Essays on Intellectual Property

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Abstract

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This dissertation consists of three essays on regulation. In the first essay, *"Firm Reputation and Screening at the Patent Office"*, we assert that the patent office is an important regulator, exerting influence on firm outcomes. Prior research argues that powerful groups such as top innovators are able to capture their regulators , gaining favorable treatment in return for either monetary contributions to legislators' political committees or hoped-for future employment of regulators in the firms they regulate or in the firms of their legal representatives. It is also argued that regulators face many audiences and attempt to maximize their legitimacy to political entities, legal entities, the general public and the firms affected by their regulation. This can introduce a lack of consistency in decision-making. Given the considerable power of many regulators, this has implications for both policy and firm strategy.

The patent office, in particular, faces considerable uncertainty about the value of the patent rights it provides. Further, patent examiners are under pressure to grant patents quickly and have no way of permanently disposing of an application other than by granting it. We argue that patent examiners tend to

look for certain signals in attempting to determine the quality of the application. We assert that the patent office's focus on helping its clients obtain intellectual property rights make their clients' prior reputations most salient. Therefore examiners tend to rely on the prominence of the applicant in the prior patent art. This can grant either a positive or negative reputation depending upon the general reputation of that field in prior patent art.

We utilize a dataset of all patents granted from 2001-2003. We use examiner-added citations to prior patent art, controlling for applicant-added citations as a measure of examiner screening. We find that firm reputation for patenting influences the level of scrutiny to which a patent application is subjected. In the conclusion we discuss the implications of these findings.

In the second essay, *"Which drugs obtain the Pediatric Exclusivity Provision"* we examine the pediatric exclusivity regulation provision. Pediatric exclusivity is designed to reward companies for conducting pediatric trials for dosage and safety with 6 months' extra monopoly on their drug. Using data from the Medical Expenditure Panel Surveys from 1996-2007 and drug data from the FDA, we find that companies appear to base the decision to conduct pediatric trials almost solely on the basis of current sales (and hence presumably future projected revenue). We find the threshold for a sharply increased probability of obtaining pediatric exclusivity is annual sales of $260 million in the prior year.

We estimate, very conservatively, that the total liability to consumers is US$ 21 billion as of end 2007.

We also find, in accordance with prior criticism, that, (barring ADHD drugs, which are marketed primarily to minors) even after controlling for the total sales, the proportion of sales to minors does not affect the probability of obtaining pediatric exclusivity. This is in concordance with regulatory capture theory which would suggest that a powerful group (i.e.. brand-name drug manufacturers) influenced Congress to pass this legislation to procure a benefit for themselves with a not-easily perceived cost to the much more diffuse group of pharmaceutical customers who pay brand-name prices for 6 more months as a result of delayed generic entry.

In the third essay *"Pediatric Exclusivity - Are the intended benefits being realized?"* we examine the underlying rationale for the pediatric exclusivity and test whether the intended benefits of pediatric exclusivity are being realized. The pediatric exclusivity rule is intended to provide benefits to pediatric patients by providing clinicians with label information regarding safety and dosage in pediatric populations. We test whether valuable and important information is being produced and disseminated by the clinical trials that are undertaken to gain pediatric exclusivity. We do this by examining the patterns of publication of clinical trials before and after pediatric exclusivity is obtained and by examining

the patterns of prescriptions to minor patients before and after pediatric exclusivity is obtained.

We find no evidence of greater dissemination of pediatric information in the peer-reviewed literature after obtaining pediatric exclusivity. We also find no evidence of changing patterns of prescriptions to minor patients after pediatric exclusivity is obtained. This leads us to question the value of the information being provided and conclude that the intended benefits of pediatric exclusivity provision are not being realized. We conclude that pediatric exclusivity legislation is an example of regulatory capture, designed primarily to increase monopoly protection of the sales of brand-name drugs without producing many tangible benefits.

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For Aneesa- my favourite, and the very best

Chapter 1: Introduction

Regulators are some of the most powerful institutions in the market. They have the powers to set the "rules of the game" for the market and allocate punishment for the infraction of those rules. The effectiveness of any institution depends upon the cost of ascertaining violations of formal and informal rules and the severity of the punishment (North 1990). The primary mechanism for regulatory control is coercive (DiMaggio and Powell 1983), but also uses it's own legitimacy (Weber 1947) , inducements and authority, i.e. coercive power within a legitimate framework of norms (Scott 1995) to impose its rules on industry. Regulators can have the power to significantly affect businesses cash flow, determining firm entry, product entry, prices[1], competitive entry, fines, etc. As such they have been studied in great detail by economists, sociologists and political scientists.

[1] As Alfred Kahn, head of the now defunct Civil Aviation Board (CAB) once observed of the decisions he had to make as head of the CAB: "May an air taxi acquire a fifty-seat plane? May a supplemental carrier carry horses from Florida to somewhere in the Northeast? Should we let a scheduled carrier pick up stranded charter customers and carry them on seats that would otherwise be empty, at charter rates? … May a carrier introduce a special fare for skiers but refund the cost of their ticket if there is no snow? May the employees of two financially affiliated airlines wear similar-looking uniforms? -Is it any wonder that I ask myself every day: Is this action necessary? Is this what my mother raised me to do?" - Greenspan, A. (2007). The Age of Turbulence- Adventures in a New World. New York, The Penguin Press.

Pigou's (1938) theory of public interest regulation holds that markets exhibit failures such as externalities and monopoly power. Regulation is therefore used by governments to serve the general interest of society and maximize social welfare (McCraw 1975) In this view, the institutions that regulate the market are viewed as Bayesian statisticians, optimizing welfare, frequently under incomplete information conditions. (Laffont and Tirole 1986). Carpenter (2010) argues that there has not been much development of this as a theory, and that it lacks an account of how regulatory politics might produce the policies it describes. He criticizes the use of the term "public interest" regulation as being less a theory than a description of previous views of regulation by critics and asserts that these critics use "public interest" purely as a straw man to contrast with theories such as regulatory capture theory (Stigler 1971).

Olson's (1965) logic of collective action where incentives to organize are higher for small groups with high stakes that are spread among fewer actors, was used by Stigler (1971) to develop the idea that an industry with few producers would be able to influence actors more than widely disbursed consumer groups. Peltzman (1976) accounted for the fact that the United States Congress occasionally passes laws that hurt large businesses and reduce protectionism by developing a model that balanced interest group support and

voter group support to legislators. This still did not account for the role of regulatory agencies in administering and enforcing rules and regulations. Laffont and Tirole (1991) developed an agency-theoretic model and argued that interest groups are more powerful when they seek to obtain inefficient regulation, where inefficiency is determined by the degree of information asymmetry between the regulated industry and the regulators.

Industry has many ways of influencing regulators. Peltzman (1976) argued that industry primarily influences legislators in Congress by providing financial support (e.g. donations to Political Action Committees) to legislators, who require both votes and money to win elections. The legislators balance the financial incentives provided by industry groups with the voting incentives provided by large groups of diffuse individuals such as consumer groups to generate optimal legislation (from their point of view). Interest groups may also directly affect the regulatory agencies by providing bribes[2], though this is likely to be more common in countries where the rule of law is relatively weak and corruption is more accepted than the US (Dal Bo and Di Tella 2003). The view that regulations are put in primarily for the benefit of politicians and bureaucrats

[2] (2010). Dynamic but dirty: A series of corruption scandals shake Indian businesses The Economist.

to collect these bribes and other incentives is sometimes referred to as the *tollbooth* view (Shleifer and Vishny 1993; Dal Bó 2006) of regulation.

In countries with more stringent rules against outright bribery, the revolving-door phenomenon contributes strongly to regulators being more pliable to industry demands. The revolving door refers to the twin facts of regulators often having held prior jobs in the industry they are regulating, and the hoped-for subsequent employment of public officials with the regulated firms or their law-firms or public-interest law firms (Laffont and Tirole 1993; Djankov, La Porta et al. 2002).

Regardless of the methods used, most models of regulatory capture predict a balance of power in favor of industrial groups that can organize more easily than diffuse groups or consumers (Peltzman 1976; Becker 1983). Laws and rules are not always in favor of the most powerful groups, but the preponderance is likely to be in the direction favored by powerful incumbents and groups. The power of the regulator depends upon its technical ability to extract information about the firm and the true value of regulation to the firm, thus reducing information asymmetry.

Carpenter (2010) , in his study on the FDA, criticizes both regulatory capture and public interest theories as categorizing officials as either "automaton or kleptocrat" (Carpenter 2010, page 43) and argues that it is the image and reputation of the regulatory organization that is the predictor of its power and influence with legislators and the regulated industry. He argues that these public beliefs about the organizations fairness, competence, etc. influence legislators to grant powers to the institution and influence industry's acceptance of institutional rules and regulations. In this construct, the agency attempts to maximize its own legitimacy thus ensuring its own increased bureaucratic power, freedom of action and survival (Kim 2007; Carpenter 2010).

In the chapters that follow we will look at the effects of the actions of the US Patent Office and its impact on innovators, and the costs and benefits of legislation passed by US Congress affecting the pharmaceutical industry and administered by the FDA. The first deals with only the actions of the regulator and the industry, with legislative action taking a background. The second deals primarily with legislative action and the consequences of pediatric exclusivity legislation. Nevertheless, this legislation is administered by the FDA.

Public interest theory (Pigou 1938) would demand that the actions of the regulator be to maximize social welfare. Evidence that the regulator is likely to favor one group over another (producers vs. consumers, powerful industry groups versus less powerful industry groups), especially if that group is smaller in number, more powerful and better organized would favor a regulatory capture view (Peltzman 1976; Becker 1983; Laffont and Tirole 1991; Laffont and Tirole 1993; Dal Bó 2006). If maintaining legitimacy and reputation of the regulator are its primary goal (Kim 2007; Carpenter 2010), then we would anticipate that the optimal action of the regulator would be to enhance its reputation in the eyes of audiences that are more salient to it. Nevertheless the organization would be less likely to take actions that may damage any bureaucratic legitimacy it possesses. However, actions that have subtle effects in the direction of salient audiences (i.e. powerful industry groups), without strong repercussions from other audiences (i.e. consumers, less powerful industry groups, potential entrants) would be expected.

In our analyses in the following three chapters we test whether the actions of the regulator affect the players in a market in a manner that is socially optimal. We anticipate finding evidence of regulatory capture and the influence of powerful groups such as top innovators and marketers of brand-name drugs. We

do not expect that our analyses will conclusively be able to determine whether the primary goal of the regulator is bureaucratic stability or whether regulatory capture has induced the regulator to favor a powerful group in either case. However, in the chapters dealing with the effects of congressional legislation on pediatric exclusivity, we do not anticipate regulatory action to ensure bureaucratic survival to be a strong factor, since almost all the specifics were written into the legislation passed by the US Congress rather than set by FDA directives.

Chapter 2: Firm Reputation and Screening at the Patent Office

Abstract

The patent office is an important regulator, exerting influence on firm outcomes. Prior research argues that powerful groups such as top innovators are able to capture their regulators , gaining favorable treatment in return for either monetary contributions to legislators' political committees or hoped-for future employment of regulators in the firms they regulate or in the firms of their legal representatives. It is also argued that regulators face many audiences and attempt to maximize their legitimacy to political entities, legal entities, the general public and the firms affected by their regulation. This can introduce a lack of consistency in decision-making. Given the considerable power of many regulators, this has implications for both policy and firm strategy.

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examiners tend to rely on the prominence of the applicant in the prior patent art. This can grant either a positive or negative reputation depending upon the general reputation of that field in prior patent art.

We utilize a dataset of all patents granted from 2001-2003. We use examiner-added citations to prior patent art, controlling for applicant-added citations as a measure of examiner screening. We find that firm reputation for patenting influences the level of scrutiny to which a patent application is subjected. In the conclusion we discuss the implications of these findings.

Firm Reputation and Screening at the Patent Office

Theories of Regulation

The patent office is an important regulator, responsible for granting twenty-year monopolies on new inventions. The decision to award — or not award — patents has significant effects on firms' revenue streams and decisions to enter product markets (Levin, Klevorick et al. 1987; Cohen, Nelson et al. 2000). The objective of this limited-time monopoly reward for invention is to benefit society by rewarding innovation, research and development.

The role of the patent office, as a regulator, is to maximize social welfare(Pigou 1938). To do so, economic welfare theory posits that it is supposed to behave as a Bayesian statistician, balancing societal costs and benefits on observable parameters when deciding whether to award patents (Laffont and Tirole 1993). It is however, not necessarily the case that the patent office (or any other regulator) actually does follow this normative theory of regulation.

Regulatory capture theory asserts that the patent office, as indeed any other regulator, can be pressurized by the industry, i.e. innovators, that it is supposed to regulate. Organizations and groups have many forms of

inducement. Firstly, the revolving-door phenomenon contributes strongly to regulators being more pliable to industry demands. The revolving door refers to the twin facts of regulators often having held prior jobs in the industry they are regulating, and the hoped-for subsequent employment of public officials with the regulated firms or their law-firms or public-interest law firms (Laffont and Tirole 1993; Djankov, La Porta et al. 2002). Secondly, patent officers may develop personal relationships with firms that repeatedly patent in their area, making them more likely to look on their work kindly. Industries may also apply pressure via legislators, who control budgets. Smaller, more tightly-knit groups like top patenters are more likely to be able to exert power, as the benefit is greater and spread among fewer participants (Peltzman 1976; Becker 1983).

The patent office, faces Knightian (Knight 1921) uncertainty about the value of patents. Innovators may have better technical knowledge of the likelihood of success of their own patents. Laffont and Tirole (1991) developed a model to show that industry had more power when it sought rules where the information asymmetry between industry and regulators is greater. This increases the likelihood that top-innovators, with the most to benefit, can lobby, pressure, or induce the patent office to treat them more liberally than the competition. This is likely to significantly distort its regulatory role.

The patent office also faces the difficulty of responding to competing demands of different audiences. Among these are patent applicants and their competitors, political entities such as the United States Congress who control budgets, the courts where patents are litigated and the general public. Prior research on other institutions suggests that the patent office, in the face of uncertainty, is likely to respond by trying to maximize its legitimacy to its audiences to increase its likelihood of survival (Kim 2007; Carpenter 2010).

In the case of the US Patent Office[3], one of the most salient and powerful audiences is patent applicants. Patent applicants currently submit approximately 450,000 applications a year. Furthermore, fees from these applicants entirely fund the US Patent Office (Merges 1999). Critics argue that this has had adverse implications for the quality of patents granted. Many complaints have been made about the large number of low quality patents granted by the US Patent Office, ranging from the silly[4], to the impossible,[5] to the unoriginal[6]. Some of these are arguably never asserted, but others could have serious anti-competitive effects.

[3] Formally the US Patents and Trademarks Office. I am not concerned with Trademarks in this chapter. I refer to it interchangeably as the USPTO, the patent office, or the US patent office
[4] US Patent 6022219 A method of painting on a work surface using the posterior of an infant
[5] US Patent 6025810 Hyper-light speed antenna
6 US Patent 5960411 – Method and system for placing a purchase order via a communications network, made famous as Amazon's "1-click" patent

There has been relatively little research on the scrutiny provided by patent examiners. Prior research on consistent decision making by patent offices has found that they are *not* consistent in assessing the quality of applications (Burke and Reitzig 2007). Some recent work (Alcacer and Gittelman 2004; Alcacer, Gittelman et al. 2008; Sampat 2009) has been done on examiner-added citations to patents, suggesting heterogeneity in the screening process. In our work, we explore one possible source of inconsistency in scrutiny: the reputation of the firm for patenting.

The Patent Process and Examiner incentives

In this chapter we argue that, in the face of uncertainty about the value of patents, the examiners at the US Patent Office tends to rely on external signals to decide how much screening a particular patent gets. The incentives of the US patent office exacerbate this. Examiners in the US Patent Office have formal quantitative incentives, in the form of a biweekly "production goal" of applications to be reviewed and actions taken (GAO 2007).

The GAO's (2007) report describes the incentives in detail, reproduced below

"Patent examiners review…applications to determine if a patent is warranted. In making this determination, patent examiners must meet two specific milestones in the patent examination process: first actions and disposals.

-*First action*. Patent examiners notify applicants about the patentability of their invention through what is called a first action. After determining if the invention is new and useful, or a new and useful improvement on an existing process or machine, patentability is determined through a thorough investigation of information related to the subject matter of the patent application and already available before the date the application was submitted, called prior art. Prior art includes, but is not limited to, publications and U.S. and international patents.

-*Disposal.* Patent examiners dispose of a patent application by determining, among other things, if a patent will be granted—called allowance—or not.

Patent examiners receive credit, called counts, for each first action and disposal, and are assigned production goals (also known as quotas) on the basis of the number of production units—composed of two counts—they are expected to achieve in a 2-week period. The counts in a production unit may be any combination of first actions and disposals."(GAO 2007 ,pages 10-11) It should,

however, be noted that patent examiners also received count credits for every 'first' action after a "Request for Continued Examination" (RCE)[7]

These goals vary by the examiner's experience and their field of expertise. Examiners receive bonuses for exceeding their goals by 10%. According to the GAO's 2007 survey of patent examiners who have left the PTO, the biweekly production goals were stated as a major factor in quitting by 67% of former patent examiners, and 70% of examiners had worked unpaid overtime in order to meet their production requirements. The assumptions underlying the quotas had not been reviewed since 1976 (GAO 2005) and were only changed somewhat in 2010. Further, there are no consequences for patent examiners if the patents are subsequently overturned on litigation (Langinier and Marcoul 2009), and in fact "no consequences for low-quality work"(GAO 2005) .

As a result, patent officers are encouraged to spend as little time as possible scrutinizing each patent (an average of 18 hours, including all refilings and editing). Although the applicant may abandon the patent filing, they can

[7] http://www.uspto.gov/patents/init_events/Count_System_changes-Overview_3-8-2010.ppt last retrieved Jun 30,

continue to file amendments, and there is no way for patent examiners to permanently dispose of a patent application except by granting it (Thomas 2001; Kesan and Gallo 2006). Patent examiners do have an incentive to get it "right first time", as a good first response will likely minimize amendments, or at least make the amendments relatively simple to grant, as they would be in line with the patent examiners' own views on the patentability of the innovation. AS their production quotas are purely quantitative, they also have a strong incentive to spend as little time on each patent as possible, and to grant patents. This lack of time to probe the technical and economic value of the patent, grants the firms greater information asymmetry, and hence more power as they seek rules in their favor (Laffont and Tirole 1991).

Given the salience of the applicants to the patent examiners, we contend that one of the most relevant external signals to the examiner is applicant firms' reputation for patenting. For reputation we use the Wilson's (1985) definition of reputation. Wilson defined reputation as a characteristic attributed by one actor (in this case the patent office, or to be more specific the patent examiner) to another actor (firm). Reputation is the history of the previously observed actions of the firm, from which future actions can be inferred (Wilson 1985).

In the case of the firms we find that firms who have patented a lot in the past in mature fields such as drugs and pharmaceuticals, where intellectual property is most powerful may have a reputation for producing a lot of quality patents, whereas firms who patent in fields that are newer, or where patents are routinely ignored, such as computers and information technology (Lemley 2007) are likely to have a reputation for producing poorer-quality patents. Consequently, if patent officers are responding to these reputations we would anticipate less scrutiny of patent applications submitted by firms with a reputation for prior patenting when they submit patents in the fields of drugs and medicine, and greater scrutiny of applicants submitted by firms with a reputation for prior patenting, when they submit patents in the fields of computers and information technology.

This article has six sections. The first section reviews prior research about regulatory capture, patenting and the patent office and patent examiner incentives. The second section advances hypotheses concerning the relations between the reputations of firms applying for patents and the examiners' screening of their patent applications. Methodological and results sections constitute the third and fourth sections. Section five discusses the significance of the results, whereas section six concludes the article.

Hypotheses

The power of regulators to coerce behavior and alter incentives faced by market participants (Laffont and Tirole 1993) makes them one of the most important institutions in a market. Regulatory effects on markets have been a subject of much research, with regulatory changes frequently used as instrumental variables in empirical work in subjects like economics, organizational theory and finance. Less work has been done on the effects of markets on regulators and their evaluation processes (but see Kim (2007) for an exception).

The role of the regulator in general is to maximize social welfare (Pigou 1938). Economic welfare theory posits that regulators act as Bayesian statisticians, maximizing social outcomes based on observable parameters (Laffont and Tirole 1993). However, many important parameters that affect the value of a patent such as the price, cost and production volume of the final product are ex-ante unobservable, especially to the patent examiner. The patent office faces Knightian (Knight 1921) uncertainty about the value of patents. It is also likely that it faces information asymmetry, in that firms are more likely to have knowledge of the potential economic value of patents to them, given their

own knowledge of their internal production processes, market research, cost of capital etc. This information asymmetry places more power in the hands of firms when persuading regulators to provide favorable treatment (Laffont and Tirole 1986; 1993).

Large innovators have many means to provide incentives to regulators. Patent examiner incentives, as reviewed above, incentivize examiners to spend as little time as possible examining patents. Patent examiners are subject to biweekly quantitative reviews of performance (GAO 2005; GAO 2007). They receive credit for the initial response to the patent, and for the final disposal of a patent, and for first response after continuation, though not for other actions they may take. Thus applicants with greater financial and legal resources may continue to apply, thus wearing down the patent examiner, who may finally obtain a second count by disposing of it in the only permanent way possible, i.e. granting the patent(Thomas 2001; Kesan and Gallo 2006). Further, the revolving door process may apply here too, (though it is not clear that it does), and patent examiners may hope for jobs either with top innovators or their law firms (Djankov, La Porta et al. 2002), thus encouraging them to treat firms with a reputation for patenting, favorably.

The pressure on patent examiners is not necessarily only from the applicants. Research on institutions argues that they face multiple audiences with competing demands. For the patent office, these include not just patent applicants, but their competitors, political entities such as the United States Congress who controls budgets, the courts where patents are litigated, academics and the general public. While patent applicants look to secure intellectual property rights as broadly and as quickly as possible, their competitors would look to denying them these rights and legal scholars might prefer patents that can be consistently upheld in court (Thomas 2002). The patent office, like other institutions faced with competing demands and uncertainty, is likely to act in ways that maximize its own legitimacy in the eyes of its audiences. This persistent threat pushes the organization to rely on market orders and reputation (Meyer and Rowan 1977).

One of the most salient audiences to regulators in general is that of the market participants who they are supposed to regulate. The focus on hierarchy among market participants can lead to regulatory capture by large firms with the most resources to lobby regulators (Stigler 1971). A less extreme explanation would be that the familiarity and visibility with high-status market participants become proxies for the underlying quality in the eyes of the regulators (Olson

1997). The implication remains that firms with positive reputations in the eyes of the patent examiners due to, say a large number of prior patents in a mature field, may enjoy advantages in the patent review process. This advantageous reputation is likely to be self-sustaining as the firms continue to produce more patents due to the advantages provided by their current reputation

Patent examination at the US Patent Office

Approximately 450,000 applications are currently submitted to the US Patent Office each year. Though there is a duty of disclosure of prior art in the United States, there is no affirmative requirement that applicants conduct prior art searches; the incentives for applicants to do so vary across inventions and industries (Sampat 2009). Most patent applications (but not all) cite some prior patent as well as non-patent art.

One issue for our analyses is whether there is any form of sorting when assigning applications to examiners at the US patent office. Lemley and Sampat (2008) provide a comprehensive account of the patent application process. In it, they assert that there is "some sorting of applications, but that familiarity with

particular technologies and docket management, rather than judgments of an application's quality or patent-worthiness, are the dominant considerations".

The patent examiner checks the application's claims for non-obviousness, searches prior art, and adds further citations if necessary. The examiner-added citations tend to be to the prior patent art rather than to non-patent literature[8] (Thomas 2001). The examiner then responds to the patent applicant, a "first response", for which the examiner obtains a "count". The application may go through multiple rounds of rejection and resubmission via "continuation applications".

Patent examiners are under intense pressure to grant patents (Thomas 2001; Kesan and Gallo 2006). Lemley (2001) notes that patent examiners devote an average of eighteen hours per patent, including all resubmissions via "continuation applications". Thomas (2001) points out that patent officers are required to provide written reasons for rejection, but none for acceptance and that the patent application can be resubmitted endlessly. There is no way to issue

[8] To get an idea of how varied the non-patent prior art can be, in 1964 the Dutch patent office refused to grant a patent to Karl Kroyer, a Danish engineer who successfully refloated a sunken ship using Ping Pong Balls. (British and German offices did grant the patent). Unfortunately for Kroyer, a 1949 Donald Duck comic *The Sunken Yacht* had used exactly the same concept, and was classified, quite literally, as prior art. http://www.octrooicentrum.nl/index.php/component/option,com_blogplus/Itemid,417/intContent_ID,1400/ - Dutch patent office statement last retrieved Jun 30, 2011, and for an English version http://www.iusmentis.com/patents/priorart/donaldduck/

a "final rejection" and that the only way to permanently dispose of a patent application is to grant the patent.

Given these strong incentives and a limited time to assess patents, we argue that patent examiners are likely to look for signals in patent applications that permit them to process applications as quickly as possible. Patent examiners might be more assured about the quality of applications conducted by firms that they perceive to have better reputations (Podolny and Stuart 1995). Under these circumstances, applications from such firms could well get lower levels of scrutiny[9]. The converse is also possibly true. Firms that have a reputation for applying for (and perhaps even getting) a lot of low-quality patents may find their applications receiving additional scrutiny. If both these patterns are the case, it can be argued that the patent office is acting more in a manner that balances it's various competing audiences (Peltzman 1976), rather than in a manner that suggests that it is completely beholden to the more powerful applicant.

[9] It is axiomatic that "No one ever got fired for buying IBM". It is quite likely that no one ever got fired for granting them a patent, either.

Citations and Quality

Burke & Reitzig (2007) discuss patent quality in terms of two dimensions, viz. techno-economic quality and legal sustainability. They argue that the first dimension is about only granting applications meeting a minimum level of technological innovation, and the second dimension about legal certainty or consistency, i.e. patents that are consistently upheld in court (Thomas 2002). They assert that patent stakeholders expect the patent office "to judge patentability requirements correctly against a given yardstick (i.e., economic dimension of quality), and reliably (or consistently) in the sense that the service can be trusted (i.e., legal dimension of quality)". Critics of the US Patent Office have frequently argued that the patent office fails on both counts, issuing many low-quality patents. A large number of these complaints center around the computer industry, particularly software patents, such as the 1-click to make purchase patent (Allison and Lemley 1998; Merges 1999).

A great deal of literature has accumulated around patent citations. One stream of this literature involves forward citations as a measure of the value of patents (Trajtenberg 1990). Backward citations of patents to the prior art have also been used to measure patent quality (Narin, Noma et al. 1987). In both cases, more citations imply higher quality.

A second stream involves citations as a measure of flows of knowledge, including regional restrictions of knowledge. This literature has treated examiner-added citations as noise. Alcacer, Gittelman & Sampat (2008) show that the signal-to-noise ratio is extremely low. They find that as many as 40% of citations are added by the patent examiner. They also find considerable heterogeneity in the number of citations added, and find that firm-level effects are one of the drivers of this heterogeneity.

While heterogeneity in examiner-added citations is certainly driven by multiple factors, we contend that this heterogeneity is related to the overall quality of screening. As part of the patent screening process the examiner generally conducts a search for prior art. The number of patents added by the examiner, conditional on the number of patents disclosed as prior art by the applicant can provide a proxy for the overall quality of screening of the application. This would be a somewhat noisy measure over time, as the number of patents added would be likely to go up as search technology improves. We use year fixed effects in our data analysis to control for this and other time trends.

Since patents are of differing quality, but only need to meet a threshold standard to be granted, "high quality" patent applications could be granted with little time and effort and the patent examiner could devote more time to patents that are nearer the threshold. While this appears obvious for the patent granting decision, it is not clear that this criterion applies in the search for prior art. Patent examiners would need to conduct a search of prior art regardless of the apparent quality of the patent application before them, and ensure that the patent granted has cited all appropriate prior art. However, the patent examiners could use the existing applicant citations to prior art as a signal of the intensity of search the applicant has already performed.

Examiner-added citations can therefore be seen as a measure of the search performed by the examiner conditional on the references disclosed by the patent applicant. As such, they are a lens to examine the amount of scrutiny given to an application by the examiner.

Firm reputation

As discussed previously, under conditions of uncertainty about the economic value of patents and the pressures on examiners to grant them, a patent office is likely to use established reputations of applicants as a signal of quality. Wilson (1985) asserts that reputation is a future-looking statement that depends on past behavior. A reputation is a belief sticking to an actor based on (possibly noisy) observations of the actor's prior behavior. The assumption is that the actor's past behavior reveals information about future (or present) behavior of the actor.

The question that arises then is what would be the behavior most visible to examiners? Since the patent office is a regulator of innovation, and patent examiners routinely conduct searches of the USPTO database, we argue that it would be the firm's prior patenting behavior that is most salient to the patent examiners. The question arises- what reputation would prior patenting behavior confer, in the eyes of patent examiners? What reputation would benefit the firm and what reputation would hurt it?

Institutional attention is gained by firms that are more prominent and visible to the institution (Wasserman and Faust 1994). Citations by other firms to a focal firm's patents are visible to the patent office. Examiners see citations made

by the applicants and also conduct their own searches of prior art. Firms that turn up more often in these searches are likely to be noticed by patent examiners. These firms are likely to have reputations in the minds of patents examiners, for better or worse, regarding their patent quality.

Given uncertainty about patent quality, the patent office is likely to be more assured about the quality of applications conducted by firms with a greater reputation for high-quality patenting. The examiners are also likely to trust the search performed by the high-status firms and put in less effort into their own additional search for prior art.

Whether turning up frequently in searches for prior art confers a positive or negative reputation for patent quality depends on the opinion of the patent examiner of the quality of patents in the area she examines. For example, patents in computer science and software receive the most criticism for bad patents and obviousness (Merges 1999). Patent officers are likely aware of this and a firm that had many patents in the prior art would have a reputation for poor-quality patenting in the eyes of the computer science examiner. This might likely trigger extra screening. Therefore we hypothesize that:

H1a: Firms with more patents will have more citations added to their "Computer Science" patents by the patent examiner than firms with fewer patents.

On the other hand, the intellectual property regime for drugs and medicine is well established. Brand-name drugs depend on the FDA and other laws to protect their monopoly products (Mossinghoff 1999; Carpenter 2010). Firms with a lot of patents in the prior art applying for a drug patent might well be perceived by a patent examiner to have a reputation for high-quality patenting. This would trigger reduced screening. In other words,

H1b: Firms with more patents will have fewer citations added to their "Drugs and Medicine" patents by the patent examiner than firms with fewer patents

The total number of external (non self-cite) citations to a firm's patents in a prior time period would provide a measure of the focal firms' quality of patenting that is visible and salient to patent examiners. However, total counts of citations to a firm are not directly visible in a search of the USPTO database, and are likely to be less salient than the number of times a firm shows up in the search itself. Nevertheless, this could also be an additional measure of the quality of patenting, even if it is not as visible to the patent examiner.

One of the key issues about status orders is that they are likely to be self-perpetuating (Gould 2002). High-status firms are likely to be able to maintain that status over time even if their objective patent quality is no different from lower firms. Further, given that high-status firms might be aware of this lower scrutiny, they might be tempted to minimize disclosure of prior art. An alternative explanation is that big firms don't care about the quality of the patents issued, just the quantity (Alcacer, Gittelman et al. 2008). If either of these behaviors is predominant, then we would expect:

H2a: Firms with greater reputations for patent quality will cite less prior art than firms with lower reputations for patent quality.

However, it could also be the case that high-status firms are acutely aware that the perception of a patent's quality is more driven by applicant's citing prior art than the firm's status. In that case, they would be able to use their superior resources to conduct better searches and cite more prior art. It is possible that the incentives to do this vary across industry. We could expect, if this behavior is predominant,

H2b: Firms with greater reputations for patent quality will cite more prior art than firms with lower reputations for patent quality

For H2a and H2b, recall that a higher patent count in "Drugs and Medicine" implies a greater reputation for patent quality, and a higher patent count in "Computers and Communications" implies a lower reputation for patent quality.

Data and Methods

In this paper, we use a database of all 502, 687 original utility patents granted from 2001 to 2003. The patent office has differentiated between citations added by the examiner and citations which were added by the applicant on the front page of the applications since January 2001. Similar data has been used in previous research on examiner added citations in several papers, notably Alcacer and Gittelman (2004) , Alcacer et al. (2008) and Sampat (2009).

This allows us to analyze the scrutiny performed by the examiner. We also use the NBER patent database (Hall, Jaffe et al. 2001) to generate variables that characterize the firm and the technology category of each patent.

Table 1 shows descriptive statistics of the dependent and independent variables, calculated at the patent level.

Independent & Dependent Variables

Examiner screening. Examiner screening is measured in terms of the effort put into the search for patent citations. Lemley and Sampat (2008) have shown that the examiner's propensity to add citations is inversely correlated with his or her propensity to grant patents. To measure examiner screening as a dependent variable, we use the count of examiner citations. We use this measure since in over 30% of cases, there are no applicant citations. The examiner share is therefore 100%, regardless of the examiner's actual search. In over 70%, there are fewer than 7 applicant citations, skewing the examiner share of citations. We use the number of applicant citations as a control variable in regressions involving examiner screening. Since the examiner citations are a count with over-dispersion we estimate a negative binomial regression (Hausman, Hall et al. 1984)

$$Y_i = \beta X_i + \varepsilon_i$$

Where Y_i is the number of examiner citations on the $_i$th patent.

X_i is a matrix of examiner and application characteristics.

Robust standard errors are used to adjust for clustering of the standard errors around the examiner.

We also do the regressions separately for each of the 6 major technology classes (explained below), to differentiate between the different effects expected in different technological areas

Applicant disclosure. We use the number of citations provided by the applicant to measure the applicant disclosure of prior patent art. This is used in different regressions as a dependent and as an independent variable.

To estimate the effects of firm characteristics on disclosure of prior art, we use the same method as above, estimating a negative binomial regression model

$$Y_i = \beta X_i + \varepsilon_i$$

Where Y_i is the number of examiner citations on the $_i$th patent.

X_i is a matrix of application characteristics.

However, in this case it is not necessary to adjust for clustering of the standard errors around the examiner, as examiner characteristics are not relevant. We also

do the regressions for each of the 6 major technology classes (explained below), to differentiate between the different effects expected in different technological areas.

Firm reputation for patent quality: Previous research shows that some institutions use the reputation of 'client' firms to guide their behaviors in the face of uncertainty (Podolny and Stuart 1995; Kim 2007) . We use two measures of the prominence of client firms in the eyes of the patent office. First, with the help of the NBER patent database, we use the number of patents the firm has had granted in the previous five years. This measures a firm's experience as well as its prominence to the patent office. We also use the external citations to a firm's work. External citations to a firm's work in prior years are used as a way of determining the position of firms in knowledge space (Podolny, Stuart et al. 1996). We use the NBER patent database (Hall, Jaffe et al. 2001) to generate the number of citations to a firm's patents in the previous five years, deliberately excluding self-citations. Since examiners view patent citations added by the applicant, search prior art and add citations, we would expect that firms who they come across regularly in their searches are more visible and possess a reputation in the eyes of patent examiners. However, we note that what that

reputation is, depends upon the overall reputation of quality that patents in that field has, viz. higher prominence in searches and citations in the area of Computer Science is likely to confer a negative reputation, whereas higher prominence in the area of Drugs and Medical patents is likely to confer a positive reputation.

One of the issues with both these measures of firm prominence is that they are very highly skewed. For example, while 27% of patents come from firms that have no patents at all, 10% of patents (50,681) come from 13 firms with over 5200 patents each in the previous 5 years. Citations are even more skewed, with the top 5% of patents coming from 7 firms over 51,700 cites from other firms to their prior art in the previous 5 years.

To deal with this, we use the log of prior patent counts plus one and prior citation counts plus one respectively as measures of status.

Controls

Whether the firm has patented before: The resources of firms differ greatly, but the fact that a firm has had a patent granted in the five-year window before indicates

some recent familiarity with the patenting process and a minimum level of resources available to pursue the patent.

Whether the firm's work was cited before: Citations to patents are a highly variable, but having at least one citation indicates that some other firm has built on the firm's patent, indicating at least a minimum level of quality for the firm's patents (Trajtenberg 1990).

Country of origin: The effect of a non-US country could be driven by several things. Applications from other countries may conform less to US Patent norms, and may be driven by the norms of the host country. They might therefore invite more careful scrutiny and exhibit more citations. On the other hand, the examination might have undergone prior screening by another patent office. In that case, additional citations made by that office show up in the data as applicant citations to prior art. Further, inventors willing to accept the additional costs of applying for and maintaining patents in an additional country may indicate a superior application (Lanjouw and Lerner 1997). We report a single variable for non-US countries, and in robustness checks, use country fixed effects to control for this effect.

Technology Categories: we use the thirty-six technology categories used in the NBER database. Each patent, based on its patent class, is assigned to a technology group (6) and subcategory (36) using the crosswalk data provided in the NBER database. We used technology fixed effects in all the overall regressions at the technology subcategory level. (Tables 2 and 4)

Class categories: We use the 421 patent classes for the technology as fixed effects in the regressions that are done in each technology category. (Tables 3 and 5)

Time trends: The number of patents added is likely to go up as search technology improves over time. We use year fixed effects in all regressions to control for this and other time trends.

Results

Tables 2-5 provide the results of the regression analyses. Tables 2 and 3 shows the factors that affect applicant-added citations. We see from the dummy variable for patenting that firms that have patented tend to cite more prior art. This holds true across all technological characteristics. This is consistent with the

idea that firms that have patenting experience are more likely to know how to craft applications, have resources to conduct searches and cite prior art.

However, firms that patent a lot, tend to cite less prior art. This holds true for four of the six categories. This implies that prominent firms are less inclined to cite prior art, supporting Hypothesis 2a. Interestingly, in the technological area of chemicals, we find that prominent firms are more inclined to cite prior art, supporting Hypothesis 2b. We find no result in the "Others category".
Firm citations do not appear to hold a similar pattern. Having some work good enough to receive a citation in the previous five years is correlated with a propensity to cite more prior patent art. However, receiving a large number of citations, a sign of a prominent firm, is not correlated with citing less prior patent art, as the effects appear equally split between positive effects, negative effects and no effect. Application citations do not appear to be very sensitive to the citations to the firms' prior art.

We find a strong negative effect for foreign inventors, supporting the suggestion that foreign inventors' lack of familiarity with the US Patents and their own countries' differing 'duty of disclosure' norms could cause them to cite less prior US patent art.

Tables 4 and 5 show the factors that affect the number of citations added by the examiner to the patent. The effect of applicant citations on examiner citations is, in general very slightly negative (4.7) and (5.1-5.6) This is consistent with Sampat (2009), and it indicates that there is very little incentive for the applicant to add citations to prior patent art. Clearly, failing to disclose prior art is very unlikely to result in the examiner adding that citation. This is some indication that the examiners are satisficing - meeting some internal norm on what constitutes an adequate search of the prior literature. This is only slightly related to the applicant citations – prior work (Alcacer, Gittelman et al. 2008) shows that firm fixed effects explain most of the variation in examiner-added citations.

We find that firms that have patented in the previous 5 years are less likely to receive examiner citations in 4 of 6 technological categories, (5.2-5.5).

Firms that have patented a lot, however elicit differing levels of scrutiny depending on which technological area the patent application is in.

Firms that have patented a lot ,applying for "Drugs and Medical" patents, are even less likely to receive examiner citations, even after controlling for

applicant citations. This provides support for H1b. This also appears to be true for “Chemical” and “Others”. However, for “Computers and Communications” and “Electrical and Electronics”, firms that have patented a lot have their patent applications subjected to extra scrutiny. This provides support for hypothesis H1a.

This is to be seen in light of Tables 2 and 3, showing that firms that have had more patents issued in the previous 5 years are less likely to disclose prior art in the first place, across the board. The exception seems to be Chemical, where firms are more inclined to disclose prior art.

Firms that are highly cited are likely to have more citations added by the examiner in some categories but not others. They are more likely to have citations added in “Drugs and Medical” This doesn’t support Hypothesis 1a. There is no effect for being highly cited in “Computers and Communication”. This doesn’t support Hypothesis 1b.

In conclusion, we find support for Hypothesis 1a and 1b and support for Hypothesis 2a, when looking at the prior patenting record of firms. We don’t find support for any of the hypotheses when looking at the patterns of citation to

the prior patents of the firms. We only find support for Hypothesis 2b in the technological area of chemicals

Discussion

From the regressions, we observe that high-reputation firms cite less patent prior art than low-reputation firms and individual inventors. Yet, patent examiners are likely to add fewer cites to patents granted to high-reputation firms, conditional on the number of applicant-added citations. This clearly implies reduced scrutiny to patents of high-reputation firms. The exception appears to be occurring in the Chemicals field, where high-reputation firms have lower scrutiny, but appear to add more applicant citations themselves. This would imply relatively efficient functioning on the part of examiners, and a sub-study of this area, and the differences between chemicals and other fields (more mature, better definitions of what is patentable) deserves exploration of it's own in some depth in future research.

The simplest explanation is that, as predicted by regulatory capture theory and theories of bureaucratic legitimacy, examiners are indeed giving benefits to high-reputation firms. However, firms that have, in effect, gained a poor reputation by patenting in certain fields, such as Computer Science and Electronics elicit a small amount of added scrutiny, though this effect is smaller

than their reduction in applicant citations. In this, examiners are performing more of a balancing act conducive to legitimacy explanations (Kim 2007; Carpenter 2010)and more general regulatory capture explanations (Peltzman 1976; Laffont and Tirole 1991)

An alternative explanation is that higher-reputation companies systematically obtain patents that *intrinsically* require fewer total citations to the existing prior art. In our regressions, we observe that high-reputation firms add fewer applicant citations than lower-reputation inventors, and yet they have fewer examiner-added citations to the prior patent literature.

In this explanation, the examiners systematically cite less prior art because there is less prior art to be found. However prior research shows that fewer patent cites to prior art indicates lower economic value (Narin, Noma et al. 1987) i.e. a lower patent quality. This explanation would imply that higher-status companies systematically obtain lower-quality patents. This would again imply the examiner granting some benefits to firm status. (Again, Chemicals appears to be exempted from all this).

These findings have strategic implications for firms heavily involved in innovation and patenting. For example, firms can have different approaches to

patenting, analogous to r/K strategies in evolutionary biology (MacArthur and Wilson 1967; Schneider 2007). Some firms (r-strategists) focus on submitting many applications with a relatively low probability of success (Schneider 2007); others may focus on fewer high-quality patents. It has been argued that both bigger and smaller firms could be K-strategists. It's possible that bigger firms are more interested in higher quality patents as they hope to reap technological benefits and would want them to withstand challenge. On the other hand, smaller firms may wish to sell or license their patents and may want them to be more resistant to legal challenge, whereas large firms are more interested in quantity rather than quality of patents. (Alcacer, Gittelman et al. 2008).

Regardless of size, these results indicate that there might be some benefits to the r-strategy in certain technological areas, but not in others.

In forthcoming research, we will look at the patent examiner's response to different indicators of status. One of the areas we intend to explore is the relationship between patent attorneys and scrutiny. A firm that invests in high-quality attorneys could be signaling its quality of patent or its willingness to persist in getting the patents approved.

We also intend to incorporate other measures of quality to better assess the magnitude of the status benefit orthogonal to quality. One good measure of patent quality would be to analyze the subset of patents that have been litigated and see if they were sustained or overturned (Thomas 2002). Another measure is whether the patent has been granted by other patent offices. For example, the European Patent Office (EPO) is widely regarded to have higher standards of innovation than the US Patent Office. In an analysis by Lemley and Sampat (2008), almost 90% of the patents approved by the EPO had been approved by the US Patent Office, whereas less than 50% of the patents approved by the US Patent Office had been approved by the EPO. These more accurate measures of assessing the quality of the patents would help in finding the magnitude of the benefit that is due to the component of firm reputation that is orthogonal to the quality of the application.

Conclusions

We find that there appear to be positive returns to a firm reputation for high-quality patenting at the patent office, as well as negative returns to a reputation for low-quality patenting. Patent examiners subject patent applications by high-reputation firms to less scrutiny. Further, many of these firms appear to be aware of this, giving them even less incentive to disclose prior

art. This appears to create a self-sustaining cycle that is beneficial to high-reputation firms and detrimental to those who do not possess that reputation in the eyes of the patent office. This is potentially anti-competitive and not consistent with stakeholders' expectation of a consistent and reliable process of patent scrutiny.

Variable	Mean	Std. Dev	Min	Max
Applicant citations to US patents	7.37	18.88	0	778
Examiner citations to US patents	5.21	4.81	0	416
Firm patents in the previous 5 years	1,291.39	2,642.94	0	14,988
Cites from other firms to patenting firms' portfolio in previous 5 years	9,492.48	22,936.46	0	152,375
Dummy Variables				
Firm has patented in the previous 5 years	0.727	0.445	0	1
Firm's work has been cited by other firms in previous 5 years	0.692	0.461	0	1
Non-US Firm	0.477	0.499	0	1

Table 1 : Description of Variables

Table 2: Applicant Search

	(1)	(2)	(3)	(4)	(5)
DV - Applicant added citations					
Log(Prior 5 years' patents+ 1)	**-0.080****	**-0.255****	**-0.294****	**-0.258****	**-0.187****
	(0.002)	(0.003)	(0.004)	(0.007)	(0.007)
Firm patented(1/0)in prior 5 years		**0.712****	**0.559****	**0.529****	**0.471****
		(0.010)	(0.011)	(0.012)	(0.011)
Firm has been cited (1/0) in prior 5 years			**0.308****	**0.341****	**0.249****
			(0.010)	(0.012)	(0.011)
Log(Prior 5 years' citations to firm patents +1)				**-0.032****	**-0.017****
				(0.006)	(0.005)
Non-US Firm (1/0)					-1.305**
					(0.005)
Constant	2.211**	1.971**	1.943**	1.939**	2.465**
	(0.043)	(0.042)	(0.042)	(0.042)	(0.040)
Observations	492895	492895	492895	492895	492895

* significant at 5%; ** significant at 1%
All regressions include dummies for 36 NBER Technological categories
All regressions include year dummies.
Logs are to base 10.

Table 3: Applicant Search by Technology Area

DV - Applicant added citations						
	(3.1)	(3.2)	(3.3)	(3.4)	(3.5)	(3.6)
Technology	Chemical	Computers and Communication	Medical and Drugs	Electrical and Electronic	Mechanical	Others
Log(Prior 5 years' patents+ 1)	**0.097****	**-0.418****	**-0.247****	**-0.312****	**-0.170****	-0.031
	(0.029)	(0.038)	(0.039)	(0.033)	(0.030)	(0.040)
Firm patented(1/0)in prior 5 years	**0.175****	**0.576****	**0.617****	**0.458****	**0.408****	**0.397****
	(0.044)	(0.054)	(0.047)	(0.041)	(0.038)	(0.041)
Firm has been cited (1/0) in prior 5 years	**0.188****	**0.301****	**0.106***	**0.116****	**0.230****	**0.372****
	(0.038)	(0.049)	(0.042)	(0.039)	(0.037)	(0.039)
Log(Prior 5 years' citations to firm patents +1)	**-0.133****	**0.080****	0.044	**0.077****	-0.002	**-0.113****
	(0.020)	(0.027)	(0.025)	(0.027)	(0.022)	(0.029)
Non-US Firm (1/0)	**-1.347****	**-1.136****	**-1.107****	**-1.358****	**-1.372****	**-1.407****
	(0.024)	(0.025)	(0.029)	(0.025)	(0.024)	(0.024)
Constant	1.299**	3.090**	2.192**	2.233**	3.006**	1.219
	(0.023)	(0.247)	(0.131)	(0.244)	(0.508)	(0.714)
Observations	68997	98849	56404	106295	85338	77012

* significant at 5%; ** significant at 1%
Robust standard errors in parentheses
All regressions include dummies for 421 NBER Technological classes
All regressions include year dummies.
Logs are to base 10.

Table 4: Examiner Scrutiny

DV- Examiner-added citations							
	(4.1)	(4.2)	(4.3)	(4.4)	(4.5)	(4.6)	(4.7)
Applicant citations	-0.002**	-0.002**	-0.003**	-0.002**	-0.002**	-0.002**	**-0.003****
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Log(Prior 5 years′ patents+ 1)		-0.025**	-0.027**	-0.005	-0.004	-0.022**	**-0.016****
		(0.002)	(0.003)	(0.003)	(0.003)	(0.006)	(0.006)
Log (Prior 5 years′ patents +1) * applicant citations			0.000*	0.000*	0.000*	0.000*	0.000
			(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Firm patented(1/0)in prior 5 years				-0.087**	-0.086**	-0.072**	**-0.072****
				(0.008)	(0.008)	(0.008)	(0.008)
Firm has been cited (1/0) in prior 5 years					-0.001	-0.016*	-0.015*
					(0.006)	(0.007)	(0.007)
Log(Prior 5 years′ citations to firm patents +1)						0.015**	**0.012****
						(0.004)	(0.004)
Non-US Firm (1/0)							**-0.079****
							(0.005)
Constant	1.213**	1.252**	1.254**	1.283**	1.283**	1.283**	1.324**
	(0.118)	(0.117)	(0.117)	(0.117)	(0.117)	(0.117)	(0.118)
Observations	492895	492895	492895	492895	492895	492895	492895

* significant at 5%; ** significant at 1%
Robust standard errors in parentheses (adjusted for clustering around the examiners.)
All regressions include dummies for 36 NBER Technological categories
All regressions include year dummies.
Logs are to base 10.

Table 5: Examiner Scrutiny by Technological Area

DV- Examiner-added citations						
Technology	Chemical	Computers and Commun-ications	Electrical and Electronic	Drugs and Medical	Mechanical	Others
	(5.1)	(5.2)	(5.3)	(5.4)	(5.5)	(5.6)
Applicant citations	**-0.003****	**-0.001***	**-0.003****	**-0.002****	**-0.004****	**-0.006****
	(0.001)	(0.000)	(0.001)	(0.000)	(0.001)	(0.001)
Log(Prior 5 years' patents+ 1)	**-0.035****	**0.018***	**0.019***	**-0.069****	-0.009	**-0.026***
	(0.013)	(0.009)	(0.009)	(0.026)	(0.010)	(0.013)
Log (Prior 5 years' patents +1) * applicant citations	0.001	-0.000	0.000	**0.001****	-0.001	**0.001***
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Firm patented(1/0)in prior 5 years	-0.009	**-0.034***	**-0.037***	**-0.067***	**-0.031***	-0.026
	(0.019)	(0.014)	(0.016)	(0.030)	(0.014)	(0.016)
Firm has been cited (1/0) in prior 5 years	-0.005	0.035**	-0.006	-0.033	-0.003	-0.051**
	(0.018)	(0.013)	(0.015)	(0.029)	(0.011)	(0.014)
Log(Prior 5 years' citations to firm patents +1)	**0.023***	-0.009	-0.006	**0.049****	0.003	**0.019***
	(0.009)	(0.006)	(0.006)	(0.015)	(0.007)	(0.009)
Non-US Firm (1/0)	**-0.042****	**-0.056****	**-0.073****	**-0.061****	**-0.075****	**-0.096****
	(0.013)	(0.006)	(0.008)	(0.019)	(0.008)	(0.008)
Constant	2.064**	1.259**	1.172**	1.702**	2.100**	1.447*
	(0.254)	(0.154)	(0.244)	(0.156)	(0.018)	(0.686)
Observations	68997	98849	106295	56404	85338	77012

* significant at 5%; ** significant at 1%
Robust standard errors in parentheses (adjusted for clustering around the examiners.)
All regressions include dummies for 421 NBER classes
All regressions include year dummies.
Logs are to base 10.

Chapter 3: Which drugs obtain the Pediatric Exclusivity Provision

Abstract

Pediatric exclusivity is designed to reward companies for conducting pediatric trials for dosage and safety with 6 months' extra monopoly on their drug. We find that companies appear to base the decision to conduct pediatric trials almost solely on the basis of current sales (and hence presumably future projected revenue). We find the threshold for a sharply increased probability of obtaining pediatric exclusivity is annual sales of $260 mn in the prior year We estimate, very conservatively, that the total liability to consumers is US$ 21 billion as of end 2007.

We also find, in accordance with prior criticism, that, (barring ADHD drugs, which are marketed primarily to minors) even after controlling for the total sales, the proportion of sales to minors does not affect the probability of obtaining pediatric exclusivity. This is in concordance with regulatory capture theory which would suggest that a powerful group (i.e.. brand-name drug manufacturers) influenced Congress to pass this legislation to procure a benefit for themselves with a not-easily perceived cost to the much more diffuse group of pharmaceutical customers who pay brand-name prices for 6 more months as a result of delayed generic entry.

Introduction

The power of regulators to coerce behavior and alter incentives faced by market participants (Laffont and Tirole 1993) makes them one of the most important institutions in a market. The United States' Food and Drug Administration (FDA) regulates, among others, the pharmaceutical industry which had annual sales of over $130 billion[10] in 2007. The FDA is an exceptionally powerful regulator and exerts a strong influence on the revenue streams of pharmaceutical firms. It must approve all drugs before they can be sold in the US, its decisions are effectively binding and very expensive to contest (Carpenter 2004)and it can grant market exclusivity for drugs over and beyond the intellectual property rights granted by patent law. In this chapter, we examine one such regulation that extends market exclusivity – the Pediatric Exclusivity provision.

Pediatric exclusivity

The Pediatric Exclusivity provision was created by Section 111 of Title I of the Food and Drug Administration Modernization Act (FDAMA) of 1997, which in turn created section 505A of the Federal Food, Drug, and Cosmetic Act (21

[10] 2007 sales data from the dataset used in this chapter

U.S.C. 355a). Section 505A permits applications to obtain an additional 6 months of market exclusivity if the sponsor submits requested information relating to the use of the active moiety in the pediatric population (FDA Guidance for Industry 1999).

Under the FDAMA, firms are rewarded with 6 months of additional market exclusivity for conducting studies specified by the Food and Drug Administration (FDA) in pediatric populations. Pediatric exclusivity attaches a 6 month period of exclusivity to the patent or market exclusivity already held by the firm. It attaches to every drug that the firm holds that contains the studied active moiety for which pediatric exclusivity has been granted.

As such it is potentially a powerful incentive for companies to conduct pediatric studies. In order to qualify for pediatric exclusivity, all that is required is that the studies agreed between the company and the FDA be conducted. There is no requirement that the studies have to be published, or that label changes must be made to the drugs. Publishing is at the discretion of the firm, and label changes are made only if the studies deem them necessary (FDA Guidance for Industry 1999). If no label changes are necessary, the firm nevertheless obtains the six month exclusivity provision.

The FDA pediatric exclusivity provision follows on from earlier legal efforts to stimulate innovation in pharmaceutical research using market exclusivity provisions. These included the Orphan Drug Act(1983) , the Waxman-Hatch Act(1984), and the Prescription Drug Fee User Act(1992) (Kesselheim 2010). The Orphan Drug Act (1983) granted seven years' market exclusivity to drugs that treated rare diseases.(Public Law 97-414)

The Waxman-Hatch Act (1984) is often credited with stimulating a vast and robust expansion in the availability of generic drugs in the US. (Grabowski and Vernon 1996; Mossinghoff 1999; Karki 2005). The Waxman-Hatch Act made it considerably easier to obtain approval for generic drugs that were bioequivalent to brand-name drugs whose protections had expired. The Act also created two market exclusivity extensions. First, it increased the effective time of market exclusivity by adding back some time lost in clinical trials and FDA review process. . Grabowski and Vernon's (2000) study found that this effectively added a total of two years to market exclusivity. The second extension was a 6-month extension for a generic manufacturer that successfully challenged a weak patent, designed to stimulate generic challenges on current brand-name pharmaceuticals (21 U.S.C. 365 bb(a)(2)). This extension has been criticized for

delaying the entry of generic pharmaceuticals (Korn, Lietzan et al. 2009). Brand name manufacturers can and do pay the generic manufacturer that challenged the patent to refrain from marketing the drug within the 180-day generic exclusivity period (Hemphill 2006).

The Prescription Drug User Fee Act (1992) responded to consumer and industry concerns about lengthy pharmaceutical reviews by reducing the FDA's review period, setting a deadline of 1 year and permitting application fees to be collected. This effectively increased the protected period for brand-name drugs. (Kesselheim 2010)

Rationale for the pediatric exclusivity provision

The pediatric exclusivity extension was provided to stimulate clinical studies in pediatric populations. Historically, efficacy and safety trials have been usually performed on adult populations. Children normally do not participate in clinical trials. There are scientific, ethical and commercial challenges. As children grow, their body size and composition, physiology, and cognitive and motor function change. The metabolism and toxicity of medications can vary substantially in children of different ages (Steinbrook 2002). Pediatric studies in

adolescents (12 to 16 years of age) may therefore not provide adequate data for, say, infants (1 month-2 years). This creates the requirement for multiple studies across different age groups. This increases the cost of the studies making pediatric studies relatively expensive compared with the size of the potential market. Further complications often cited include the difficulty of finding enough patients to participate, and inadequate numbers of quality pediatric pharmacology investigators (Caldwell, Murphy et al. 2004).

The ethical issues associated with studying children are complex. Informed consent of children's parents is not the same as consent of an adult (Committee on Bioethics 1995) . As a result federal regulations impose a greater oversight role on review boards for pediatric trials versus adult trials. (Steinbrook 2002). All these issues add up to fewer pediatric trials, and fewer patients in individual pediatric trials, thus giving them less statistical power than for adult patients.

This translates into a lack of dosage and safety information for pediatric patients on the drug labels. Doctors wishing to prescribe these drugs for children must prescribe them "off-label", i.e. for a purpose or to a population that has not been specifically approved in clinical trials by the FDA. The FDA has long

maintained the general position that although physicians may freely prescribe drugs for off-label uses, drug manufacturers may not promote such uses. (Mello, Studdert et al. 2009). Clinical practice on pediatric populations has often involved “off-label” prescriptions. (Conroy, Choonara et al. 2000; McIntyre, Conroy et al. 2000; 't Jong, Eland et al. 2002; O'Donnell, Stone et al. 2002; Schirm, Tobi et al. 2003).

To address the issue of a lack of pediatric information, the FDA first published a pediatric rule in 1979 requiring pediatric dosage information. This was followed by a rule in 1994 requiring manufacturers to survey their current data to determine if any pediatric dosage information was given. Neither of these rules succeeded in providing much information – in the case of the 1994 rule, because there were so few studies being conducted on children, the only statement that was added to the labeling in most cases was one similar to the following: "Safety and effectiveness in pediatric patients below the age of <weeks/years/months> has not been established." (Cooper 2002)

In 1998, the FDA added a new Pediatric Rule that granted it the power to require studies from manufacturers of drugs if there is a substantial use in the pediatric population or the significant therapeutic benefit. Currently, however,

the FDA "will not require studies of approved drugs except if approved by the Center Director. Instead, FDA will seek to have manufacturers voluntarily submit studies for marketed drugs under the incentives provided by FDAMA". (i.e. pediatric exclusivity)[11]

Obtaining pediatric exclusivity

In order for pediatric exclusivity to be granted, the FDA must first issue a Written Request for pediatric studies. It is important to note that a firm may (and in our data, most often does) request a Written Request for pediatric studies from the FDA. Once the FDA has issued the Written Request, the firm responds, and the firm and the FDA negotiate the terms of the pediatric studies to be conducted (FDA Guidance for Industry 1999). This can be a long-drawn out process, taking several years, including requests for extensions of deadlines.

If the firm wishes to obtain exclusivity, it must provide results of studies that take place after the written request is issued. Once the FDA accepts the studies as a sufficient response to the written request, any label changes required are made and pediatric exclusivity is granted. Note that there is no requirement

[11] Frequently Asked Questions of Pediatric Exclusivity, The Pediatric "Rule" and their Interaction http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm

to make public or publish these studies in scientific journals, and that in practice, dissemination of these studies is limited (Benjamin, Smith et al. 2006)

This paper is organized into five parts. In the first part, we introduced the concept of pediatric exclusivity and provide background information. In the second part we review the extant relevant literature on regulators and regulatory capture and deduce our hypotheses. In the third part we explain our data and methods. In the fourth part we present our results and findings. In the fifth and final part we discuss our findings and discuss our conclusions.

Theory

As we discussed in the introduction, pediatric exclusivity provides for a 6-month extension of current market protection provided by patents and other market exclusivities granted by the FDA. The value of this extension can be considerable.

Pigou's (1938) theory of public interest regulation holds that markets exhibit failures such as externalities and monopoly power. Regulation is therefore used by governments to serve the general interest of society and maximize social welfare (McCraw 1975) In this view, the institutions that

regulate the market are viewed as Bayesian statisticians, optimizing welfare, frequently under incomplete information conditions. (Laffont and Tirole 1986).

Olson's (1965) logic of collective action where incentives to organize are higher for small groups with high stakes that are spread among fewer actors, was used by Stigler (1971) to develop the idea that an industry with few producers would be able to influence actors more than widely disbursed consumer groups. Peltzman (1976) accounted for the fact that the United States Congress occasionally passes laws that hurt large businesses and reduce protectionism by developing a model that balanced interest group support and voter group support to legislators. Laffont and Tirole (1991) pointed out that groups seeking to produce legislation that increased information asymmetry had even more power. This regulatory capture model predicts legislation that favors small powerful groups with information advantages over large diffuse groups.

Pediatric exclusivity legislation appears at first to fit this model. It favors incumbent brand-name drugs against generic competitors with valuable 6-month extensions. Brand-name drugs depend on monopoly pricing for profitability. It is notable that pediatric exclusivity is a "carrot" rule, providing an incentive with

no “sticks” or penalties for not providing pediatric information, an option that is always open to the firm.

Coercive rules had been attempted before to address the issue of a lack of pediatric information. The FDA first published a pediatric rule in 1979 requiring pediatric dosage information. This was followed by a rule in 1994 requiring manufacturers to survey their current data to determine if any pediatric dosage information was given. Neither of these rules succeeded in providing much information – in the case of the 1994 rule, because there were so few studies being conducted on children, the only statement that was added to the labeling in most cases was one similar to the following: "Safety and effectiveness in pediatric patients below the age of <weeks/years/months> has not been established." (Cooper 2002)

In 1998, the FDA added a new Pediatric Rule that granted it the power to require studies from manufacturers of drugs if there is a substantial use in the pediatric population or the significant therapeutic benefit. Currently, however, the FDA “will not require studies of approved drugs except if approved by the Center Director. Instead, FDA will seek to have manufacturers voluntarily submit studies for marketed drugs under the incentives provided by FDAMA”.

(i.e. pediatric exclusivity)[12] . Again the pattern appears to be that Congress and the FDA will not apply rules that force the pharmaceutical companies into doing pediatric studies, without any monetary benefit.

It has been argued the benefits of the drugs towards children and pediatric prescriptions are worth the cost (although we have not found any estimate for the cost to consumer in the extant literature) This argument has been made by several groups including the American Association for Pediatricians (Cooper 2002), as well as strongly criticized in academic literature. (Benjamin, Smith et al. 2006; Boots, Sukhai et al. 2007). We make a first attempt at finding out what this cost is in the current chapter and will assess the pediatric benefits in the next chapter.

The benefit-cost ratio of pediatric exclusivity can be enormously favorable. Li et al. found that median costs per written request of pediatric studies for a cohort of drugs in 2002-04 were approximately $12mn (range $5-$44 million). As against these costs, the benefits to the firm depend on the anticipated profits during those extra 6 months with exclusivity protection versus the anticipated profits without it. "Blockbuster" drugs are those whose sales exceed $1bn a year,

[12] Frequently Asked Questions of Pediatric Exclusivity, The Pediatric "Rule" and their Interaction http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm

providing an extra $500 million in sales during an additional six months of exclusivity.

Brand-name drugs are exceedingly dependent on these monopoly protections. Generic competition can severely dent the market share of the drug. After generic entry, generic prices fall to between 35% and 40% of the brand-name drug in two years, and subsequently to about 10-20% of the brand-name drug (Grabowski and Vernon 1992; Frank and Salkever 1997). Brand name drugs typically do not respond by dropping their prices, but lose market share.

Grabowski and Vernon (1996) in their study on the effectiveness of the Waxman-Hatch Act found that, for the 1984-85 cohort of generic entrants, brand name drugs typically retained 55% of the market share two years after going generic. By the 1991-92 cohort, this had dropped to 28%. They attributed this to increased price-sensitivity brought about by managed care. Mortimer's (1997) work supported these conclusions by finding that demand for drugs in managed care is more price-elastic than in other sectors, such as the demand by patients who pay the entire cost of drugs themselves.

The market share retained by the brand-name drugs is also affected by the original market size. The greater the original market size, the lower the market share retained by the brand-name drug. (Grabowski and Vernon 1992; Grabowski and Vernon 1996; Saha, Grabowski et al. 2006).

Saha, Grabowski et al. (2006) found that the number of generic entrants strongly affects market share retained by the brand name drug. Of those with 20 or more entrants, on average the brand name drug retained 20% of market share within one year of losing its market exclusivity protections. Saha, Grabowski et al. (2006)and Scott Morton (2000) also found that market size (i.e. brand-name drug sales prior to expiry of exclusivity protections) increased the likelihood of generic entry.

Thus we see a strong market threat to brand name drugs, i.e. generic competition. A 6-month delay can be very valuable to the brand-name pharmaceutical industry, and , coupled with the exceedingly low cost of conducting the trials relative to the potential benefits is potentially evidence of regulatory capture.

The attractiveness of a drug's current sales to potential generic competitors, and the inability of brand-name drugs to maintain market share in the face of stiff price competition from generic manufacturers increase the potential value of the 6 -month pediatric exclusivity as the sales of the drug increases. We therefore hypothesize that:

H1: The higher (lower) the sales of a drug, the greater(lesser) the likelihood of obtaining pediatric exclusivity.

The primary stated rationale behind pediatric exclusivity is to stimulate pediatric drug trials in patients. One of the key criticisms of pediatric exclusivity is that the pediatric studies conducted for pediatric exclusivity are conducted with the primary purpose of increasing exclusivity for drugs that have a large market in the adult population (Boots, Sukhai et al. 2007) . As adults represent over 90% of the sales of drugs, any drug with a large market would primarily sell to the adult population. Boots, Sukhai et al.'s (2007) study described prescription patterns across different categories of drugs and found that the majority of drugs granted pediatric exclusivity are those that treat central nervous system, cardiovascular, alimentary, and metabolism disorders, all of which are relatively

rarely used by children. Drug categories frequently used by children, such as respiratory drugs, anti-infectives for systemic use, and dermatologicals are underrepresented in the pediatric trial data. These findings are entirely consistent with regulatory capture theory (Stigler 1971; Peltzman 1976), as the legislation does not require that drugs are primarily marketed to children, only that the required clinical trials have been conducted.

However, once we control for the total sales of the drug, we would find that a larger proportion of pediatric populations would imply higher total prescriptions (and consequently, sales attributed to those prescriptions) that are occurring off-label. Companies that wish to aggressively market pediatric uses of drugs, particularly to consumers, would therefore be more likely to seek pediatric exclusivity. Therefore, we hypothesize:

H2a: Controlling for total sales, the higher (lower) the proportion of prescriptions of a drug to minors, the greater(lesser) the likelihood of the firm conducting the necessary studies and obtaining pediatric exclusivity

And

H2b: Controlling for total sales, the higher(lower) the proportion of sales of a drug to minors, the greater(lesser) the likelihood of the firm conducting the necessary studies obtaining pediatric exclusivity

The FDA had historically restricted drug companies from promoting off-label uses of their drugs. However, according to the latest guidance, companies are allowed to distribute peer-reviewed scientific articles and texts describing off-label uses to medical practitioners, subject to certain conditions, primarily regarding accuracy, completeness of the article, not highlighting any sections and separation of the articles from promotional materials (Mello, Studdert et al. 2009). This would certainly give the firms more leeway in promoting off-label use and might attenuate the effects anticipated above in H2a and H2b.

We recall that pediatric exclusivity adds only to the end of the current period of market protection (via patents or other exclusivity provisions). It is likely that firms would be able to estimate the economic benefits of pediatric exclusivity (i.e. predicted sales and hence profits during the extra six months of exclusivity) more accurately the nearer the date of expiry of current market exclusivity. The firms would be able to carry out more accurate cost-benefit analyses. This leads us to hypothesize that:

H3: The less (more) the time to expiry of exclusivity, the greater (lesser) the likelihood of obtaining pediatric exclusivity.

Data and Methods

The Medical Expenditure Panel Survey (MEPS) is conducted annually by the Agency for Healthcare Research and Quality, part of the United States Department of Health and Human Services. The Household Component of the Medical Expenditure Panel Survey (MEPS-HC) is designed to produce national and regional estimates of the health care use, expenditures, sources of payment, and insurance coverage of the U.S. civilian non-institutionalized population. The sample design of the survey includes stratification, clustering, multiple stages of selection, and disproportionate sampling (Machlin, Yu et al. 2005) . We use data from the Household Component of the MEPS from 1996 to 2007 to compute prescription counts and expenditures. The MEPS sample size differs each year and ranges from 8,655 families (21,571 individuals) to 14,828 families (37,418 individuals) in our dataset.

The data from the household components of MEPS was merged with new drug application data from the FDA Electronic Orangebook. As the FDA Orangebook only holds data for all currently valid therapeutics, Multum Lexicon

was also used to provide data for some drugs that had appeared in the household survey but had expired. Pediatric exclusivity data was obtained from the FDA Orangebook and crosschecked with the FDA list of drugs granted pediatric exclusivity[13]. Expenditure data from MEPS covered a total of 519 drugs. 155 drugs were granted exclusivity by Dec 31, 2009.

Variables

Granting of pediatric exclusivity

Using the date of pediatric granting data from the FDA list we generate dummy variables for the following

a. *Pediatric exclusivity ever granted*

(1/0) variable that Takes the value 1 if the drug is granted pediatric exclusivity before Dec 31, 2009.

b. *Pediatric exclusivity granted during the year* – (1/0) variable that takes the value 1 if pediatric exclusivity was granted during the year.

c. *Pediatric exclusivity already granted* - (1/0 variable that takes the value 1 if pediatric exclusivity has been granted during the year or was granted in a previous year

[13] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm

Annual sales for each drug

The Household component of the MEPS provides overall medical expenditure data, for each medical event. Each prescription event for each patient has a drug assigned. Each patient has a separate id, and each patient's age is identified. Each patient has a personal sampling weight that represents the prevalence for their particular conditions in the population.

We use the following variables:

a. *Total annual sales for each drug to adult patients* – The weighted sum of the total expenditure per event for all patients aged 18 or over for each drug for the year
b. *Total annual sales for each drug to minor patients* - The weighted sum of the total expenditure per event for all patients aged below 18 for each drug for the year
c. *Total annual sales for each drug* - The weighted sum of the total expenditure per prescription event for all patients for each drug for the year

Time to expiry

The firm that owns the rights to the drug is more likely to seek pediatric exclusivity nearer the end of expiry of current exclusivity. This is due to the

increased certainty in the sales that will be obtained in the "extra" 6 months at the end of the normal patent-protected period.

We define time to expiry as the number of years until the final expiry of the drug. This variable has some noise in the data, as the expiry date at the time of granting pediatric exclusivity is not always available.

Control variables

We control for several factors, such as a large fraction of prescriptions being written for minor patients, which would make some pediatric trials desirable to address the large market of minors. Firms would be more likely to seek pediatric exclusivity for trials that they are likely to perform anyway.

Therefore we control for:

1. Fraction of annual prescriptions to minor patients

The total prescriptions to minor patients for each drug for the year divided by total prescriptions to all patients for each drug for the year.

2. *Fraction of annual sales to minor patients*

The total sales to minor patients for each drug for the year divided by total sales to all patients for each drug for the year.

Age of drug

The older the drug, the more likely that the drug already has a safe off-label use among minors and that non-clinical trial information is available to doctors. It is possible that these drugs are low-profit as newer drugs have already superseded them for many purposes. This would reduce the incentive provided by the pediatric exclusivity provision. It is also possible that these drugs are nearer expiry, which would increase the attention being incentive provided by the pediatric exclusivity provision. The firm owning the rights to the drug would also be likely to focus on immediate results from extensions. The effect of age could therefore be in either direction, and we control for it, in our analyses.

We use the number of years since the drug was first approved by the FDA. This is left-censored by the orangebook at 1982, so all drugs first approved before January 1, 1982, are assumed to be approved on January 1, 1982.

Number of years under pediatric exclusivity regime

As the drug could not have been approved before 1997, this is defined as the number of years since 1997 that the drug has been approved by the FDA

Time trends

Drug sales have increased steadily with time. Further, as time has passed since 1997, there has been more time to conduct studies and obtain pediatric approval. We use year fixed effects in all regressions to control for this and other time trends.

Methods

In order to estimate the effects of variables on the drug obtaining pediatric exclusivity, we use a panel data logistic regression model

$$Y_{it} = \beta X_{it} + \varepsilon_{it}$$

Where Y is a dummy variable indicating whether the 'i'th pharmaceutical had received pediatric exclusivity at time 't'

And X_{it} is a series of independent and control variables

And where β is estimated using a panel logit regression where standard errors ε_{it} are allowed to cluster around the 'i'th drug.

We also estimate the obtaining of pediatric exclusivity using a hazard rate model (Tuma and Hannan 1984). The hazard rate ($h(t)$) is defined as follows:

$$h(t) = \lim \frac{P[\text{Obtaining exclusivity between } t \text{ and } t+\Delta t \mid \text{No exclusivity at } t]}{}$$

$\Delta t \to 0$ Δt

where P(.) is the probability of a drug obtaining pediatric exclusivity during time period at time[t, t+Δt] conditional on not having obtained pediatric exclusivity at time 't'. We follow Barron et al. (1994) and specify a piece-wise exponential model which allows us to model age dependence without making strong assumptions regarding its functional form. As it was not possible to obtain pediatric exclusivity before 1997, we use time under the pediatric exclusivity regime as our age variable.

Results:

Descriptive Tables: Table 1 describes the key variables in our data, and table 2 presents the correlation matrix. Annual prescriptions and sales are highly correlated and the fraction of sales to minors and fraction of prescriptions to minors are even more so. Tables 3 to 6 break down annual total and mean (per drug) sales and prescriptions by drugs having obtained pediatric exclusivity and by the patients who they are sold to- adults or minors. It quickly becomes apparent that the mean sales of a drug that has obtained pediatric exclusivity is much higher than of one that hasn't. For example, in 2006 the mean sales of a drug with pediatric exclusivity is just over US$ 670 million, whereas that of a

drug without pediatric exclusivity is just under US$ 200 million. A similar pattern can be seen in the total number of prescriptions.

However, it must be appreciated that it takes time to correspond with the FDA regarding written requests, agree on trials to be conducted, and conduct the clinical trials. If H1 is correct, companies that commence the process may well be doing so on the anticipation of future sales. Further, since pediatric exclusivity adds to the end of the current period, there is no compelling reason to obtain exclusivity urgently, other than the possibility of the pediatric exclusivity provision not being renewed. (It has so far been renewed for 5 year intervals under the Best Pharmaceuticals for Children Act 2002 and again in 2007 (@). As a result, in the earlier years of the pediatric exclusivity regime, the data showing higher mean sales is not as compelling- in fact in 1998 and 1999, the mean sales and prescriptions are lower for drugs with pediatric exclusivity than for drugs without them. (Table 4 and 6)

In tables 7-10 we describe data where we have back-coded future obtaining of pediatric exclusivity. Thus the data are now split by drugs that have ever received pediatric exclusivity. This allows us to see differences in sales and prescriptions of drugs that had not at the time obtained pediatric exclusivity, but would do so later. The difference in sales increases most for earlier data, but even

in our 2006 example above, the mean sales of drugs that would obtain pediatric exclusivity before 2010 is now US$ 688 million, and those that had not yet done so is US$ 146 million. These data clearly indicate that H1 is likely to be supported.

The ADHD Trio - outliers

The data in Tables 3-10 also show some preliminary evidence of support for H2a and b. The fraction of sales and prescriptions to minors appears to be slightly higher for drugs that have obtained pediatric exclusivity. These results, however, are strongly driven by three outliers, Adderall, Concerta and Strattera. Three drugs are approved to treat Attention Deficit Hyperactivity Disorder, (ADHD) and for all three drugs, over 2/3rds of their prescriptions and sales are to minors. Table 11 summarizes the data for the ADHD trio. After dropping these outliers, we repeat tables 3 through 10 as tables 12 through 19. These outliers are also dropped in all the t-statistics and regression tables.

We see that the differences in fractions of prescriptions and sales to minors are considerable attenuated in tables 12 through 19. We test the difference in fractions of prescriptions and sales of drugs with and without pediatric exclusivity in Table 20. We find very limited support for hypotheses 2a and 2b. Obtaining pediatric exclusivity does not seem to increase or decrease the fraction

of sales or prescriptions to minors. Contrary to H2a and H2b, drugs that obtained pediatric exclusivity before 2010 have a statistically significantly lower fraction of prescriptions and sales than drugs that did not obtain pediatric exclusivity. This supports the Boots et al. (2007) criticism that pediatric exclusivity has been obtained by drug companies on drugs that are primarily prescribed to (Boots, Sukhai et al. 2007)s. It could be argued that it is possible that that these drugs have been by and large, found to be unsuitable for minors thanks to the pediatric exclusivity testing. The final set of comparisons in Table 20, however, refute this possible explanation, showing that, within the set of drugs that obtained pediatric exclusivity, there was an increase in prescriptions and sales to minor patients after pediatric exclusivity was obtained.

To test all our hypotheses, we used panel-data logit regressions(Tables 21-24 as well as survival-time regressions (Tables 25 and 26). Since annual sales of drugs has a distribution with high skewness(6.94) and kurtosis (80.85), we opted to split the variable into deciles, the split points being shown in Table 20. We find very strong support for H1 across all the regressions. The panel-data regressions (Tables 21-24) show an increased probability of a drug obtaining pediatric exclusivity if its annual sales are in excess of $33mn, with a sharply increased probability if the drugs' annual sales are in excess of $260mn.

Although the decision to obtain pediatric exclusivity is not strongly affected by timing, since the exclusivity is obtained only at the end of the time to expiry, the survival-time regressions show that a drug having annual sales in excess of $260mn is, statistically significantly, over 20 times more likely to obtain pediatric exclusivity than one with annual sales below $3.3mn.

The regressions show no support for H2a or H2b, with coefficients on all the relevant fully-specified regressions: 21.2, 22.7, 24.6 or 28.4 for H2a , or 21.3, 23.7 and 29.4 for H2b being insignificantly different from zero.

The survival-time regressions (25.4) and (26.4) show no support for H3 either, and neither do any of the panel-data regressions. This may also be due to a limitation in our data- we have the information for the current protection expiry dates, including all exclusivities and extensions and patents, not the expiry of protection at the time that pediatric exclusivity was obtained, or to be completely accurate, at the time the decision to obtain exclusivity was taken.

To recap, we find strong support for hypothesis H1, but no support for hypotheses H2a, H2b, or H3.

Discussion and Conclusion

It appears from our results that obtaining pediatric exclusivity is driven primarily, if not solely, by the total sales of the drug, especially once it's beyond a certain threshold. In our analyses, we found this to be about $260 mn in annual sales. We can compare this to the cost of a trial in Li, Eisenstein et al's (2007) research. They estimated that the cost of a pediatric drug trial to comply with the exclusivity provisions ranged from $5-$43 million (median $12.5 million). Since, after patent expiry, generic product prices stabilize at about 30% of the brand-name product (Saha, Grabowski et al. 2006) we can conclude that at least a 70% net contribution margin exists. Under this assumption, to recover the median $12.5 million would require additional sales of merely $18 million in the 6 months. At first glance, our threshold of $260 mn appears to be very high, and might be interpreted as reluctance of firms to conduct pediatric exclusivity trials unless sales are already high. However since pediatric exclusivity applies at the end of the current patent protections, the additional provisions are being added on several years (in some cases over 10 years) in the future , the discounting required for future income is likely to explain a lot of this difference. A LEXIS-NEXIS and FDA.gov search for a representative sample of the drugs that had at least one year of annual sales over $300 mn but never obtained pediatric exclusivity showed either a) their patents had been invalidated or b) they had

reached a generic agreement due to lawsuits or c) their patents were being legally challenged or d) their current protections had not yet expired, and they still had the opportunity to gain pediatric exclusivity.

Prior research (Li, Eisenstein et al. 2007) has focused on potential returns on investment for the firms. It is not simple, however, to interpret a firm's returns on investment on pediatric trials from a regulatory policy perspective. A lower return on investment can be interpreted as a firm viewing pediatric exclusivity trials as a low-risk investment. With a lower threshold of sales required, more drugs might obtain exclusivity. This may be desirable from the objective of increasing pediatric trials but would increase total cost to the adult consumer, who does not benefit in any way from the tests. The quality of the information obtained from the clinical trials is the key to balancing this decision. Higher quality trials may involve higher risks (e.g. with larger number of patients, greater chance of something going wrong) and costs and the sponsoring firm might require a higher return on investment.

One of the outstanding issues regarding pediatric exclusivity is the actual cost to the consumer of the legislation. Since this cost is highly diffused and paid by no one consumer or group, there has been little focus on it. Using our data, we

can make a first estimate of the cost. If we accept the findings of Saha et al. (2006), the price of generics stabilizes at about 30% of the brand-name drug and at about 80% of the market within two years of entry. Six months delay in generic entry implies a premium of 28% of annual sales of the drug at the time of the extended exclusivity[14]. While this cannot be calculated easily for drugs with unknown future projected sales and prices, or brought to a net present value at different expiry times (and no doubt discount rates) from Table 7, we can see a figure of $76 billion in sales for drugs that obtained pediatric exclusivity in 2010. A very conservative the estimated excess bill to consumers is 28% of that, i.e. approximately US$ 21 billion in undiscounted dollars at current sales rates. This figure does not include growth in sales, nor does it include all the drugs that have been approved since then.

It is clear from our inability to find any support for hypotheses 2a and 2b, that the drugs being selected for pediatric exclusivity (with the exception of the ADHD outliers) are not those that have significant pediatric use, but rather have similar or lower pediatric use (see first set of comparisons in Table 20) than the general set of drugs.

[14] 80% market share * 70% price difference * 0.5 years = 28% of annual sales

The above findings are not at all consistent with Pigou's (1938) economic welfare idea that regulation is about maximizing social welfare, even if there is information asymmetry. Pediatric exclusivity has been renewed in 2002 and 2007, even after data has been collected on which drugs it has been obtained for, their sales, and the pediatric benefits. It is far more consistent with the idea that there has been regulatory capture by a small powerful group of brand-name drug manufacturers to extend their monopoly protections by erecting barriers to entry to generic competitors, with a diffuse set of consumers to shoulder the$ 21 bn cost. (Stigler 1971; Peltzman 1976; Dal Bó 2006)

Our study has several limitations. We only have partial data as to which drugs were studied at the initial request of the FDA and which were studied at the initial request of the firms. This would enable more precise information as to the motivation of the firms. We do not have data where the FDA has issued Written Requests and the responses to the Written Requests are pending. We have very limited data on the length of time firms spent responding and negotiating with the FDA on the studies to be conducted. These would serve to differentiate drugs into categories which could be studied separately. We have no data on future sales projection data of firms or their cost of capital which they would take into consideration in their cost-benefit calculations. Although a

paucity of researchers skilled in pediatric trials has been stated as a constraint (Caldwell, Murphy et al. 2004), we do not have any information as to how precisely this affects a single firm's decision to conduct trials for pediatric exclusivity.

Table 1 Data description

Variable	Mean	SD	Min	Max
Annual sales ($ million)	235.85	530.0	0	9,562.9
Annual prescriptions (millions)	2.63	5.80	0	84.61
Fraction of sales to minors (%)	8.34%	19.1%	0	1
Fraction of prescriptions to minors (%)	8.48%	19.1%	0	100%
Age of drug (years)	7.74	6.00	0	25
Time under pediatric exclusivity regime (years)	4.42	2.97	0	10

Table 2: Correlation matrix

	Annual sales ($ million)	Annual prescriptions (millions)	Fraction of sales to minors (%)	Fraction of prescriptions to minors (%)	Age of drug (years)
Annual prescriptions (millions)	0.8984				
Fraction of sales to minors (%)	-0.0619	-0.0608			
Fraction of prescriptions to minors (%)	-0.0603	-0.0577	0.9852		
Age of drug (years)	0.0436	0.0759	0.0338	0.0310	
Time under pediatric exclusivity regime (years)	0.1442	0.0916	0.0054	0.0071	0.5826

Table 3: Total sales of drugs with and without pediatric exclusivity

	Without pediatric exclusivity			After being granted pediatric exclusivity		
Year	**Total sales for drugs (minors) - USD millions** *(%)*	**Total sales of drugs (adults) – USD millions** *(%)*	**Total sales of drugs – USD millions** *(%)*	**Total sales of drugs (minors) - USD millions** *(%)*	**Total sales of drugs (adults) - USD millions** *(%)*	**Total sales of drugs – USD millions** *(%)*
1996	930.73	24,057.03	24,987.76	-	-	-
	3.72%	*96.28%*	*100.00%*			
1997	1,425.62	27,991.18	29,416.80	-	-	-
	4.85%	*95.15%*	*100.00%*			
1998	1,675.32	34,199.88	35,875.20	7.02	64.49	71.52
	4.67%	*95.33%*	*100.00%*	*9.82%*	*90.18%*	*100.00%*
1999	1,963.75	41,746.75	43,710.49	37.59	297.39	334.97
	4.49%	*95.51%*	*100.00%*	*11.22%*	*88.78%*	*100.00%*
2000	2,297.66	41,746.33	44,043.99	468.27	6,447.42	6,915.69
	5.22%	*94.78%*	*100.00%*	*6.77%*	*93.23%*	*100.00%*
2001	2,548.01	50,148.75	52,696.75	791.35	10,977.62	11,768.97
	4.84%	*95.16%*	*100.00%*	*6.72%*	*93.28%*	*100.00%*
2002	2,433.57	43,337.65	45,771.22	1,312.10	26,401.90	27,713.99
	5.32%	*94.68%*	*100.00%*	*4.73%*	*95.27%*	*100.00%*
2003	2,705.62	49,967.41	52,673.04	2,286.39	29,384.31	31,670.69
	5.14%	*94.86%*	*100.00%*	*7.22%*	*92.78%*	*100.00%*
2004	2,357.96	53,743.49	56,101.45	2,944.34	36,400.28	39,344.61
	4.20%	*95.80%*	*100.00%*	*7.48%*	*92.52%*	*100.00%*
2005	3,423.62	65,632.89	69,056.51	3,621.32	44,085.43	47,706.75
	4.96%	*95.04%*	*100.00%*	*7.59%*	*92.41%*	*100.00%*
2006	3,680.18	62,550.04	66,230.22	4,143.68	45,477.41	49,621.09
	5.56%	*94.44%*	*100.00%*	*8.35%*	*91.65%*	*100.00%*
2007	2,382.67	73,272.96	75,655.63	4,622.91	50,832.16	55,455.08
	3.15%	*96.85%*	*100.00%*	*8.34%*	*91.66%*	*100.00%*

Table 4: Mean sales of drugs with and without pediatric exclusivity

	Without pediatric exclusivity			After being granted pediatric exclusivity		
Year	Mean sales per drug (minors) - USD millions (%)	Mean sales per drug (adults) – USD millions (%)	Mean sales per drug – USD millions (%)	Mean sales per drug (minors) – USD millions (%)	Mean sales per drug (adults) – USD millions (%)	Mean sales per drug – USD millions (%)
1996	5.85	151.30	157.16	-	-	-
	3.72%	*96.28%*	*100.00%*			
1997	7.02	137.89	144.91	-	-	-
	4.85%	*95.15%*	*100.00%*			
1998	7.32	149.34	156.66	7.02	64.49	71.52
	4.67%	*95.33%*	*100.00%*	*9.82%*	*90.18%*	*100.00%*
1999	7.98	169.70	177.68	9.40	74.35	83.74
	4.49%	*95.51%*	*100.00%*	*11.22%*	*88.78%*	*100.00%*
2000	8.29	150.71	159.00	46.83	644.74	691.57
	5.22%	*94.78%*	*100.00%*	*6.77%*	*93.23%*	*100.00%*
2001	9.23	181.70	190.93	37.68	522.74	560.43
	4.84%	*95.16%*	*100.00%*	*6.72%*	*93.28%*	*100.00%*
2002	8.42	149.96	158.38	39.76	800.06	839.82
	5.32%	*94.68%*	*100.00%*	*4.73%*	*95.27%*	*100.00%*
2003	9.02	166.56	175.58	48.65	625.20	673.84
	5.14%	*94.86%*	*100.00%*	*7.22%*	*92.78%*	*100.00%*
2004	7.58	172.81	180.39	49.90	616.95	666.86
	4.20%	*95.80%*	*100.00%*	*7.48%*	*92.52%*	*100.00%*
2005	10.41	199.49	209.90	54.87	667.96	722.83
	4.96%	*95.04%*	*100.00%*	*7.59%*	*92.41%*	*100.00%*
2006	11.08	188.40	199.49	56.00	614.56	670.56
	5.56%	*94.44%*	*100.00%*	*8.35%*	*91.65%*	*100.00%*
2007	7.20	221.37	228.57	55.03	605.14	660.18
	3.15%	*96.85%*	*100.00%*	*8.34%*	*91.66%*	*100.00%*

Table 5: Total prescriptions of drugs with and without pediatric exclusivity

	Without pediatric exclusivity			After being granted pediatric exclusivity		
Year	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions
	(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	19.10	407.00	426.10	-	-	-
	4.48%	*95.52%*	*100.00%*			
1997	25.80	447.00	472.80	-	-	-
	5.46%	*94.54%*	*100.00%*			
1998	31.60	535.00	566.60	0.60	4.38	4.98
	5.58%	*94.42%*	*100.00%*	*12.01%*	*87.99%*	*100.00%*
1999	37.00	596.00	633.00	0.80	6.85	7.65
	5.85%	*94.15%*	*100.00%*	*10.44%*	*89.56%*	*100.00%*
2000	33.20	589.00	622.20	7.59	82.20	89.79
	5.34%	*94.66%*	*100.00%*	*8.45%*	*91.55%*	*100.00%*
2001	38.20	648.00	686.20	10.90	133.00	143.90
	5.57%	*94.43%*	*100.00%*	*7.57%*	*92.43%*	*100.00%*
2002	34.10	561.00	595.10	18.50	294.00	312.50
	5.73%	*94.27%*	*100.00%*	*5.92%*	*94.08%*	*100.00%*
2003	31.70	507.00	538.70	28.80	319.00	347.80
	5.88%	*94.12%*	*100.00%*	*8.28%*	*91.72%*	*100.00%*
2004	30.20	565.00	595.20	34.80	378.00	412.80
	5.07%	*94.93%*	*100.00%*	*8.43%*	*91.57%*	*100.00%*
2005	33.00	622.00	655.00	40.10	446.00	486.10
	5.04%	*94.96%*	*100.00%*	*8.25%*	*91.75%*	*100.00%*
2006	32.10	553.00	585.10	42.60	484.00	526.60
	5.49%	*94.51%*	*100.00%*	*8.09%*	*91.91%*	*100.00%*
2007	19.30	502.00	521.30	36.90	422.00	458.90
	3.70%	*96.30%*	*100.00%*	*8.04%*	*91.96%*	*100.00%*

Table 6: Mean prescriptions of drugs with and without pediatric exclusivity

	Without pediatric exclusivity			After being granted pediatric exclusivity		
Year	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug - millions	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug - millions
	(%)	(%)	(%)	(%)	(%)	(%)
1996	0.12	2.56	2.68	-	-	-
	4.47%	*95.53%*	*100.00%*			
1997	0.13	2.20	2.33	-	-	-
	5.47%	*94.53%*	*100.00%*			
1998	0.14	2.34	2.47	0.60	4.38	4.98
	5.59%	*94.41%*	*100.00%*	*12.01%*	*87.99%*	*100.00%*
1999	0.15	2.42	2.57	0.20	1.71	1.91
	5.84%	*94.16%*	*100.00%*	*10.44%*	*89.56%*	*100.00%*
2000	0.12	2.13	2.25	0.76	8.22	8.98
	5.33%	*94.67%*	*100.00%*	*8.45%*	*91.55%*	*100.00%*
2001	0.14	2.35	2.49	0.52	6.35	6.86
	5.57%	*94.43%*	*100.00%*	*7.53%*	*92.47%*	*100.00%*
2002	0.12	1.94	2.06	0.56	8.91	9.47
	5.73%	*94.27%*	*100.00%*	*5.92%*	*94.08%*	*100.00%*
2003	0.11	1.69	1.80	0.61	6.79	7.40
	5.87%	*94.13%*	*100.00%*	*8.27%*	*91.73%*	*100.00%*
2004	0.10	1.82	1.91	0.59	6.40	6.99
	5.08%	*94.92%*	*100.00%*	*8.45%*	*91.55%*	*100.00%*
2005	0.10	1.89	1.99	0.61	6.76	7.36
	5.04%	*94.96%*	*100.00%*	*8.24%*	*91.76%*	*100.00%*
2006	0.10	1.67	1.76	0.58	6.53	7.11
	5.49%	*94.51%*	*100.00%*	*8.09%*	*91.91%*	*100.00%*
2007	0.06	1.52	1.58	0.44	5.03	5.47
	3.70%	*96.30%*	*100.00%*	*8.03%*	*91.97%*	*100.00%*

Table 7: Total sales of drugs granted and never granted pediatric exclusivity (before 2010)

	No Pediatric exclusivity before 2010			Pediatric exclusivity before 2010		
Year	Total sales for drugs (minors) - USD millions	Total sales of drugs (adults) - millions	Total sales of drugs - millions	Total sales of drugs (minors) - USD millions	Total sales of drugs (adults) - millions	Total sales of drugs - millions
	(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	556.60	9,447.79	10,004.38	374.13	14,609.25	14,983.38
	5.56%	*94.44%*	*100.00%*	*2.50%*	*97.50%*	*100.00%*
1997	654.45	11,137.45	11,791.90	771.17	16,853.73	17,624.90
	5.55%	*94.45%*	*100.00%*	*4.38%*	*95.62%*	*100.00%*
1998	735.61	13,234.92	13,970.53	946.74	21,029.44	21,976.18
	5.27%	*94.73%*	*100.00%*	*4.31%*	*95.69%*	*100.00%*
1999	877.08	16,799.78	17,676.86	1,124.25	25,244.35	26,368.60
	4.96%	*95.04%*	*100.00%*	*4.26%*	*95.74%*	*100.00%*
2000	1,208.52	15,081.17	16,289.69	1,557.41	33,112.58	34,669.99
	7.42%	*92.58%*	*100.00%*	*4.49%*	*95.51%*	*100.00%*
2001	945.56	18,434.72	19,380.29	2,393.79	42,691.64	45,085.43
	4.88%	*95.12%*	*100.00%*	*5.31%*	*94.69%*	*100.00%*
2002	1,080.31	21,528.98	22,609.28	2,665.37	48,210.57	50,875.93
	4.78%	*95.22%*	*100.00%*	*5.24%*	*94.76%*	*100.00%*
2003	1,549.32	26,368.78	27,918.10	3,442.69	52,982.94	56,425.63
	5.55%	*94.45%*	*100.00%*	*6.10%*	*93.90%*	*100.00%*
2004	1,609.65	29,636.66	31,246.31	3,692.65	60,507.10	64,199.76
	5.15%	*94.85%*	*100.00%*	*5.75%*	*94.25%*	*100.00%*
2005	2,241.30	37,197.83	39,439.13	4,803.64	72,520.49	77,324.13
	5.68%	*94.32%*	*100.00%*	*6.21%*	*93.79%*	*100.00%*
2006	2,245.87	42,053.01	44,298.88	5,577.99	65,974.44	71,552.43
	5.07%	*94.93%*	*100.00%*	*7.80%*	*92.20%*	*100.00%*
2007	1,875.55	52,528.03	54,403.58	5,130.03	71,577.09	76,707.12
	3.45%	*96.55%*	*100.00%*	*6.69%*	*93.31%*	*100.00%*

Table 8 : Mean sales of drugs granted and never granted pediatric exclusivity (before 2010)

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Mean sales per drug (minors) - millions	Mean sales per drug (adults) – millions	Mean sales per drug - millions	Mean sales per drug (minors) - millions	Mean sales per drug (adults) - millions	Mean sales per drug - millions
	(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	5.01	85.12	90.13	7.79	304.36	312.15
	5.56%	*94.44%*	*100.00%*	*2.50%*	*97.50%*	*100.00%*
1997	4.51	76.81	81.32	13.30	290.58	303.88
	5.55%	*94.45%*	*100.00%*	*4.38%*	*95.62%*	*100.00%*
1998	4.51	81.20	85.71	14.13	313.87	328.00
	5.27%	*94.73%*	*100.00%*	*4.31%*	*95.69%*	*100.00%*
1999	4.93	94.38	99.31	15.61	350.62	366.23
	4.96%	*95.04%*	*100.00%*	*4.26%*	*95.74%*	*100.00%*
2000	5.98	74.66	80.64	18.32	389.56	407.88
	7.42%	*92.58%*	*100.00%*	*4.49%*	*95.51%*	*100.00%*
2001	4.57	89.06	93.62	26.60	474.35	500.95
	4.88%	*95.12%*	*100.00%*	*5.31%*	*94.69%*	*100.00%*
2002	4.74	94.43	99.16	28.35	512.88	541.23
	4.78%	*95.22%*	*100.00%*	*5.24%*	*94.76%*	*100.00%*
2003	6.32	107.63	113.95	33.75	519.44	553.19
	5.55%	*94.45%*	*100.00%*	*6.10%*	*93.90%*	*100.00%*
2004	6.10	112.26	118.36	34.84	570.82	605.66
	5.15%	*94.85%*	*100.00%*	*5.75%*	*94.25%*	*100.00%*
2005	7.76	128.71	136.47	45.32	684.16	729.47
	5.68%	*94.32%*	*100.00%*	*6.21%*	*93.79%*	*100.00%*
2006	7.44	139.25	146.69	53.63	634.37	688.00
	5.07%	*94.93%*	*100.00%*	*7.80%*	*92.20%*	*100.00%*
2007	6.01	168.36	174.37	49.81	694.92	744.73
	3.45%	*96.55%*	*100.00%*	*6.69%*	*93.31%*	*100.00%*

Table 9: Total prescriptions of drugs granted and never granted pediatric exclusivity (before 2010)

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions
(%)	(%)	(%)	(%)	(%)	(%)	(%)
1996	11.70	213.00	224.70	7.36	194.00	201.36
	5.21%	*94.79%*	*100.00%*	*3.65%*	*96.35%*	*100.00%*
1997	13.30	223.00	236.30	12.60	224.00	236.60
	5.63%	*94.37%*	*100.00%*	*5.33%*	*94.67%*	*100.00%*
1998	15.20	261.00	276.20	17.00	278.00	295.00
	5.50%	*94.50%*	*100.00%*	*5.76%*	*94.24%*	*100.00%*
1999	19.10	276.00	295.10	18.70	327.00	345.70
	6.47%	*93.53%*	*100.00%*	*5.41%*	*94.59%*	*100.00%*
2000	16.20	269.00	285.20	24.50	402.00	426.50
	5.68%	*94.32%*	*100.00%*	*5.74%*	*94.26%*	*100.00%*
2001	17.80	294.00	311.80	31.20	487.00	518.20
	5.71%	*94.29%*	*100.00%*	*6.02%*	*93.98%*	*100.00%*
2002	17.40	305.00	322.40	35.20	550.00	585.20
	5.40%	*94.60%*	*100.00%*	*6.02%*	*93.98%*	*100.00%*
2003	21.90	291.00	312.90	38.60	536.00	574.60
	7.00%	*93.00%*	*100.00%*	*6.72%*	*93.28%*	*100.00%*
2004	23.70	330.00	353.70	41.40	612.00	653.40
	6.70%	*93.30%*	*100.00%*	*6.34%*	*93.66%*	*100.00%*
2005	26.00	370.00	396.00	47.10	699.00	746.10
	6.57%	*93.43%*	*100.00%*	*6.31%*	*93.69%*	*100.00%*
2006	24.80	379.00	403.80	49.90	658.00	707.90
	6.14%	*93.86%*	*100.00%*	*7.05%*	*92.95%*	*100.00%*
2007	16.40	378.00	394.40	39.70	546.00	585.70
	4.16%	*95.84%*	*100.00%*	*6.78%*	*93.22%*	*100.00%*

Table 10: Mean prescriptions of drugs granted and never granted pediatric exclusivity (before 2010)

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug - millions	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug – millions
	(%)	(%)	(%)	(%)	(%)	(%)
1996	0.11	1.91	2.02	0.15	4.05	4.20
	5.22%	*94.78%*	*100.00%*	*3.64%*	*96.36%*	*100.00%*
1997	0.09	1.54	1.63	0.22	3.87	4.08
	5.63%	*94.37%*	*100.00%*	*5.31%*	*94.69%*	*100.00%*
1998	0.09	1.60	1.69	0.25	4.16	4.41
	5.52%	*94.48%*	*100.00%*	*5.76%*	*94.24%*	*100.00%*
1999	0.11	1.55	1.66	0.26	4.54	4.80
	6.48%	*93.52%*	*100.00%*	*5.40%*	*94.60%*	*100.00%*
2000	0.08	1.33	1.41	0.29	4.73	5.02
	5.69%	*94.31%*	*100.00%*	*5.75%*	*94.25%*	*100.00%*
2001	0.09	1.42	1.51	0.35	5.41	5.76
	5.72%	*94.28%*	*100.00%*	*6.02%*	*93.98%*	*100.00%*
2002	0.08	1.34	1.41	0.37	5.85	6.22
	5.39%	*94.61%*	*100.00%*	*6.02%*	*93.98%*	*100.00%*
2003	0.09	1.19	1.28	0.38	5.26	5.63
	6.99%	*93.01%*	*100.00%*	*6.72%*	*93.28%*	*100.00%*
2004	0.09	1.25	1.34	0.39	5.77	6.17
	6.69%	*93.31%*	*100.00%*	*6.33%*	*93.67%*	*100.00%*
2005	0.09	1.28	1.37	0.44	6.59	7.03
	6.57%	*93.43%*	*100.00%*	*6.32%*	*93.68%*	*100.00%*
2006	0.08	1.26	1.34	0.48	6.32	6.80
	6.15%	*93.85%*	*100.00%*	*7.05%*	*92.95%*	*100.00%*
2007	0.05	1.21	1.27	0.39	5.30	5.69
	4.17%	*95.83%*	*100.00%*	*6.78%*	*93.22%*	*100.00%*

Table 11: The three outliers – The ADHD trio of Adderall, Concerta and Strattat

Name	Adderall	Concerta	Strattera
Approval year	1996	2000	2002
Pediatric exclusivity granted	2004	2003	2001
Total sales to minors ($mn)	3,131.52	3,285.54	1,367.83
Fraction of sales to minors	67.4%	80.3%	67.9%
Total sales (1996-2007)	4,647.85	4,092.48	2,015.41
Mean annual sales to minors ($mn)	260.96	410.69	273.57
Mean annual sales	387.32	511.56	403.08
Total prescriptions to minors (mn)	42.70	33.30	12.60
Fraction of prescriptions to minors	71.6%	81.0%	67.4%
Total prescriptions (mn)	59.60	41.10	18.70
Mean annual prescriptions to minors	3.56	4.17	2.52
Mean annual prescriptions	4.96	5.14	3.74

Table 12: Sales of drugs with and without pediatric exclusivity excluding the ADHD Trio

	Without pediatric exclusivity			After obtaining pediatric exclusivity		
Year	Total sales for drugs (minors) - USD millions	Total sales of drugs (adult s) – USD millions	Total sales of drugs - millions	Total sales of drugs (minors) - USD millions	Total sales of drugs (adults) – USD millions	Total sales of drugs – USD millions
	(%)	(%)	(%)	(%)	(%)	(%)
1996	556.599	9447.785	10004.38	0	0	0
	5.56%	94.44%	100.00%			
1997	654.451	11137.45	11791.9	0	0	0
	5.55%	94.45%	100.00%			
1998	735.609	13234.92	13970.53	7.024	64.492	71.516
	5.27%	94.73%	100.00%	9.82%	90.18%	100.00%
1999	877.081	16799.78	17676.86	37.586	297.388	334.974
	4.96%	95.04%	100.00%	11.22%	88.78%	100.00%
2000	1208.522	15081.17	16289.69	468.27	6447.422	6915.692
	7.42%	92.58%	100.00%	6.77%	93.23%	100.00%
2001	945.563	18434.72	19380.29	791.346	10977.62	11768.97
	4.88%	95.12%	100.00%	6.72%	93.28%	100.00%
2002	1080.305	21528.98	22609.28	1312.097	26401.9	27713.99
	4.78%	95.22%	100.00%	4.73%	95.27%	100.00%
2003	1549.319	26368.78	27918.1	1739.572	29231.38	30970.95
	5.55%	94.45%	100.00%	5.62%	94.38%	100.00%
2004	1609.647	29636.66	31246.31	1771.84	35893.44	37665.28
	5.15%	94.85%	100.00%	4.70%	95.30%	100.00%
2005	2241.3	37197.83	39439.13	2371.252	43569.05	45940.3
	5.68%	94.32%	100.00%	5.16%	94.84%	100.00%
2006	2245.874	42053.01	44298.88	2734.467	44905.59	47640.06
	5.07%	94.93%	100.00%	5.74%	94.26%	100.00%
2007	1875.553	52528.03	54403.58	3053.445	50104.13	53157.58
	3.45%	96.55%	100.00%	5.74%	94.26%	100.00%

Table 13: Mean annual sales of drugs, with and without pediatric exclusivity, excluding the ADHD Trio

	Without pediatric exclusivity			After obtaining pediatric exclusivity		
Year	Mean sales per drug (minors) - USD millions	Mean sales per drug (adults) - USD millions	Mean sales per drug - USD millions	Mean sales per drug (minors) - USD millions	Mean sales per drug (adults) - USD millions	Mean sales per drug - USD millions
	(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	5.014405	85.11518	90.12959	0	0	0
	5.56%	*94.44%*	*100.00%*			
1997	4.513455	76.81001	81.32347	0	0	0
	5.55%	*94.45%*	*100.00%*			
1998	4.512939	81.19586	85.70879	7.024	64.492	71.516
	5.27%	*94.73%*	*100.00%*	*9.82%*	*90.18%*	*100.00%*
1999	4.927421	94.38081	99.30823	9.3965	74.347	83.7435
	4.96%	*95.04%*	*100.00%*	*11.22%*	*88.78%*	*100.00%*
2000	5.982782	74.65924	80.64202	46.827	644.7422	691.5692
	7.42%	*92.58%*	*100.00%*	*6.77%*	*93.23%*	*100.00%*
2001	4.567937	89.05663	93.62457	37.68314	522.7438	560.4269
	4.88%	*95.12%*	*100.00%*	*6.72%*	*93.28%*	*100.00%*
2002	4.73818	94.42534	99.16352	39.76052	800.0574	839.8179
	4.78%	*95.22%*	*100.00%*	*4.73%*	*95.27%*	*100.00%*
2003	6.323751	107.6277	113.9514	38.65716	649.5862	688.2433
	5.55%	*94.45%*	*100.00%*	*5.62%*	*94.38%*	*100.00%*
2004	6.097148	112.2601	118.3572	31.64	640.9544	672.5944
	5.15%	*94.85%*	*100.00%*	*4.70%*	*95.30%*	*100.00%*
2005	7.755363	128.7122	136.4676	37.63892	691.5722	729.2111
	5.68%	*94.32%*	*100.00%*	*5.16%*	*94.84%*	*100.00%*
2006	7.436669	139.2484	146.685	38.51362	632.4731	670.9867
	5.07%	*94.93%*	*100.00%*	*5.74%*	*94.26%*	*100.00%*
2007	6.011388	168.3591	174.3705	37.69685	618.5696	656.2664
	3.45%	*96.55%*	*100.00%*	*5.74%*	*94.26%*	*100.00%*

Table 14 : Total prescriptions with and without pediatric exclusivity excluding the ADHD Trio

Without pediatric exclusivity			After obtaining pediatric exclusivity		
Total prescript-tions (minors) - millions	**Total prescrip-tions (adults) - millions**	**Total prescrip-tions - millions**	**Total prescrip-tions (minors) - millions**	**Total prescrip-tions (adults) - millions**	**Total prescriptions – millions**
(%)	***(%)***	***(%)***	***(%)***	***(%)***	***(%)***
11.70	213.00	224.00	-	-	-
937.09%	*5.49%*	*100.00%*			
13.30	223.00	236.00	-	-	-
895.52%	*5.96%*	*100.00%*			
15.20	261.00	276.00	0.60	4.38	4.98
5.51%	*94.57%*	*100.00%*	*12.01%*	*87.99%*	*100.00%*
19.10	276.00	295.00	0.80	6.85	7.65
6.47%	*93.56%*	*100.00%*	*10.44%*	*89.56%*	*100.00%*
16.20	269.00	285.00	7.59	82.20	89.80
5.68%	*94.39%*	*100.00%*	*8.45%*	*91.54%*	*100.00%*
17.80	294.00	312.00	10.90	133.00	144.00
5.71%	*94.23%*	*100.00%*	*7.57%*	*92.36%*	*100.00%*
17.40	305.00	322.00	18.50	294.00	313.00
5.40%	*94.72%*	*100.00%*	*5.91%*	*93.93%*	*100.00%*
21.90	291.00	312.00	22.00	318.00	340.00
7.02%	*93.27%*	*100.00%*	*6.47%*	*93.53%*	*100.00%*
23.70	330.00	354.00	22.60	373.00	395.00
6.69%	*93.22%*	*100.00%*	*5.72%*	*94.43%*	*100.00%*
26.00	370.00	396.00	27.70	441.00	468.00
6.57%	*93.43%*	*100.00%*	*5.92%*	*94.23%*	*100.00%*
24.80	379.00	404.00	29.40	477.00	506.00
6.14%	*93.81%*	*100.00%*	*5.81%*	*94.27%*	*100.00%*
16.40	378.00	395.00	24.00	416.00	440.00
4.15%	*95.70%*	*100.00%*	*5.45%*	*94.55%*	*100.00%*

Table 15: Mean annual prescriptions with and without pediatric exclusivity excluding the ADHD Trio

	Without pediatric exclusivity			After obtaining pediatric exclusivity		
Year	Mean prescrip-tions per drug (minors) – millions	Mean prescrip-tions per drug (adults) - millions	Mean prescrip-tions per drug - millions	Mean prescrip -tions per drug (minors) - millions	Mean prescrip-tions per drug (adults) - millions	Mean prescrip-tions per drug - millions
	(%)	(%)	(%)	(%)	(%)	(%)
1996	0.11	1.91	2.02	-	-	-
	5.22%	*94.78%*	*100.00%*			
1997	0.09	1.54	1.63	-	-	-
	5.63%	*94.37%*	*100.00%*			
1998	0.09	1.60	1.69	0.60	4.38	4.98
	5.52%	*94.48%*	*100.00%*	*12.01%*	*87.99%*	*100.00%*
1999	0.11	1.55	1.66	0.20	1.71	1.91
	6.48%	*93.52%*	*100.00%*	*10.44%*	*89.56%*	*100.00%*
2000	0.08	1.33	1.41	0.76	8.22	8.98
	5.69%	*94.31%*	*100.00%*	*8.45%*	*91.55%*	*100.00%*
2001	0.09	1.42	1.51	0.52	6.35	6.86
	5.72%	*94.28%*	*100.00%*	*7.53%*	*92.47%*	*100.00%*
2002	0.08	1.34	1.41	0.56	8.91	9.47
	5.39%	*94.61%*	*100.00%*	*5.92%*	*94.08%*	*100.00%*
2003	0.09	1.19	1.28	0.49	7.06	7.55
	6.99%	*93.01%*	*100.00%*	*6.48%*	*93.52%*	*100.00%*
2004	0.09	1.25	1.34	0.40	6.65	7.06
	6.69%	*93.31%*	*100.00%*	*5.73%*	*94.27%*	*100.00%*
2005	0.09	1.28	1.37	0.44	6.99	7.43
	6.57%	*93.43%*	*100.00%*	*5.91%*	*94.09%*	*100.00%*
2006	0.08	1.26	1.34	0.41	6.72	7.13
	6.15%	*93.85%*	*100.00%*	*5.80%*	*94.20%*	*100.00%*
2007	0.05	1.21	1.27	0.30	5.14	5.43
	4.17%	*95.83%*	*100.00%*	*5.46%*	*94.54%*	*100.00%*

Table 16: Total sales of drugs granted and never granted pediatric exclusivity (before 2010) excluding the ADHD Trio

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Total sales for drugs (minors) - USD millions	Total sales of drugs (adults) - millions	Total sales of drugs - millions	Total sales of drugs (minors) - USD millions	Total sales of drugs (adults) - millions	Total sales of drugs - millions
	(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	556.60	9,447.79	10,004.38	372.17	14,609.25	14,981.42
	5.56%	*94.44%*	*100.00%*	*2.48%*	*97.52%*	*100.00%*
1997	653.68	11,137.05	11,790.72	745.88	16,850.55	17,596.42
	5.54%	*94.46%*	*100.00%*	*4.24%*	*95.76%*	*100.00%*
1998	735.61	13,234.92	13,970.53	886.33	21,024.64	21,910.97
	5.27%	*94.73%*	*100.00%*	*4.05%*	*95.95%*	*100.00%*
1999	861.55	16,799.19	17,660.74	1,008.02	25,225.22	26,233.24
	4.88%	*95.12%*	*100.00%*	*3.84%*	*96.16%*	*100.00%*
2000	1,190.33	15,075.59	16,265.92	1,353.18	33,066.47	34,419.66
	7.32%	*92.68%*	*100.00%*	*3.93%*	*96.07%*	*100.00%*
2001	928.18	18,434.72	19,362.91	1,856.45	42,578.04	44,434.49
	4.79%	*95.21%*	*100.00%*	*4.18%*	*95.82%*	*100.00%*
2002	1,080.31	21,528.98	22,609.28	2,033.50	48,031.03	50,064.53
	4.78%	*95.22%*	*100.00%*	*4.06%*	*95.94%*	*100.00%*
2003	1,549.32	26,368.78	27,918.10	2,636.37	52,700.39	55,336.75
	5.55%	*94.45%*	*100.00%*	*4.76%*	*95.24%*	*100.00%*
2004	1,609.65	29,636.66	31,246.31	2,520.16	60,000.27	62,520.43
	5.15%	*94.85%*	*100.00%*	*4.03%*	*95.97%*	*100.00%*
2005	2,241.30	37,197.83	39,439.13	3,553.57	72,004.11	75,557.68
	5.68%	*94.32%*	*100.00%*	*4.70%*	*95.30%*	*100.00%*
2006	2,245.87	42,053.01	44,298.88	4,168.77	65,402.62	69,571.39
	5.07%	*94.93%*	*100.00%*	*5.99%*	*94.01%*	*100.00%*
2007	1,875.55	52,528.03	54,403.58	3,560.56	70,849.06	74,409.63
	3.45%	*96.55%*	*100.00%*	*4.79%*	*95.21%*	*100.00%*

Table 17 : Mean sales of drugs granted and never granted pediatric exclusivity (before 2010) excluding the ADHD Trio

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Mean sales per drug (minors) - millions	Mean sales per drug (adults) – millions	Mean sales per drug - millions	Mean sales per drug (minors) - millions	Mean sales per drug (adult s) - millions	Mean sales per drug - millions
(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	5.01	85.12	90.13	7.92	310.84	318.75
	5.56%	*94.44%*	*100.00%*	*2.48%*	*97.52%*	*100.00%*
1997	4.57	77.88	82.45	13.32	300.90	314.22
	5.54%	*94.46%*	*100.00%*	*4.24%*	*95.76%*	*100.00%*
1998	4.51	81.20	85.71	13.43	318.56	331.98
	5.27%	*94.73%*	*100.00%*	*4.05%*	*95.95%*	*100.00%*
1999	4.87	94.91	99.78	14.20	355.28	369.48
	4.88%	*95.12%*	*100.00%*	*3.84%*	*96.16%*	*100.00%*
2000	5.92	75.00	80.92	16.30	398.39	414.69
	7.32%	*92.68%*	*100.00%*	*3.93%*	*96.07%*	*100.00%*
2001	4.51	89.49	93.99	21.10	483.84	504.94
	4.79%	*95.21%*	*100.00%*	*4.18%*	*95.82%*	*100.00%*
2002	4.74	94.43	99.16	22.10	522.08	544.18
	4.78%	*95.22%*	*100.00%*	*4.06%*	*95.94%*	*100.00%*
2003	6.32	107.63	113.95	26.63	532.33	558.96
	5.55%	*94.45%*	*100.00%*	*4.76%*	*95.24%*	*100.00%*
2004	6.10	112.26	118.36	24.47	582.53	606.99
	5.15%	*94.85%*	*100.00%*	*4.03%*	*95.97%*	*100.00%*
2005	7.76	128.71	136.47	34.50	699.07	733.57
	5.68%	*94.32%*	*100.00%*	*4.70%*	*95.30%*	*100.00%*
2006	7.44	139.25	146.69	41.27	647.55	688.83
	5.07%	*94.93%*	*100.00%*	*5.99%*	*94.01%*	*100.00%*
2007	6.01	168.36	174.37	35.61	708.49	744.10
	3.45%	*96.55%*	*100.00%*	*4.79%*	*95.21%*	*100.00%*
1996	5.01	85.12	90.13	7.92	310.84	318.75

Table 18: Total prescriptions of drugs granted and never granted pediatric exclusivity (before 2010) excluding the ADHD Trio

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions	Total prescriptions (minors) - millions	Total prescriptions (adults) - millions	Total prescriptions - millions
(%)	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
1996	11.71	212.54	224.24	7.28	194.47	201.74
	5.22%	*94.78%*	*100.00%*	*3.61%*	*96.39%*	*100.00%*
1997	13.25	222.58	235.82	11.77	224.11	235.88
	5.62%	*94.38%*	*100.00%*	*4.99%*	*95.01%*	*100.00%*
1998	15.24	260.77	276.01	14.75	278.26	293.01
	5.52%	*94.48%*	*100.00%*	*5.03%*	*94.97%*	*100.00%*
1999	18.64	276.02	294.66	15.23	326.70	341.93
	6.33%	*93.67%*	*100.00%*	*4.45%*	*95.55%*	*100.00%*
2000	15.76	269.03	284.79	19.31	401.31	420.62
	5.53%	*94.47%*	*100.00%*	*4.59%*	*95.41%*	*100.00%*
2001	17.30	294.10	311.40	23.39	485.21	508.60
	5.55%	*94.45%*	*100.00%*	*4.60%*	*95.40%*	*100.00%*
2002	17.37	304.97	322.33	26.82	547.58	574.40
	5.39%	*94.61%*	*100.00%*	*4.67%*	*95.33%*	*100.00%*
2003	21.85	290.59	312.45	28.58	533.34	561.91
	6.99%	*93.01%*	*100.00%*	*5.09%*	*94.91%*	*100.00%*
2004	23.68	330.35	354.03	29.18	607.17	636.35
	6.69%	*93.31%*	*100.00%*	*4.59%*	*95.41%*	*100.00%*
2005	25.98	369.55	395.52	34.75	693.34	728.09
	6.57%	*93.43%*	*100.00%*	*4.77%*	*95.23%*	*100.00%*
2006	24.84	379.07	403.91	36.67	651.30	687.96
	6.15%	*93.85%*	*100.00%*	*5.33%*	*94.67%*	*100.00%*
2007	16.45	378.42	394.87	26.87	539.96	566.83
	4.17%	*95.83%*	*100.00%*	*4.74%*	*95.26%*	*100.00%*

Table 19: Mean prescriptions of drugs granted and never granted pediatric exclusivity (before 2010) excluding the ADHD Trio

	Pediatric exclusivity not obtained before 2010			Pediatric exclusivity obtained before 2010		
Year	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug - millions	Mean prescriptions per drug (minors) - millions	Mean prescriptions per drug (adults) - millions	Mean prescriptions per drug – millions
1996	0.11	1.91	2.02	0.15	4.14	4.29
	5.22%	*94.78%*	*100.00%*	*3.61%*	*96.39%*	*100.00%*
1997	0.09	1.56	1.65	0.21	4.00	4.21
	5.62%	*94.38%*	*100.00%*	*4.99%*	*95.01%*	*100.00%*
1998	0.09	1.60	1.69	0.22	4.22	4.44
	5.52%	*94.48%*	*100.00%*	*5.03%*	*94.97%*	*100.00%*
1999	0.11	1.56	1.66	0.21	4.60	4.82
	6.33%	*93.67%*	*100.00%*	*4.45%*	*95.55%*	*100.00%*
2000	0.08	1.34	1.42	0.23	4.84	5.07
	5.53%	*94.47%*	*100.00%*	*4.59%*	*95.41%*	*100.00%*
2001	0.08	1.43	1.51	0.27	5.51	5.78
	5.55%	*94.45%*	*100.00%*	*4.60%*	*95.40%*	*100.00%*
2002	0.08	1.34	1.41	0.29	5.95	6.24
	5.39%	*94.61%*	*100.00%*	*4.67%*	*95.33%*	*100.00%*
2003	0.09	1.19	1.28	0.29	5.39	5.68
	6.99%	*93.01%*	*100.00%*	*5.09%*	*94.91%*	*100.00%*
2004	0.09	1.25	1.34	0.28	5.89	6.18
	6.69%	*93.31%*	*100.00%*	*4.59%*	*95.41%*	*100.00%*
2005	0.09	1.28	1.37	0.34	6.73	7.07
	6.57%	*93.43%*	*100.00%*	*4.77%*	*95.23%*	*100.00%*
2006	0.08	1.26	1.34	0.36	6.45	6.81
	6.15%	*93.85%*	*100.00%*	*5.33%*	*94.67%*	*100.00%*
2007	0.05	1.21	1.27	0.27	5.40	5.67
	4.17%	*95.83%*	*100.00%*	*4.74%*	*95.26%*	*100.00%*
1996	0.11	1.91	2.02	0.15	4.14	4.29

Table 20: Annual Sales percentiles used in regressions (excluding ADHD trio)

Percentile	$ mn
0	0
10	3.28
20	9.31
30	19.17
40	33.38
50	53.96
60	88.52
70	146.60
80	261.09
90+	619.91

Table 21: Factors that affect drugs ever obtaining pediatric exclusivity

	(21.1)	(21.2)	(21.3)	(21.4)
Dependent variable: Pediatric exclusivity obtained before 2010 (1/0)				
Fraction of prescriptions to minors		-0.119		-0.197
		(0.816)		(3.319)
Fraction of total sales to minors			-0.108	0.078
			(0.794)	(3.229)
10% < Annual sales percentile < 25%	0.342	0.341	0.340	0.341
	(0.537)	(0.537)	(0.538)	(0.538)
25% < Annual sales percentile < 30%	0.571	0.567	0.567	0.567
	(0.555)	(0.556)	(0.556)	(0.556)
30% < Annual sales percentile < 40%	0.861	0.857	0.858	0.857
	(0.553)	(0.553)	(0.553)	(0.553)
40% < Annual sales percentile<50%	**1.237***	**1.232***	**1.232***	**1.232***
	(0.556)	(0.557)	(0.557)	(0.557)
50% < Annual sales percentile < 60%	**1.501****	**1.495****	**1.496****	**1.495****
	(0.552)	(0.553)	(0.553)	(0.553)
60 %< Annual sales percentile < 70%	**1.689****	**1.682****	**1.683****	**1.683****
	(0.558)	(0.559)	(0.560)	(0.560)
70% < Annual sales percentile < 80%	**2.374****	**2.367****	**2.368****	**2.368****
	(0.565)	(0.567)	(0.567)	(0.567)
80% < Annual sales percentile<90%	**3.106****	**3.100****	**3.100****	**3.100****
	(0.577)	(0.579)	(0.579)	(0.579)
Annual sales percentile>90%	**4.595****	**4.587****	**4.587****	**4.587****
	(0.655)	(0.658)	(0.658)	(0.658)
Constant	-4.373**	-4.361**	-4.362**	-4.361**
	(0.607)	(0.612)	(0.612)	(0.612)
Observations	3656	3654	3654	3654
Number of Drugs	517	517	517	517

All regressions include year fixed effects
Standard errors in parentheses
* significant at 5%; ** significant at 1%

Table 22: Factors affecting obtaining pediatric exclusivity

	(22.1)	(22.2)	(22.3)	(22.4)	(22.5)	(22.6)	(22.7)
Dependent variable :	**Pediatric exclusivity granted (1/0)**						
Fraction of prescriptions to minors		0.444	0.461	0.461	0.542	0.549	0.529
		(0.793)	(0.797)	(0.797)	(0.812)	(0.815)	(0.815)
Age of drug			**0.114****	**0.114****	0.026		0.027
			(0.028)	**(0.028)**	(0.042)		(0.043)
Time under pediatric exclusivity regime					**0.253****	**0.297****	**0.252****
					(0.090)	**(0.059)**	**(0.090)**
Time to expiry of exclusivity protections						0.004	0.007
						(0.033)	(0.034)
10% < Annual sales percentile < 20%	0.808	0.809	0.834	0.834	0.809	0.801	0.806
	(0.629)	(0.634)	(0.633)	(0.633)	(0.638)	(0.638)	(0.637)
20% < Annual sales percentile < 30%	0.111	0.129	0.070	0.070	0.043	0.041	0.043
	(0.695)	(0.702)	(0.711)	(0.711)	(0.716)	(0.716)	(0.716)
30% < Annual sales percentile < 40%	**1.478***	**1.495***	**1.469***	**1.469***	**1.457***	**1.456***	**1.454***
	(0.626)	(0.630)	(0.633)	(0.633)	(0.638)	(0.639)	(0.638)
40% < Annual sales percentile<50%	**1.335***	**1.358***	**1.347***	**1.347***	**1.299***	**1.290***	**1.296***
	(0.628)	(0.635)	(0.636)	(0.636)	(0.640)	(0.640)	(0.640)
50% < Annual sales percentile < 60%	**1.509***	**1.534***	**1.484***	**1.484***	**1.417***	**1.404***	**1.410***
	(0.623)	(0.629)	(0.632)	(0.632)	(0.635)	(0.636)	(0.636)
60 %< Annual sales percentile < 70%	**1.604***	**1.638***	**1.631***	**1.631***	**1.568***	**1.552***	**1.560***
	(0.646)	(0.653)	(0.653)	(0.653)	(0.659)	(0.660)	(0.660)
70% < Annual sales percentile < 80%	**1.986****	**2.021****	**1.926****	**1.926****	**1.881****	**1.875****	**1.872****
	(0.626)	(0.631)	(0.635)	(0.635)	(0.640)	(0.641)	(0.641)
80% < Annual sales percentile<90%	**2.860****	**2.902****	**2.885****	**2.885****	**2.852****	**2.835****	**2.841****
	(0.605)	(0.611)	(0.612)	(0.612)	(0.616)	(0.618)	(0.618)
Annual sales percentile>90%	**4.179****	**4.230****	**4.311****	**4.311****	**4.318****	**4.296****	**4.309****
	(0.625)	(0.633)	(0.636)	(0.636)	(0.640)	(0.642)	(0.641)
Constant	-30.956	-31.006	-31.829	-31.829	-7.042**	-31.002	-31.253
	(9,465)	(9,390)	(9,843)	(9,843)	(0.744)	(9,813)	(9,993)
Observations	3656	3654	3654	3654	3654	3654	3654
Number of Drugs	517	517	517	517	517	517	517

All regressions include year fixed effects

Standard errors in parentheses

* significant at 5%; ** significant at 1%

Table 23: Factors affecting obtaining pediatric exclusivity

	(23.1)	(23.2)	(23.3)	(23.4)	(23.5)	(23.6)	(23.7)
Pediatric exclusivity granted (1/0)							
Fraction of sales to minors		0.506	0.529	0.529	0.594	0.599	0.583
		(0.764)	(0.768)	(0.768)	(0.782)	(0.785)	(0.784)
Age of drug			**0.114****	**0.114****	0.026		0.028
			(0.028)	(0.028)	(0.042)		(0.043)
Time under ped. exclusivity regime					**0.253****	**0.297****	**0.252****
					(0.090)	(0.059)	(0.090)
Time to expiry of current protections						0.004	0.007
						(0.033)	(0.034)
10% < Annual sales percentile < 20%	0.808	0.813	0.838	0.838	0.813	0.805	0.810
	(0.629)	(0.634)	(0.634)	(0.634)	(0.638)	(0.639)	(0.638)
20% < Annual sales percentile < 30%	0.111	0.129	0.069	0.069	0.039	0.038	0.040
	(0.695)	(0.702)	(0.711)	(0.711)	(0.716)	(0.716)	(0.716)
30% < Annual sales percentile < 40%	**1.478***	**1.495***	**1.469***	**1.469***	**1.457***	**1.455***	**1.454***
	(0.626)	(0.631)	(0.634)	(0.634)	(0.639)	(0.639)	(0.639)
40% < Annual sales percentile<50%	**1.335***	**1.362***	**1.351***	**1.351***	**1.302***	**1.293***	**1.299***
	(0.628)	(0.635)	(0.637)	(0.637)	(0.640)	(0.640)	(0.640)
50% < Annual sales percentile < 60%	**1.509***	**1.536***	**1.486***	**1.486***	**1.418***	**1.405***	**1.412***
	(0.623)	(0.629)	(0.632)	(0.632)	(0.635)	(0.636)	(0.636)
60 %< Annual sales percentile < 70%	**1.604***	**1.645***	**1.639***	**1.639***	**1.576***	**1.560***	**1.568***
	(0.646)	(0.653)	(0.654)	(0.654)	(0.659)	(0.661)	(0.660)
70% < Annual sales percentile < 80%	**1.986****	**2.027****	**1.931****	**1.931****	**1.886****	**1.880****	**1.878****
	(0.626)	(0.632)	(0.635)	(0.635)	(0.640)	(0.641)	(0.641)
80% < Annual sales percentile<90%	**2.860****	**2.907****	**2.891****	**2.891****	**2.856****	**2.840****	**2.846****
	(0.605)	(0.612)	(0.612)	(0.612)	(0.616)	(0.618)	(0.618)
Annual sales percentile>90%	**4.179****	**4.235****	**4.317****	**4.317****	**4.323****	**4.302****	**4.315****
	(0.625)	(0.633)	(0.636)	(0.636)	(0.641)	(0.642)	(0.641)
Constant	-30.956	-31.014	-31.840	-31.840	-7.051**	-31.005	-31.259
	(9,465)	(9,415)	(9,846)	(9,846)	(0.743)	(9,817)	(10,00)
Observations	3656	3654	3654	3654	3654	3654	3654
Number of Drugs	517	517	517	517	517	517	517

All regressions include year fixed effects

Standard errors in parentheses

* significant at 5%; ** significant at 1%

Table 24: Factors affecting the timing of obtaining pediatric exclusivity

	(24.1)	(24.2)	(24.3)	(24.4)	(24.5)	(24.6)
Dependent Variable	**Pediatric exclusivity granted during year**					
Fraction of prescriptions to minors		-0.476	-0.503	-0.488	-0.552	-0.555
		(0.929)	(0.934)	(0.933)	(0.945)	(0.945)
Age of drug			0.014	0.007	0.008	0.008
			(0.021)	(0.029)	(0.029)	(0.029)
Time under pediatric exclusivity regime				0.027	0.031	0.031
				(0.072)	(0.073)	(0.073)
Time to expiry of exclusivity protections					0.013	0.012
					(0.025)	(0.026)
10% < Annual sales percentile < 20%	0.926	0.903	0.908	0.904	0.895	0.903
	(0.842)	(0.842)	(0.842)	(0.842)	(0.843)	(0.843)
20% < Annual sales percentile < 30%	-17.081	-17.105	-17.090	-17.092	-18.213	-18.205
	(3,590)	(3,588)	(3,588)	(3,587)	(6,295)	(6,296)
30% < Annual sales percentile < 40%	0.681	0.649	0.650	0.647	0.658	0.669
	(0.871)	(0.872)	(0.872)	(0.872)	(0.872)	(0.873)
40% < Annual sales percentile<50%	0.941	0.904	0.902	0.895	0.900	0.913
	(0.842)	(0.843)	(0.843)	(0.844)	(0.844)	(0.844)
50% < Annual sales percentile < 60%	1.245	1.204	1.202	1.190	1.181	1.199
	(0.807)	(0.809)	(0.809)	(0.810)	(0.810)	(0.811)
60 %< Annual sales percentile < 70%	0.446	0.409	0.407	0.397	0.380	0.410
	(0.918)	(0.919)	(0.919)	(0.920)	(0.920)	(0.923)
70% < Annual sales percentile < 80%	1.234	1.192	1.180	1.173	1.157	1.184
	(0.823)	(0.824)	(0.824)	(0.825)	(0.825)	(0.827)
80% < Annual sales percentile<90%	**2.362****	**2.319****	**2.321****	**2.300****	**2.271****	**2.297****
	(0.752)	(0.754)	(0.754)	(0.756)	(0.758)	(0.760)
Annual sales percentile>90%	**3.015****	**2.964****	**2.969****	**2.954****	**2.916****	**2.942****
	(0.739)	(0.742)	(0.742)	(0.743)	(0.746)	(0.749)
Constant	-24.425	-24.360	-24.435	-5.113**	-25.691	-25.677
	(7,089)	(7,090)	(7,096)	(0.860)	(13,913)	(13,914)
Observations	3,350	3,348	3,348	3,348	3,348	3,348
Number of Pharmaceuticals	511	511	511	511	511	511

All regressions include Year Fixed effects

Standard errors in parentheses

* significant at 5%; ** significant at 1%

N.B. Once pediatric exclusivity is obtained, drug exits data used for above reressions.

Table 25: Survival-time piecewise-constant hazard rate regressions (Failure =granting of pediatric exclusivity)

	(28.1)	**(28.2)**	**(28.3)**	**(28.4)**
Fraction of prescriptions to minors		-0.649	-0.552	-0.722
		(0.972)	(0.961)	(0.983)
Age of Drug			-0.045	-0.042
			(0.030)	(0.030)
Time to expiry of exclusivity protections				0.031
				(0.025)
10% < Annual sales percentile < 20%	1.701	1.673	1.637	1.624
	(1.55)	(1.096)	(1.096)	(1.096)
20% < Annual sales percentile < 30%	-14.183	-14.207	-14.241	-14.233
	(0.01)	(1,353)	(1,351)	(1,355)
30% < Annual sales percentile < 40%	1.571	1.535	1.504	1.539
	(1.40)	(1.119)	(1.119)	(1.119)
40% < Annual sales percentile<50%	1.739	1.690	1.665	1.668
	(1.59)	(1.097)	(1.097)	(1.097)
50% < Annual sales percentile < 60%	1.882	1.831	1.784	1.743
	(1.74)	(1.081)	(1.082)	(1.082)
60 %< Annual sales percentile < 70%	1.225	1.187	1.145	1.084
	(1.06)	(1.156)	(1.156)	(1.157)
70% < Annual sales percentile < 80%	1.968	1.922	1.892	1.839
	(1.82)	(1.081)	(1.081)	(1.082)
80% < Annual sales percentile<90%	**3.020****	**2.970****	**2.873****	**2.787****
	(1.028)	(1.029)	(1.030)	(1.032)
Annual sales percentile>90%	**3.542****	**3.482****	**3.404****	**3.288****
	(1.018)	(1.019)	(1.020)	(1.024)
Observations	5538	5534	5534	5534

All regressions include year fixed effects
Standard errors in parentheses
* significant at 5%; ** significant at 1%

Table 26 : Survival-time piecewise-constant hazard rate regressions (Failure = granting of pediatric exclusivity)

Survival-time piecewise regressions (failure = granting of pediatric exclusivity)

	(29.1)	(29.2)	(29.3)	(29.4)
Fraction of sales to minors		-0.576	-0.487	-0.638
		(0.976)	(0.965)	(0.984)
Age of Drug			-0.045	-0.043
			(0.030)	(0.030)
Time to expiry of exclusivity protections				0.030
				(0.025)
10% < Annual sales percentile < 20%	1.701	1.675	1.638	1.624
	(1.096)	(1.096)	(1.096)	(1.096)
20% < Annual sales percentile < 30%	-14.183	-14.203	-14.238	-14.231
	(1,356)	(1,355)	(1,352)	(1,356)
30% < Annual sales percentile < 40%	1.571	1.538	1.505	1.538
	(1.119)	(1.119)	(1.119)	(1.119)
40% < Annual sales percentile<50%	1.739	1.694	1.668	1.670
	(1.096)	(1.097)	(1.097)	(1.097)
50% < Annual sales percentile < 60%	1.882	1.836	1.788	1.747
	(1.081)	(1.081)	(1.082)	(1.082)
60 %< Annual sales percentile < 70%	1.225	1.189	1.147	1.086
	(1.156)	(1.156)	(1.156)	(1.157)
70% < Annual sales percentile < 80%	1.968	1.925	1.894	1.842
	(1.081)	(1.081)	(1.082)	(1.082)
80% < Annual sales percentile<90%	**3.020****	**2.973****	**2.875****	**2.790****
	(1.028)	(1.029)	(1.030)	(1.033)
Annual sales percentile>90%	**3.542****	**3.487****	**3.407****	**3.292****
	(1.018)	(1.019)	(1.020)	(1.024)
Observations	5538	5534	5534	5534

All regressions include year fixed effects

Standard errors in parentheses

* significant at 5%; ** significant at 1%

Chapter 4: Pediatric Exclusivity - Are the intended benefits being realized?

Abstract

The pediatric exclusivity rule is intended to provide benefits to pediatric patients by providing clinicians with label information regarding safety and dosage in pediatric populations. We test whether valuable and important information is being produced and disseminated by the clinical trials that are undertaken to gain pediatric exclusivity. We do this by examining the patterns of publication of clinical trials before and after pediatric exclusivity is obtained and by examining the patterns of prescriptions to minor patients before and after pediatric exclusivity is obtained.

We find no evidence of greater dissemination of pediatric information in the peer-reviewed literature after obtaining pediatric exclusivity. We also find no evidence of changing patterns of prescriptions to minor patients before and after pediatric exclusivity is obtained. This leads us to question the value of the information being provided and conclude that the intended benefits of pediatric exclusivity provision are not being realized. We conclude that pediatric exclusivity legislation is an example of regulatory capture, designed primarily to increase monopoly protection of the sales of brand-name drugs without producing many tangible benefits.

Introduction

In the previous chapter, we estimated the cost of the pediatric exclusivity questions at over US$ 21 billion in current undiscounted dollars. In this chapter we examine whether the intended benefits provided by the legislation are indeed being realized.

In the analyses conducted in the prior chapter, we found evidence to suggest that the likelihood of pharmaceutical companies conducting pediatric exclusivity tests is strongly correlated to the sales of the drugs. Further, we also found that the proportion of prescriptions to minors did not appear to be a factor in obtaining pediatric exclusivity. [15] These factors affecting selection of drugs supports Boots et al.'s (2007) findings that the majority of drugs granted pediatric exclusivity are those that treat central nervous system, cardiovascular, alimentary and metabolism disorders, which are relatively rarely used by children. Boots et al. found that drug categories frequently used by children, such as respiratory drugs, anti-infectives for systemic use and dermatologicals

[15] The possible exceptions to this being the ADHD trio of outliers- Adderall, Concerta and Strattera (over 50% of prescriptions to minors) which were excluded from our analyses.

are underrepresented in the pediatric trial data. However, it should be noted that in the previous chapter, on average, we found no significant difference between the ratios of drugs prescribed to children for drugs with and without pediatric exclusivity. Drugs with pediatric exclusivity had higher sales and a higher number of prescriptions. Therefore, drugs with overall higher prescriptions were prescribed to children at a higher volume (if not a higher rate), and the information provided due to tests on pediatric exclusivity is therefore applicable to a larger number of prescriptions. This can clearly be classified as an intended benefit of the legislation. Nevertheless, we concluded at the end of the last chapter, that pediatric exclusivity appears to show all the symptoms of Stigler's (1971) theory of regulatory capture. It provides large transfers (up to a few billions of dollars in sales per drug, and presumably large profits) from diffuse consumers to a small number of producers, at the relatively small cost of clinical trials (tens of millions of dollars) (Li, Eisenstein et al. 2007).

This chapter is comprised of four parts. In the first part, we develop our theory and hypotheses regarding regulatory capture and the benefits of pediatric exclusivity regulations In the second part we describe our data and the methods used to test our hypotheses. In the third part we present our findings. Finally, we

discuss our results and present our conclusions and suggestions for future research.

Theory

The FDA is one of the most powerful market regulators with sweeping powers to deny or permit sales of all drugs in the US, as well as grant extensions of market exclusivities (Carpenter 2010) . The FDA must answer,however to many audiences including the US Congress which passes legislation changing its powers and controls its budget (Kim 2007). Pediatric exclusivity is one such provision created by US Congress in 1997 and renewed in 2002 and 2007. (21 U.S.C. 365 bb(a)(2)).

The FDA's role as regulator (and Congress's as legislator) is theoretically one of maximizing social welfare (Pigou 1938; McCraw 1975). the institutions that regulate the market are viewed as Bayesian statisticians, optimizing welfare, frequently under incomplete information conditions (Laffont and Tirole 1986).

Political theories of regulation differ from this account, arguing that is in the interest of all groups to attempt to influence regulation for their benefit. Olson's (1965) logic of collective action where incentives to organize are higher for small groups with high stakes that are spread among fewer actors, was used

by Stigler (1971) to develop the idea that an industry with few producers would be able to influence actors more than widely disbursed consumer groups. Peltzman (1976) accounted for the fact that the United States Congress occasionally passes laws that hurt large businesses and reduce protectionism by developing a model that balanced interest group support and voter group support to legislators, who require both money and votes to win re-election. Laffont and Tirole (1991) developed an agency-theoretic model of regulatory capture and argued that interest groups are more powerful when they seek to obtain inefficient regulation, where inefficiency is determined by the degree of information asymmetry between the regulated industry and the regulators.

Evidence for regulatory capture can be found in the legislation that Congress produces (and in the enforcement by the FDA) favoring one group over another, specifically favoring small financially powerful groups over diffuse groups (Peltzman 1976; Becker 1983). In Chapter 2, we identified reasons that pediatric exclusivity legislation was an example that showed capture of Congressional legislation by the brand-name pharmaceutical industry. First, unlike previous attempts to produce data on pediatric safety, it involved no requirements or demands upon the industry. Everything could be done at the pace of the firm, (other than the fact that some current exclusivity must exist) and at the option of the firm, except for labeling after the trials were complete.

Second, it provided incentives of a 6-month pediatric exclusivity, potentially worth billions (a blockbuster drug is an industry term for a drug with over $1bn in sales) against clinical trials that required outlays in the tens of millions. (Li, Eisenstein et al. 2007). Third, the transfers were coming from diffuse groups in the form of adults (getting no benefits from the trials) and children (who might be getting some benefits) who bought the drug and who had a 6-month delay in getting a lower-priced one. The calculations of cost-to-consumer are opaque and not easily appreciated by the individual.

While we calculate an undiscounted cost-to-consumer in excess of $21 billion, in order to decide if it is regulatory capture by the brand-name pharmaceutical industry, if the Peltzman (1976) balance that the legislators have to accomplish between finance and votes is firmly tilted towards the small financially powerful group, we need to ask whether we can quantify any tangible benefits that might be weighed against the cost to adult and pediatric consumers. In the rest of the section we will hypothesize the benefits implied by the legislation and then test our data to see whether these are realised

Reasons for pediatric exclusivity legislation

Pediatric exclusivity was enacted by the US Congress with the stated goal of remedying the paucity of data on safety of drugs on children. Doctors wishing to prescribe these drugs for children must prescribe them "off-label", i.e. for a purpose or to a population that has not been specifically approved in clinical trials by the FDA. The FDA has long maintained the general position that although physicians may freely prescribe drugs for off-label uses, drug manufacturers may not promote such uses. (Mello, Studdert et al. 2009). Clinical practice on pediatric populations has often involved "off-label" prescriptions. (Conroy, Choonara et al. 2000; McIntyre, Conroy et al. 2000; 't Jong, Eland et al. 2002; O'Donnell, Stone et al. 2002; Schirm, Tobi et al. 2003).

Prescribing drugs for children is not a simple matter. As children grow, their body size and composition, physiology, and cognitive and motor function change. The metabolism and toxicity of medications can vary substantially in children of different ages (Steinbrook 2002). This creates a more pressing need for reliable clinical trial data. At the same time, there are scientific, ethical and commercial challenges to conducting clinical trials on children. First, due to the variations in metabolism and toxicity, studies in adolescents (12 to 16 years of age) may therefore not provide adequate data for, say, infants (1 month-2 years). This creates the requirement for multiple studies across different age groups.

This increases the cost of the studies making pediatric studies relatively expensive compared with the size of the potential market. Further complications often cited include the difficulty of finding enough patients to participate, and inadequate numbers of quality pediatric pharmacology investigators (Caldwell, Murphy et al. 2004).

There are also complex ethical issues associated with studying children. Informed consent of children's parents is not the same as consent of an adult (Committee on Bioethics 1995) . As a result federal regulations impose a greater oversight role on review boards for pediatric trials versus adult trials. (Steinbrook 2002). All these issues add up to fewer pediatric trials, and fewer patients in individual pediatric trials, thus giving them less statistical power than for adult patients.

To address this, the FDA has tried various "stick" approaches, publishing pediatric rules in 1979, and 1994 requiring dosage information. Neither of these rules succeeded in providing much information – in the case of the 1994 rule, because there were so few studies being conducted on children, the only statement that was added to the labeling in most cases was one similar to the following: "Safety and effectiveness in pediatric patients below the age of

<weeks/years/months> has not been established." (Cooper 2002). The "carrot-only" approach has been used by the pediatric exclusivity provision in granting an extra 6 months' market exclusivity in return for specific clinical trials conducted by the drug sponsor in consultation with the FDA[16]. It has had somewhat better success at getting companies to do these studies – up until the end of 2009, 155 drugs had been granted pediatric exclusivity.

Hypotheses

One of the underlying assumptions of the pediatric exclusivity provision is that the information provided by the studies that led to these drugs being granted pediatric exclusivity is both new and reliable information. Benjamin, Smith et al. (2006) , however, found that, from 1998 to 2004 only 45% of clinical trials conducted for pediatric exclusivity were published in peer-reviewed journals. They found that trials with positive labeling requirements were more likely to be published, and that publication usually took place within three years of submitting the data to the FDA.

[16] The FDA issues a Written Request for studies, which the firm then responds to and the final parameters are mutually agreed upon.

Pediatric exclusivity cannot be granted on studies already completed before the FDA's Written Request (FDA Guidance for Industry 1999). We have seen that in the interests of disseminating positive information about their products, firms are likely to publish at least some of the results of the trials conducted for pediatric exclusivity, in peer-reviewed publications, *after* obtaining pediatric exclusivity (Benjamin, Smith et al. 2006). However, given the inherent difficulties in conducting pediatric clinical trials described above firms are therefore not likely to have done many, if any clinical trials, unless the value of the pediatric market alone made it worthwhile for them to do so without the effective subsidy of a pediatric exclusivity extension. As we have noted, this lack of data was, in fact, the original rationale for the Pediatric Exclusivity provision. We would therefore find it likely that firms have not published (or have published very few) pediatric trials in peer-reviewed publications *before* submitting data for pediatric exclusivity.

We would therefore hypothesize that:

H1: The number of peer-reviewed articles published on pediatric trials of a drug is likely to increase after the drug has obtained pediatric exclusivity

Many other factors could increase (or their absence decrease) the number of clinical trials such as the drug being used for a variety of therapeutic purposes, different forms of taking the drug (pill vs injection), etc. Some of these factors would also likely increase (or decrease) the number of clinical trials in adults. Therefore it might be appropriate to also test for the ratio of clinical trials performed on minors to the number of clinical trials performed on adults. Therefore we hypothesize that:

H2: The ratio of peer-reviewed articles published on pediatric trials to the number of peer-reviewed articles published on adult clinical trials of a drug is likely to increase after the drug has obtained pediatric exclusivity

Peer-reviewed articles are the first step towards dissemination of information and are not the only source of information for doctors. The dissemination of information is a complex and faulty process and doctors may not always be aware of the latest developments(Stross and Harlan 1979). Obtaining FDA approval for pediatric uses of a drug would permit companies to include such information on promotional material both to doctors and consumers. Any negative information would also show up in the labeling changes required by the FDA when granting pediatric exclusivity.

If the information is both high-quality and important to doctors, we would expect it to generate impact on prescriptions to minors. Doctors would be less likely to prescribe drugs that are ineffective, or have been shown to have strong side effects, and more likely to prescribe drugs that have been shown to be safe with appropriately tested doses. In either case, therefore, regardless of the results of the clinical trials, the information should change the prescribing patterns of doctors, and consquently the sales patterns.

Therefore we hypothesize that

H3a: The proportion of prescriptions of drugs to minors is likely to change after obtaining pediatric exclusivity

and

H3b: The proportion of sales of drugs to minors is likely to change after obtaining pediatric exclusivity

Data Description:

We use data on papers published about clinical trials by searching PubMed's archives for all data on clinical trials for adults and those that focused only on minors. We collected clinical trial data on all drugs that obtained pediatric exclusivity before Jan 1, 2010. We commence recording clinical trial

data from 1992, 5 years before pediatric exclusivity was introduced in 1997 via Section 111 of the FDAMA. We use data on the number of papers published for the period 1992 - 2009. We also obtain sales and prescription data from the household component of the Medical Expenditure Panel Survey from 1996-2007, as described in the previous chapter. We merged this, as before, with new drug application data from the FDA Electronic Orangebook. Pediatric exclusivity data was also obtained from the FDA Orangebook and crosschecked with the FDA list of drugs granted pediatric exclusivity[17]. For all our analyses, we drop the three outliers identified in the previous chapter- Adderall, Concerta and Strattera.

Variables

The Federal Drug Modernization Act's pediatric exclusivity extension, 1997, and the subsequent renewal in the Best Pharmaceuticals for Children Act 2002 were intended to stimulate pediatric research and provide benefits for children (Roberts, Rodriguez et al. 2003). These benefits have been questioned by various researchers (Benjamin, Smith et al. 2006; Boots, Sukhai et al. 2007). We use the following variables to determine if the information provided by the trials conducted to obtain pediatric exclusivity and subsequent labeling generate

[17] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm

information that changes patterns of prescriptions and sales of pharmaceuticals to minors.

Dependent and Independent variables:

We conducted a PubMed search to count the number of human clinical trials for each drug that was granted pediatric exclusivity before Jan 1, 2010. For pediatric data, we use the clinical trial data that focuses on pediatric patients and not adults. We did this because the "adult" age classification in pubmed is 19+ and minor is 0-18. We found that trials conducted on subjects aged 18 and up were frequently classified into the "both minor and adult"category. On a random subsample, the appearance of 18 year olds only appeared to be the vast majority of the publications that had both minors and adults in the study. From the data thus collected we generated, for each year,:

a. *The number of papers published on clinical trials*
b. *The number of papers published on clinical trials on minors, and*
c. *Fraction of papers published on clinical trials of minors*

To address the impact of pediatric exclusivity, we used (in different regressions), as dependent and independent variables,

Fraction of annual prescriptions to minor patients

The total prescriptions to minor patients for each drug for the year divided by total prescriptions to all patients for each drug for the year.

Fraction of annual sales to minor patients

The total sales to minor patients for each drug for the year divided by total sales to all patients for each drug for the year.

In order to determine whether the ratio of publications of clinical trials on minors to publications of clinical trials on adults increases as a result of the granting of pediatric exclusivity, we calculate the difference in the fraction of publication of trials on minor patients for each drug generated at the point of granting pediatric exclusivity. Using Benjamin et al's (2006) findings that almost all of the publications occurred within three years of the date of submission to the FDA as our guideline, we use the difference over a time period up to three years.

Difference in fraction of annual publications on clinical trials on minor patients over periods before and after time 't'

a. *Year over previous year at time 't'*

The difference between the fraction of annual publications on clinical trials on minors for a drug in the current year and the previous year (t-1).

b. Two year period over prior two year period at time 't'

The difference between the mean fraction of annual publications on clinical trials on minors for a drug in the current year t and the next year t+1 and the mean fraction of annual publications on clinical trials on minors for a drug in the previous two years t-1 and t-2

c. Three year period over prior three year period at time 't'-

The difference between the mean fraction of annual publications on clinical trials on minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual publications on clinical trials on minors for a drug in the previous three years t-1 ,t-2, and t-3.

As a robustness check, we also use the *difference in fraction of annual publications on clinical trials on minor patients between periods before and after and not including the current year 't'*

a. Next year versus prior year at time 't'

The difference between the fraction of annual publications on clinical trials on minors for a drug in the next year (t+1) and the previous year (t-1).

b. Next two years versus previous two years at time 't'

The difference between the mean fraction of annual publications on clinical trials on minors for a drug during the next two years t+1 and t+2 and the mean fraction of annual prescriptions to minors of the drug in the previous two years t-1 and t-2

c. Next three years versus previous three years at time 't'

The difference between the mean fraction of annual publications on clinical trials on minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual publications on clinical trials on minors for a drug in the previous three years t-1 ,t-2, and t-3.

In order to determine whether the rate of prescriptions of the drugs to minors change as a result of the granting of pediatric exclusivity, we calculate the difference in the fraction of annual prescriptions to minor patients for each drug generated at the point of granting pediatric exclusivity. As it is possible that for some drugs the rate of prescriptions changes positively and for others negatively, we also use the square of the difference in the fraction of annual prescriptions to minor patients for each drug at the point of pediatric exclusivity.

Difference in fraction of annual prescriptions of minor patients over periods before and after time 't'

a. *Year over previous year at time 't'*

The difference between the fraction of annual prescriptions to minors for a drug in the current year and the previous year (t-1).

b. *Two year period over prior two year period at time 't'*

The difference between the mean fraction of annual prescriptions to minors for a drug in the current year t and the next year t+1 and the mean fraction of annual prescriptions to minors of the drug in the previous two years t-1 and t-2

c. *Three year period over prior three year period at time 't'-*

The difference between the mean fraction of annual prescriptions to minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual prescriptions to minors of the drug in the previous three years t-1 ,t-2, and t-3.

As a robustness check, we also use the *difference in fraction of annual prescriptions of minor patients between periods before and after and not including the current year 't' as well as its second moment(square).*

a. *Next year versus prior year at time 't'*

The difference between the fraction of annual prescriptions to minors for a drug in the next year (t+1) and the previous year (t-1).

b. Next two years versus previous two years at time 'ti

The difference between the mean fraction of annual prescriptions to minors for a drugs during the next two years t+1 and t+2 and the mean fraction of annual prescriptions to minors of the drug in the previous two years t-1 and t-2

c. Next three years versus previous three years at time 't'

The difference between the mean fraction of annual prescriptions to minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual prescriptions to minors of the drug in the previous three years t-1 ,t-2, and t-3.

For hypothesis 2b, we also determine whether the sales of the drugs to minors changes as a result of the granting of pediatric exclusivity and we calculate the difference in the fraction of annual sales to minor patients for each drug generated at the point of granting pediatric exclusivity. As before, we are interested in seeing whether there is a change. It is possible that some changes are positive and some are negative, and we would see an overall null effect. To test for this we also use the square of the difference in the fraction of annual sales

for minor patients for each drug generated at the point of granting pediatric exclusivity.

Difference in fraction of annual sales of minor patients over periods before and after time 't'

a. *Year over previous year at time 't'*

The difference between the fraction of annual sales to minors for a drug in the current year and the previous year (t-1).

b. *Two year period over prior two year period at time 't'*

The difference between the mean fraction of annual sales to minors for a drug in the current year t and the next year t+1 and the mean fraction of annual sales to minors of the drug in the previous two years t-1 and t-2

c. *Three year period over prior three year period at time 't'-*

The difference between the mean fraction of annual sales to minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual sales to minors of the drug in the previous three years t-1 ,t-2, and t-3.

As a robustness check, we also use the *difference in fraction of annual sales of minor patients between periods before and after and not including the current year 't'*

a. *Next year versus prior year at time 't'*

The difference between the fraction of annual sales to minors for a drug in the next year (t+1) and the previous year (t-1).

b. *Next two years versus previous two years at time 'ti*

The difference between the mean fraction of annual sales to minors for a drugs during the next two years t+1 and t+2 and the mean fraction of annual sales to minors of the drug in the previous two years t-1 and t-2

c. *Next three years versus previous three years at time 't'*

The difference between the mean fraction of annual sales to minors for a drug in the current year 't' and the next two years t+1 and t+2 and the mean fraction of annual sales to minors of the drug in the previous three years t-1 ,t-2, and t-3.

Control variables

Age of drug

The older the drug, the more likely that the drug already has a safe off-label use among minors and that non-clinical trial information is available to

doctors. This would tend to reduce the likelihood of new information having significant changes in prescription patterns.

It is also possible that these drugs are nearer the date of expiration of their current patent or market exclusivity protections, which would decrease the likelihood that pharmaceutical companies would invest in aggressively changing their marketing literature, and doctors would have to obtain information by way of peer-reviewed journals, if the trials were published or labeling changes, if any. Due to these effects, we control for age in our analyses.

We use the number of years since the drug was first approved by the FDA. This is left-censored by the Orangebook at 1982, so all drugs first approved before January 1, 1982, are assumed to be approved on January 1, 1982.

Number of years under pediatric exclusivity regime

As the drug could not have been approved before 1997, this is defined as the number of years since 1997 that the drug has been approved by the FDA

Time trends.

As time has passed since 1997, there has been more time to conduct studies and obtain pediatric approval. We use year fixed effects in all regressions to control for this and any other time trends.

Methods:

We use a series of t-tests to estimate the difference between the fraction of publications on pediatric clinical trials in a 1, 2 and 3 year period before and after pediatric exclusivity.

We also do t-tests to estimate the difference between the change in prescriptions to minors in a 1,2 and 3 year period before and after the point of pediatric exclusivity versus the average changes observed in the 1,2, and 3 year periods around all other points.

It is possible that for some drugs, this change is positive, due to information indicating, for example, that the drugs are safe for pediatric use or need to be taken for longer period . On the other hand, other drugs may be contra-indicated for pediatric use. It is possible that if the first moment average is used, we may find an overall null effect. To eliminate this possibility, we also estimate the second moment, i.e. the difference in the squares of the change in prescriptions to minors in a 1,2 and 3 year period before and after the point of

pediatric exclusivity versus the mean squares of changes observed in the 1,2, and 3 year periods around all other points.

We also conduct a fractional two-stage probit analysis using Papke and Wooldridge's (2008) technique for fractional response variables using panel data with endogenous explanatory variables. For example, in one of the two-step procedures, we first estimate the reduced form equation for the endogenous explanatory variable $X_{it,}$ where X_{it} is the fraction of pediatric prescriptions of the 'i'th drug at time 't'. We obtain the residuals for each i,t pair ν_{it}. In the second step, we use the pooled probit quasi-maximum likelihood estimator to calculate,

$$Y_{jt} = \beta_1 X_{it} + \beta_2 z_{it} + \beta_3 \nu_{it} + \varepsilon_{it}$$

Y_{it} is the ratio of articles published about pediatric trials to the total articles on adult trials conducted on the 'i'th drug at time t.

Results

Table 1 describes the key variables in our data, and Table 2 presents the correlation matrix. We see that the fraction of prescriptions and the fraction of sales to minors are highly correlated. The fraction of sales to minors is also slightly correlated with the fraction of articles published on pediatric trials. Table

3 presents the number of papers published on pediatric and adult clinical trials. While we have per-drug data for all the drugs with pediatric exclusivity, we only collect aggregate data for the drugs that did not obtain pediatric exclusivity. Collecting individual data for these (several thousand) drugs is a project for future work. We note that the fraction of articles published on pediatric trials of drugs that did obtain pediatric exclusivity is actually lower than for drugs that have not obtained pediatric exclusivity, barring in 2008 and 2009. Table 4 presents data on the number of pediatric trials published before and after obtaining pediatric exclusivity. We see that, contrary to our *a priori* expectations, that drugs have indeed had some pediatric trials before being granted pediatric exclusivity, in some cases many years before the provision even existed. In Specifically, out of the 155 drugs that did obtain pediatric exclusivity before 2010, 105 drugs had articles on pediatric trials that were published before they had obtained pediatric exclusivity, and 43 had more than 10 articles on pediatric clinical trials published before obtaining pediatric exclusivity.

H1 is first tested using t-statistics in table 5. We see that in table 5, only the change in fraction of papers published between years 't+1' and 't-1' is statistically significant. This could well be an artifact of the data, and we conclude initially that there is no support for H1. Our two-stage regression

analyses confirm this in Table 11, with none of the regressions showing any support for H1. The factor "pediatric exclusivity already granted" is statistically insignificant across all regressions, including the fully specified models 11.3 and 11.6 (Fraction of prescriptions and fractions of sales are kept in separate regressions as they are so highly correlated). We conclude that there is no support for H1 and that the extra clinical trials being conducted for the pediatric exclusivity provision are either not being published in adequate numbers, or, as the companies are publishing clinical trials on the same drugs before and after obtaining exclusivity, may well likely have conducted for these specific drugs anyway.

To test H2a and H2b, we also use t-tests to differentiate whether the changes in the fraction of prescriptions to minors (Tables 7 and 9) and sales to minors (Tables 8 and 10) during the period where pediatric exclusivity was obtained were substantially different. We find no support for H2a or H2b. In tables 6,7,8,9, and 10 we do not find any consistent support for evidence of any change in prescriptions or sales around the time of obtaining pediatric exclusivity. In fact using the second moments in table 8 and 10 we find strong evidence in the opposite direction, i.e. that changes in the rate of prescriptions and sales are much *lower* around the year of obtaining pediatric exclusivity

versus similar periods around other years. We do not know why this should be so.

The two-stage regression analyses in Table 12 and 13 do not show any effect of obtaining pediatric exclusivity on either the fraction of prescriptions to minors (Full regression 12.3) or sales to minors (full regression 13.3). All the regressions in Table 11,12,and 13 do support a strong correlation between the fraction of articles published on pediatric clinical trials and the fraction of prescriptions to minors as well as the fraction of sales to minors. We can interpret this correlation as greater information on minors providing a greater likelihood of prescriptions, or the demand for prescriptions in minors providing the companies with the financial incentive to conduct and publish clinical trials on minors. However, this does not appear to be correlated with the pediatric exclusivity provision as we don't find any effect of having obtained pediatric exclusivity. To recap, none of our analyses provide support for either H1, H2a or H2b, and there is evidence of statistically significant effects in the opposite direction predicted by H2a and H2b.

Discussion and Conclusion

We were unable to detect any change in publishing patterns as a result of obtaining pediatric exclusivity. We observed *lower* changes in prescription patterns to minors around the period where pediatric exclusivity was obtained. This strongly suggests that there is limited, if any, additional information being made available to clinical practitioners as a result of pediatric exclusivity. It is possible that the prescription patterns are not being affected because dissemination of off-label prescription practices (Mello, Studdert et al. 2009) is efficiently providing doctors with the necessary information. It is also possible that the trials themselves do not have the statistical power to add enough new information. Either or both these processes may be occurring, and are not distinguishable from our data. Nevertheless, this is disturbing as it cuts at the very heart of the rationale for stimulating pediatric testing- that the testing is important and provides valuable relevant information.

The FDA has many audiences. Almost all these audiences would prefer pediatric testing. The perception of the FDA as public safety guardian and it's own desire to increase it's reputation guides a safety-first mentality and a desire to minimize Type 1 errors (Kim 2007). While the costs are borne by a fragmented set of consumers and are difficult to calculate, the benefits to the consumer too appear to be difficult to aggregate. The benefits for the

pharmaceutical companies are tangible and clear. The FDA thus faces an audience that would perhaps prefer the intangible idea of "safety for children", a pharmaceutical audience looking for tangible rewards, and a relatively diffuse (and consequently less likely to be engaged) audience bearing the costs.

The ability to change labels and provide some information allow the FDA to address it's audiences of the general public and the pediatricians.

The FDA's audience of pharmaceutical companies would prefer to continue to be given profitable incentives to conduct trials and to be able to negotiate low-cost trials with short time periods and the minimum number of participants, reducing the statistical power and the likelihood of information being provided.

In their Guidance to Industry, 1999, the FDA has stated that they do not currently enforce the provision that allows them to require pediatric testing of a drug. Under the pediatric exclusivity provision, the 6-month extension can be granted so long as the drug is currently under patent or other market exclusivity. As patent exclusivity lasts for 20 years (and other provisions may extend this further), this permits the trials to be conducted anytime during this period, and

consequently, the information can be delayed until the pharmaceutical firm that owns the drugs decides that the incentives are sufficient for it to conduct trials.

If the information provided from trials was expected to be essential to patient safety, it would be more likely that the FDA would choose a more even balance between the "carrot" of pediatric exclusivity and the potential "stick" of requiring pediatric testing. The absence of the "stick" in the FDA's approach therefore lends some weight to the supposition that it is not expected by the FDA that very critical information is provided and that only some minor information regarding dosing and side effects may be provided by these trials.

During the passage of the 2002 BPC, the American Association of Pediatricians (AAP), a non-profit group dedicated to pediatric healthcare issues, stated in its testimony before Congress that " the AAP does not take lightly to adding costs to the health care of individuals, but we strongly believe that a parent or grandparent would be agreeable to spending a few dollars for more than six months in order to ensure that a drug their child or grandchild was taking had the appropriate dosing, safety and effectiveness information"(pg 542, (Cooper 2002))

Unfortunately, we don't find any evidence that valuable information, not previously available, is provided by these trials. Nevertheless the entire population, adults included, pays heavily for the 6-month extensions granted through costs of delayed generic availability. In other words, those "few dollars" mentioned soon add up. Our very conservative estimate in the prior chapter of approximately US$ 21 billion in undiscounted dollars of consumer liability at the end of 2007 is not a small amount, even set against the $130 billion in annual pharmaceutical expenditure(2007)

Our study has many strengths, in terms of the multi-year nature of the data, the repeated questioning and sampling of the AHRQ survey and the comprehensiveness of the Orange Book information. The study also has its limitations. First, it is possible that the reason we cannot detect changes in prescription patterns is that they are too subtle to be detected at a macro level. It may not be that the information being passed is of relatively small importance, rather it may be because the changes required are of a fine order, such as a small adjustment in dosage, being watchful for certain side-effects or reducing or increasing the time of the regimen.

Much work remains to be done in this area. The effectiveness of regulatory stimulation for research in pharmaceuticals can be assessed in many ways. One possible area for future study would be to assess the actual tests conducted for the pediatric exclusivity provision for power, long-term follow up and compare them to similar adult tests. A further project for future research would be to study the sales and prescription patterns of the drugs that the FDA has issued written requests for, but whose studies were delayed by the pharmaceutical firm or have not been conducted at all.

Table 1 : Data description

Variable	Mean	SD	Min	Max
Articles published on human clinical trials in a year	31.40	44.29	0	281
Fraction of articles published on pediatric trials	6.26%	10.84%	0	100%
Fraction of sales to minors (%)	8.34%	19.1%	0	100%
Fraction of prescriptions to minors (%)	8.48%	19.1%	0	100%
Age of drug (years)	7.74	6.00	0	25
Time under pediatric exclusivity regime (years)	4.42	2.97	0	10

Table 2: Correlation matrix

	Articles published on human clinical trials in a year	Fraction of articles published on pediatric trials	Fraction of sales to minors (%)	Fraction of prescriptions to minors (%)	Age of drug (years)
Fraction of articles published on pediatric trials	0.0517				
Fraction of sales to minors (%)	-0.0254	0.3561			
Fraction of prescriptions to minors (%)	-0.0142	0.3208	0.9705		
Age of drug (years)	0.2672	0.0844	0.0338	0.0296	
Time under pediatric exclusivity regime	0.1954	0.0219	0.0241	0.0283	0.6180

(years)

Table 3 : Papers published on pediatric and adult clinical trials

Year	Obtained Pediatric exclusivity before 2010			Pediatric exclusivity not obtained before 2010		
	Pediatric	Total	Ratio	Pediatric	Total	Ratio
1992	102	1,880	5.43%	287	3,333	8.61%
1993	140	2,056	6.81%	345	3,443	10.02%
1994	166	2,662	6.24%	410	3,753	10.92%
1995	200	3,234	6.18%	377	3,701	10.19%
1996	222	3,273	6.78%	342	3,399	10.06%
1997	302	3,395	8.90%	389	3,518	11.06%
1998	290	3,789	7.65%	382	3,539	10.79%
1999	292	4,375	6.67%	386	3,382	11.41%
2000	332	4,629	7.17%	294	3,110	9.45%
2001	349	4,678	7.46%	358	3,034	11.80%
2002	396	4,976	7.96%	308	3,265	9.43%
2003	396	5,800	6.83%	397	3,511	11.31%
2004	460	6,485	7.09%	353	3,542	9.97%
2005	493	6,936	7.11%	410	4,146	9.89%
2006	493	6,868	7.18%	455	4,365	10.42%
2007	573	7,278	7.87%	428	4,822	8.88%
2008	602	7,040	8.55%	343	4,995	6.87%
2009	556	6,355	8.75%	363	5,472	6.63%

Table 4 : Papers published on pediatric and adult clinical trials of drugs that were granted pediatric exclusivity before 2010

Year	Before obtaining pediatric exclusivity			After being granted pediatric exclusivity		
	Pediatric	Total	Fraction	Pediatric	Total	Fraction
1992	102	1,880	3.10%	-	-	-
1993	140	2,056	3.90%	-	-	-
1994	166	2,662	4.72%	-	-	-
1995	200	3,234	4.10%	-	-	-
1996	222	3,273	5.80%	-	-	-
1997	302	3,395	6.98%	-	-	-
1998	253	3,603	5.53%	37	186	13.94%
1999	235	3,807	4.20%	57	568	10.85%
2000	204	3,561	6.29%	128	1,068	9.84%
2001	176	2,970	5.10%	173	1,708	11.56%
2002	167	2,479	4.19%	229	2,497	10.11%
2003	118	2,376	3.91%	278	3,424	7.42%
2004	124	2,228	4.69%	336	4,257	6.85%
2005	114	2,047	4.22%	379	4,889	7.57%
2006	128	1,508	5.68%	365	5,360	7.98%
2007	65	773	6.45%	508	6,505	7.55%
2008	14	342	4.67%	588	6,698	8.45%
2009	-	-	-	556	6,355	8.59%

Table 5: t-statistics comparing fraction of papers published on pediatric trials of drugs with and without pediatric exclusivity at time t

	Drugs that obtained pediatric exclusivity at year 't'			
	Other years 't'	Year drug obtained pediatric exclusivity 't'		
Variable	**Mean**	**Mean**	**Welch's df**	**t-stat**
Change in fraction of papers published on pediatric trials between years 't' and 't-1'	0.29%	1.41%	174.4	-1.50
Change in average fraction of papers published on pediatric trials between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.54%	1.01%	157.0	-0.97
Change in average fraction of papers published on pediatric trials between three year period 't' to t+2' vs three-year period 't-3' to 't-1'	0.69%	0.97%	144.1	-0.55
Change in fraction of papers published on pediatric trials between years 't+1' and 't-1'	0.49%	2.07%	171.1	**-2.38***
Change in average fraction of papers published on pediatric trials between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.83%	1.23%	140.2	-0.65
Change in average fraction of papers published on pediatric trials between three year period 't+1' to t+3' vs three-year period 't-3' to 't-1'	0.80%	1.42%	119.7	-1.02

Note: The above analyses in this table are restricted to drugs that obtained pediatric exclusivity before 2010

Table 6: t-statistics comparing fractions of prescriptions to minors and fractions of sales of minors of drugs with and without pediatric exclusivity

			Fraction of prescriptions to minors	Fraction of sales to minors
All drugs	**Drugs that did not obtain pediatric exclusivity before 2010**	**Mean**	**8.53%**	**8.41%**
	Drugs that obtained pediatric exclusivity before 2010	**Mean**	6.95%	6.78%
		Welch's df	2744.5	2708.7
		t-statistic	**2.76***	**2.82***
All drugs	**Drugs without pediatric exclusivity**	**Mean**	7.95%	7.80%
	Drugs that have obtained pediatric exclusivity	**Mean**	9.36%	9.29%
		Welch's df	515.6	511.6
		t-statistic	-1.61	-1.66
Only drugs that have obtained pediatric exclusivity at some time before 2010	**Drugs without pediatric exclusivity**	**Mean**	5.46%	5.23%
	Drugs that have obtained pediatric exclusivity	**Mean**	**9.36%**	**9.29%**
		Welch's df	606.6	604.4
		t-statistic	**-4.21****	**-4.29****

Table 7 : t-statistics comparing changes in prescriptions to minors at time of obtaining pediatric exclusivity

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	Other years 't' Mean	Year drug obtained ped. Exclus-ivity 't' Mean	Welch's df	t-stat	Other years 't' Mean	Year drug obtained ped. Exclusive-ity 't' Mean	Welch's df	t-stat
Change in fraction of prescriptions to minors between years 't' and 't-1'	0.067%	-0.51%	95.2	0.82	0.128%	-0.51%	119.1	0.86
Change in mean fraction of prescriptions to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.13%	-0.003%	69.9	0.21	0.28%	-0.003%	90.0	0.402
Change in mean fraction of prescriptions to minors between three year period 't' to t+2' vs three-year period 't-3' to 't-1'	0.075%	0.97%	50.6	-0.93	0.25%	0.97%	57.63	-0.72

(Table is continued on next page)

Table 7 (cont'd)

	All drugs				Only drugs that obtained pediatric exclusivity			
	Other years 't'	Year drug obtained ped. exclusivity 't'			Other years 't'	Year drug obtained ped. exclusivity 't'		
Variable	**Mean**	**Mean**	**Welch's df**	**t-stat**	**Mean**	**Mean**	**Welch's df**	**t-stat**
Change in fraction of prescriptions to minors between years 't+1' and 't-1'	0.21%	0.39%	71.6	-0.19	0.29%	0.39%	88.5	-0.10
Change in mean fraction of prescriptions to minors between two year period 't+1' and t+2 vs two-year period 't-1' and 't-2'	0.11%	1.34%	53.3	-1.22	0.16%	1.34%	61.6	-1.12
Change in mean fraction of prescriptions to minors between three year period 't+1' to t+3' vs three-year period 't-3' to 't-1'	0.13%	**2.5%**	43.8	**-2.01***	0.45%	2.5%	51.2	-1.67

Table 8: t-statistics comparing changes in sales to minors at time of obtaining pediatric exclusivity

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	**Other years 't'** **Mean**	**Year drug obtained ped. exclusivity 't'** **Mean**	**Welch's df**	**t-stat**	**Other years 't'** **Mean**	**Year drug obtained ped. exclusivity 't'** **Mean**	**Welch's df**	**t-stat**
Change in fraction of sales to minors between years 't' and 't-1'	0.005%	-1.03%	83.07	1.04	0.11%	-1.03%	93.8	1.05
Change in mean fraction of sales to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.16%	0.14%	67.9	0.02	0.36%	0.14%	85.9	0.26
Change in mean fraction of sales to minors between three year period 't' to t+2' vs three-year period 't-3' to 't-1'	0.07%	1.24%	50.9	-1.16	0.19%	1.24%	59.1	-1.09

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Table 8 cont'd

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**
Change in fraction of sales to minors between years 't+1' and 't-1'	0.22%	0.31%	67.6	-0.07	0.36%	0.31%	78.8	0.04
Change in mean fraction of sales to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.14%	1.89%	53.2	-1.59	0.21%	1.89%	61.9	-1.46
Change in mean fraction of sales to minors between three year period 't+1' to t+3' vs three-year period 't-3' to 't-1'	0.11%	2.91%	43.5	**-2.11***	0.28%	2.91%	50.5	-1.91

Table 9: t-statistics comparing squares of changes in prescriptions to minors at time of obtaining pediatric exclusivity

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	**Other years 't'**	**Year drug obtained ped. exclusivity 't'**			**Other years 't'**	**Year drug obtained ped. exclusivity 't'**		
	Mean	**Mean**	**Welch's df**	**t-stat**	**Mean**	**Mean**	**Welch's df**	**t-stat**
Square of the change in fraction of prescriptions to minors between years 't' and 't-1'	1.81%	0.31%	685.6	**7.28****	0.96%	0.31%	536.7	**3.11****
Square of change in mean fraction of prescriptions to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	0.89%	0.23%	144.7	**5.29****	0.61%	0.23%	182.1	**2.89****
Square of change in mean fraction of prescriptions to minors between three year period 't' to t+2' vs three-year period 't-3' to 't-1'	0.59%	0.41%	50.0	0.63	0.43%	0.41%	52.1	0.05

(Table is continued on next page)

Table 9 (cont'd)

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**
Square of change in fraction of prescriptions to minors between years 't+1' and 't-1'	1.94%	0.50%	167.1	**5.26****	1.27%	0.50%	212.1	**2.62***
Square of change in mean fraction of prescriptions to minors between two year period 't+1' and t+2 vs two-year period 't-1' and 't-2'	0.91%	0.49%	53.9	1.26	0.67%	0.49%	56.4	0.53
Square of change in mean fraction of prescriptions to minors between three year period 't+1' to t+3' vs three-year period 't-3' to 't-1'	0.67%	0.60%	42.5	0.15	0.58%	0.60%	45.9	-0.05

Table 10 : t-statistics comparing square of changes in sales to minors at time of obtaining pediatric exclusivity.

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	Other years 't' Mean	Year drug obtained pediatric exclusivity 't' Mean	Welch's df	t-stat	Other years 't' Mean	Year drug obtained pediatric exclusivity 't' Mean	Welch's df	t-stat
Square of change in fraction of sales to minors between years 't' and 't-1'	2.02%	0.76%	135.9	**3.61****	1.11%	0.76%	137.6	0.96
Square of change in mean fraction of sales to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	1.02%	0.30%	109.6	**4.38****	0.73%	0.30%	165.7	**2.35***
Square of change in mean fraction of sales to minors between three year period 't' to t+2' vs three-year period 't-3' to 't-1'	0.69%	0.45%	50.4	0.72	0.53%	0.46%	56.6	0.21

(This table is continued on next page)

Table 10 cont'd

	All drugs				Only drugs that obtained pediatric exclusivity			
Variable	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**	**Other years 't'** **Mean**	**Year drug obtained pediatric exclusivity 't'** **Mean**	**Welch's df**	**t-stat**
Square of change in fraction of sales to minors between years 't+1' and 't-1'	2.15%	0.83%	87.5	**2.94***	1.43%	0.83%	100.2	1.29
Square of change in mean fraction of sales to minors between two year period 't' and t+1 vs two-year period 't-1' and 't-2'	1.04%	0.60%	53.8	1.18	0.81%	0.59%	59.4	0.54
Square of change in mean fraction of sales to minors between three year period 't+1' to t+3' vs three-year period 't-3' to 't-1'	0.77%	0.76%	42.6	0.04	0.69%	0.76%	-0.14	47.4

Table 11: Factors affecting the fraction of articles published on clinical trials that were on pediatric clinical trials – two stage regression

DV : Fraction of articles on pediatric clinical trials						
	(11.1)	**(11.2)**	**(11.3)**	**(11.4)**	**(11.5)**	**(11.6)**
Fraction of prescriptions to minors	**2.787****	**2.827****	**2.820****			
	(0.331)	(0.352)	(0.355)			
Fraction of sales to minors				**2.698****	**2.757****	**2.754****
				(0.353)	(0.381)	(0.383)
Pediatric exclusivity already granted	0.099	0.070	0.070	0.105	0.073	0.073
	(0.086)	(0.087)	(0.090)	(0.088)	(0.089)	(0.091)
Age of drug		0.014	0.013		0.015	0.015
		(0.010)	(0.013)		(0.011)	(0.014)
Time under pediatric exclusivity			0.002			-0.004
			(0.038)			(0.038)
Constant	-1.667**	-1.606**	-1.956**	-1.647**	-1.604**	-1.922**
	(0.104)	(0.187)	(0.260)	(0.104)	(0.186)	(0.259)
Observations	992	992	946	992	992	946

Robust standard errors in parentheses
* significant at 5%; ** significant at 1%

All regressions include year fixed effects

Table 12 : Factors affecting the fraction of prescriptions to minors- two stage regression

	(12.1)	(12.2)	(12.3)
	DV: Fraction of prescriptions to minors		
Fraction of articles published on pediatric clinical trials	**6.264****	**6.373****	**5.893****
	(0.629)	(0.618)	(0.530)
Pediatric exclusivity already granted	0.105	0.135	0.135
	(0.116)	(0.110)	(0.110)
Age of drug		-0.010	-0.003
		(0.013)	(0.016)
Time under pediatric exclusivity			-0.018
			(0.053)
Constant	-2.081**	-2.248**	-1.992**
	(0.121)	(0.121)	(0.365)
Observations	992	992	946

Robust standard errors in parentheses
* significant at 5%; ** significant at 1%
All regressions include year fixed effects

Table 13 : Factors affecting the fraction of sales to minors- two stage regression

	(13.1)	(13.2)	(13.3)
	DV: Fraction of sales to minors		
Fraction of articles published on pediatric clinical trials	5.963**	6.088**	5.644**
	(0.644)	(0.613)	(0.525)
Pediatric exclusivity already granted	0.134	0.167	0.166
	(0.117)	(0.111)	(0.112)
Age of drug		-0.012	-0.007
		(0.013)	(0.017)
Time under pediatric exclusivity			-0.012
			(0.053)
Constant	-2.071**	-2.210**	-2.003**
	(0.145)	(0.127)	(0.361)
Observations	992	992	946

Chapter 5: Conclusions

In the previous three chapters, we first looked at the various theories of regulation. Economic welfare theory posited that the regulator, be it a legislative entity like Congress or a bureaucratic entity such as the FDA or the patent office existed to maximize social welfare, and acts like a Bayesian statistician, taking decisions under uncertainty. (Pigou 1938; McCraw 1975; Laffont and Tirole 1986). This theory was criticized for not having much development as to *how* these rules would be made from a political process. Here, regulatory capture theory takes over, from Olson's (1965) logic of collective action where incentives to organize are higher for small groups with high stakes that are spread among fewer actors.

Stigler (1971) and Peltzman (1976) argued from this that small groups of industries could sway legislative and regulatory bodies, as diffuse groups of consumers would find it hard to organize and had lower-powered incentives for doing so. While Stigler and Peltzman focused primarily on legislative bodies, Laffont and Tirole's (1991) agency-theoretic model accounted for bureaucratic regulators like the USPTO and the FDA, showing that interest groups are more powerful when they seek to obtain inefficient regulation, where inefficiency is determined by the degree of information asymmetry between the regulated industry and the regulators.

The means by which these groups exercise power are primarily financial support to legislators (Peltzman 1976; Becker 1983; Dal Bo and Di Tella 2003) and the revolving-door, i.e. hoped-for financial support in the form of future jobs in industry for bureaucratic regulators. (Laffont and Tirole 1993; Djankov, La Porta et al. 2002).

The results that regulatory capture theory predicts are socially inefficient legislation and socially inefficient bureaucratic rule-enforcing, both in favour of small groups with large incentives to be spread over few actors, at the cost of diffuse groups. We looked at the latter, first in Chapter 2. The USPTO is a bureaucratic organization focused on policing innovation by awarding 20-year monopolies. Examiners are tied to quantitative production quotas and neither rewarded for quality nor punished for the lack of it. They are under extreme pressure to produce and are looking for any signals in the patent application to give them a quick resolution. Regulatory capture theory would predict that we would find benefits to top innovators, i.e. the relatively small groups that patent a lot. These groups would be salient to examiners, likely to have aggressive legal representation, and possibly a case can be made to superiors that they do good patents. What we actually found was that patent examiners appeared to grant patents to top innovators with less scrutiny in fields which had strong intellectual property protections like pharmaceuticals and medicine. The

converse was true in Computers and Communications, a field where most criticisms of bad patents have been made(Merges 1999), and in Electronics, where innovators routinely ignore ptents(Lemley 2007). This effect is nearer what would be predicted by Carpenter's (2010) model of reputation, where the bureaucratic organization tries to maximize it's own authority and legitimacy by taking actions that maximize it's legitimacy in the eyes of all it's audiences. Nevertheless regulatory capture theories (Peltzman 1976; Becker 1983) do include the regulator balancing the competing pressures of different groups with different aims, and it is not possible from our analyses to distinguish this balancing act from the framework proposed by Carpenter.

The story is very different when we come to the legislative body, the US Congress in Chapter 3 and Chapter 4. Here we see that pharmaceutical firms did not conduct pediatric trials for years, and all methods to force them, like not allowing them to market drugs to pediatric markets, failed. Once a carrot-only method granting 6 months' monopoly rights was adopted, 155 drugs were tested in the next 12 years, at an estimated median cost of $12mn. This will result (some of it already has) in over $21 billion being transferred from the very diffuse group of all consumers of 155 drugs to the far more concentrated group of owners of those drugs, in line with Stigler's (1971) theories. Worse, we were unable to find any tangible benefit to pediatric patients in terms of additional

information in published journals or any evidence of more changes (either increase or decrease) in the prescription patterns by doctors. All this is in line with what would be predicted by the strong versions Stigler's (1971) theories of regulatory capture, without the influence of consumers in the balancing theories of Peltzman(1976) , Becker(1983) or Laffont and Tirole(1986). We conclude that it is highly likely that this is a case of regulatory capture, with pediatric exclusivity legislation and rules specifically designed to protect brand-name incumbents and keep out lower-cost generic competition at a final cost to the consumer, for a vague and intangible benefit.

References

(1983). Public Law 97--414. 96 STAT 2049. U. S. Congress.

(1999). Guidance for Industry -Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA. Rockville, MD.

(2008). 21. U. S. C. **365 bb(a) (2)**.

(2010). Dynamic but dirty: A series of corruption scandals shake Indian businesses The Economist.

't Jong, G. W., I. A. Eland, et al. (2002). "Unlicensed and off label prescription of drugs to children: population based cohort study." BMJ **324**(7349): 1313-1314.

Alcacer, J. and M. Gittelman (2004). How do I Know what you Know? Patent Examiners and the Generation of Patent Citations, SSRN.

Alcacer, J., M. Gittelman, et al. (2008). "Applicant and Examiner Citations in US Patents: An Overview and Analysis " Working paper.

Allison, J. R. and M. A. Lemley (1998). Empirical Evidence on the Validity of Litigated Patents, SSRN.

Barron, D. N., E. West, et al. (1994). "A Time to Grow and a Time to Die: Growth and Mortality of Credit Unions in New York City, 1914-1990." American Journal of Sociology **100**(2): 381-421.

Becker, G. S. (1983). "A Theory of Competition Among Pressure Groups for Political Influence." The Quarterly Journal of Economics **98**(3): 371-400.

Benjamin, D. K., P. B. Smith, et al. (2006). "Peer-Reviewed Publication of Clinical Trials Completed for Pediatric Exclusivity." JAMA: The Journal of the American Medical Association **296**(10): 1266-1273.

Boots, I., R. Sukhai, et al. (2007). "Stimulation programs for pediatric drug research – do children really benefit?" European Journal of Pediatrics **166**(8): 849-855.

Burke, P. F. and M. Reitzig (2007). "Measuring patent assessment quality-Analyzing the degree and kind of (in) consistency in patent offices' decision making." Research Policy **36**(9): 1404.

Caldwell, P. H. Y., S. B. Murphy, et al. (2004). "Clinical trials in children." The Lancet **364**(9436): 803-811.

Carpenter, D. P. (2004). "The Political Economy Of FDA Drug Review: Processing, Politics, And Lessons For Policy." Health Affairs **23**(1): 52-63.

Carpenter, D. P. (2010). Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA. Princeton, NJ, Princeton University Press.

Cohen, W. M., R. R. Nelson, et al. (2000). "Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)." Working paper.

Committee on Bioethics, A. A. o. P. (1995). "Informed consent, parental permission, and assent in pediatric practice." Pediatrics **95**: 314-317.

Conroy, S., I. Choonara, et al. (2000). "Survey of unlicensed and off label drug use in paediatric wards in European countries." BMJ **320**(7227): 79-82.

Cooper, K. J. (2002). "Pediatric Marketing Exclusivity - As Altered by the Best Pharmaceuticals for Children Act of 2002." Food and Drug Law Journal **57**: 542.

Dal Bó, E. (2006). "Regulatory Capture: A Review." Oxford Review of Economic Policy **22**(2): 203-225.

Dal Bo, E. and R. Di Tella (2003). "Capture by Threat." The Journal of Political Economy **111**(5): 1123-1154.

DiMaggio, P. J. and W. W. Powell (1983). "The Iron Cage Revisited: Institutional Isomorphism and Collective Rationality in Organizational Fields." American Sociological Review **48**(2): 147-160.

Djankov, S., R. La Porta, et al. (2002). "The Regulation of Entry." The Quarterly Journal of Economics **117**(1): 1-37.

Frank, R. G. and D. S. Salkever (1997). "Generic Entry and the Pricing of Pharmaceuticals." Journal of Economics & Management Strategy **6**(1): 75-90.

GAO (2005). Intellectual Property: USPTO Has Made Progress in Hiring Examiners, But Challenges to Retention Remain. U. G. A. Office. Washington, DC.

GAO (2007). Hiring Efforts are Not Sufficient to Reduce the Patent Application Backlog. U. G. A. Office. Washington, DC.

Gould, R. V. (2002). "The origins of status hierarchies: A formal theory and empirical test." The American Journal of Sociology **107**(5): 1143.

Grabowski, H. G. and J. M. Vernon (1992). "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act." Journal of Law and Economics **35**(2): 331-350.

Grabowski, H. G. and J. M. Vernon (1996). "Longer Patents for Increased Generic Competition: the Waxman-Hatch Act after One Decade." SSRN eLibrary.

Grabowski, H. G. and J. M. Vernon (2000). "Effective patent life in pharmaceuticals." International Journal of Technology Management **19**(1-2): 98-120.

Greenspan, A. (2007). The Age of Turbulence- Adventures in a New World. New York, The Penguin Press.

Hall, B. H., A. B. Jaffe, et al. (2001). The NBER Patent Citation Data File: Lessons, Insights and Methodological Tools, NBER Working Paper Series.

Hall, B. H., A. B. Jaffe, et al. (2001). "The NBER Patent Citations Data File: Lessons, Insights, and Methodological Tools."

Hausman, J. A., B. H. Hall, et al. (1984). "Econometric Models for Count Data With an Application to the Patent R&D Relationship." Econometrica **52**(4): 909-938.

Hemphill, C. S. (2006). "Paying for delay: Pharmaceutical patent settlement as a regulatory design problem." New York University Law Review **81**(5): 1553-1623.

Karki, L. (2005). "Review of FDA Law Related to Pharmaceuticals: The Hatch-Waxman Act, Regulatory Amendments and Implications for Drug Patent Enforcement." Journal of Patent and Trademark Office Society **87**: 602.

Kesan, J. P. and A. Gallo (2006). Why 'Bad' Patents Survive in the Market and How Should We Change? - The Private and Social Costs of Patents, SSRN.

Kesselheim, A. S. (2010). "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation." New England Journal of Medicine **363**(19): 1855-1862.

Kim, J. (2007). "Arbiter of Science: Institutionalization and Status Effects in FDA Drug Review 1990-2004." Working paper.

Knight, F. H. (1921). Risk, Uncertainty and Profit. Boston, Houghton Mifflin Company.

Korn, D. E., E. Lietzan, et al. (2009). "A New History and Discussion of 180-Day Exclusivity." Food and Drug Law Journal **64**: 335.

Laffont, J.-J. and J. Tirole (1986). "Using Cost Observation to Regulate Firms." The Journal of Political Economy **94**(3): 614-641.

Laffont, J.-J. and J. Tirole (1991). "The Politics of Government Decision-Making: A Theory of Regulatory Capture." The Quarterly Journal of Economics **106**(4): 1089-1127.

Laffont, J.-J. and J. Tirole (1993). A theory of incentives in procurement and regulation. Cambridge, MA, MIT Press.

Langinier, C. and P. Marcoul (2009). "Monetary and Implicit Incentives of Patent Examiners." Working paper.

Lanjouw, J. O. and J. Lerner (1997). "The Enforcement of Intellectual Property Rights: A Survey of the Empirical Literature." NBER Working Paper **No. W6296**.

Lemley, M. and B. Sampat (2008). "Examiner Characteristics and the Patent Grant Rate." Working paper.

Lemley, M. A. (2001). Rational Ignorance at the Patent Office, SSRN.

Lemley, M. A. (2007). "Ignoring Patents." SSRN eLibrary.

Levin, R. C., A. K. Klevorick, et al. (1987). "Appropriating the Returns from Industrial Research and Development." Brookings Papers on Economic Activity **18**(1987-3): 783-832.

Li, J. S., E. L. Eisenstein, et al. (2007). "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program." JAMA: The Journal of the American Medical Association **297**(5): 480-488.

MacArthur, R. H. and E. O. Wilson (1967). The theory of Island biogeography. Princeton, NJ, Princeton University Press.

Machlin, S., W. Yu, et al. (2005). Computing Standard Errors for MEPS Estimates. A. f. H. R. a. Quality. Rockville, MD.

McCraw, T. K. (1975). "Regulation in America: A Review Article." The Business History Review **49**(2): 159-183.

McIntyre, J., S. Conroy, et al. (2000). "Unlicensed and off label prescribing of drugs in general practice." Archives of Disease in Childhood **83**(6): 498-501.

Mello, M. M., D. M. Studdert, et al. (2009). "Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals." New England Journal of Medicine **360**(15): 1557-1566.

Merges, R. P. (1999). "As Many as Six Impossible Patents Before Breakfast: Property Rights for Business Concepts and Patent System Reform." Berkeley Technology Law Journal **14**: 577-615.

Meyer, J. W. and B. Rowan (1977). "Institutionalized Organizations: Formal Structure as Myth and Ceremony." American Journal of Sociology **83**: 340-368.

Mortimer, R. K. (1997). "Demand for Prescription Drugs: The Effects of Managed Care Pharmacy Benefits." University of California-Berkeley Working Papers.

Mossinghoff, G. J. (1999). "Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process " Food and Drug Law Journal **54**: 187.

Narin, F., E. Noma, et al. (1987). "Patents as indicators of corporate technological strength." Research Policy **16**(2): 143-155.

North, D. (1990). Institutions, Institutional Change and Economic Performance. Cambridge, UK, Cambridge University Press.

O'Donnell, C. P. F., R. J. Stone, et al. (2002). "Unlicensed and Off-Label Drug Use in an Australian Neonatal Intensive Care Unit." Pediatrics **110**(5): e52-.

Olson, M. (1965). The Logic of Collective Action: Public Interest and the Theory of Groups. Cambridge, MA, Harvard University Press.

Olson, M. K. (1997). "Firm Characteristics and the Speed of FDA Approval." Journal of Economics & Management Strategy **6**(1): 377-401.

Papke, L. E. and J. M. Wooldridge (2008). "Panel data methods for fractional response variables with an application to test pass rates." Journal of Econometrics **145**: 121-133.

Peltzman, S. (1976). "Toward a More General Theory of Regulation." Journal of Law and Economics **No. 19**(2): 211-240.

Pigou, A. C. (1938). The Economics of Welfare. London, MacMillan.

Podolny, J. M. and T. E. Stuart (1995). "A Role-Based Ecology of Technical Change." American Journal of Sociology **100**(5): 1224-1260.

Podolny, J. M., T. E. Stuart, et al. (1996). "Networks, Knowledge, and Niches: Competition in the Worldwide Semiconductor Industry, 1984-1991." American Journal of Sociology **102**(3): 659-689.

Roberts, R., W. Rodriguez, et al. (2003). "Pediatric Drug Labeling." JAMA: The Journal of the American Medical Association **290**(7): 905-911.

Saha, A., H. G. Grabowski, et al. (2006). "Generic Competition in the U.S. Pharmaceutical Industry." International Journal of the Economics of Business **13**(1): 15-38.

Salacer, J., M. Gittleman, et al. (2008). "Applicant and Examiner Citations in US Patents: An overview and analysis." Working paper.

Sampat, B. (2009). "When do applicants search for prior art?"" Journal of Law and Economics **Forthcoming**.

Schirm, E., H. Tobi, et al. (2003). "Risk Factors for Unlicensed and Off-Label Drug Use in Children Outside the Hospital." Pediatrics **111**(2): 291-295.

Schneider, C. (2007). "The Determinants of Patent Applications Outcomes - Does Experience Matter?" MPRA Paper No. 3359.

Scott Morton, F. M. (2000). "Barriers to entry, brand advertising, and generic entry in the US pharmaceutical industry." International Journal of Industrial Organization **18**(7): 1085-1104.

Scott, W. R. (1995). Institutions and Organizations. Foundations for Organizational Science. Thousand Oaks, CA, Sage**:** xvi, 178.

Shleifer, A. and R. W. Vishny (1993). "Corruption." The Quarterly Journal of Economics **108**(3): 599-617.

Steinbrook, R. (2002). "Testing Medications in Children." New England Journal of Medicine **347**(18): 1462-1470.

Stigler, G. J. (1971). "The Theory of Economic Regulation." The Bell Journal of Economics and Management Science(2): 3-21.

Stross, J. K. and W. R. Harlan (1979). "The Dissemination of New Medical Information." JAMA: The Journal of the American Medical Association **241**(24): 2622-2624.

Thomas, J. R. (2001). "Collusion and Collective Action in the Patent System:

A Proposal for Patent Bounties." " University of Illinois Law Review **2001**(1): 305-353.

Thomas, J. R. (2002). "The responsibility of the rulemaker: comparative approaches to patent administration reform." Berkeley Technology Law Journal **17**(2): 728-761.

Trajtenberg, M. (1990). "A penny for your quotes: patent citations and the value of innovations." RAND Journal of Economics **21**(1): 172-187.

Tuma, N. B. and M. T. Hannan (1984). Social Dynamics: Models and Methods. Orlando, FL, Academic Press.

Wasserman, S. and K. Faust (1994). Social network analysis : methods and applications. New York, Cambridge University Press.

Weber, M. (1947). The theory of social and economic organization. Oxford, Oxford University Press.

Wilson, R. (1985). Reputations in games and markets. Game-theoretic models of bargaining. A. E. Roth. Cambridge, UK, Cambridge University Press: 27-62.