THE SIGNALING EFFECTS OF FDA DRUG DESIGNATIONS

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ABSTRACT

Kathleen L. Miller: The Signaling Effects of FDA Drug Designations
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Investors in pharmaceutical firms face substantial information asymmetries. Only a small fraction of drugs that enter development are ever approved by the U.S. Food and Drug Administration (FDA), causing uncertainty for investors. While investors desire information regarding a drug's potential likelihood of a successful approval, firms are limited in their ability to share any proprietary information, because in doing so they may lose their competitive advantage. Instead, firms may use signals to indicate to investors the likelihood of success of drugs in their pipeline.

One such signal is FDA drug designations. Firms apply for the designations from the FDA, and receive them if their drug meets certain federally mandated criteria. The firms can then publicly announce the receipt of a designation to their investors, thereby reducing information asymmetries about a drug's potential market success. Using an event-study methodology utilizing the market model, this dissertation examines three questions regarding the signaling effects of the fast-track designation, the Orphan designation, and stacked designations. In the event study methodology, the strength of a signal is measured by the change in the stock price of a firm after an announcement. This change, aggregated across all events, is known as the cumulative abnormal returns (CARs).

In the first chapter, this dissertation examines whether the fast-track designation acted as a signal to investors (between 1998 and 2012 with n= 196 firms), and finds CARs of 6.53% after the announcement of a fast-track designation. In the second chapter, this dissertation examines whether the Orphan designation acted as a signal to investors (between 1985 and 2012 with n= 246 firms), and finds CARs of 3.66% after the announcement of an Orphan designation. In the third chapter, this dissertation analyzes whether the announcement of a stacked designation (a fast-track designation with a prior Orphan designation) produce higher CARs than non-stacked fast-track destinations (between 1998 and 2012 with n= 30 stacked designations and n= 166 non-stacked designations). The analysis finds CARs of 7.47% for the stacked designations, and CARs of 6.63% for non-stacked designations. Each chapter also analyses longitudinal differences in CARs, as well as differences in CARs based on firm size.

To the two who began this journey with me, but who are not here to see the end:
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LIST OF ABBERVIATIONS

BLA	Biologic License Agreement
CARs	Cumulative Abnormal Returns
CRSP	Center for Research in Security Prices
FDA	US Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
IND	Investigational New Drug
NDA	New Drug Application
NME	New Molecular Entity
ODA	Orphan Drug Act
OLS	Ordinary Least Squares
R&D	Research and Development

Chapter 1 – Introduction

Modern drug development began in the early part of the 20th century, with the creation of the first antimicrobials and vaccines. Since then, the degree of complexity of drug development has increased significantly to now include biologic drugs created from cell lines, as well as targeted and genomic therapies. With these advances came lowered mortality rates, higher life expectancies, and a higher standard of health. However, there are still diseases for which there is no cure, or where current treatments are not as safe or effective as would be desired. Continuing to stimulate drug development is therefore critical if advances in health are to be sustained.

Advances in drug development are affected by market forces. It has been estimated that the current total cost of bringing a drug to market is close to $1 billion (including the cost of failed development projects). This suggests that firms and investors will only choose to develop drugs that they believe will recoup this cost. Therefore, drugs are more likely to be developed if the affected population requiring the drug is large, the expected price of the drug is high, or both. As a result, advances in drug development for certain conditions are sometimes stymied due to market limitations. These market limitations can include low reimbursement rates (e.g. antimicrobials), small worldwide population sizes (e.g. Orphan diseases), and small domestic population sizes (e.g. tropical diseases). Where market limitations for drug development exist, public policy can step in to incentivize development.

Public policy measures for encouraging drug development fall into two primary categories: designations, which are given during the development process, and prizes, which are awarded once a drug has gained marketing approval. The Hatch-Waxman Act of 1985, that created a regulatory pathway for generic drugs, is the earliest example of a prize. The prize created by this legislation was market exclusivity; a new drug was rewarded five years of market exclusivity after approval before generic entry could begin. The prize was created to allay fears that the entry of generic drugs would cause a decrease in drug development because firms would not be able to recoup their full investment costs before generic entry.

The second public policy measure, and the topic of this dissertation, is designations. Designations are given during the drug development process, and may contain prizes as part of the award package. For example, one of the first designations was the Orphan drug designation, created in 1983. The Orphan designation is awarded to drugs that are indicated to treat a rare disease, defined as affecting 200,000 or fewer patients in the US. This designation provides multiple tangible benefits, including a prize of two extra years of exclusivity on the indication if the drug is approved. The Orphan designation also makes some clinical trial costs for the drug tax-deductible, provides more defined access to the FDA to discuss clinical trial design and other regulatory matters, and waives user fees if a drug submits a marketing application.

However, not all designations contain prizes. For example, the fast-track designation, created in 1998, only provides benefits that are related to the regulatory approval process. A drug can receive this designation if it meets an unmet medical need, and is used to treat a serious or life-threatening condition. Once a drug has received the fast-track designation, the

sponsoring firm can take advantage of more frequent communication with the FDA, as well as a rolling review. The rolling review allows the firm to submit pieces of its marketing approval application as they are completed, rather than all at once, which is standard. A drug that receives a fast-track designation is also potentially eligible for an accelerated approval or priority review, although these programs are also available to non-fast-track drugs.

Assessing the impact of these designations is an important component of the public policy process. New designations, such as the Breakthrough designation, continue to be created, yet minimal research has been done to determine the effectiveness of the current programs. Some studies have looked at the impact of a single piece of legislation; for example, Yin (2008) assessed the Orphan Drug Act. Other studies such as Alefantis, Kulkarni, and Vora (2005) and Anderson and Zhang (2010) looked at the impact of a single designation, specifically the fast-track designation.(1-3) However, the focus of these assessments has not been on examining current programs with an eye for predicting the success of future policies.

The purpose of this dissertation is to begin to address this deficiency in the literature. Specifically, the following chapters will attempt to determine whether investors believe the Orphan and fast-track designations bring value to a firm. But why do investors matter in this space? If the purpose of creating the designations is to speed drug development for clinically meaningful drugs, or drugs for diseases where a market failure exists, shouldn't the number of drugs which have been approved through the mechanism matter most? Yes and no. While it is important to determine whether the designations have been successful in inducing the development of drugs that make it through the entire development process, it is equally

important to step back and assess the effects of the designation at the beginning of the drug development process.

Investors are a central piece of the drug development process. For both public and private firms, investors bring in needed capital. And given the high costs of drug development, this capital outlay is substantial. Without investors, drug development projects would never get off the ground, as seen in the rare disease space before the Orphan Drug Act was passed. However, to get investors interested in a drug, some information needs to be conveyed regarding the drug's quality, i.e. its likelihood of producing a future profit. However, not all of the information regarding a drug's potential can be conveyed to investors, due to proprietary concerns. For example, information such as a drug's molecular structure, and advantage over other drugs under development, cannot be conveyed publicly because other firms may use the information to further their own development projects. This information asymmetry between firms and investors can be reduced using signals.

Signals convey to investors salient information regarding a drug, without actually disclosing any proprietary information. To be effective, these signals must be both observable, and costly enough that firms without meaningful quality information cannot imitate high quality firms. Designations can provide such a signal to investors because applying for them requires the input of both financial resources and time, and the receipt of the designation can be publicly announced by firms to investors. The proprietary information is vetted through the FDA, and therefore not made public, but the receipt of the designation may be perceived by investors as conveying information about a drug's future profitability. Additionally, some designations provide the added benefit of financial incentives or prizes for development.

To determine how investors perceive designations (i.e., whether or not designations are effective signals), an event study methodology will be used. The event study assesses how much a firm's stock price changes after an announcement of the receipt of a designation, thereby acting as a proxy for investors' perceptions of the designation. This methodology works well with designations for multiple reasons. First, many of the designations are publicly announced, making them visible to both investors and researchers. Second, the designations are discrete events, thereby increasing the validity that the designation has the impact on stock price. Lastly, most of the designation announcements are specifically tailored to investors, increasing the likelihood that they will see them and that they will add the information contained within them to their valuation of the firm.

This study covers three policies, correlating to each of its chapters. The first chapter studies the fast-track designation, the second the Orphan designation, and the third the stacked designation (a fast-track designation which has a prior Orphan designation). Each of the chapters tests three main research hypotheses: (1) whether the announcement of a designation has an overall effect on stock price; (2) whether this effect has changed over time; and, (3) whether the effect is different for different sized firms. The specific hypotheses are outline below.

Aim 1: To determine whether the fast-track designation is an effective signal.

Hypothesis 1A: The fast-track designation does provide a signal to investors.

Hypothesis 1B: The strength of the average fast-track signal decreases over time.

Hypothesis 1C: The strength of the average fast-track signal will be higher for smaller firms than for larger firms.

Aim 2: To determine whether the Orphan designation is an effective signal.

Hypothesis 2A: The Orphan designation does provide a signal to investors.

Hypothesis 2B: The strength of the average Orphan signal increases over time.

Hypothesis 2C: The strength of the average Orphan signal will be higher for smaller firms than for larger firms.

Aim 3: To determine whether having a prior Orphan designation increases the strength of a subsequent fast-track signal.

Hypothesis 3A: Having a stacked designation increases the strength of the signal, compared to a non-stacked designation.

Hypothesis 3B: The strength of the average stacked designation signal increases over time.

Hypothesis 3C: The strength of the average stacked designation signal will be higher for smaller firms than for larger firms.

It would be nearly impossible to assess the entire impact and success of these designation programs in one study. This dissertation, therefore, has focused on one particular aspect of impact and success: the degree to which investors value these designations. The results of these studies should provide policymakers and regulators one piece of the assessment puzzle, to help inform whether these programs are working as predicted, and what characteristics would be most beneficial for future programs. Assessing this one piece of the designations is not holistic, but it is a necessary first step. Future research should focus on studying other aspects of the designation programs to fully assess the impact and degree of success they are having on encouraging innovative and clinically meaningful drug development.

Chapter 2 – The Signaling Effects of the Fast-Track Designation

Abstract

Investors in pharmaceutical firms face substantial information asymmetries. Only a small fraction of drugs that enter clinical development are ever approved by the U.S. Food and Drug Administration (FDA), causing severe uncertainty for investors. While investors would desire information regarding a drug's potential likelihood of a successful approval, firms are limited in their ability to share any proprietary information, because in doing so they may lose their competitive advantage. Instead, firms may use signals to indicate to investors the likelihood of success of drugs in their pipeline. One such signal is the FDA fast-track designation, which was created in 1998. Firms apply for the designation from the FDA, and receive it if their drug meets certain federally mandated criteria. The firms can then publicly announce the receipt of the designation to their investors, thereby reducing information asymmetries about a drug's potential market success. Using an event-study methodology with stock and market data extracted from the Center for Research in Security Prices (CRSP), this analysis examines three questions regarding the signaling effects of the fast-track designation. In the event study methodology, the strength of a signal is measured by the change in the stock price of a firm after an announcement. This change, aggregated across all events, is known as the cumulative abnormal return (CAR). In the first section, the study examines whether the fast-track designation acted as a signal to investors (between 1998 and 2012 with n=196 firms), and finds

CARs of 6.53% after the announcement of a fast-track designation. In the second section, the study examines whether the strength of the fast-track signal changed over time due to investors updating their priors regarding the quality of the fast-track signal (between 1998 and 2004 for n=86 firms and 2005-2012 for n=110 firms). Findings suggest a decrease in CARs of almost 50% between the first years of the fast-track program, and the later years of the program. In the last section, the study analyzes whether the strength of the fast-track signal differs based on firm size. It finds CARs of 12.01% for the smallest firms and CARs of only 0.13% for the largest firms, possibly indicating significant differences in information asymmetries between different sized firms.

Introduction

Pharmaceuticals have evolved over the last hundred years from vaccines and antimicrobials to include everything from monoclonal antibodies to targeted therapies. It has been estimated that pharmaceutical innovation was the catalyst for over 40% of the longevity gains in the United States between 1970 and 1991.(4) In recent years, over $250 billion has been spent on prescription drugs annually in the United States, and pharmaceutical firms have spent over $65 billion a year on research and development (R&D).(5, 6) Pharmaceutical innovation, therefore, represents an important part of both the public's health and the economy, and encouraging further innovation is an important policy objective.

Pharmaceutical innovation is uncertain and expensive, however, and typically requires equity investment by both individuals and organizations to share in the risk. Although there is potential for significant return on investment, encouraging investment in drug development has been challenged by the fact that pharmaceutical firms and their investors face significant

information asymmetries. Specifically, it is difficult for investors to determine whether a drug will eventually be approved and brought to market. Although by 2008 over 100 approved drugs had reached the level of blockbusters, grossing over $1 billion a year in sales, this is the exception, not the rule; only one in nine new drugs to be studied in humans (investigational new drugs, INDs) ever gains regulatory approval. (7-10) Having a drug approved by the U.S. Food and Drug Administration (FDA) is the most important outcome of a development project, because if the drug fails, R&D costs cannot be recouped, and future profits cannot be used to fund new projects. If a drug is not going to be approved, it is desirable for it to fail early in the development process, as each stage of R&D costs more than previous ones.(11) Despite the importance of information regarding a drug's likelihood of success to investors, pharmaceutical firms cannot share all drug development information due to the fear that other companies might utilize proprietary information for their own projects. For example, this could include sharing the molecular structure of a drug, or when patents on the drug are expected to expire. In order to overcome this information asymmetry, pharmaceutical firms may have used FDA drug designations to signal a drug's likelihood of approval to investors.

This study analyzed the signaling effects of the FDA fast-track designation. The fast-track designation was created by Congress in 1997 to enable faster development for needed drugs. Firms could receive a fast-track designation for their drug if it treated a serious or life-threatening condition, and met an unmet medical need.(12) Once a firm obtained this designation for a drug, it could signal to investors by publicly announcing the receipt of this designation, thereby potentially decreasing the information asymmetries. The information gained by the signal should have induced an increase in investors' expectations regarding the

likelihood of the drug's potential success, and led to an increase in the stock price of the firm. Therefore, an event study methodology was used to determine the strength of the signal provided by a fast-track designation, where signal strength was measured by an abnormal increase in the stock price of a firm after the announcement occurred.

The study investigated three questions regarding the signaling effects of the fast-track designation. The first aim of this analysis was to determine whether the fast-track designation acted as a signal to investors over the period 1998 to 2012. The second aim of this research was to determine whether the strength of the average fast-track designation signal had changed over time. As new information became available, investors were able to see how well this designation predicted the future success of a drug, and thus they were likely to update their priors regarding how well this designation signaled the drug's likelihood of approval.(13-15) The third aim of this research was to determine whether the fast-track designation had differing signaling effects for different sized firms. It was hypothesized that small firms benefited more from the fast-track designation than larger firms. These small firms may have had a limited or nonexistent track record for bringing drugs to market, and therefore there may have been greater information asymmetries between these firms and their investors. The announcement of a designation would therefore have caused a greater reduction in the information asymmetries, resulting in stronger signaling effects.

The Fast-Track Designation

The fast-track designation was enacted in 1997 through the Food and Drug Administration Modernization Act of 1997 (FDAMA). It was originally created as a mechanism to give patients faster access to new HIV and cancer drugs, by speeding up the regulatory

process for approval.(16) The FDA had the ability to grant a fast-track designation to a drug if it met two criteria. First, the drug must have been used to treat a serious or life-threatening condition. Second, the drug must have met an unmet medical need.(12) A drug could meet an unmet medical need if it treated a condition for which no other therapy existed, or the drug provided a significant improvement over existing therapies. If a drug was indicated for multiple conditions that met the criteria for the designation, a firm could apply for fast-track designations for each of the conditions. The application process involved the firm submitting a written request for the designation to the FDA, along with supporting documentation regarding the drug's indication and how it fills an unmet medical need. The FDA would review these materials to determine whether the drug met the congressionally mandated requirements for designation. As of 2008, the percent of applications for fast-track designation that subsequently received the designation was 74.5% for pharmaceuticals and 63.6% for biologics.(17) As of December 31st, 2012, there had been 712 fast-track designations conferred, on 669 unique drugs.(18)

Firms typically applied to the FDA for the designation during the early stages of clinical development, while the drug was in the investigational new drug (IND) phase. However, the main benefits of applying for the fast-track designation were not realized until the drug had finished its required clinical trials. The fast-track designation conferred three primary benefits. First was that the firms could choose to utilize a rolling review of the drug's marketing application.(16) When a drug had finished its required clinical trials, the sponsoring firm submitted either a New Drug Application (NDA), for a pharmaceutical drug, or a Biologic License Agreement (BLA), for a biologic drug. This marketing application would be reviewed by the FDA

to determine whether the drug would be approved for public use. A rolling review would allow the firm to submit sections of the NDA/BLA for review at different times, rather than submitting the entire NDA/BLA at one time, as was standard. This process could have allowed the application to be reviewed more expediently. A second incentive of the fast-track designation was that it allowed firms to have pre-NDA/BLA conferences with the FDA to discuss clinical trial designs and the composition of the NDA/BLA application.(17) While historically any firm was able to meet with the FDA to discuss clinical trial design, or any other concerns, the fast-track designation created a built-in mechanism for firms to request these meetings, by formally requiring the FDA to provide them when requested. Lastly, most fast-track drugs were also eligible for a priority review.(19) A priority review was given to drugs which treated serious conditions and demonstrated significant improvement, in safety or efficacy, over existing therapies. If the FDA granted a priority review, the time the FDA spent reviewing the drug was reduced to six months, from the standard ten months. This meant that, if approved, a drug could reach the market four months earlier, and was therefore able to generate profits sooner.(16)

Investor Reactions to Drug Development Announcements: Previous Studies

Numerous studies have used an event study methodology to determine how public announcements are used by pharmaceutical firms as signals for their investors. Dedman, et al. (2008) investigated R&D announcements by pharmaceutical firms along the entire length of the drug development pipeline.(20) Their main finding was that drug development announcements, such as clinical trial results, had a larger impact on stock price than earnings announcements. Three studies investigated the market response to the announcement of a drug approval by the

FDA. Sharma and Lacey (2004) found average abnormal returns (the assessed change in stock price due to the announcement) of 0.48% on the day of an approval announcement(21) while Sarkar and Jong (2006) found average abnormal returns of 0.35%.(22) Strum, Dowling, and Roder (2007) found average abnormal returns of 0.74% and 0.25% for biotech and pharmaceutical firms, respectively, on the day of announcement.(23) The authors suggested that these low abnormal returns may have been evidence that most of the information regarding the likelihood of an approval was incorporated before the official announcement.

Ahmed, Gardella, and Nanda (2002) studied the wealth effects on firms when an announcement of a drug withdrawal occurred.(13) They found abnormal returns of -7.85% on the day before and day of the announcement; but also found that the negative abnormal returns were much greater for firms whose drug had not yet been approved (-18.69%), than for those drugs which were withdrawn during post-market surveillance (-1.83%). Together, the results of previous studies suggest that much of the wealth effect created by a successful drug was already incorporated into the stock price before the drug was approved. Therefore, it was likely that early announcements in the drug development pipeline would be stronger signals to investors than announcements occurring later in development.

Two studies in the literature examined the signaling effects of the fast-track designation. Anderson and Zhang (2010) aimed to determine whether a fast-track designation announcement improved investor's perceptions of firm value.(2) Their sample was limited to any drug that received a fast-track designation between 1998 and 2004 (n=109). Anderson and Zhang found that investors responded favorably to fast-track announcements, as indicated by positive abnormal stock returns of about 9%. The authors also split the announcements into

quartiles based on firm size, using market value of equity as the proxy. They found significantly higher abnormal returns for the smallest quartile than for the largest quartile. Alefantis, Kulkarni, and Vora (2005) also aimed to determine whether a fast-track designation would increase the stock price of a given firm. (3) Their sample was limited to any drug receiving a fast-track designation between 1998 and 2001 (n=26). The authors found an average positive stock price increase of 10.2%.

In sum, previous research suggested that between 1998 and 2004, announcement of a fast-track designation by pharmaceutical firms resulted in average abnormal returns of between 9 and 10.2 percent. Announcements of any event early in the drug development process were more likely to convey meaningful information to investors, as were announcements by smaller firms relative to larger firms. Building on these findings, this study examined the signaling effects of fast-track designations, contributing to existing knowledge in two significant ways. First, the sample period was increased to include the years 1998-2012. And second, a longitudinal analysis was performed to determine whether the strength of the fast-track signal had changed over time.

Study Theory Development

Signaling Theory

In the pharmaceutical industry, information asymmetry has long been a problem in the investor-firm relationship. Firms have been limited in the amount of information about their R&D pipeline that they can divulge to investors, primarily due to the need to safeguard their primary competitive advantage: their proprietary drug development information.(15) These problems have been magnified in R&D intensive industries, such as the pharmaceutical

industry, for three central reasons. First, because most R&D projects (such as drug development projects) were unique to a firm, the R&D performance of a given firm in an industry did not convey any information regarding the R&D performance of other firms in the industry. Second, there were no organized markets for R&D, and therefore no set prices for it from which an investor could glean information. Lastly, accounting and reporting rules surrounding R&D were not set up to provide any indication of the value or productivity of the R&D expenditures.(24) These information asymmetries created the potential for adverse selection, where low quality pharmaceutical firms were able to act as high quality pharmaceutical firms to investors, and investors needed to use trial and error to determine which firms were high quality.(25, 26) Because this was not an optimal equilibrium for either investors or the high quality pharmaceutical firms, high quality firms needed to find a way to demonstrate the quality of drugs in their R&D pipeline to investors without divulging proprietary information. To demonstrate this, high quality pharmaceutical firms could use signals to show investors their true quality.

For a signal to achieve its desired outcome, it must fulfill two properties.(27) First, the signal needs to be observable; investors must be able to notice the signal in order to be able to act on it. Second, the signal needs to be costly; a cost must be involved in obtaining or using the signal. The cost of the signal could be in terms of time costs, such as preparing the paperwork for a designation, or in monetary costs, such as paying to submit a designation. While it is obvious that a signal must be observable to have an impact on investors, it is crucial that a signal be costly. Without this element of cost, low quality pharmaceutical firms would have had no reason not to signal as well, which would render the signal useless to investors.(27, 28) Thus,

for a signal to separate high and low quality pharmaceutical firms for investors, it must be both observable and costly.

The standard signaling timeline is typically split into four periods: the first period, in which the signal has not yet been sent; the second period, in which the signaler has sent the signal to the receiver; the third period, in which the receiver has received the signal; and the final period, in which the receivers update their priors regarding the quality of the signal. (27) In event studies, the second and third periods are collapsed into a single period following the semi-strong form of the efficient market hypothesis. This hypothesis states that all information regarding a firm is immediately incorporated into its stock valuation as soon as the information becomes available.

The Fast-Track Designation as a Signal to Investors

This study examined the fast-track designation as a firm's signal to investors about a drug's likelihood of being approved by the FDA, and therefore its future profits. The signaling literature on R&D intensive industries suggested that the information asymmetries between investors and firms lay within intangibles in the R&D process. For pharmaceutical firms, this translated to uncertainty about whether a drug was likely to be approved, and therefore uncertainty regarding its ability to create profits for the firm and investors. At its introduction, investors believed that the fast-track designation conveyed information regarding the FDA's likelihood of approving the drug, and in turn, the drug's potential to produce profits (later referred to as "drug quality").(11, 29) This theory led to the first aim of this research, the central hypothesis of which was:

Hypothesis 1: *Investors perceived the fast-track designation as a positive signal of a drug's quality over the period 2008 to 2012.*

The fast-track designation satisfied all the theoretical criteria needed for being considered a signal of a drug's future profits. Specifically, the designation was both costly and observable. Firms applied to the FDA for the designation, which was costly in terms of both employee time and monetary costs. While the monetary costs were fairly low to submit an application, they were not zero.(11) Additionally, firms were able to publicly announce the receipt of the designation, making it easily observable. Importantly, the FDA was a neutral, third-party gatekeeper with access to all current data on the drug. The firms were able to provide proprietary information to the FDA, which could not be revealed to investors, due to the FDA's strict non-disclosure policies. The FDA also had no incentive to approve designations for drugs that did not meet the congressionally mandated standards for the designation. These two features ensured that the integrity of the fast-track signal was not compromised, and that firms with low-quality drugs could not easily (that is, at low cost) imitate those with high-quality drugs.

Supporting the conceptualization of the fast-track designation as a signal, evidence has suggested that firms may have been using it solely as a signal to investors.(30) While, like other FDA drug designations, a fast-track designation conveys multiple tangible benefits (for example, a rolling review), many firms have not taken advantage of these benefits, and many of the benefits were already available to firms without the designation.(18) This behavior suggests that firms may have been applying for this designation solely for the signaling benefits.

For this analysis, the signaling environment for the fast-track designation was conceptualized as comprising two parties and three time periods. The two parties were the signaler (the pharmaceutical firm that wished to show its underlying R&D pipeline quality) and the receiver (the investors who were deciding which firms to invest in). The signal was the announcement of the receipt of the fast-track designation. The three time periods were the period prior to the announcement of the fast-track designation, the period when the signal was sent by the firm and received by investors, and the period during which investors updated their priors regarding the quality of the signal's information. Assuming the semi-strong form of the efficient market hypothesis means the value of the fast-track designation should be incorporated into a firm's stock price as soon as the announcement is made. The second study question, discussed below, extends the final period, when receivers update their priors, to incorporate a longitudinal learning component.

Longitudinal Changes in the Strength of the Fast-Track Signal

The purpose of the fast-track designation was to signal to investors that a firm had a high quality drug, that is, a drug that had a high likelihood of generating future profits. However, over time there may have been a learning component to the investor's evaluation of the signal's informational quality.(15, 26) Specifically, if the average fast-track designation was not highly correlated with subsequent marketing approval, and therefore the ability to generate profits, then investor's perceptions of the value of information conveyed by the signal may have decreased over time.

When it was first introduced, the fast-track designation was considered a strong indicator of a drug's likelihood of future approval. Primarily, this was because the designation

was given to drugs that were used to treat a serious or life-threatening condition, which typically had a lower regulatory approval hurdle.(19) However, the actual regulatory outcomes of fast-track drugs were significantly lower than expectations. As of 2008, of the drugs that had received a fast-track designation, only 10.6% of the pharmaceuticals and 17.7% of the biologics were subsequently approved.(17) In comparison, during approximately the same time period, the overall Investigational New Drug (IND; clinical trial phase of drug development) success rate was 20.9%.(7) Therefore, over time, investors were able to see that drugs that received a fast-track designation actually had a lower rate of approval than the average new drug that did not receive a fast-track designation. It was then likely that, acting as rational actors, investors updated their priors regarding their perception of the fast-track designation as a signal of drug quality. The second aim of this research was to determine whether, over time, the strength of the fast-track signal changed as investors updated their priors regarding the quality of the signal's information. This led to the second hypothesis:

Hypothesis 2: *The magnitude of the fast-track signal was higher for the earlier announcements than it was for later announcements.*

The process of investors updating their priors about the quality of the fast-track signal's information likely occurred after each drug with a fast-track designation was either approved, or failed in development. This process would therefore be ongoing, but immediate once new information was available. However, for the purposes of this analysis, it was important to determine a theoretically plausible cutoff point to compare the signaling effects over time, as determining the effects of each incremental piece of information was not empirically feasible. Therefore, it was necessary to determine at what time period it was likely that investors had

accumulated the aggregate amount of information necessary for them to have reassessed their prior that the fast-track designation had positive predictive power that a drug would be subsequently approved.

Two assumptions were made to determine the time needed for investors to fully integrate the outcomes of fast-track designated drugs into their priors regarding the fast-track signal's informational quality. First, it was assumed that most drugs took between 4-5 years after receiving the fast-track designation to either be approved for use, or to fail in development. This assumption was based on the fact that most fast-track drugs received their designations during the Phase II clinical trial portion of the drug development timeline. Once a drug had entered this phase of trials, the average time to finish development and be reviewed by the FDA was 4-5 years. As the first fast-track designations were conferred in 1998, that would imply that the first drugs receiving the designation would have either failed in development, or been approved, by 2002 or 2003. This average development time for fast-track drugs was confirmed using internal FDA data. Second, it was assumed that investors needed multiple examples of fast-track drugs either failing or succeeding in clinical development for them to have fully integrated the new quality of the fast track signal's information. The prior that the fast-track designation would be a strong predictor of subsequent approval was a strongly held belief in the investing community.(11) Therefore, it would have likely taken multiple examples of fast-track drugs failing to obtain marketing approval, at rates higher than non-fast-track new drugs, for investors to fully abandon their strong priors. Given these two assumptions, this analysis used the year 2004 as the time period in which investors should have fully updated their priors regarding the quality of the fast-track signal's information. The

analysis was therefore split into pre- and post-2004 time periods to compare the strength of the fast-track signal.

The Strength of the Fast-Track Signal by Firm Size

A central ancillary benefit of the fast-track designation signal was to reduce information asymmetries between firms and investors. The previous aims of this study set out to determine the magnitude of the signal, as a proxy of investor's perceptions of its quality. This third aim of the research was undertaken to determine whether the magnitude of the signal differed by firm size. Such a finding would suggest heterogeneity in information asymmetries between different sized firms and investors. (2, 31-33)

There may have existed greater information asymmetries between small firms and investors, than larger firms and investors, for multiple reasons. First, smaller firms likely had a more limited, or nonexistent, history of successful drug development. If a firm had never brought a drug to market, then investors did not have any prior information on which to assess the likelihood that a firm would be able to successfully bring the fast-track designated drug to market. Second, each individual drug in a small firm's pipeline carried more weight than any individual drug in a large firm's pipeline. A large firm may have needed successful new innovations simply to stay competitive with other large firms. A small firm may have needed successful new innovations to survive as a company.(34) The loss of even a single drug in a small firm that had no other drugs on the market could have led to the loss of investor funding, and therefore the end of the firm. Third, the relative value of any successful drug achieving a given level of profitability would be greater for a small sized firm than a larger one.(35) For example, if a small firm with annual profit of $100 million had a drug approved which would

produce another $100 million in annual profit, then the firm had increased its annual profit by 100%, and investors should have appreciated the gain accordingly. In contrast however, if a large firm, with annual profit of $1 billion were to bring the same drug to market, the annual profit would have only increased by 10%, an entire order of magnitude lower. And while investors should have responded positively to this approval, the magnitude of the response would likely be lower than for the smaller firm.

Lastly, investors may have already expected larger firms to go after these designations, as they had the infrastructure and institutional knowledge to be able to successfully apply for them.(36) Therefore the information conveyed by an announcement of the receipt of a fast-track designation by a larger firm would have conveyed less unanticipated information, causing a decrease in the magnitude of the market response compared to a smaller firm. In contrast, the announcement of the receipt of a designation by a smaller firm would likely have been met with a higher market response as obtaining the designation was likely more costly, and investors gained more unanticipated information from the fast-track signal for a small firm. The theory surrounding differences in the fast-track signal by firm size led to the third hypothesis:

Hypothesis 3: *The magnitude of the fast-track signal was higher for the smallest firms than it was for the largest firms.*

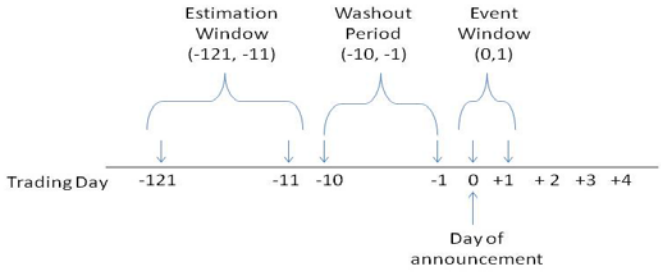
Methods

Defining the Event Timeline

For all three study questions, the event timeline was split into two periods: the estimation window and the event window. (Figure 2.1 provides a graphical representation of the event timeline.) The estimation window was used to calculate the predicted value of the

stock at the time of the announcement of the fast-track designation. For this analysis, an estimation window of 110 trading days (*t*= -121, -11) was used, where *t*= 0 was the day of the announcement.(22) The event window encompassed the days over which the abnormal returns precipitated by the announcement were expected to occur, and an event window of *t*= 0, 1 was used. While the semi-strong form of the efficient market hypothesis theorized that all public information should have been immediately incorporated into a stock price after the fast-track designation was announced, the trading day after the announcement was included in the event window due to the sometimes obscure nature of the announcement, and to stay consistent with the literature in using a multi-day event window.(15)

Figure 2.1 Event Study Timeline



Calculating the Expected Returns

Following the literature on event studies in the pharmaceutical industry, the expected returns of a stock were estimated using the market model.(3, 13, 15, 20-23, 37) A benefit to using the market model was that it picked up less cross-correlation from the residuals than did the Fama-French model (an alternative model of asset pricing).(38) As the data used for this

analysis had multiple instances of fast-track announcements on the same or close days, which could cause cross-correlation in the residuals, the market model was deemed the best fit.

The market model for a single event was calculated as expressed in Equation 1. In this model, $R_{i,t}$ and $R_{m,t}$ were the period t returns on the stock of firm i and the representative market portfolio, respectively. Conceptually, if a perfect linear relationship between the market return and an individual stock return were expected, α_i (the intercept term) and β_i (the slope term) should have perfectly predicted the individual stock return $R_{i,t}$, and $\epsilon_{i,t}$ should therefore have been mean zero. Unexplained deviations from this relationship would be picked up by the error term, which was the basis for calculating the abnormal returns.

$$R_{i,t} = \alpha_i + \beta_i R_{m,t} + \epsilon_{i,t} \qquad (1)$$

The S&P 500 Composite Index was used to measure the market return. This index has been widely used in the literature, and had the added benefit of containing numerous pharmaceutical and biotech firms, ensuring that it picked up both market and industry effects.(21, 35, 39)

Calculating the Cumulative Abnormal Returns

The abnormal returns, $\hat{\epsilon}_{i,t}$, were calculated using Equation 2.(37, 40, 41)

$$\hat{\epsilon}_{i,t} = R_{i,t} - \hat{a}_{i,t} - \hat{b}_{i,t} R_{m,t} \qquad (2)$$

The abnormal returns were then aggregated by individual firms across time and then aggregated across both firms and time, to produce the measure known as the cumulative abnormal returns (CARs).

The GRANK-T Significance Test

The standard method of testing the statistical significance of CARs in the event study literature involved parametric tests. However, as abnormal stock returns are typically non-normally distributed, evidence suggests that nonparametric tests should be used for significance testing in event studies.(40) A limitation of previous nonparametric tests was that they could not be accurately extended to encompass multiple event days.(42, 43) This shortcoming was addressed in the nonparametric generalized rank t-test, known as the GRANK-T test, described in Kolari and Pynnonen (2011).(38) This test accounted for the multiple event days problem by condensing all the CARs of multiple event days into one observation, which was then used to conduct the significance test. The authors showed that the empirical power of their test was stronger than other popular parametric and nonparametric tests of CARs that had been used previously. Additionally, the test was found to be robust against the cross-correlation caused by event day clustering. As there were multiple instances in the data where this occurred, this was a further benefit of choosing this particular test. This test was used to determine the statistical significance of the CARs for all three hypotheses.

The Wilcoxon Rank Sum Significance Test

The Wilcoxon rank sum test was used to test the difference in means between the CARs of the longitudinal analysis, to determine whether there was a statistically significant difference between the two time periods. This test is also a nonparametric rank test, with a z-statistic as output. The Wilcoxon rank sum test worked by determining whether two independent samples were drawn from the same underlying population distribution. Therefore, the test was able to

test the hypothesis that there were statistically significant longitudinal changes in the CARs between 1998-2004 and 2005-2012.

Data

The announcements of the receipt of a fast-track designation were found via a systematic, manual search of LexisNexis using the search terms “fast track” and “FDA”. A total of 442 announcements were found, spanning the time period 1998-2012. Stock data were extracted from the Center for Research in Securities Prices (CRSP). Data included both the daily returns for individual firms, as well as the daily returns for the S&P 500 Composite Index used as the market return. Market capitalization, the market value of the firm’s trading and non-trading share issues, was used as the proxy for firm size.(44) The market cap data from the year the designation was announced were extracted from the “market value” variable in Compustat.

Exclusion Criteria

Once the announcements of a fast-track designation were gathered, the following exclusion criteria were applied to ensure that the event study methodology could be used.

First, designations for drugs that had been previously approved by any worldwide drug regulatory agency were excluded because they were likely inherently different from announcements for drugs which had not been approved. Approved drugs were much less uncertain to investors, as their safety and efficacy profiles were public and well known. A total of 22 announcements were excluded for this reason.

Next, remaining firms were excluded if daily stock data were not available for the entire estimation and event windows. There were two possible reasons that the stock data were not available. The first was that the firm was private, and therefore stock information did not exist.

The second was that data for the full time period were not available from CRSP. (There were many possible reasons for this, including the firm going public sometime during the time period, or getting acquired during the time period.) A total of 168 announcements were excluded due to this exclusion criterion.

Lastly, the remaining firms were excluded if another significant event occurred during the event window (t= 0, 1). This was to ensure that there were no confounding events within the event window. Observations were excluded if one of the following was announced during the event window: (a) general drug news (e.g., clinical trial results, patent received, drug approved, grant received, other designation received); (b) financing news (e.g., common stock offering, credit downgraded, debt financing); (c) leadership news (e.g., senior leadership resigning, being hired, or optioning stock); (d) firm news (e.g., merger/acquisition announced or finalized, partnership deal announced, licensing deal announced). A total of 55 announcements were excluded due to this criterion.

Additionally, one announcement was excluded from the analyses because it was an outlier in its abnormal returns. In event studies, it is necessary to check for outliers because they are inherently different from the other events, and biased CARs can strongly affect the conclusion of a study.(35, 45)

Final Data

Once the exclusion criteria were applied, a total of 196 announcements remained, spanning the entire desired time period 1998-2012. For the longitudinal analysis, there were 86 announcements in the 1998-2004 time period, and 110 announcements in the 2005-2012 time period. For the firm size analysis, 42 additional firms were excluded due to unavailable market

cap data, resulting in a total sample size of 154 firms. Of those firms, 12 were classified as nano-cap (market cap less than $50 million), 48 were classified as micro-cap (market cap between $50 and $250 million), 71 were classified as small-cap (market cap between $250 million and $2 billion), and 23 were classified as mid-cap (market cap between $2 and $10 billion). There were no firms in the final sample with a market cap greater than $10 billion.

Average daily returns calculated during the estimation window (*t*= -121, -11) showed minimal abnormal returns (Table 2.1). The returns were especially small for the nano-cap firms, as well as for the second time period of the longitudinal analysis. Average daily returns calculated during the event window (*t*= 0, 1) showed substantial increases in daily returns, except for the largest firms (Table 2.2).

Table 2.1 Average Daily Returns for Estimation Window (-121, -11)

Study	**Average Daily Returns**	**Standard Deviation of Average Daily Returns**
Aim 1		
Overall (n= 196)	0.24%	9.1%
Aim 2		
1998-2004 (n= 86)	0.34%	11.5%
2005-2012 (n= 110)	0.16%	6.7%
Aim 3		
Nano-cap: Market cap <$50m (n= 12)	0.01%	6.0%
Micro-cap: Market cap >$50m & <$250m (n= 48)	0.22%	6.7%
Small-cap: Market cap >$250m & <$2b (n= 71)	0.33%	7.4%
Mid-cap: Market cap >$2b and <$10b (n= 23)	0.14%	3.2%

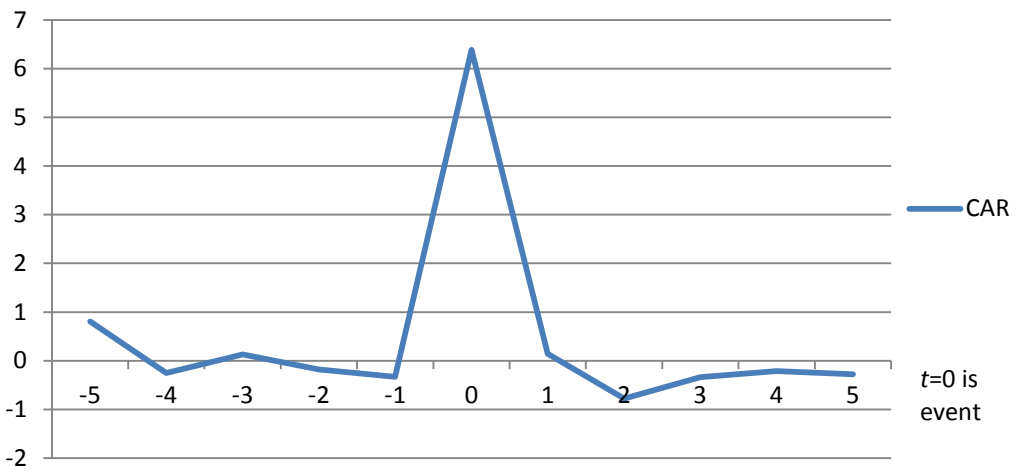
Table 2.2 Average Daily Returns for Event Window (0, 1)

Study	Average Daily Returns	Standard Deviation of Average Daily Returns
Aim 1		
Overall (n= 196)	3.89%	12.5%
Aim 2		
1998-2004 (n= 86)	5.28%	16.0%
2005-2012 (n= 110)	2.80%	8.9%
Aim 3		
Nano-cap: Market cap <$50m (n= 12)	7.29%	21.5%
Micro-cap: Market cap >$50m & <$250m (n= 48)	5.64%	15.9%
Small-cap: Market cap >$250m & <$2b (n= 71)	2.47%	6.5%
Mid-cap: Market cap >$2b and <$10b (n= 23)	0.02%	2.8%

Results and Discussion

The cumulative abnormal returns found over the entire time period were 6.53%, which was statistically significant at the 10% level (Table 2.3 and Figure 2.2). This result implied that the announcement of a fast-track designation caused the average firm's stock price to increase by 6.53% over what it would have been had the announcement not occurred. Although statistical significance was weak, this finding provided some support for the first hypothesis: that investors perceived the fast-track designation as a positive signal of drug quality. The 6.53% CARs were substantially greater than those found when a drug was approved, and were similar in absolute value to those found when a drug was withdrawn from the market, as previously discussed. This suggests that investors perceived the fast-track designation as conveying about as much positive information as a drug withdrawal provided negative information.

Figure 2.2 Graph of Cumulative Abnormal Returns Between (-5, 5)



These results deviated substantially from the previous event studies of the fast-track designation, where Anderson and Zhang, and Alefantis, Kulkarni, and Vora found CARs of between 9% and 10% after the announcement of a fast-track designation. Abnormal returns found in this analysis were between 2.5 and 3.5 percentage points lower, or about 50% lower on average. This discrepancy may have been caused by the small time frame utilized in the previous studies (four to seven years versus the 15 years used by this study), particularly if investors lost confidence in the positive signal of the fast-track designation over time.

Table 2.3 Results of Main Analyses

Study	Cumulative Abnormal Returns	GRANK-T Test Statistic
Aim 1		
Overall (n= 196)	6.53%	1.69*
Aim 2		
1998-2004 (n= 86)	8.63%	1.79*
2005-2012 (n= 110)	4.89%	1.35
Aim 3		
Nano-cap: Market cap <$50m (n= 12)	12.01%	2.36**
Micro-cap: Market cap >$50m & <$250m (n= 48)	9.27%	3.92***
Small-cap: Market cap >$250m & <$2b (n= 71)	4.42%	1.10

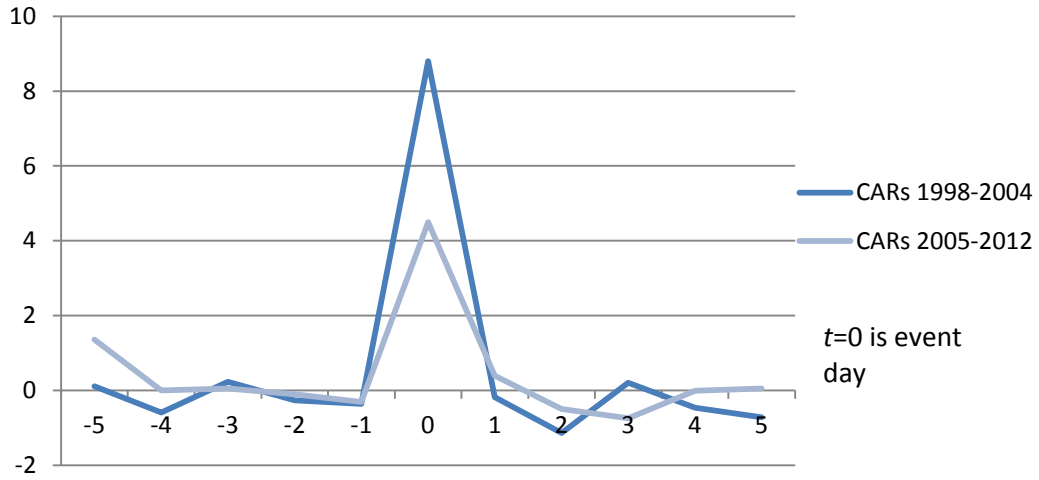
Mid-cap: Market cap >$2b and <$10b (n= 23)	0.13%	0.24
***statistically significant at the 1% level; **statistically significant at the 5% level; *statistically significant at the 10% level		

Longitudinal Analysis

There was some evidence to support the second hypothesis of a longitudinal change in investor perceptions of the fast-track designation (Table 2.3 and Figure 2.3). During the first seven years of fast-track designation (1998-2004), this study found CARs of 8.63%, which was statistically significant at the 10% level, and almost identical to the approximately 9% CARs found by Anderson and Zhang during the same time period. However, in the most recent eight years of the fast-track designation (2005-2012), this study found CARs of only 4.89% (not statistically significant). Although the Wilcoxon rank sum test did not identify a statistically significant difference between the two CARs (z = -0.90), practically, this difference, a decrease of almost 50% in the cumulative abnormal returns, was large.

The results of the longitudinal analysis suggest that investors changed their perceptions of the fast-track designation over time, updating their priors about how well the designation signaled drug quality. While it was not particularly surprising that investors learned over time, this finding suggests that the signaling environment for the fast-track designation was dynamic. It is therefore critically important that drug developers and policy makers monitor the changing environment to discern whether this drug designation program is continuing to accomplish its goals. The results of this study suggest that while investors still perceive the fast-track designation as a positive signal of drug quality, the overall strength of the signal has declined over time.

Figure 2.3 Graph of the Longitudinal Cumulative Abnormal Returns Between (-5, 5)



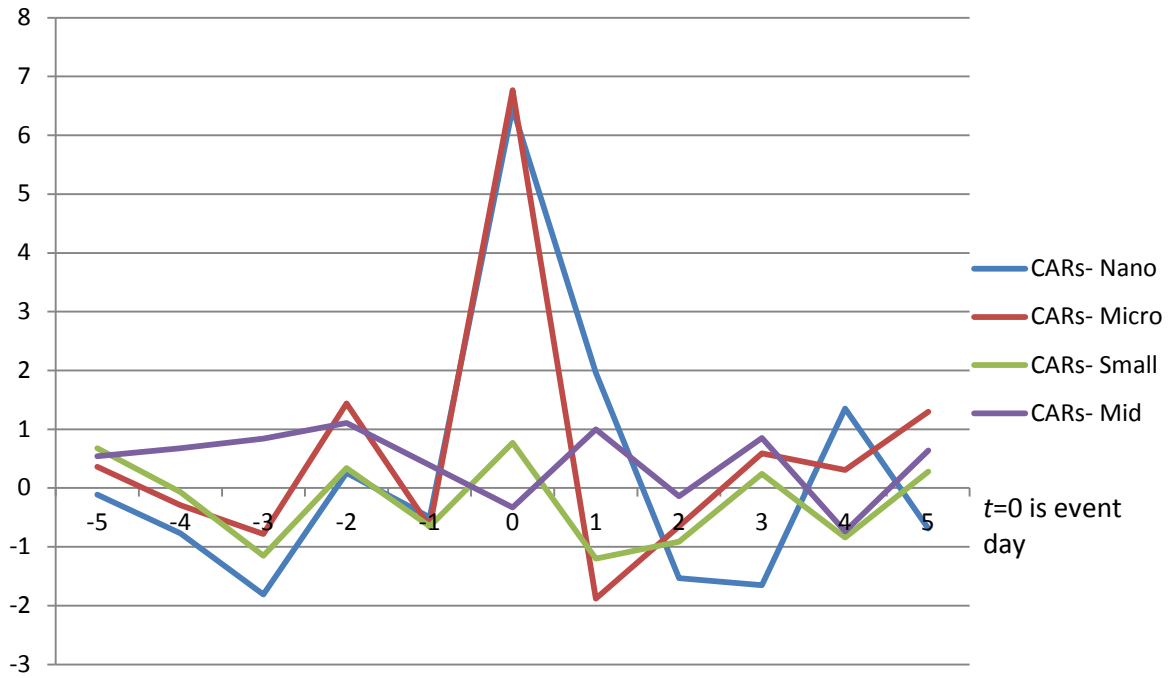
Firm Size Analysis

The results of the analysis of signal strength by firm size were striking, and provided strong support for the third hypothesis. The smallest firms, the nano-caps with a market cap of less than $50 million, had CARs of 12.01% after a fast-track designation was announced, and the result was statistically significant at the 5% level (Table 2.3 and Figure 2.4). These CARs were almost twice as large as those found for the study sample overall. The magnitude of the CARs fell only slightly for the micro-caps to 9.27% relative to the nano-caps, and the result was statistically significant at the 1% level. The CARs for the small-cap and mid-cap firms were 4.42% and 0.13%, respectively, and neither result was statistically significant.

These results suggest significant heterogeneities by size of firm for the signaling effects of the fast-track designation, and therefore provide compelling support for the hypothesis that there are different levels of asymmetric information between investors and firms based on firm size. The theory suggested that the information asymmetries between smaller firms and investors would be greater than those for larger firms. Smaller firms may have had a smaller, or

non-existent, history of producing successful drugs. Therefore, investors would have had less overall information with which to assess a particular drug's likelihood of successful development by a smaller firm. The results of the study supported this hypothesis. The difference of almost 12 percentage points in CARs between the largest firms and the smallest firms indicated that investors valued the information provided by the fast-track designation significantly more for small firms. This suggested that the fast-track designation reduced investor information asymmetries substantially for the smaller firms, while providing no statistically significant reduction in asymmetries for the largest firms.

Figure 2.4 Graph of the Cumulative Abnormal Returns by Firm Size Between (-5, 5)



Sensitivity Analyses

Sensitivity analyses for the first hypothesis indicated that the overall CARs were robust to extensions of the event window after the event occurred (Table 2.4). No additional increases in CARs were observed after the announcement of a fast-track designation. However, when the

event window was extended to include the day prior to the event, a gain in CARs of approximately 0.2 percentage points was observed. The CARs during the (-1, 1) event window were 6.72%, and were statistically significant at the 1% level. This was most likely due to the different sample of firms that was included in the analysis when the event window was extended. Sixteen firms were removed because they had concurrent events during *t*= -1. During the (0, 1) window, the removed firms had CARs of 1.84%, while the remaining sample, which was used in the (-1, 1) window, had CARs of 6.95%. This indicated that the removal of these firms possibly caused a spurious inflation of the CARs in the (-1, 1) event window. However, it cannot be ruled out that part of this result was caused by some form of early information on the part of investors.(24) Multiple other event studies of the pharmaceutical industry also found abnormal returns on the day prior to an event.(13, 15, 21-23, 37)

Sensitivity analyses for the second hypothesis substantiated the hypothesized break point of 2004-2005 in the longitudinal analysis (Table 2.4). Analyses comparing the 1998-2003 vs. 2003-2012 and 1998-2006 vs. 2007-2012 time periods also found substantially decreasing CARs, although the declines continued to be statistically insignificant. As these sensitivity results did not differ substantially from the originally hypothesized break point, the original break point was deemed reasonable.

Table 2.4 Results of Main Sensitivity Analyses

Sensitivity Analysis	**Cumulative Abnormal Returns**	**GRANK-T Test Statistic**
(-1, 1) event window (n=180)	6.72%	5.92***
(0, 4) event window (n=165)	5.55%	3.94***
(-1, 4) event window (n=154)	5.69%	3.64***
		Wilcoxon Rank Sum Test Statistic

1998-2002 (n=40)	8.43%	-1.30
2003-2012 (n=156)	6.04%	
1998-2006 (n=134)	7.25%	0.76
2007-2012 (n=62)	4.97%	
		***statistically significant at the 1% level

A sensitivity analysis was also conducted around data overlaps, that is, when a firm had an announcement occur during the estimation window of a separate announcement by the firm. It was possible that this data overlap would cause bias in the coefficients, although other event studies of the pharmaceutical industry did not find any bias.(37, 45) There were 14 occurrences (28 observations) of overlap in the data. Removing the first of the overlapping announcements led to overall CARs of 6.61%, and removing the second of the overlapping announcements led to overall CARs of 6.66%. This very limited difference from the overall CARs of 6.53% indicated that bias due to data overlap was not a serious threat to this analysis.

A last sensitivity analysis was conducted to determine whether the overall CARs were affected by co-developed drugs.(2) Many pharmaceuticals have been co-developed by two or more pharmaceutical firms, to decrease R&D costs and share propriety information regarding the project. However, investors may have reacted differently to announcements of co-developed drugs, as firms would also have had to share profits if the drug was subsequently approved. There were 13 instances (26 observations) of this in the data. This sensitivity analysis averaged the abnormal returns of the co-developers, and returned that single averaged number to form the overall CARs, which were 6.64%. This was slightly larger than the overall CARs of the study of 6.53%, indicating that announcements of co-developed drugs likely had lower average abnormal returns then singly developed drugs.

Limitations

One limitation of this study was that it was possible that the manual search for the fast-track announcements failed to find some early announcements, and therefore the date of announcement set for the analysis was mis-specified. It was also possible that the manual search for announcements failed to find some of the announcements that occurred. However, as long as there was no systematic failure in finding announcements, this should not cause bias in the results.

A second limitation of this study was its generalizability. The exclusion criteria limited the sample to firms which were: (1) publicly traded in the United States; and (2) had no other announcements during the event window. The first part of this criteria excluded private firms, as well as international firms, limiting the generalizability of the study to U.S. firms. In the initial sample of announcements, 53 announcements stated that the announcing firm was privately held, and 39 announcements indicated that the announcing firm was listed on an international exchange. In contrast, 11 announcements indicated that the firm was listed on an OTC exchange, 30 announcements indicated that the firm was listed on the NYSE, and 213 announcements indicated that the firm was listed on the NASDAQ exchange. (86 announcements did not indicate any affiliation.) These numbers from the initial sample indicated that, while having to remove the private and international observations from the data reduced the generality of the sample, the vast majority of the announcements came from firms which were publicly traded on a US exchange. Therefore, this should not be considered a major limitation.

A third limitation arises from the second part of the exclusion criteria that limited the sample to only firms that had no other announcements during the event window. It is possible that this excluded larger firms disproportionally, and therefore the results are not generalizable to the largest firms that received the fast-track designation. A simple calculation was conducted to identify whether large firms, defined as those with brand name recognition at the time of announcement, were more likely to be excluded from the sample. In the sample of announcements which remained after the first exclusion criteria was applied (that firms must be publicly listed on a US exchange), approximately 11% of the sample was composed of these large firms. In the final sample, once the event window exclusion criteria had been applied, this figure had decreased to approximately 4%. These results indicate that the proportion of large firms that was in the sample may have declined by as much as two-thirds due to concurrent events. This limitation in generalizability may therefore be substantial, and the results of this study may not apply to the largest of pharmaceutical firms.

While the limitations described above may limit the generality of the results, they are a known cost of using the event study methodology. Future research should focus on determining the effects of the designation on large firms, private firms, and foreign firms, which may involve a mixed-methods approach.

One important policy limitation this study was unable to address was whether these increases in investments were sustained over time. If investment in firms increased on the days surrounding the announcements, but the gains were not sustained over time, then the usefulness of the announcement was limited. However, even if these gains were not sustained, the fast-track designation would still have been useful in reducing information asymmetries and

increasing investor awareness of lesser known firms. Further analysis should be done to determine the long-term effects of this designation on investment.

Conclusion

Publicly traded pharmaceutical firms and their investors have always faced information asymmetries. The intensive R&D nature of the pharmaceutical industry has created valid concerns about releasing propriety information that could reduce information asymmetries, but could also be used to co-opt a firm's competitive advantage in drug development. Since continued investment was critical to funding the drug development projects of these pharmaceutical firms, firms needed to signal to investors that there was value in the investment. This was especially true for smaller firms that did not have a history of successfully approved drugs that could both inform investors and provide a source of cash flow for funding current projects. This study analyzed whether the FDA fast-track designation was effectively used to signal to investors the value of a drug in development. Utilizing an event study methodology and a non-parametric test for statistical significance, the analysis found that the announcement of a fast-track designation did act as a signal to investors. Additionally, it found that the strength of the signal changed over time, as investors updated their priors regarding the value of the designation after observing the success, or failure, of previous designated drugs. Finally, the study found that the fast-track designation reduced investor information asymmetries substantially for the smallest firms, while providing no statistically significant reduction in asymmetries for the largest firms.

The results of this study lead to two important policy implications. First, the declining signaling effects of the fast-track designation raise the question of whether the goals of the

designation continued to be met. Congress's goal in creating the fast-track destination was to speed drug development for serious or life-threatening conditions for which there was an unmet medical need. The implicit impact of this speed was that more drugs would be approved, to be used by patients. The degree to which investors react to the designation is a rough proxy for how successful these drugs are in obtaining marketing approval. The declining signaling effects of the designation may have implied that investors felt less confident in the information a fast-track designation supplied: which would be a strong correlation between receiving the designation and receiving a speedy regulatory pathway and approval. This implies that the fast-track designation may be failing to meet its goal of supporting clinically needed drug development. Second, the results of the firm size analysis suggested that the signaling benefits of the fast-track designation were disproportionately going to the smallest firms. This was not necessarily outside the intended actions of the designation, but policymakers should be aware that this has been its effect, and adjust future policies as needed.

Future empirical research should be undertaken to discern whether the increases in investment due to the announcements were sustained over time, and future qualitative research should be undertaken to interview policymakers, regulatory agencies, and investors regarding whether the fast-track designation continues to be a valuable tool to encourage drug development.

Chapter 3 – The Signaling Effects of the FDA Orphan Designation

Abstract

The Orphan drug designation was created by Congress in 1983 to encourage drug development for rare diseases. The designation provided multiple financial incentives that aimed to decrease the costs to pharmaceutical firms of developing these drugs. It was hoped that the incentives would increase the amount of investment in rare disease drug development programs by allaying investors' fears that the costs of developing these drugs would far outweigh the expected profits of the drugs. This study sought to determine whether investors perceived the awarding of an Orphan designation as a signal of the drug's expected profits. Using an event study methodology, the analysis found that, on average, a firm's stock price increased by 3.66% after the awarding of the designation was announced, as compared to what it would have been had there been no announcement. The study also found that investors' perceptions of the designation improved over time, and that the designation increased the stock price more for smaller firms than for larger firms. Therefore, the results implied that the Orphan designation was successful in increasing investor's perceptions of a drug's expected profits, and therefore was also potentially successful in its goal of increasing investment in drug development for rare diseases.

Introduction

A central public health goal of the US Food and Drug Administration (FDA) is encouraging innovative drug development, especially for diseases which currently have no

treatments. Since its creation through the Food, Drug and Cosmetics Act of 1938, the FDA has undertaken numerous public policy initiatives to foster this goal. These initiatives range from public-private partnerships, to greater transparency of FDA processes, to special designations that provide incentives for drug development in areas of unmet medical need.

A central part of encouraging innovative drug development was encouraging initial, and continuing, investment in drug development projects. This was especially true for drug development for rare diseases, where the potential market size for a drug was typically too small to justify the research and development (R&D) costs necessary to bring a drug to market. In 1983, Congress created a special designation for drugs in development that were indicated to treat a rare disease.(46) This was the Orphan designation, and it also conveyed tangible financial incentives to the developer of the drug (such as making some clinical trial expenses tax deductible).

Assessing the direct effect of the Orphan designation on new drug development has proved difficult. Lichtenberg (2011) estimated that the introduction of drugs to treat rare diseases had caused a substantial reduction in the potential years of life lost to rare diseases.(47) Additionally, Yin (2008) found that the introduction of Orphan designation led to a significant increase in the number of new clinical trials being conducted for rare diseases.(1) However, neither of these studies were able to show whether the creation of the Orphan designation translated into more drugs for rare disease patients. Partly, this was because the counterfactual (that more drugs for rare disease would still have been developed even without the Orphan designation) was impossible to determine, historical drug development data were often unavailable, and the overall measure of innovative new drug development success -- the

number of new molecular entities (NMEs), or new innovative drugs, approved yearly – has been relatively stable since the 1980s.(48)

This analysis evaluated how investors responded to the Orphan designation over time, thereby acting as a proxy for how successful the designation was in generating investment in drugs for rare diseases. An event study methodology was used to determine whether investors viewed the Orphan designation as increasing the expected profits of a drug, as measured by increasing investment in the firm once the awarding of an Orphan designation was announced. If investors perceived the Orphan designation as increasing expected profits, then there may have been greater investment in innovative rare disease drug development, consistent with the aim of this FDA program.

Background

History of the Orphan Drug Designation

The Orphan drug designation was created in 1983 when Congress passed the Orphan Drug Act (ODA). The goal of the ODA was to encourage more drug development for rare diseases, which in the US were defined as diseases affecting fewer than 200,000 individuals. In the 1970s, only 10 drugs had been approved for rare diseases in the US, and there were few financial incentives for pharmaceutical firms to develop drugs for these relatively tiny markets, where the likelihood of recouping R&D costs was small.(49) However, in the early 1980s patient advocacy groups for rare diseases such as HIV/AIDS, which at the time had a low enough prevalence to be considered a rare disease, lobbied Congress to create tangible incentives for rare disease drug development.(50) The outcome of this lobbying was the ODA and the creation of the Orphan designation.

To receive an Orphan designation, a firm submits a standardized application to the FDA to request the designation, along with supporting documentation that shows rare disease status for the disease that drug is being indicated to treat. There were no additional requirements for receiving the designation. If a firm was successful in applying for the designation, it was eligible for multiple financial benefits.(51) First, some clinical trial expenditures for the development of the drug were made tax deductible. This was a less important benefit for small firms, which usually did not have any, or had low, tax liabilities as they were not yet profitable. However, for larger firms, this could have helped make the development of these drugs less costly to develop. Second, if the firm submitted the drug for regulatory approval, the user fees were waived. This decreased the cost of development significantly for both large and small firms. Average user fees in fiscal year 2014 for submission with clinical trial data were over $2 million.(52) Last, if the drug was eventually approved, it received seven years of marketing exclusivity, which was two years more than for new drugs without an Orphan designation. This increased the potential profit stream for both large and small firms. In addition to conferring direct financial incentives, drugs with an Orphan designation were generally eligible for a priority review, and some were eligible for an accelerated approval, both of which shortened the potential time to market.

Advances in basic science, in conjunction with advances in personalized medicine and genomics, along with the decline of the 'blockbuster' drug, led numerous pharmaceutical firms to begin or expand their Orphan drug development programs, helping to increase interest in, and lend importance to, the Orphan designation. In the thirty years since the ODA was enacted (1983-2012), 2,739 designations were conferred, and 191 new molecular entities (NMEs) with

an Orphan designation were approved.(53) Additionally, since 2002, approximately 30% of all approved NMEs have been Orphan drugs.(53)

The Literature on FDA Designation Event Studies

An extensive search of the literature did not find any previous studies that examined how investors responded to an Orphan designation using an event study methodology. However, there have been two studies that have examined the signaling effects of the fast-track designation, another FDA designation given to drugs that are for serious or life-threatening conditions and treat an unmet medical need. While not looking at the Orphan designation, these studies could provide a starting point from which to compare investor reactions to FDA designation.

Anderson and Zhang (2010) aimed to determine whether a fast-track designation announcement improved investor's perceptions of firm value.(2) Using an event study methodology, they looked at four measures of perception: trading volume, short-term and long-term stock price changes, institutional ownership and analyst coverage. Their sample was limited to any drug that received a fast-track designation between 1998 and 2004 that they were able to identify through a news database search (n=109). Anderson and Zhang found that investors responded favorably to fast-track announcements. In particular, they found positive abnormal stock returns of about 9%, and concluded that the fast-track designation does convey positive information regarding a drug's quality. Alefantis, Kulkarni, and Vora (2005) aimed to determine whether a fast-track designation would increase the stock price of a given firm, also using an event study methodology.(3) Their sample was limited to any drug that received a fast-

track designation between 1998 and 2001 that they were able to identify through a news database search (n=26). The authors found an average positive stock price increase of 10.2%.

Conceptual Framework

In this study, the Orphan designation was conceptualized as signaling unobserved information about a drug's potential profitability. Information asymmetry, where firms have more information about a drug's potential for success than investors, has always been a critical problem in the investor-firm relationship. Firms are limited in the amount of information they can divulge to investors due to the need to safeguard proprietary information. These problems are magnified in R&D intensive industries, such as the pharmaceutical industry. This information asymmetry creates the potential for adverse selection, where low quality firms are able to portray themselves as high quality firms to investors, and investors must use trial and error to determine which firms are high quality. Because this is not an optimal equilibrium for either investors or the high quality firms, high quality firms need to find a way to demonstrate their quality to investors without giving up proprietary information. To demonstrate this, these firms can use signals to show investors their true quality.

The Orphan Designation as a Signal to Investors

Before the ODA was passed, there was too little investment devoted to the development of drugs for rare diseases. Firms and their investors had little interest in developing drugs for these diseases because their small market size implied small expected profits, which meant limited ability to recoup R&D costs and fund new development projects. The Orphan designation was created to help correct this market failure by both decreasing the

cost of developing the drugs, and allowing for an extended earnings stream if the drug reached the market, thereby increasing the expected profits of Orphan drugs.

Because of the design of the incentives, however, many of the tangible benefits of the Orphan designation were only valuable at later stages of a drug's development. Therefore, the immediate value of the designation was dependent on its ability to signal to investors information about a drug's lifetime expected profits. If investors viewed the Orphan designation as increasing a drug's expected profits, then investors were expected to respond favorably to a firm's announcement of receipt of the designation by increasing their investment in the firm. This framework led to the study's first hypothesis: announcement of the receipt of an Orphan designation provided a positive signal about expected profits to investors.

The Strength of the Orphan Designation Signal Over Time

The Orphan designation has made substantial gains since its introduction in 1983: from being a new and unknown tool at its inception, the Orphan designation is now a part of 30% of all NME approvals. This statistic alone shows that Orphan drugs have become a substantial part of the overall drug development pipeline. Additionally, Orphan drugs have become more financially successful than anticipated. Beginning in the early 2000's, numerous scientific breakthroughs in Orphan conditions were beginning to finish clinical development, and many Orphan drugs saw tremendously high reimbursement rates from insurers, in the hundreds of thousands of dollars per patient, per year.(54)

For these reasons, it was probable that, over time, investors changed the way they responded to the announcement of an Orphan designation. Specifically, it would seem logical that the greater the amount of proven experience, the more confidence investors would have

felt about the Orphan designation's ability to signal increased expected profits. This confidence would translate into greater investment in firms that received an Orphan designation in later years. Because 2000 was the year before Orphan designated drugs became a major sector of the drug development pipeline, after 2000 investors would have been expected to place more value on an Orphan designation. This development led to the study's second hypothesis: the strength of the Orphan signal was greater in the most recent years of the designation than in the initial years.

The Strength of the Orphan Designation Signal by Firm Size

While the Orphan designation conveyed tangible financial benefits to any recipient firm, these benefits may have been more valuable to some firms than others. Specifically, these benefits were likely more valuable to smaller firms than larger ones. In large firms, the financial benefits conveyed by the designation offset some of the initial costs of development, and the additional exclusivity ensured that profitability would be extended if the drug were approved. However, while important, the overall magnitude of these benefits was not particularly large when compared to the sales volume of most of these firms. In contrast, the value to smaller firms may have been significant.

Many small pharmaceutical firms had a very short, or non-existent, track record of successful drug development. Without any profits coming in from past, successful drugs, providing funding for current development projects was more difficult. The financial benefits of the Orphan designation could therefore be critically important for a small firm. The ability to reduce tax liabilities could be carried over multiple years, and waived user fees could save millions of dollars in development costs.

Investors in small pharmaceutical firms may therefore have found the award of an Orphan designation relatively more important as a signal of the drug's expected profits. The designation decreased the amount the firm would have to spend developing the drug, and therefore decreased the risk of the firm becoming insolvent and increased the speed at which the development process could progress, both of which would have significantly increased the drug's expected profits. Therefore, investors should have reacted more favorably to an Orphan designation received by a smaller pharmaceutical firm than a larger pharmaceutical firm. This led to the study's third hypothesis: the strength of the Orphan signal was greater for smaller firms than for larger firms.

Methods

To evaluate whether investors perceived the Orphan designation as an effective signal (i.e., adding positive value to a firm), this analysis utilized an event study methodology. An 'event' was defined as a publicly visible occurrence that affected either a single firm, or multiple firms. For example, other events that have been used with this methodology included a firm announcing that its drug had been approved for market use, withdrawn from market use or, as previously discussed, that one of its drugs received a fast-track designation.(13, 22) For this study, the 'event' was defined as a firm publicly announcing that it had received an Orphan designation. The event study first predicted what a firm's stock price would have been at the time of the event, in the absence of the event occurring, known as the expected return. Next, the predicted stock price was subtracted from the actual stock price at the time of the event to find the abnormal return. The abnormal return was deemed to be the effect of the event on investor's perceptions of the firm.

The event timeline included three periods: the estimation window, the washout period, and the event window (Figure 2.1). The estimation window was defined as a period of time prior to the event, and was used to estimate the expected return. This analysis used the 120 trading days prior to the public announcement by a firm of award of the Orphan designation, through the 11 trading days prior to the event, as the estimation window (*t*= -121,-11).(22) The washout period was defined as the 10 days before the event occurred (*t*= -10,-1), and was used to provide a buffer between the estimation window and event window, to ensure that the expected returns were not biased by any near-event occurrences. The event window was the period of time during which the effects of the event were expected to be reflected in the firm's stock price. For this analysis, the event window was defined as the day of the event (*t*= 0) plus the day after the event (*t*= 1). The day after the announcement of the Orphan designation was included in the event window to capture any residual reactions from investors.

To estimate the expected return of a stock consistent with the literature, this analysis used the market model, which is a standard Ordinary Least Squares (OLS) regression model, expressed in Equation 1.(3, 13, 22, 23, 37, 55) In this model, $R_{i,t}$ and $R_{m,t}$ were the period t returns on the stock of firm i and the representative market portfolio, respectively. Following previous research, the S&P 500 Composite Index was used as the respective market portfolio.(21, 35) Conceptually, if a perfect linear relationship is expected between the market return and an individual stock return, α_i (the intercept term) and β_i (the slope term) should have perfectly predicted the individual stock return, $R_{i,t}$; $\epsilon_{i,t}$, the error term, should therefore be mean zero. Unexplained deviations from this relationship would be picked up by the error term, which would be the basis for calculating the abnormal returns.

$$R_{i,t} = \alpha_i + \beta_i R_{m,t} + \epsilon_{i,t} \qquad (1)$$

The abnormal returns, $\hat{\epsilon}_{i,t}$, were calculated using Equation 2.(40, 41) The abnormal returns could be interpreted as the investors' reaction to the event for the individual firm.

$$\hat{\epsilon}_{i,t} = R_{i,t} - \hat{a}_{i,t} - \hat{b}_{i,t} R_{m,t} \qquad (2)$$

Finally, the abnormal returns were aggregated by individual firms across time and then aggregated across both firms and time, known as the cumulative abnormal returns. The cumulative abnormal returns were interpreted as the investors' reactions to the event at large; the average reaction to the event over all firms.

Specifications for Longitudinal and Firm Size Analyses

The time period covered by the study was 1983-2012. The longitudinal analysis examined the difference in cumulative abnormal returns in the two time periods 1983-2000 and 2001-2012, with break point determined as outlined in the conceptual framework.

In the firm size analysis, market capitalization, the market value of the firm's trading and non-trading issues, was used as the proxy for firm size.(44) Firms were stratified into four sizes based on market cap: less than $50 million, known as nano-cap firms; between $50 and $250 million known as micro-cap firms; between $250 million and $2 billion, known as small-cap firms; and, between $2 and $14 billion, known as mid-cap firms. Cumulative abnormal returns were analyzed separately for each firm size category, and the differences between them were compared.

Significance Testing

The statistical significance of the cumulative abnormal returns was determined using a GRANK-T test as outlined in Kolari and Pynnonen (2011).(38) As it has been shown that stock

returns are not normally distributed, a standard t-test, which relies on the normal distribution, could not be used to test for significance. Therefore, the GRANK-T test was used as a non-parametric, generalized rank, t-test. This test used the respective rankings of the abnormal returns, by firm, which generated an underlying distribution from which it conducted the significance test. This test was used for the overall test of significance of the cumulative abnormal returns of the sample, as well as each individual test of significance for the cumulative abnormal returns of the longitudinal and firm size analyses.

The statistical significance of the difference in cumulative abnormal returns between the two periods in the longitudinal analyses was tested using a Wilcoxon rank sum test. Like the GRANK-T test, the Wilcoxon rank sum test is also a non-parametric rank test; however it produces a z-statistic, rather than a t-statistic. The Wilcoxon rank sum test used the difference in sample distributions of the cumulative abnormal returns for each of the two time periods to determine whether the difference was statistically significant.

Data

The announcements of the award of an Orphan designation were found via a systematic manual search of LexisNexis. A total of 715 announcements were found, spanning the time period 1985-2012. Stock data were extracted from the Center for Research in Securities Prices (CRSP). Data included both the daily returns for individual firms, as well as the daily returns for the S&P 500 Composite Index used as the market return. Market cap data were extracted from Compustat.

Exclusion Criteria

To construct the final study sample, the following exclusion criteria were applied.

First, designations for drugs that had been previously approved were excluded because they were likely inherently different from announcements for drugs which had not been approved. Approved drugs were much less uncertain to investors, as their safety and efficacy profiles were public and well known. Additionally, the drugs had already cleared the largest hurdle in the eyes of investors: approval by the FDA. A total of 64 announcements were excluded for this reason.

Next, remaining firms were excluded if stock data were not available for the entire estimation and event windows. There were two possible reasons that the stock data were not available. The first was that the firm was private, and therefore stock information did not exist. The second was that data for the full time period were not available from CRSP. (There were many possible reasons for this, including the firm going public sometime during the time period, or getting acquired during the time period.) A total of 324 announcements were excluded due to this criterion.

Lastly, the remaining firms were excluded if another significant, potentially confounding, event occurred during the event window (t= 0, 1). Observations were excluded if one of the following was announced during the event window: (a) any drug news (e.g., clinical trial results, patent received, drug approved, grant received, other designation received); (b) financing news (e.g., 8-k filed, royalty payment received, common stock offering, credit downgraded, debt financing); (c) leadership news (e.g., new leadership, leadership leaving, leadership optioning stock); (d) firm news (e.g., merger/acquisition announced or finalized, partnership deal announced, licensing deal announced). A total of 80 announcements were excluded due to this criterion.

Additionally, one announcement was excluded from the analyses because it was an outlier. In event studies, outliers can strongly affect the conclusions of the study, causing bias because they are inherently different from the other events.(35, 45) This outlier had an abnormal return of 97%, which was over eight standard deviations above the mean. It was also over three standard deviations above than the next largest abnormal return.

Final Study Sample

Once the criteria were applied, a total of 246 announcements remained, spanning the time period 1985-2012. For the longitudinal analysis, there were 71 announcements in the 1985-2000 time period, and 175 announcements in the 2001-2012 time period. (No announcements were found between 1983 and 1985; therefore the longitudinal analysis was adjusted accordingly.) For the firm size analysis, 67 firms were excluded due to unavailable market cap data, and one firm was excluded as an outlier in size of market cap, resulting in a total sample size of 178 firms. Of those firms, there were 29 firms which were classified as nano-cap (market cap less than $50 million), 77 firms which were classified as micro-cap (market cap between $50 and $250 million), 59 firms which were classified as small-cap (market cap between $250 million and $2 billion), and 13 firms which were classified as mid-cap (market cap between $2 and $14 billion).

Average daily returns calculated during the estimation window (t= -121, -11) showed minimal abnormal returns (Table 3.1). The returns were especially small for the nano-cap and mid-cap firms, as well as for the second time period of the longitudinal analysis. Average daily returns calculated during the event window (t= 0, 1) showed substantial increases in daily returns, except for the two largest firm sizes (Table 3.2).

Table 3.1 Average Daily Returns for Estimation Window (-121, -11)

Study	Average Daily Returns	Standard Deviation of Average Daily Returns
Aim 1		
Overall (n= 246)	0.20%	6.7%
Aim 2		
1985-2000 (n= 71)	0.33%	6.1%
2001-2012 (n= 175)	0.15%	7.0%
Aim 3		
Nano-cap: Market cap <$50m (n= 29)	0.21%	12.2%
Micro-cap: Market cap >$50m & <$250m (n= 77)	0.19%	6.6%
Small-cap: Market cap >$250m & <$2b (n= 59)	0.36%	4.9%
Mid-cap: Market cap >$2b & <$14b (n= 13)	0.17%	4.6%

Table 3.2 Average Daily Returns for Event Window (0, 1)

Study	Average Daily Returns	Standard Deviation of Average Daily Returns
Aim 1		
Overall (n= 246)	2.25%	8.9%
Aim 2		
1985-2000 (n= 71)	2.11%	8.9%
2001-2012 (n= 175)	2.32%	9.0%
Aim 3		
Nano-cap: Market cap <$50m (n= 29)	4.56%	11.5%
Micro-cap: Market cap >$50m & <$250m (n= 77)	3.04%	11.5%
Small-cap: Market cap >$250m & <$2b (n= 59)	0.41%	5.9%
Mid-cap: Market cap >$2b & <$14b (n= 13)	0.27%	2.8%

Results

The cumulative abnormal returns over the entire study period were 3.66% (Table 3.3 and Figure 3.1). This meant that, on average, the announcement of an Orphan designation for a new drug in development increased a firm's stock price by 3.66% over what it would have been had the announcement not occurred. The GRANK-T test corresponding to this estimate was significant at the 1% level (t-statistic= 2.73).

Figure 3.1 Graph of Cumulative Abnormal Returns Between (-5, 5)

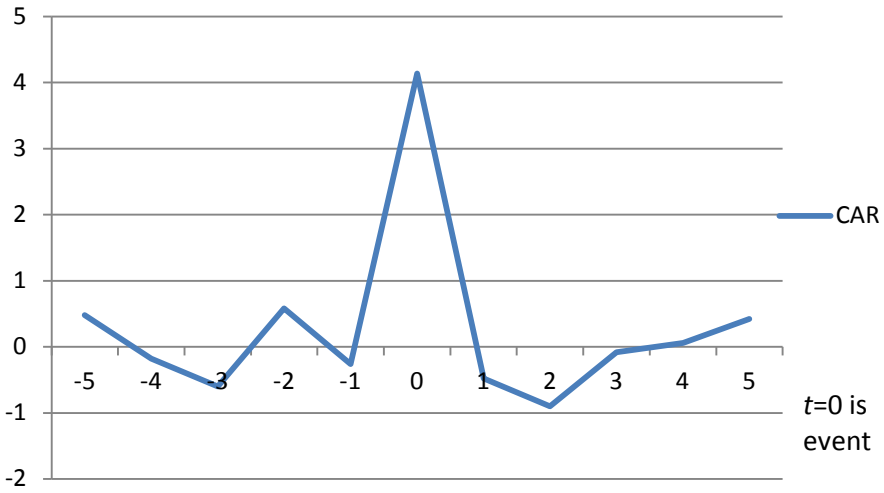
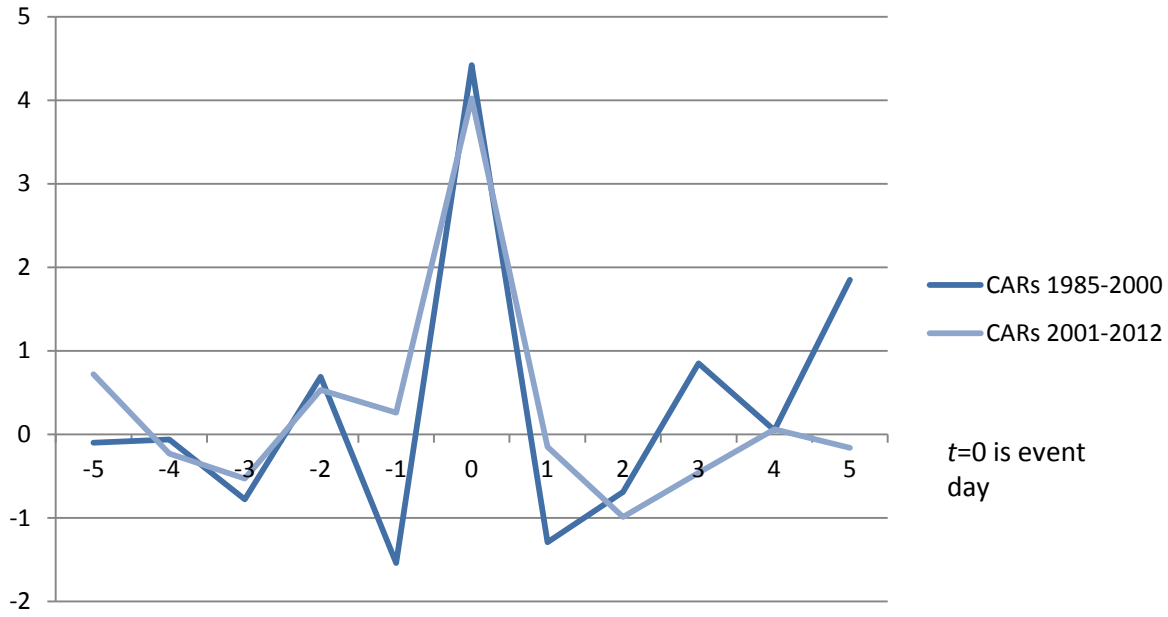


Table 3.3 Results of Main Analyses

Study	Cumulative Abnormal Returns	GRANK-T Test Statistic
Aim 1		
Overall (n= 246)	3.66%	2.73***
Aim 2		
1985-2000 (n= 71)	3.13%	3.63***
2001-2012 (n= 175)	3.87%	2.13**
Aim 3		
Nano-cap: Market cap <$50m (n= 29)	8.42%	2.60***
Micro-cap: Market cap >$50m & <$250m (n= 77)	4.90%	1.57
Small-cap: Market cap >$250m & <$2b (n= 59)	-0.43%	0.10
Mid-cap: Market cap >$2b & <$14b (n= 13)	0.67%	-0.49
***statistically significant at the 1% level; **statistically significant at the 5% level		

Between 1985 and 2000, the cumulative abnormal returns were 3.13% (Table 3.3 and Figure 3.2), and the GRANK-T test was significant at the 1% level (t-statistic= 3.63). Between 2001 and 2012, the cumulative abnormal returns were 3.87%, and the GRANK-T test was significant at the 5% level (t-statistic= 2.13). The cumulative abnormal returns in the later period of 2001-2012 reflected a 24% increase in cumulative abnormal returns over the initial period of 1985-2000. However, the Wilcoxon rank sum test did not show a statistically significant difference between these two cumulative abnormal returns (z-statistic= -0.50).

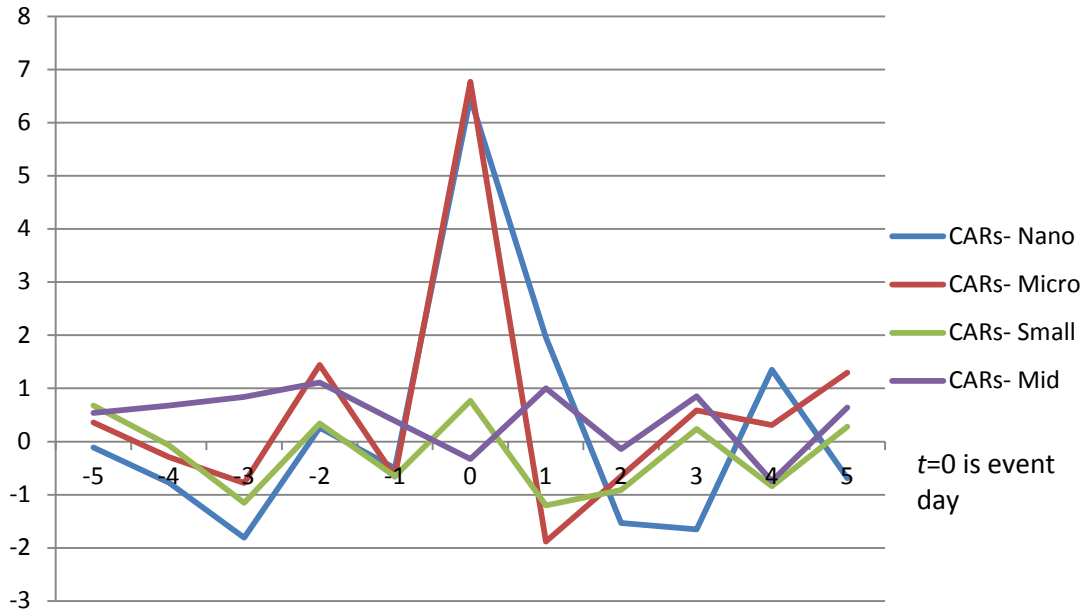
Figure 3.2 Graph of Longitudinal Cumulative Abnormal Returns Between (-5, 5)



Nano-cap firms with a market cap of less than $50 million had cumulative abnormal returns of 8.42% (Table 3.3 and Figure 3.3), and the result was statistically significant at the 1% level (t-statistic= 2.60). Cumulative abnormal returns became progressively smaller as market cap increased. Micro-cap firms with a market cap of between $50 and $250 million had

cumulative abnormal returns of 4.90%; small-cap firms with a market cap of between $250 million and $2 billion had cumulative abnormal returns of -0.43%; and mid-cap firms with a market cap of between $2 and $14 billion had cumulative abnormal returns of 0.67%. None of these results were statistically significant.

Figure 3.3 Graph of Cumulative Abnormal Returns by Firm Size Between (-5, 5)



Sensitivity Analyses

Four sensitivity analyses were conducted to determine whether the results were robust to alternative specifications. The first set of analyses looked at whether the event window of (0, 1) was correctly specified. Specifically, event windows of (-1, 1), (0, 4), and (-1, 4) were tested. These corresponded to an event window including the day before the event (*t*= -1), an event window including the four days after the event (*t*= 4), and an event window from the day before the event to four days after the event. None of the changes in the event window resulted in an increase in CARs compared to the main results. Therefore, it was unlikely that any

of these other trading days were affected by the announcement. (The full sensitivity results are presented in Table 3.4.)

The second analysis was run to determine whether the dates for the longitudinal analyses were correctly specified. The data was separated and analyzed using the dates 1985-2002 v. 2003-2012, and 1985-2005 v. 2006-2012. These results were consistent with the original longitudinal analysis results.

Table 3.4 Results of Sensitivity Analyses

Sensitivity Analysis	**Cumulative Abnormal Returns**	**GRANK-T Test Statistic**
(-1, 1) event window (n=231)	3.27%	2.93***
(0, 4) event window (n=213)	2.79%	2.64***
(-1, 4) event window (n=201)	2.24%	2.49**
		Wilcoxon Rank Sum Test Statistic
1985-2002 (n=96)	3.44%	-0.59
2003-2012 (n=150)	3.80%	
1985-2005 (n=134)	3.37%	0.45
2006-2012 (n=112)	3.99%	
***statistically significant at the 1% level; **statistically significant at the 5% level		

Third, a sensitivity analysis was conducted around data overlaps; that is, when a firm had an announcement occur during the estimation window of a separate announcement by the firm. It was possible that this data overlap would cause bias in the coefficients, although other event studies of the pharmaceutical industry did not find any bias.(37, 45) There were 20 occurrences (42 observations) of this in the data. Two occurrences had three announcements overlapping; the middle announcement was removed for both sensitivity tests. Removing the first of the overlapping announcements led to overall CARs of 3.69%, and removing the second

of the overlapping announcements led to overall CARs of 3.74%. These results were consistent with the CARs of 3.66% found in the primary analysis, suggesting little bias due to data overlap.

Finally, a sensitivity analysis was conducted to determine whether the overall CARs were affected by co-developed drugs.(2) Many pharmaceuticals have been co-developed by two or more pharmaceutical firms, to decrease R&D costs and share propriety information regarding the project. However, investors may have reacted differently to announcements of co-developed drugs, as firms would also have had to share profits if the drug was subsequently approved. There were 7 instances (14 observations) of this in the data. This sensitivity analysis averaged the abnormal returns of the co-developers, and then used those averaged returns when computing the overall CARs for the entire study sample. Results of the sensitivity analysis returned CARs of 3.65% -- virtually identical to the CARs of 3.66% found in the primary analysis.

Discussion

The central question of this analysis was whether investors viewed the award of an Orphan drug designation for a new drug in development as positive news for a firm. The goal of the designation was to encourage investment in drug development for rare diseases. In order to encourage this investment, investors needed to perceive the Orphan designation as increasing a drug's expected profits. The results of the overall cumulative abnormal returns led to the conclusion that investors did see the designation as increasing this value, evidenced by the finding of overall cumulative abnormal returns of 3.66%. Comparing this to previous evidence showing 0.35% average abnormal returns on the day a drug was approved, and 2.20% average abnormal returns on the day after an approvable letter was announced, suggested that

investors may have viewed the Orphan designation as providing substantial information regarding a drug likelihood of being approved.(22)

It is important to note that this cumulative abnormal return of 3.66% might have actually underestimated the value to investors of an Orphan designation. The only requirement to receiving the designation was that the drug be indicated to treat a rare disease. Therefore, investors with scientific knowledge may have been able to predict whether a drug would receive the designation, and may therefore have incorporated this knowledge into their valuation of the firm before the designation was announced. This would mean that not all of the investor perceptions of the designation would be picked up by the CARs, and therefore they may have underestimated the true value of the designation.

The longitudinal analysis of this study attempted to determine whether investor's perceptions of the Orphan designation had changed over time. The overall time period of 1985-2012 was split into two time periods: 1985-2000 and 2001-2012. The break point was hypothesized to be 2000-2001 because that was the time period just prior to when Orphan drugs first gained 'blockbuster' status, and therefore investors may have perceived that there was potentially more payoff in the rare disease market than had been previously thought. The results of the analysis weakly supported this conclusion. Cumulative abnormal returns were found to be 3.13% and 3.87%, respectively, and were statistically significant at the 1% level and 5% level, respectively. While the difference between these two findings was not statistically significant, the magnitude of the difference did lend some support to the hypothesis that changes in the overall market for Orphan drugs had led investors to perceive more value in the

Orphan designation over time. The fact that the sensitivity analyses also supported this trend lent additional support to this conclusion.

The firm size analysis of this study attempted to determine whether investor's reactions to an Orphan designation differed depending on firm size. The results of this analysis showed that investors reacted much more strongly to announcements by small firms than they did for larger firms. For the smallest firms, the nano-cap firms, the cumulative abnormal returns were 8.42%, which was statistically significant at the 1% level. This result was notable, especially when compared to the cumulative abnormal returns for the entire sample, which were 3.66%. A difference of this magnitude seemed to indicate that investors perceived the Orphan designation as providing much more positive value to the smallest firms.

There were two possible reasons for this. First, the tangible financial rewards of the Orphan designation (e.g., user fees are waived) may have provided relatively greater benefits to encouraging drug development for the smallest firms. Investors may have believed that these benefits decreased the risk of small firms developing drugs for these rare disease markets, and therefore made investing in these small firms less risky. Second, it might have been possible that there were greater information asymmetries between small firms and their investors, and this designation reduced these asymmetries more than it might have for larger firms. Because smaller firms were less likely to have a drug development track-record, whether positive or negative, investors may have known less about the likelihood of the success for drugs developed by these small firms. These two reasons for investors responding more positively to Orphan designation announcements from small firms were not mutually exclusive; it may have

been that both were involved in creating the notable increase in cumulative abnormal returns for the smallest firms, compared to firms of other sizes.

The medium-sized pharmaceutical firms, the micro-cap firms, had cumulative abnormal returns of 4.90%, although this result was not statistically significant. This result was the closest in value to the of the cumulative abnormal returns for the entire sample than any other market cap group; which was not wholly surprising as this group of firms represented the largest proportion of the total sample. However, this also represented a drop of more than 65% off the cumulative abnormal returns of the small firms. This result seemed to indicate that while investors perceived the Orphan designation as providing strong positive value to medium-sized firms; it provided significantly greater value to small-sized firms.

The cumulative abnormal returns for the small-cap firms were substantially lower than those of the micro-sized firms. The cumulative abnormal returns for these firms were actually negative at -0.43%, and this result was not statistically significant. The returns for the largest pharmaceutical firms in the data, the mid-cap firms, saw an equally precipitous decline, with cumulative abnormal returns of 0.67%. This result was also not statistically significant. These results together suggested that investors perceived the Orphan designation as an overall neutral announcement for the larger firms.

This study had several limitations. First, the results for the small- and mid-cap firms may not have been as precisely estimated as the results for the smallest firms. The largest firms were more likely than smaller firms to have confounding announcements occurring on the same day as the announcement of an Orphan designation. Because of this, they were more likely to be excluded from the analysis, possibly skewing the results for the largest firms. The

direction of the skewness was also impossible to precisely determine, although it seemed most likely, given the results for the other firm sizes, that they were biased downward. Second, due to the exclusion criteria required to implement the event study methodology, the results of this study may not be generalizable to all pharmaceutical firms that received an Orphan designation. For example, the results are not generalizable to privately held firms or international firms because they were excluded from the study. Still, this study was the first to examine the signaling effect of the Orphan designation in a large sample of U.S. pharmaceutical firms.

Conclusion

This analysis sought to determine how well the Orphan drug designation worked to increase investment in developing drugs for rare diseases, by signaling to investors an increase in a drug's expected profits. Three central results were found. First, investors had an overall positive response to the announcement of an Orphan designation, with the cumulative abnormal returns over the entire 1985-2012 study period being 3.66%. Second, over time, investors have had a more positive response to the designation. Cumulative abnormal returns between 1983 and 2000 were 3.13%, while the returns from 2001 through 2012 were 3.87%. Lastly, investors had a much stronger reaction to an announcement from the smallest firms (cumulative abnormal returns of 8.42%) than those from the largest firms (cumulative abnormal returns of 0.67%).

From a policy perspective, the main results of this study were that investors responded positively to the announcement of a designation, particularly those by the smallest firms, and the response became slightly stronger over time. However, a limitation of this study was that it

could not discern which part, or parts, of the Orphan designation investors were responding to. The Orphan designation confers multiple tangible incentives, such as exclusivity and fee waivers, and may also confer information about future profitability because of historically high reimbursement rates and blockbuster status of some Orphan drugs. A qualitative study, which interviews investors as to their perceptions of the designation, or a similar quantitative survey of investors, could ascertain the answer to the question of which part, or parts, of the designation investors value most. This type of information would allow policymakers to tailor the designation and the benefits it confers in a way that would maximize future investment in drug development for rare diseases by all firms, large and small.

Still, the importance of the success of the designation to date cannot be overlooked. Investment in rare disease research was chronically underfunded before the designation was created, due primarily to the market failure which existed for Orphan drugs. The designation created incentives which decreased the cost of R&D, thereby making the development of Orphan drugs more attractive by increasing Orphan drug's expected profitability. The drugs that had been approved with an Orphan designation went to patients who, in many cases, previously had no other existing therapies to treat their disease. While other studies evaluated the drugs approved with an Orphan designation, this study took a step back, and evaluated the effect of the designation on investors in firms with early stage Orphan drugs in development. The results indicated that the Orphan designation was viewed by investors as a positive signal of an Orphan drug's expected profits. Therefore, on this measure, the Orphan drug designation has been successful in accomplishing its goal.

Chapter 4 – The Signaling Effects of Stacked FDA Designations

Abstract

Since 1983, the US Food and Drug Administration (FDA) has offered special designation programs for certain types of drugs in development. Some pharmaceutical and biotech companies have taken advantage of these programs by obtaining multiple designations for a single drug; a practice known as 'stacking' or 'layering' designations. This analysis studied whether investors in the stocks of pharmaceutical firms reacted differently to stacked designations versus non-stacked designations. Specifically, it examined whether there was a difference in stock price changes following announcement of a fast-track designation for a drug which had received a prior Orphan designation (the stacked designations), versus the announcement of a fast-track designation without a prior Orphan designation (the non-stacked designations). The results of the analysis indicated that investors respond more favorably to stacked designations; however, the difference was not statistically significant. Additionally, the magnitude of the difference appeared to have decreased over time, and appeared to be much more pronounced for smaller companies than for larger companies. Findings suggested that while stacked designations may have been important for the smallest pharmaceutical companies, larger companies should have considered whether the benefit of obtaining multiple designations outweighed the costs of applying for them.

Introduction

Drug development had been fraught with uncertainty; while some drugs had received marketing approval and become 'blockbusters', most drugs failed in development. (7-10) This uncertainty was compounded for investors in publicly traded pharmaceutical companies. Not only did investors not know whether a company's drugs would ultimately receive approval and become successful, but they also had been unable to observe all of the information that might have helped predict the outcome. This was because publicly traded pharmaceutical companies were unable to provide propriety information regarding the drugs to investors, for fear of increasing competition.

One way pharmaceutical firms could have decreased these unknowns with investors was to use signals such as the public announcement of a company-level event. A signal would have conveyed to investors some piece of knowledge regarding a drug's likelihood of success, without having to divulge any proprietary information. This study examined the signaling effects of public announcements of US Food and Drug Administration (FDA) drug designations. Specifically, this study investigated whether multiple designations for a single drug, known as stacked designations, provided a stronger signal to investors than single, or non-stacked, designations.

Two FDA designations were included in the study: the fast-track designation and the Orphan designation. The fast-track designation was created in 1998 to decrease the development and review time for clinically needed drugs. In order to receive the designation, a company needed to show that a drug was for a serious or life-threatening condition, and met an unmet medical need. The Orphan designation was created in 1983 to promote drug

development for rare diseases. To receive an Orphan designation, a company needed to show that the drug was intended to treat a rare disease, defined in the US as affecting fewer than 200,000 patients.

This study examined whether there was a difference in stock price changes following announcement of a fast-track designation for a drug with a prior Orphan designation versus announcement of a fast-track designation without a prior designation. The fast-track designation was selected as the stacked, or second, designation because it was typically conferred later in the development process than an Orphan designation. Therefore, if a drug were going to receive an Orphan designation, it would typically have been conferred by the time it also received a fast-track designation.

Multiple studies have estimated the magnitude of investor's reactions to the fast-track designation. Early event studies of the fast-track designation found that the stock price of a company rose 9-10% after the announcement of the receipt of the designation.(2, 3) The most recent analysis of the designation, presented in Chapter 2 of this dissertation, found that, between 1998 and 2012, the average stock price of a company increased 6.35% after the announcement of the designation, and the magnitude of the stock price increase after announcement had decreased over time.

Conceptual Framework

The ability to stack FDA designations had been available to companies since the creation of the fast-track designation in 1998, which could have been stacked onto a prior Orphan designation. Although available since the late 90s, it is possible that the practice of stacking designations as a strategy to appeal to investors was more recent.(56) The advent of the

internet, with the accompanying instantaneous availability of information, increased the need for firms to supply investors with a stream of development news. Obtaining multiple designations on a drug was one way to increase the number of signals that a company could send to its investors. Additionally, obtaining a fast-track designation after an Orphan designation provided investors with additional valuable information regarding a drug's development prospects. Investors could have observed that a drug was progressing through the development pipeline, and, in the process, was receiving attention from the FDA. While the designations themselves did not imply anything about a drug's likelihood of being approved by the FDA for marketing, investors may still have believed that the designations conferred some information of this kind.

This study explored whether investors reacted differently to announcements of fast-track designations for drugs that received a prior Orphan designation, compared with fast-track designations for drugs that had not received a prior Orphan designation. While the information provided by the Orphan designation should have already been incorporated into a firm's stock price prior to the announcement of the fast-track designation, it was predicted that this prior Orphan designation would increase the magnitude of the fast-track signal. The magnitude of the increases would be expressed as an additional premium in the signal for the fast-track designation announcement; i.e. the fast-track signal would be proportionally increased by the prior Orphan designation, as compared to fast-track designations without a prior Orphan designation.

Additionally, this study examined whether the magnitude of these reactions had changed over time. While previous evidence suggested that, overall, investor's perceptions of

the quality of the fast-track designation had decreased over time, it is possible that reactions to stacked designations may have differed. The analysis was divided into two time periods to observe any differences: 1998-2004 and 2005-2012. This split was chosen because 2004 and 2005 was when investors would have seen whether the first fast-track drugs either received marketing approval or failed in development and therefore been able to fully assess the fast-track program.

Lastly, this study investigated whether the magnitude of investor's reactions to stacked designations differed by company size. It was possible that stacked designation were more important to investors in smaller companies, which had a limited track record of successful drug development, and therefore possibly more inherent risk in the success of their drugs.

Methods and Data

To determine whether investors believed that the announcement of a drug designation provided valuable information regarding a drug in development, this analysis utilized an event study methodology. The event study determined whether a public announcement of receipt of a designation correlated to an increase in a company's stock price, controlling for fluctuations in the overall stock market and any confounding company-level events. Any increase in stock price was called the abnormal returns of an individual event, and the aggregate abnormal returns over all events were known as the cumulative abnormal returns (CARs).

The event study covered two distinct time periods. The first was the estimation window, which was used to predict what the stock price would have been, had the event not occurred. The estimation window encompassed the 110 trading days before the event occurred. If the event date was set at t= 0, the estimation window was then t= -121, -11. A washout period of

the ten days prior to the event was added to further ensure that there were no confounding events immediately prior to the event day. The second period of the event study was the event window, which was the period over which the event was predicted to have affected the company's stock price. The event window was set to the day of the event, plus the day after the event; *t*= 0, 1.

The expected return of a stock was estimated using the market model, and standard Ordinary Least Squares (OLS) regression, as expressed in Equation 1. (3, 13, 22, 23, 37, 55) In this model, $R_{i,t}$ and $R_{m,t}$ were the period t returns on the stock of firm i and the representative market portfolio, respectively. Following previous research, the S&P 500 Composite Index was used as the respective market portfolio.(21, 35)

$$R_{i,t} = \alpha_i + \beta_i R_{m,t} + \epsilon_{i,t} \qquad (1)$$

The abnormal returns, $\hat{\epsilon}_{i,t}$, were calculated using Equation 2.(40, 41) The abnormal returns could be interpreted as investors' reaction to the event for the individual firm.

$$\hat{\epsilon}_{i,t} = R_{i,t} - \hat{a}_{i,t} - \hat{b}_{i,t} R_{m,t} \qquad (2)$$

The abnormal returns were then aggregated by individual firms across time and then aggregated across both firms and time, to create the CARs. The CARs were interpreted as the average investor reaction to the announcement over all firms.

To test the statistical significance of the CARs, a nonparametric generalized rank test, specifically the GRANK-T test, was used.(38) A nonparametric test was necessary because the stock returns were not normally distributed; a test which utilized the normal distribution would therefore have been inappropriate. To test whether there were differences between the stacked and non-stacked designations, and differences between the longitudinal time periods, a

Wilcoxon rank sum test was used. This tested the difference in sample distributions between the two samples, to determine whether there was a statistically significant difference.

Stock data were extracted from the Center for Research in Securities Prices (CRSP). Data included both the daily returns for individual firms, as well as the daily returns for the S&P 500 Composite Index.

Market capitalization, or market cap, was used to proxy company size. Market cap was the total market value of a company's outstanding shares. Companies were split into two groups based on market size: those with a market cap less than $250 million, and those with a market cap greater than $250 million. The upper limit of market cap in the sample was less than $10 billion. Market cap data were extracted from Compustat, and the market cap from the year of the designation was used.

Study Sample and Exclusion Criteria

The fast-track announcements were gathered via a systematic manual search of Lexis-Nexis. A fast-track designation was determined to be stacked if the announcement noted the drug's prior receipt of an Orphan designation. The search yielded 442 fast-track announcements, 88 of which were for a stacked designation. Several exclusion criteria were applied to the announcements to ensure that they conformed to the event study methodology:

1. Announcements were excluded if they were for a drug which had been previously approved. This removed 18 observations for the non-stacked announcements, and 4 observations for the stacked announcements.

2. Announcements were excluded if stock data was not available for the entire study period. This removed 124 observations for the non-stacked announcements, and 44 observations for the stacked announcements.
3. Announcements were excluded if the firm had another significant announcement occur during the event window (t= 0, 1). For example, this included an announcement of a change in company senior leadership, or clinical trial results. This removed 45 observations for the non-stacked announcements, and 10 observations for the stacked announcements.

Additionally, one non-stacked announcement was removed from the sample because it was determined to be an outlier and could have biased the overall results. In the firm size analysis, 39 non-stacked announcements and 3 stacked announcements were excluded because market cap data were unavailable during the study period.

The final sample included 196 observations: 166 observations of non-stacked announcements, and 30 observations of stacked announcements. In the first time period of the longitudinal analysis, 1998-2004, there were 78 non-stacked announcements and 8 stacked announcements, and in the second time period, 2005-2012, there were 88 non-stacked announcements and 22 stacked announcements. For the company size analysis, there were 49 non-stacked announcements and 11 stacked announcements from companies with a market cap of less than $250 million (nano-cap and micro-cap companies). There were 78 non-stacked announcements and 16 stacked announcements from companies with a market cap of greater than $250 million (small-cap and mid-cap companies).

Average daily returns calculated during the estimation window (*t*= -121, -11) showed minimal abnormal returns (Table 4.1). The returns were smaller overall for the stacked designations as compared to the non-stacked designations, and the returns were especially small for the stacked designations in the second time period of the longitudinal analysis. Average daily returns for the event window (*t*= 0, 1) showed overall substantial increases in daily returns (Table 4.2).

Table 4.1 Average Daily Returns for Estimation Window (-121, -11)

Study	**Average Daily Returns**	**Standard Deviation of Average Daily Returns**
Aim 1		
Fast-track with prior Orphan (n= 30)	0.13%	5.1%
Fast-track without prior Orphan (n= 166)	0.26%	9.6%
Aim 2		
1998-2004		
Fast-track with prior Orphan (n= 8)	0.37%	6.9%
Fast-track without prior Orphan (n= 78)	0.33%	11.8%
2005-2012		
Fast-track with prior Orphan (n= 22)	0.05%	4.2%
Fast-track without prior Orphan (n= 88)	0.19%	7.2%
Aim 3		
Nano-cap and Micro-cap: Market cap <$250m		
Fast-track with prior Orphan (n= 11)	0.15%	6.6%
Fast-track without prior Orphan (n= 49)	0.19%	6.6%
Small-cap and Mid-cap: Market		

cap >$250m		
Fast-track with prior Orphan (n= 16)	0.20%	3.9%
Fast-track without prior Orphan (n= 78)	0.30%	7.1%

Table 4.2 Average Daily Returns for Event Window (0, 1)

Study	Average Daily Returns	Standard Deviation of Average Daily Returns
Aim 1		
Fast-track with prior Orphan (n= 30)	4.48%	14.6%
Fast-track without prior Orphan (n= 166)	3.78%	12.1%
Aim 2		
1998-2004		
Fast-track with prior Orphan (n= 8)	8.06%	26.2%
Fast-track without prior Orphan (n= 78)	4.99%	14.6%
2005-2012		
Fast-track with prior Orphan (n= 22)	3.18%	6.8%
Fast-track without prior Orphan (n= 88)	2.71%	9.3%
Aim 3		
Nano-cap and Micro-cap: Market cap <$250m		
Fast-track with prior Orphan (n= 11)	8.10%	22.6%
Fast-track without prior Orphan (n= 49)	5.49%	15.7%
Small-cap and Mid-cap: Market cap >$250m		
Fast-track with prior Orphan (n= 16)	1.67%	5.2%
Fast-track without prior Orphan (n= 78)	1.91%	6.1%

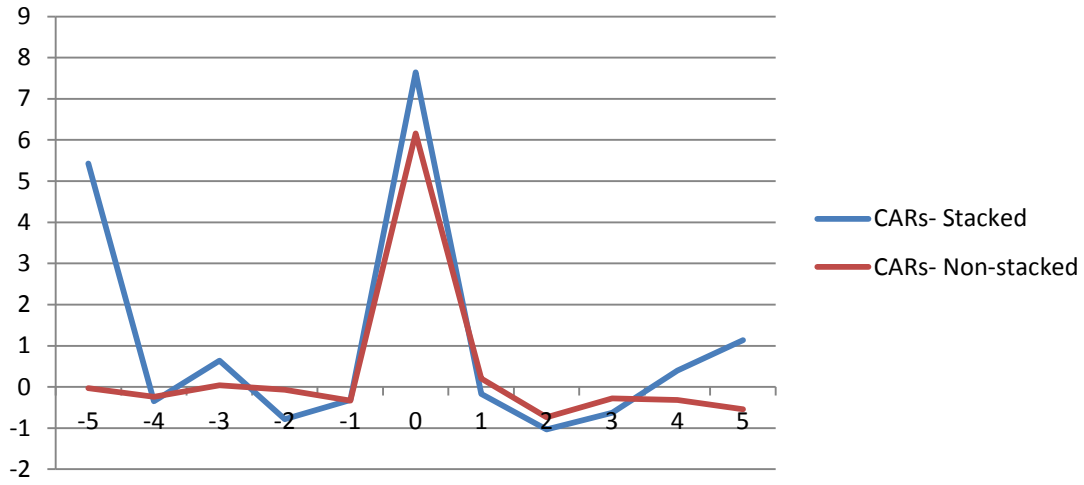
Results

Results from the overall analysis found cumulative abnormal returns (CARs) of 7.47% for the stacked designations, which was statistically significant at the 1% level, and CARs of 6.36% for the non-stacked designations, which was not statistically significant (Table 4.3 and Figure 4.1). These results indicated that the stacked designations caused an approximately one percentage point higher increase in the stock price than did a fast-track designation without a prior Orphan designation. However, the Wilcoxon rank sum test between these two values was not statistically significant (z= 0.474), indicating that the two CARs were not statistically different from one another.

Table 4.3 Results of Overall Analysis

Study	Cumulative Abnormal Returns	GRANK-T Test Statistic
Fast-track with prior Orphan (n= 30)	7.47%	2.69***
Fast-track without prior Orphan (n= 166)	6.36%	1.38
***statistically significant at the 1% level		

Figure 4.1 Graph of Cumulative Abnormal Returns Between (-5, 5)



The results of the longitudinal analysis showed a decline in CARs for both the stacked and non-stacked designations over time. The analysis found CARs of 12.51% for stacked

designations in the early time period (1998-2004), which was not statistically significant (which is not surprising given the small sample size), and CARs of 5.64% in the later period (2005-2012), which was statistically significant at the 1% level (Table 4.4). This was a decline of more than 50%. However, the difference between these two values was not statistically significant (*z*= 0.334).

The study found CARs of 8.23% for the non-stacked designations in the early time period, and CARs of 4.70% in the later time period, neither of which was statistically significant. This was a decline of almost 50%. However, as for the stacked designations, this decline was not statistically significant (*z*= 0.929).

Table 4.4 Results of Longitudinal Analysis

Study	**Cumulative Abnormal Returns**	**GRANK-T Test Statistic**
1998-2004		
Fast-track with prior Orphan (n= 8)	12.51%	1.42
Fast-track without prior Orphan (n= 78)	8.23%	1.46
2005-2012		
Fast-track with prior Orphan (n= 22)	5.64%	2.66***
Fast-track without prior Orphan (n= 88)	4.70%	1.24
***statistically significant at the 1% level		

The results of the company size analysis showed substantially larger CARs for the small firms than for the larger firms, for both the stacked and non-stacked designations (Table 4.5). The CARs for the companies with a market cap of less than $250 million were 12.51% for the stacked designations, and 9.21% for the non-stacked designations, both of which were statistically significant at the 1% level. However, the CARs for the larger companies were approximately 75% smaller for the stacked designations and approximately 60% smaller for the non-stacked designations. The CARs for the companies with a market cap of greater than $250

million were 3.22% for the stacked designations, and 3.40% for the non-stacked designations. These two values were almost identical, and neither was statistically significant.

Table 4.5 Results of Company Size Analysis

Study	Cumulative Abnormal Returns	GRANK-T Test Statistic
Nano-cap and Micro-cap: Market cap <$250m		
Fast-track with prior Orphan (n= 11)	12.51%	2.99***
Fast-track without prior Orphan (n= 49)	9.21%	3.97***
Small-cap and Mid-cap: Market cap >$250m		
Fast-track with prior Orphan (n= 16)	3.22%	1.57
Fast-track without prior Orphan (n= 78)	3.40%	0.91
***statistically significant at the 1% level		

Sensitivity Analyses

A sensitivity analysis was performed around the dates of the longitudinal analysis. Two additional longitudinal splits were tested: 1998-2002 vs. 2003-2012 and 1998-2006 vs. 2007-2012 (Table 4.6). Results indicated that the earliest years of the fast-track program saw the highest CARs for the stacked designations, and the most recent years of the fast-track program saw the lowest CARs for the non-stacked designations. However, while these results differed in magnitude from the central longitudinal analysis, they did not differ in directionality. It appears that the very earliest years of the designation elicited the highest response from investors, and the decline in response may have begun even earlier than anticipated.

Table 4.6 Results of Longitudinal Sensitivity Analyses

Study	Cumulative Abnormal Returns	GRANK-T Test Statistic
Longitudinal Sensitivity Analysis 1		
1998-2002		
Fast-track with prior Orphan (n= 5)	18.90%	1.43
Fast-track without prior Orphan (n= 35)	6.94%	0.48
2003-2012		

Fast-track with prior Orphan (n= 25)	5.19%	2.83***
Fast-track without prior Orphan (n= 131)	6.21%	1.47
Longitudinal Sensitivity Analysis 2		
1998-2006		
Fast-track with prior Orphan (n= 17)	7.99%	1.57
Fast-track without prior Orphan (n= 117)	7.16%	2.03***
2007-2012		
Fast-track with prior Orphan (n= 13)	6.79%	2.37***
Fast-track without prior Orphan (n= 49)	4.49%	0.98
***statistically significant at the 1% level		

Discussion

The results of the primary analysis in this study suggested that investors responded more positively to the stacked announcement of a fast-track designation compared with the announcement of a fast-track destination alone. While the difference between the CARs for these two announcements was not statistically significant, the magnitude of the difference, over one percentage point, was large for an event study. It therefore appeared that stacking designations was perceived by investors as bringing more value to a drug, and provided a premium on the fast-track signal. The exact nature of this premium could not be determined by this study. It is possible that investors viewed this additional information as increasing their ability to predict whether a drug would subsequently gain marketing approval. Alternatively, investors may have believed that the additional designations were, in fact, predictive of increased likelihood of a subsequent approval.

The results of the longitudinal analysis confirmed that the strength of investor reactions to both stacked and non-stacked fast-track designations decreased substantially over time. By the second period, CARs for the stacked designations had decreased by more than half, and

CARs for the non-stacked designations had decreased by almost fifty percent. However, even with these decreases, the stacked designations had CARs of almost one percentage point greater than the CARs of the non-stacked designations, although this was down from a difference of almost four percentage points greater in the earlier period. The substantial decrease seen in CARs for the stacked designations may imply that investors had learned over time that the stacking of designations did not provide significantly more information over non-stacked designations. However, this could also have been a remnant of the decrease in investor reactions for the fast-track designation overall.

The results of the company size analysis indicated that investors' reactions were the strongest for both stacked and non-stacked designations announced by the smallest companies. A market cap of below $250 million was reflective of an extremely small company, which likely did not have any marketed products. Therefore, the success of any one drug was vitally important, and investors seemed to have been acting accordingly when valuing the information provided by the announcements. The CARs of the stacked designations were much greater in magnitude, almost three percentage points, than the CARs of the non-stacked designations for these small companies. The most surprising result was that there was virtually no difference in CARs between stacked and non-stacked designations for the larger companies. This would seem to indicate that there was no stacking premium placed on the prior Orphan designation for these fast-track announcements: investors did not believe that these designations provided much valuable information regarding these drugs for the larger companies. The reason for this lack of premium was not fully determined by this analysis. It may have been that investors were more confident that these companies would be able to

bring a drug to market, and did not need the additional information provided by the designations. However, this may also have been caused by a depreciating effect from the prior Orphan designation. An Orphan drug was likely to have provided less revenue to a company than a non-Orphan drug and investors may have viewed a larger company's development of this kind of drug as a poor use of capital.

Limitations

The primary limitation of this study was the small sample size for the stacked designations. Although event studies are often powered by sample sizes as small as thirty observations, the sample sizes of fewer than twenty found in the longitudinal and company size analyses were small, even for an event study. Therefore, conclusions drawn from these analyses should be measured. While the directionality may be a reasonable reflection of investors' reactions to the stacked designation signal, the exact magnitude of the signal cannot be precisely estimated.

Conclusion

The results of this study showed that investors responded more favorably to stacked designations than to non-stacked designations. The difference was not statistically significant, but higher CARs were seen for the stacked designations in all but one analysis. These findings implied that investors may have believed that drugs which received both an Orphan and fast-track designation were more likely to be successful: gaining marketing approval by the FDA and generating profits for the company. This was especially true for the smallest companies, which may not have had a strong track record in bringing drugs to market.

However, the results for the stacked designations were not all favorable. The longitudinal analysis indicated that the value investors placed on a stacked designation had decreased substantially over time, as had the value investors placed on the non-stacked designations. However, the decline was slightly more substantial for the stacked designations. Additionally, the value of the stacked designation seen for small companies did not seem to translate for larger companies. The CARs for the large companies in the sample were virtually identical for stacked and non-stacked designations.

Investor relations departments within pharmaceutical and biotech companies should be aware of the changing perception of the value of stacked designations over time. The smallest firms may still find benefit in applying for, and receiving, multiple designations. However, the time and cost of applying for multiple designations may no longer be attractive to larger companies, whose investors may find little added value in them.

Chapter 5 – Conclusion

The goal of this dissertation was to examine the signaling effects of three types of FDA drug designations: the fast-track designation, Orphan designation, and stacked designations. Overall, the results of all three studies of the designations were consistent with the initial hypotheses outlined in the first chapter of this dissertation. Positive, statistically significant, overall cumulative abnormal returns were found for all three types of designations. The returns for the fast-track and stacked designations decreased substantially over time, while the Orphan designation saw a slight increase. Additionally, for all three analyses, returns were significantly higher for the smallest firms compared to the larger firms. The conclusions of the studies were that investors found positive signaling benefits from the designations, although the magnitude of the responses was substantially different over firms and times. These results led to three central conclusions.

The first implication of this research was that only the smallest firms saw statistically significant investor reactions after the announcement of a designation. In all three studies, on average, a firm with a market cap of over $250 million saw no statistically significant abnormal change in stock price after the announcement of a designation; only firms with a market capitalization of under $250 million saw statistically significant abnormal returns. These small firms are the most entrepreneurial firms: firms of this size typically do not have any approved drugs on the market, and may only have one or two drugs under development. Therefore, the

conclusion of these analyses is that the abnormal returns generated by the announcement of the designations are the greatest for the smallest firms.

It unlikely that this result is caused by these small market caps firms having the smallest stock price (and therefore greater ability to cause large returns), as stock price and market cap are not strongly correlated with each other even for the smallest firms. (For firms in the fast-track sample with a market cap of less than $250 million, the correlation between market cap and stock price is 33%.) It seems likely then that the results seen here are caused by intrinsic differences between the information asymmetries present in these different sized firms and the importance of information about single drugs, as outlined in the conceptual framework sections of the chapters of this dissertation. From a policy perspective, this result may or may not be highly relevant. It is unlikely that policymakers are extremely concerned with what types of firms are developing the drugs and using the incentives, as long as the incentives lead to increased drug development. However, as the organization of the industry continues to evolve, with greater entry by smaller firms, these investor-related implications may become more important for policymakers to consider, as it appears that the investor's reactions to the designations affect primarily the smallest firms.

The second implication, examined in the fourth chapter of this dissertation, was the importance investors place on stacked designations. While the analysis could not identify the manner in which stacked designations provide additional information to investors, the results suggest a multiplicative effect of up to 1.30. Specifically, the overall abnormal returns for the stacked designations were 7.47%, which is approximately equal to the value of a non-stacked fast-track designation (6.36%) plus a third of the value of an Orphan designation (1.10=

0.30*3.66%). While this is an imprecise estimate, and likely represents the maximum effect of a stacked designation of this type, results suggest some incremental benefit to obtaining multiple designations. Policymakers should consider whether providing further opportunities for stacking, for example by creating multiple designations with narrower designation criteria, could contribute to the FDA's mission of encouraging drug development, particularly for diseases and conditions where there are significant market limitations.

Lastly, the results suggest two implications for the design of FDA drug designations. First, the strong decline in the signaling effects of the fast-track designation was striking when compared to the stability of the signal from the Orphan designation over time. There are several possible explanations. The difference may have resulted from the difference in the benefits awarded by the two designations. While the Orphan designation conferred multiple tangible financial benefits on firms, the fast-track designation did not provide any similar benefits (although it typically is correlated with the conferral of other regulatory benefits which can provide tangible financial benefits). Therefore, it may be possible that investors find greater value in the financial benefits of designations than in the drug development information that they convey. From a policy perspective, this would imply that future designations should include financial benefits to firms (such as extended exclusivity), rather than solely informational or signaling benefits, if policymakers wish to attract investors to the space.

Alternatively, it is possible that this difference over time between the two designations was caused by the scope of drugs to which each designation might apply. The fast-track and Orphan designations differ markedly in the specificity of their respective inclusion criteria. A drug which receives an Orphan designation must fulfill a very specific criterion: that it is

indicated to treat a disease which affects fewer than 200,000 people in the US. The fast-track designation, on the other hand, has more broadly defined criteria: that the drug meets an unmet medical need and is indicated to treat a serious or life-threatening disease. Therefore, it is possible that there is a diluting effect of the signal based on a broad inclusion criterion. A broader inclusion criterion may lessen the information that is conveyed by the designation, by allowing low-quality firms to receive a designation, thus decreasing the overall signaling quality of the designation. From a policy perspective, this would imply that future designations should be designed with criteria that ensure that low-quality firms are unable to obtain them, thereby offsetting the dilution of the signal.

While this research has made a significant contribution to existing knowledge about the signaling effects of FDA drug designations, there remain opportunities to extend and advance the field. For example, future studies could expand on the current analysis by including internationally based firms. This would allow for a comparison of international versus domestic investor reactions to a U.S. based designation, providing information to the FDA about the global reach of its programs. Studies could also be conducted to compare the signaling effects of FDA designations to the signaling effects of designations granted by the European Medicines Agency (EMA), the European drug regulatory authority.

Additionally, analyses should be conducted to explore the differences in investor reactions to designations received by approved and unapproved drugs. Approved drugs were excluded from the analysis because it was hypothesized that there were fewer information asymmetries related to these drugs. However, future research could provide evidence to inform this question. Finally, many other FDA designations and regulatory programs remain

unexplored using this methodology. Specifically, the new Breakthrough therapy designation, created in 2012, should be analyzed once an ample sample size has been reached. This designation is similar to the fast-track designation, in that it does not provide any prizes or financial incentives to the recipient firm. However, unlike both the fast-track and Orphan designations, the Breakthrough therapy designation is tantamount to a 'seal of approval' from the FDA. Receiving the designation means that the FDA believes that the drug is critically important, and will likely use multiple regulatory means to speed its approval. Evidence on the value investors place on this level of FDA engagement (and its ability to truly separate high quality drugs from others) would perhaps aid in understanding the upper bound of investor reactions for this type of signal. The evidence could also help inform whether investors value this type of FDA engagement more than financial incentives for designations. Lastly, if investors strongly value the Breakthrough therapy designation, it may dilute the value of the fast-track or Orphan designations. Future research could evaluate whether there is a decrease, or cannibalization, of signaling effects for earlier designations due to the introduction of the Breakthrough therapy designation.

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