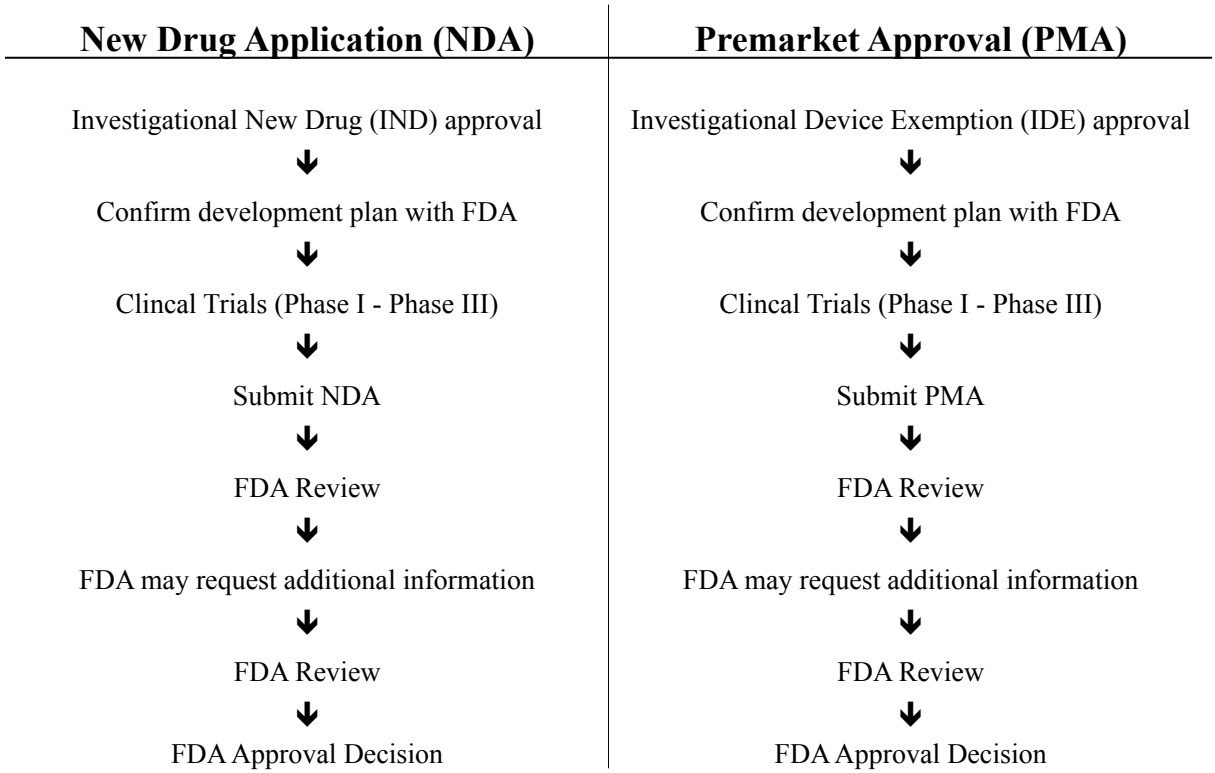
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Tables and Figures:

Figure 1: Steps in Regulation of Drugs and Devices



This figure shows the parallel chronologies of the steps leading up to the New Drug Application (NDA) decision for pharmaceutical drugs and the Premarket Approval (PMA) decision for high-risk medical devices. Descriptions of these processes can be found in Sections 2.2 and 2.3, respectively.

Figure 2: Regulation of Drugs vs. Devices

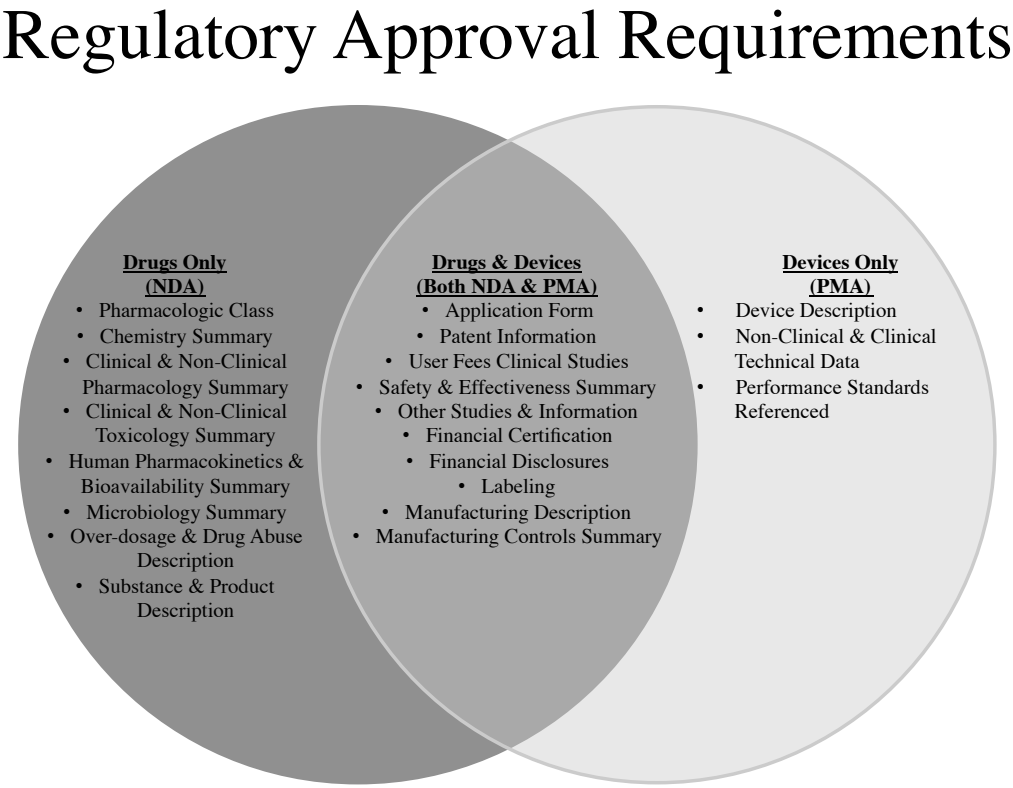


Figure 3: Organization and Examples

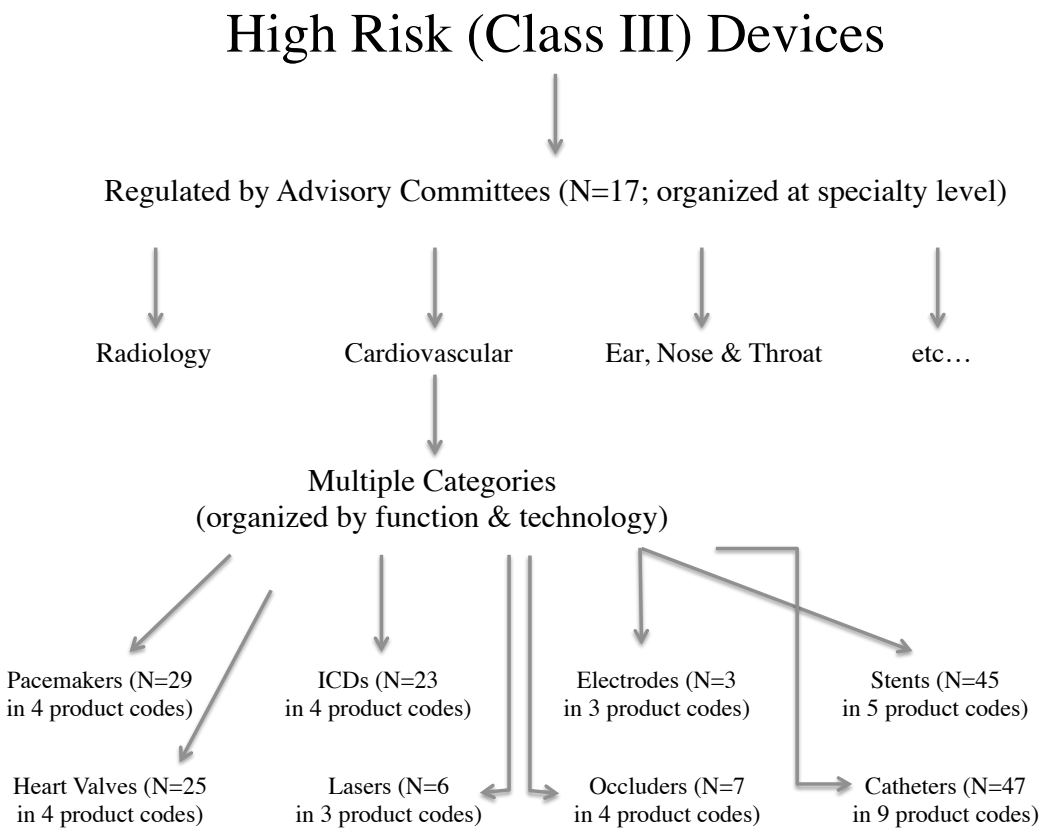


Table 1: Summary Statistics

New Drug Applications (NDAs) - Drugs: N=693 Premarket Applications (PMAs) - Devices: N=847 Premarket Applications (Cardiovascular Devices): N=241						
	Drugs		Devices		CV Devices	
Variable	Mean	S.D.	Mean	S.D.	Mean	S.D.
Approval Time (Months)	23.54	17.67	18.12	15.84	17.31	12.96
Approval Time (1st Product)	19.31	14.40	21.48	16.77	23.07	18.16
Entry Order	13.64	17.81	6.37	8.79	5.06	4.32
Priority Review	0.44	0.50	0.10	0.30	0.10	0.29
New Applications (Current)	7.68	7.78	15.32	20.63	27.57	25.92
Submission Year	1991	7.42	1994	8.46	1995	7.98
Firm	57 FEs	–	32 FEs	–	15 FEs	–
Disease Group / Product Code	187 FEs	–	249 FEs	–	55 FEs	–

Summary statistics for the 693 drugs and 847 medical devices used in the empirical analyses, as well as separate descriptive statistics for the subset of (241) cardiovascular devices alone. Approval Time measures months from PMA/NDA submission until FDA approval. Entry Order is based on the chronological ordering of PMA or NDA submissions. Priority Review is an indicator for whether a product was eligible for expedited FDA review. New Applications (Current) is a firm-specific, time-varying count of successful new product applications that the applicant firm has completed at the time of a given submission. Submission year is the calendar year in which an application was sent to the FDA. Firm contains a set of dummy variables for each firm in the data set or a dummy indicator for being a "small" firm – i.e. one with fewer than five new applications over the entire period of observation.

Table 2: New Devices by Advisory Committee (Specialty)

Advisory Committee	New Devices	Percent
Circulatory System	241	28.45
Opthalmic	160	18.89
Microbiology	74	8.74
General and Plastic Surgery	60	7.08
Gastroenterology-Urology	53	6.26
Orthopedic and Rehabilitation	53	6.26
Immunology	38	4.49
Obstetrics and Gynecology	33	3.90
Radiology	28	3.31
General Hospital and Personal use	23	2.72
Clinical Chemistry and Toxicology	17	2.01
Dental	15	1.77
Ear, nose and throat	13	1.53
Neurology	13	1.53
Anesthesiology	12	1.42
Physical Medicine	8	0.94
Hematology and pathology	6	0.71
(Total)	847	100.00

This table shows the distribution of all 847 new devices analyzed in this study by FDA (specialty-specific) Advisory Committee.

Table 3: Entry order and Approval Times

Outcome = Ln Time to Approval				
	(1) (Log-Linear) Drugs	(2) (Log-Linear) Devices	(3) (Cox Hazard) Drugs	(4) (Cox Hazard) Devices
Entry Order	0.0200**	-0.0098*	-0.0207***	0.0265***
	(0.0074)	(0.0047)	(0.0057)	(0.0063)
Controls	X	X	X	X
N	693	847	693	847
R^2	0.3587	0.1048		
F-test	P[$(\beta_1) = (\beta_2)$] = 0.000		P[$(\beta_3) = (\beta_4)$] = 0.000	

* p<0.05, ** p<0.01, *** p<0.001

This table shows the average relationships between product entry order and approval times for drugs and devices.

Columns 1 and 2 represent the results from a (parametric) log-normal model. Columns 3 and 4 present the results form a (semi-parametric) Cox hazard model. Columns 1 and 3 consider new drug approvals and columns 2 and 4 consider new device approvals. The dependent variable in all models is the natural log of approval time from submission.

All models include firm and product type fixed effects and a time trend (year) Results presented are robust to the exclusion/inclusion of firm fixed effects and to the use of year fixed effects rather than a time trend. All models also include controls for whether a product was granted "priority" (expedited) review as well as a count of the applicant firm's total approved applications at the time of submission. Standard errors are clustered at the product level.

Table 4: Truncated Samples and Approval Times

Outcome = Ln Time to Approval for Products of Entry Order >Z					
	(0)	(1) Z=1	(2) Z=2	(3) Z=4	(4) Z=6
Drugs					
Product Entry Order	0.0200**	0.0195*	0.0236**	0.0295***	0.0303**
	(0.0074)	(0.0076)	(0.0072)	(0.0084)	(0.0092)
Controls	X	X	X	X	X
N	693	581	497	394	337
R^2	0.3587	0.3824	0.4365	0.4938	0.4927
Devices					
Product Entry Order	-0.0098**	-0.0054	0.0014	-0.0050	-0.0069
	(0.0047)	(0.0062)	(0.0069)	(0.0090)	(0.0148)
Controls	X	X	X	X	X
N	847	608	479	330	234
R^2	0.1048	0.1253	0.1400	0.1478	0.1682

* p<0.05, ** p<0.01, *** p<0.001

Column 1 replicates the log-linear results in column 3 of Table 3. Subsequent columns answer the question: "what is the relationship between entry order and approval times when considering only entrants *beyond the Zth* product?" Columns 2 - 5 show results for an increasingly later group of entrants into a product code as one reads from left to right.

All models include firm and advisory committee fixed effects and a time trend (year). Results presented are robust to the exclusion/inclusion of firm fixed effects and to the use of year fixed effects rather than a time trend. All models also include controls for whethera product was granted "priority" (expedited) review as well as a count of the applicant firm's total approved applications at the time of submission. Standard errors are clustered at the product level.

Table 5: Quantifying Early Mover Disadvantage

Outcome = Device Approval Time (Months)				
	(1) Ln Approval Time	(2) Approval Time (Months)	(3) Ln Approval Time	(4) Approval Time (Months)
First in Product Code	0.2157**	5.7158***	0.3376***	7.1993***
	(0.0890)	(1.5015)	(0.0914)	(1.3238)
Second in Product Code	-0.0705	0.1781		
	(0.0887)	(1.3966)		
Third in Product Code	0.1208	4.7995		
	(0.1235)	(3.4273)		
Fourth in Product Code	0.0039	1.6371		
	(0.0694)	(1.7781)		
Greater than 5th in Product Code	-0.0536	0.9762		
	(0.0732)	(1.0754)		
Full Sample	X	X		
Restricted Sample (1st + 1st Follow-on Only)			X	X
N	847	847	342	342
R^2	0.0934	0.1073	0.1105	0.0986

* p<0.05, ** p<0.01, *** p<0.001

Column 1 shows the relationship between the listed entry order dummies and the log of approval time. Column 2 converts these results into months. Column 3 considers only the difference in approval times between the first applicant (the pioneer) and the first unambiguous follow-on innovator in the same product code. Column 4 converts these results into months.

All models include firm and advisory committee fixed effects and a time trend (year) and are robust to the exclusion/inclusion of year fixed effects rather than a time trend. All models also include controls for whether a product was granted "priority" (expedited) review as well as a count of the applicant firm's total approved applications at the time of submission. Standard errors are clustered at the product level.

Table 6: Functional Category Composition
(Cardiovascular Devices)

Device Function (Category)	Number of Unique Product Codes	Number of Unique Devices (Total)
1. Pacemaker	4	29
2. Catheter	9	47
3. ICD	4	23
4. Electrodes	3	3
5. Stents	5	45
6. Valves	4	25
7. Laser for Angioplasty	3	6
8. Occluder	4	7

This table presents the eight functional categories evaluated in Section 5.4. Each of the categories contains multiple unique product codes, making each a useful setting for comparing technologically similar products.

Table 7: Technological Novelty in Cardiovascular Devices

	(1) Ln Approval Time	(2) Approval Time (Months)	(3) Approval Time (Months)
Panel A: Cardiovascular Subsample Only (by Prod. Code)			
First in Product Code	0.2334*	5.1143**	6.8224**
	(0.1292)	(2.4862)	(2.6205)
N	183	183	163
R^2	0.5009	0.4372	0.4118
Panel B: Devices in 8 Functional Categories			
First in Category	0.1624	2.7185	9.0857
	(0.2767)	(5.3434)	(5.8699)
N	183	183	179
R^2	0.4899	0.4206	0.4218
Panel C: Controlling for Technological Uncertainty			
First in Product Code	0.2327*	5.2872**	7.1890**
	(0.1376)	(2.6466)	(2.8121)
First in Category	0.0041	-1.1056	-2.1300
	(0.2934)	(5.6446)	(5.7774)
N	183	183	163
R^2	0.5009	0.4374	0.4125

* p<0.05, ** p<0.01, *** p<0.001

This table looks at first entrants and their respective approval delays in a) product codes b) functional categories and c) both in the same model.

All models include firm and year fixed effects. Models also include controls for whether a product was granted "priority" (expedited) review and a count of the applicant firm's approved applications at the time of submission.

Column 1 presents a log-linear model, while Column 2 translates the result into months. Column 3 restricts the sample to only the first entrant plus those subsequent entrants who submitted applications *after* the first entrant's approval decision was finalized.

Table 8: Case Studies, Publication of Objective Regulatory Guidance

Product Type	Date Published	Product Code(s) Affected	Pre-Guidance Approval Time (Months)	Post-Guidance Approval Time (Months)	N (obs)
Drug-Eluting Stents	(3/1/2008)	1	15.38	8.75	9
Intravascular Stents	(4/18/2010)	4	13.50	8.02	42
Heart Valves	(1/20/2010)	3	11.83	9.00	6
Catheter Ablation Devices	(8/5/2008)	1	14.29	9.36	7
			(N=49)	(N=15)	(N=64)

This table summarizes four recent cases in which objective regulatory guidelines were published by the FDA for major categories of cardiovascular devices. In each of the cases, regulatory delays fall substantially in the period after guidance is published. The data are raw and un-adjusted for potentially relevant covariates.

Table 9: Publication of Objective Regulatory Guidance
Outcome = Approval Time

	(1)	(2)	(3)	(4)
Post-Guidance	-10.0515**	-8.3711†		
	(4.7666)	(4.9293)		
ATE (Post-Guideance)			-6.0696***	
			(0.8577)	
ATT (Post-Guideance)				-8.5193***
				(3.0972)
Controls	X	X	X	X
Excluding first 2 Entrants		X		
Pre-Post Analysis	X	X		
Matched Analysis			X	X
N	64	51	192	192
R^2	0.3401	0.3944		

†p<0.10 * p<0.05, ** p<0.01, *** p<0.001
This table shows the covariate-controlled results of a regression model of the relationship between new device approval times and the publication of regulatory guidance for the four cases presented in Table 8.

All models include product code fixed effects and controls for whether a product was granted "priority" (expedited) review, application year, and a count of the applicant firm's approved applications at the time of submission.

Columns 1 and 2 present results from a pre-post analyses of guidance publication. Column 1 shows results for all devices in affected categories. Column 2 excludes the first entrants so as not to bias the results by including a group that is known to have longer approval times in the pre-guidance average.

Columns 3 & 4 presents results from a "nearest neighbor" matching analysis in which each device in a "treated" product code is matched to two other "untreated" devices based on observables including entry order, submission year, submissions in the product code at the time of a given application, and average approval times in the product code. Both the averagetreatment effect (ATE) and average treatment effect on the treated (ATT) from this analysis are presented.

Table 10: Financially Constrained Firms' Market Entry Strategies

	(1) Pioneer Entrants	(2) Follow-On Entrants	(3) P[(1) = (2)]†
Definition 1	17.2%	23.0%	0.3169
Definition 2	10.3%	19.4%	0.0657
Definition 3	6.9%	14.3%	0.0751

† P-values are from a 2-sided t-test with unequal variances.

A financially constrained firm as one that is not a) publicly listed, b) does not have revenues of more than $500 million per year, and c) is not a subsidiary of firms of type a or b.

Definition 1: only those firms that were defined as "financially constrained" at least one year before an application was submitted.
Definition 2: excludes those firms that were or became subsidiaries of established firms within five years of a given PMA submission.
Definition 3: firms that never met criteria a, b, or c above.

Appendix A: Firm Experiences in the PMA Process

Case 1: A Protracted Review Process for a New Device

The company CardioMEMS is the developer of the Champion Heart Failure Monitoring System device. This device is a permanently implantable pressure measurement system that sits in the pulmonary artery of heart failure patients and monitors pressure and heart rate, transmitting data wirelessly. It is intend to assist in the ambulatory management of heart failure and reduce associated hospital stays (Loh et. al., 2013).

The device was evaluated in the CHAMPION Trial in which 550 patients were randomized into treatment or control groups. In the treatment group, physicians were provided access to patients' pulmonary artery pressure and all physicians were instructed in the adjustment of heart failure medications. According to CardioMEMS,

> *"The CHAMPION trial achieved all pre-specified primary efficacy and safety endpoints. Specifically, the rate of adjudicated hospitalizations for heart failure was significantly lower in the Treatment Arm (0.32) compared to the Control Arm (0.44) (28% reduction, p=0.0002), and the device exhibited an excellent safety and performance profile. All pre-specified secondary endpoints were also achieved."*

The results of this trial were submitted in the company's Premarket Application to the FDA on December 14th, 2010. The reviewing panel raised concerns about potential bias in the efficacy analysis as well as concerns about the efficacy of the device in some subpopulations and the device was not approved following the first meeting at which it was considered in December, 2011 (Husten, 2013). CardioMEMS continued to pursue FDA approval, having completed an additional follow-up study, but at the next review in 2013, the reviewer reported that the FDA still found it "difficult to draw conclusions based on unrandomized and unblinded followup data of a segment of the original trial population" (Husten, 2013). On May 28, 2014 the FDA approved the CardioMEMs device and on May 30, just two days later, St. Jude reported that it closed its acquisition of the product, adding a payout of $375 to the $60 million (19% stake) it had already acquired in 2010[30].

[30] http://media.sjm.com/newsroom/news-releases/news-releases-details/2014/St-Jude-Medical-Completes-Acquisition-of-CardioMEMS/default.aspx

Case 2: Requests for Additional Information Following PMA Submission and Completion of Pivotal Trials

EnteroMedics is a medical device company that develops neuroscience based technologies to treat obesity and metabolic disease. Its VBLOC therapy device is intended to help obese patients lose weight more comfortably by intermittently blocking the vagus nerve, which resides just above the intersection of the stomach and esophagus. This is accomplished by two small laparoscopically implanted electrodes that are put in contact with the vagus nerve.

EnteroMedics completed a randomized, double-blind, sham-controlled, multicenter pivotal clinical trial of the effectiveness of the VBLOC device in 239 patients at 10 sites (The control group received a non-functional device during the trial period). In February of 2013, EnteroMedics announced a statistically significant and clinically meaningful effect of the device on weight loss and "an excellent safety profile" of the device in trials. The results suggested excess weight loss of approximately 25 percent among treated patients, with over half of patients achieving at least 20 percent excess weight loss. Based on the results of the pivotal trial, a Premarket Application was submitted to the FDA.

In late September of 2013, EnteroMedics reported that it had "received a formal response...from the Food and Drug Administration (FDA) with regard to its Premarket Approval Application (PMA) for approval of the Maestro Rechargeable System as a treatment for obesity." According to a press release by EnteroMedics, "the response contains follow-up questions related to the application, pertaining primarily to device testing and clinical data, including training programs for users and a post approval study." (EnteroMedics, September 24, 2013) EnteroMedics said that it would respond to the FDA's follow-up questions within the weeks immediately following the communication. The Premarket Application for the VBLOC device is still under review at the FDA and EnteroMedics hopes for an approval in 2014.

Case 3: Emerging Classes of Medical Technology and Procedural Uncertainty

There are several classes of emerging medical technologies that do not yet have formal regulatory approval pathways in place for entering U.S. Markets. Two examples (biosimilars and cellular and gene therapies) are presented below. These can be thought of as *extreme* cases of procedural uncertainty – that is, the complete absence of rules for regulating these new technologies has meant that they are not yet available to patients in the United States.

I. Biosimilars

Biologics are a group of large, complex and heterogeneous proteins derived from living organisms, which are often the primary component of vaccines and cancer therapies. Because they are more complex and derived from living cells, biologic drugs are regulated separately from chemical drugs. Bio*similars* or follow-on biopharmaceuticals differ from chemical drug generics in terms of their physical characteristics as well as in how they are regulated. Generic versions of chemically manufactured small molecule drugs are based on bioequivalence – that is, containing the same quantity of active substance(s) as the reference product. These generic drugs can be used in the same dose to treat the same disease with equal expected efficacy. Biosimilars, on the other hand, are much larger molecules and follow-on products are based on *similarity* to the reference product, such as biologically manufactured recombinant proteins (Manheim et. al. 2006; Rovira et. al., 2011).

At present, the FDA's Center for Biologics Evaluation and Research (CBER) is considering how to regulate follow-on biological products and the United States has no established industry for biosimilars. Europe, in contrast, has had biosimilars since 2006 following the establishment of a formal regulatory pathway for their approval. On February 9, 2012, the FDA issued three draft guidance documents on biosimilar product development and the FDA is currently accepting public comments these documents. There remains a fair amount of debate as to what FDA will require of biosimilars in particular with respect to requirements to prove interchangeability (GaBI, 2012). In a February 2012 editorial, The Lancet urged the FDA "to integrate the data, experience, and lessons learned by the

European Medicines Agency, which has approved a dozen biosimilars since 2006." At present, the absence of regulatory processes for approving biosimilars has meant that patients in the United States have no access to these products.

II. Cellular and Gene Therapies

Several new cellular and gene therapies also provide examples of extreme procedural uncertainty. As is the case for biologics, the applications of cellular and gene therapies are regulated by the FDA's Center for Biologics Evaluation and Research (CBER). Specific products and applications, in turn, are typically regulated following the publication of, and in accordance with, CBER guidance[31] documents. As a corollary, the absence of CBER guidance on a specific therapeutic application typically means that it is unavailable to U.S. patients.

An example is that of retinal ganglion cell gene therapy for visual system repair. In this application, the cells in the retina are genetically modified using viral vectors in order to benefit patients with certain inherited degenerative conditions that compromise visual function (Hellström and Harvey, 2011). Several recent clinical trials have demonstrated that genetic modification can be of meaningful therapeutic benefit to patients and there is now evidence for the long-term expression of genes delivered through the vector, suggesting extended therapeutic effects of the therapy, following a single treatment/dose. However, clinical trials to-date have been heterogeneous in their use of viral vs. non-viral gene therapy vectors and even within viral vector therapies, multiple vectors have been studied in clinical trials (Hellström and Harvey, 2011). In the absence of FDA guidance on the regulation of such therapies and despite evidence of their effectiveness, no rental repair gene therapies are currently approved by the FDA for use outside of clinical trials.

[31] All cellular and gene therapy guidance documents are available at http://www.fda.gov/BiologicsBlood Vaccines/guidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm

Appendix B: Approval Regulation given a Farsighted Regulator

The first model tested in Section 5 is an extension of Carpenter et. al.'s (2010), model of the FDA drug approval process. In this model, drugs are indexed by i, diseases by j, and firms by k. I generalize this model to apply to multiple categories of medical technology products (e.g. drugs, devices, and others) and a common regulator, the FDA. New products can then be characterized by two parameters:

1. γ_{ij} (where $0 < \gamma_{ij} \leq 1$) is the *curing probability* of the product. Assume γ_{ij} is fixed and known with certainty throughout agency's decision problem.

2. μ_i is the *danger* of the drug or the expected number of people who will be harmed or killed by it over an interval of time, which can be normalized to 1 such that μ_i can be thought of as the rate of harming consumers. The greater is μ_i, the more its approval will harm the regulator's reputation.

   Note: for simplicity, it is helpful to assume that $\text{cov}(\mu_i, \gamma_{ij}) = 0$ – that is, danger and curing power are independently distributed.

The agency observes information (e.g. clinical trials) in which a product either harms or does not harm the consumer. Harm evolves according to a Wiener process $X_{it} = X(t)$ a linear function of underlying danger (μ) plus a random component:

$$X(t) = \mu t + \sigma z(t)$$

where μ and $\sigma > 0$ are constants and where $z(t)$ is a standard normal variable with mean 0 and variance t. Then the agency applies Bayes' Rule to the stochastic history of X(t) to learn about μ. In this model, assume that σ is the same across products, but that μ (normally distributed) differs across them and has a mean, m and variance s. Then, Carpenter et. al. (2010) note that for any product review of time t and accumulated harm $X(t) = x$, $[x, t]$ constitutes a sufficient statistic for the agency's problem.

Bayseian estimates of μ are then:

$$PosteriorMean \equiv E_{xt}(\mu) = \hat{\mu} = \frac{m/s + x/\sigma^2}{1/s + t/\sigma^2}$$

And

$$PosteriorVariance \equiv S(t) = \frac{1}{1/s + t/\sigma^2}$$

Where the posterior variance can be thought of as the FDA's uncertainty about μ, the harm the product may induce (Carpenter et. al., 2010).

Approval Payoff

Scholars of the political economy of FDA drug approvals have found that the FDA may be more responsive to the demands of lobby groups representing (potential) drug consumers, such as cancer or AIDS organizations (Olson, 1995; Carpenter 2002; Carpenter et. al., 2010) and that individual firms may also exert pressure on the FDA. Once can think of a general model of payoff for the regulator as follows:

$$A_{ijk} = g(\gamma_N, N_J, \rho_K, \theta_J, \chi)$$

where:

- γ_N is the curing probability, as noted above
- $N_J - 1$ is the number of products in the same product category that have already applied for FDA approval
- ρ_K is the "political clout" of the submitting firm, K
- θ_J is a disease-specific factor that may represent the disease's prevalence and/or the strength of its political lobby[32]
- χ is a set of relevant specialty area and time-varying effects that may affect the payoff associated with product approval

[32]Note that in contrast to Carpenter et. al. (2009), I am not interested in identifying the disease-specific effects *per se*. Rather, knowing that they may exist for some subset of illnesses, I control for them when estimating other model coefficients.

Agency Decision-Making

As in Carpenter et. al. (2010), I can write an agency objective function, in which the Agency wants to maximize its approval payoff given information about $\hat{\mu}$:

$$\max Ee^{\delta(T)}\{A - E_{\mu,t}\int_{t}^{\infty} e^{-\delta(y-t)}\mu * (y,\omega)dy\}$$

where δ is the discount factor, T is approval time, $\mu*$ is the agency's estimate of danger at the optimal stopping time for clinical trials and other data collection, ω represents an elementary event in probability space Ω and y is a variable of integration.

Early Entrant Advantages

In a model like the one used above, early entrant protection should be observed within a product category. All else equal, this is a result of a regulator making approval decisions in the present while expecting a discounted pipeline of future innovations. For example, given two products $i = N$ and $i = N + 1$ with the same expected levels of danger ($\mu_N = \mu_{N+1}$) and curing probability, then the Nth product should have a shorter expected approval time. This result is, of course, in the absence of regulatory uncertainty, which is introduced and discussed in Section 3.

Appendix C: Product Code Examples

Examples of unique cardiovascular products:

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES
PART 870 CARDIOVASCULAR DEVICES

Subpart A--General Provisions
§ 870.1 - Scope.
§ 870.3 - Effective dates of requirement for premarket approval.
§ 870.9 - Limitations of exemptions from section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act).

Subpart B--Cardiovascular Diagnostic Devices
§ 870.1025 - Arrhythmia detector and alarm (including ST-segment measurement and alarm).
§ 870.1100 - Blood pressure alarm.
§ 870.1110 - Blood pressure computer.
§ 870.1120 - Blood pressure cuff.
§ 870.1130 - Noninvasive blood pressure measurement system.
§ 870.1140 - Venous blood pressure manometer.
§ 870.1200 - Diagnostic intravascular catheter.
§ 870.1210 - Continuous flush catheter.
§ 870.1220 - Electrode recording catheter or electrode recording probe.
§ 870.1230 - Fiberoptic oximeter catheter.
§ 870.1240 - Flow-directed catheter.
§ 870.1250 - Percutaneous catheter.
§ 870.1270 - Intracavitary phonocatheter system.
§ 870.1280 - Steerable catheter.
§ 870.1290 - Steerable catheter control system.
§ 870.1300 - Catheter cannula.
§ 870.1310 - Vessel dilator for percutaneous catheterization.
§ 870.1330 - Catheter guide wire.
§ 870.1340 - Catheter introducer.
§ 870.1350 - Catheter balloon repair kit.
§ 870.1360 - Trace microsphere.
§ 870.1370 - Catheter tip occluder.
§ 870.1380 - Catheter stylet.

Example product code definition for an implantable pacemaker pulse generator:

[CITE: 21CFR870.3610]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 870 -- CARDIOVASCULAR DEVICES

Subpart D--Cardiovascular Prosthetic Devices

Sec. 870.3610 Implantable pacemaker pulse generator.

(a) *Identification.* An implantable pacemaker pulse generator is a device that has a power supply and electronic circuits that produce a periodic electrical pulse to stimulate the heart. This device is used as a substitute for the heart's intrinsic pacing system to correct both intermittent and continuous cardiac rhythm disorders. This device may include triggered, inhibited, and asynchronous modes and is implanted in the human body.

(b) *Classification.* Class III (premarket approval).

(c) *Date PMA or notice of completion of PDP is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before September 20, 2012, for any implantable pacemaker pulse generator device that was in commercial distribution before May 28, 1976, or that has, on or before September 20, 2012, been found to be substantially equivalent to any implantable pacemaker pulse generator device that was in commercial distribution before May 28, 1976. Any other implantable pacemaker pulse generator device shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

[45 FR 7907, Feb. 5, 1980, as amended at 52 FR 17736, May 11, 1987; 77 FR 37576, June 22, 2012]