

Fossett, Sarah J.; Wunnava, Phanindra V.

Working Paper

Active Ingredients: Exploring the Key Factors Affecting the Rising Cost of Developing New Drugs

IZA Discussion Papers, No. 10817

Provided in Cooperation with:

IZA – Institute of Labor Economics

Suggested Citation: Fossett, Sarah J.; Wunnava, Phanindra V. (2017) : Active Ingredients: Exploring the Key Factors Affecting the Rising Cost of Developing New Drugs, IZA Discussion Papers, No. 10817, Institute of Labor Economics (IZA), Bonn

This Version is available at:

<https://hdl.handle.net/10419/170801>

Standard-Nutzungsbedingungen:

Die Dokumente auf EconStor dürfen zu eigenen wissenschaftlichen Zwecken und zum Privatgebrauch gespeichert und kopiert werden.

Sie dürfen die Dokumente nicht für öffentliche oder kommerzielle Zwecke vervielfältigen, öffentlich ausstellen, öffentlich zugänglich machen, vertreiben oder anderweitig nutzen.

Sofern die Verfasser die Dokumente unter Open-Content-Lizenzen (insbesondere CC-Lizenzen) zur Verfügung gestellt haben sollten, gelten abweichend von diesen Nutzungsbedingungen die in der dort genannten Lizenz gewährten Nutzungsrechte.

Terms of use:

Documents in EconStor may be saved and copied for your personal and scholarly purposes.

You are not to copy documents for public or commercial purposes, to exhibit the documents publicly, to make them publicly available on the internet, or to distribute or otherwise use the documents in public.

If the documents have been made available under an Open Content Licence (especially Creative Commons Licences), you may exercise further usage rights as specified in the indicated licence.

DISCUSSION PAPER SERIES

IZA DP No. 10817

**Active Ingredients: Exploring the Key Factors
Affecting the Rising Cost of Developing
New Drugs**

Sarah J. Fossett
Phanindra V. Wunnava

JUNE 2017

DISCUSSION PAPER SERIES

IZA DP No. 10817

Active Ingredients: Exploring the Key Factors Affecting the Rising Cost of Developing New Drugs

Sarah J. Fossett

Credit Suisse

Phanindra V. Wunnava

Middlebury College and IZA

JUNE 2017

Any opinions expressed in this paper are those of the author(s) and not those of IZA. Research published in this series may include views on policy, but IZA takes no institutional policy positions. The IZA research network is committed to the IZA Guiding Principles of Research Integrity.

The IZA Institute of Labor Economics is an independent economic research institute that conducts research in labor economics and offers evidence-based policy advice on labor market issues. Supported by the Deutsche Post Foundation, IZA runs the world's largest network of economists, whose research aims to provide answers to the global labor market challenges of our time. Our key objective is to build bridges between academic research, policymakers and society.

IZA Discussion Papers often represent preliminary work and are circulated to encourage discussion. Citation of such a paper should account for its provisional character. A revised version may be available directly from the author.

ABSTRACT

Active Ingredients: Exploring the Key Factors Affecting the Rising Cost of Developing New Drugs*

What makes prescription drugs cost so much? The media and Congress say it is corporate greed, while pharmaceutical firms blame federal regulations and an expensive drug development process. This study focuses on R & D (R&D) expenditures at global pharmaceutical firms and explores the driving factors behind what makes R&D for prescription drugs so costly. By combining variables that represent the news media's claims (i.e. CEO compensation) and the pharmaceutical firms' rebuttals (i.e. late-stage drug development), this study attempts to add empirical evidence to the growing debate surrounding the high and rising cost of prescription drugs. The results suggest that there is some truth to both sides of the argument- specifically; both CEO compensation and phase II development are positively correlated with R & D expenditures. However, we have reason to believe that CEO compensation is more of an indicator of business strategy than greed. Finally, this study proposes possible research extensions for continued study.

JEL Classification: I11, J33, L10

Keywords: prescription drugs, CEO compensation, drug development, price earnings ratio, profitability, employee effect, Research & Development

Corresponding author:

Phanindra V. Wunnava
David K. Smith '42 Chair in Applied Economics
Department of Economics
Middlebury College
Warner Hall 502F
Middlebury, VT 05753
USA
E-mail: wunnava@middlebury.edu

* Authors would like to thank Sanjay Wunnava for his editorial suggestions and comments. The usual caveats apply.

“Active Ingredients: Exploring the Key Factors Affecting the Rising Cost of Developing New Drugs”

I. Introduction

For nearly a decade, the citizens of the United States have been bystanders in what many have dubbed “the U.S. Healthcare Crisis.” Undoubtedly, one of the most troubling trends in the U.S. economy is the rapid growth of health expenditures following WWII.¹ Within the healthcare landscape, the rate of increase to the costs associated with drug development is even greater.

In recent years, high and rising drug prices have brought pharmaceutical companies under intense fire from the media and the government. In Congressional hearings, politicians from both sides of the matter at hand have publicly attacked the pharmaceutical industry for price gouging. Even President Trump, an avid supporter of aggressive deregulation, has stated that he believes that pharmaceutical companies “are getting away with murder.”² The narrative often focuses on “greedy” company CEOs and their outsized compensation packages as the cause behind astronomical drug prices.³ However, pharmaceutical companies argue that their industry faces increasing R & D costs associated with heightened regulatory requirements, and that their profits on successful drugs are not outsized.⁴

Yet even after extensive media coverage and Congressional investigations, there is little definitive evidence supporting one reason over the other. At a time when overall healthcare spending is nearly 18% of America’s GDP, and spending on prescription drugs is increasing faster than all other healthcare spending at approximately 10% each year, understanding which factors are affecting R & D expenditures in the pharmaceutical industry is imperative.⁵ This paper will seek to provide evidence to that end.

For the proposed project, we will use a combination of Bloomberg terminal data and annual audited financial reports from a sample of 11 global pharmaceutical companies. Due to constraints imposed by the data, each of the companies in the sample is publically traded and has a headquarters located in the Western Hemisphere. The study period covers the six years ranging from 2010 to 2015.

This data will be used to analyze the most significant factors affecting R & D expenditures at a firm level over the duration of the study period. R & D expenditures are widely thought of as the most important and costly segment of the drug development process, and thus are essential to understanding the overall debate on drug costs.

This project will seek to answer questions such as; does CEO compensation affect R & D expenditure dollars? What is the impact of phase II and III trials on R & D costs? Do drugs in certain therapeutic categories cost significantly more to develop than others? Does a company’s profitability affect R & D spending? Through this project, we hope to provide economic evidence to the public debate on the high costs of prescription drugs, as well as to the body of academic literature on the economics of pharmaceutical drug development.

¹ Fuchs, 2012.

² Leonard, 2017.

³ Mangan, 2016.

⁴ CNBC, 2016.

⁵ Centers for Medicare & Medicaid, accessed 2017.

II. Insights from the Literature

Understanding what is affecting the costs associated with developing a new drug is key to cracking the code of what is driving high prescription drug prices. On an aggregate level, pharmaceutical firms record these costs on their income statements under the “R & D” line item. A firm’s R & D expenditures can run in the millions if not billions of dollars annually, begging the question as to what makes developing new drugs so expensive.

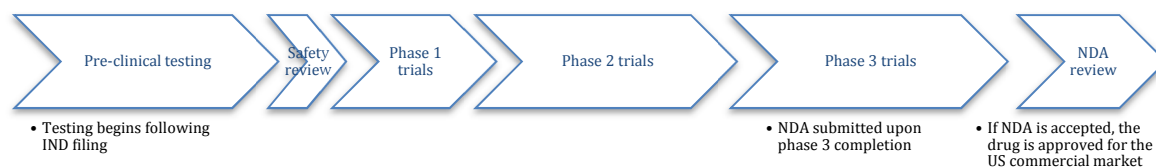
There is a large body of academic literature concerning R & D costs in the pharmaceutical industry. This section provides a review of the various qualitative and quantitative factors that influence overall R & D costs, as well as a review of the key economic studies on the topic. Important factors that influence overall R & D costs include the length of time a drug spends in clinical trials, the risk associated with developing a new drug, competition for market share for a newly approved drug, as well as macroeconomic indicators affecting the entire pharmaceutical industry and CEO compensation, business strategy and firm decision-making.

1. Time Spent in Clinical Development

The clinical development process is both risky and time-consuming.⁶ As a result, the time a drug spends in development is an important driver of R & D costs associated with a given new chemical entity (NCE).⁷

For an NCE to be approved for commercial markets in the United States, the proposed compound must go through a series of formal tests and regulatory reviews designed by the Food and Drug Administration (FDA) to prove certain standards of safety and efficacy.⁸

Figure 1:



To summarize, the clinical development process begins with preclinical testing, which involves running a series of laboratory and animal tests to better understand how the drug works and whether it is likely to be safe and effective in human subjects.⁹ If the preclinical test results are promising, the drug company or sponsor will file an investigational New Drug Application (IND). If the FDA approves the IND, then researchers may begin human testing with phase I clinical trials. The goal of phase I trials is to identify the frequency and severity

⁶ Dickson and Gagnon, 2004.

⁷ Dickson and Gagnon, 2004.

⁸ NCEs must go through a similar process in most other major markets, however the scope of this project is limited to drugs undergoing development for marketing approval in the United States.

⁹ Food and Drug Administration (FDA), 2017.

of any side effects, and to understand how the drug is metabolized and excreted by studying the drug in a small number of healthy human subjects.¹⁰ If the results of the phase I study show acceptable toxicities and generally promising data, the compound moves to phase II clinical trials. In phase II clinical trials, the focus pivots from safety to efficacy. The goal of phase II trials is to gather preliminary insights on whether or not the compound in question is effective in subjects with a certain disease or condition.¹¹ If phase II data shows favorable effectiveness results, the company or sponsor can make the decision to advance the compound to phase III trials. Phase III trials are generally the largest and most complex studies of the three trial phases. To be successful, phase III trials must show safety and efficacy in different dosages, across varying populations, and in combination with other drugs.¹² Once phase III trials are completed, the drug company or sponsor will file all of the trial results in a New Drug Application (NDA) with the FDA. The NDA is a formal application asking the FDA to consider a New Chemical Entity (NCE) for marketing approval in the United States commercial market.¹³ If the application is approved following a rigorous review of the evidence, then the drug company can begin manufacturing the NCE for commercial consumption.¹⁴

Altogether, the R & D process can last over ten years.¹⁵ In the most recent DiMasi et al. study, the mean time from the start of clinical testing to the filing of an NDA with the FDA is estimated at 80.8 months (6.7 years).¹⁶ However, estimates of the amount of time a drug spends in clinical development should include both the time spent in clinical trials, and time spent in review and approval processes.¹⁷ When the review and approval processes representing the period of time between filing for an NDA and receiving marketing approval are considered, this time estimate increases to 96.8 months (8.1 years).¹⁸ Other studies estimate that development times can extend up to 10 – 20 years with an average of 9 – 12 years.¹⁹

Notably, historical trends show that the amount of time spent in preclinical development is increasing. DiMasi and associates assess that their estimates of time spent in clinical development have increased over study periods by at least 7%.^{20,21} Increased time

¹⁰ Food and Drug Administration (FDA), 2017.

¹¹ Food and Drug Administration (FDA), 2017.

¹² Food and Drug Administration (FDA), 2017.

¹³ Food and Drug Administration (FDA), 2017.

¹⁴ Food and Drug Administration (FDA), 2017.

¹⁵ DiMasi et al., 2016.

¹⁶ DiMasi et al., 2016.

¹⁷ DiMasi et al., 2016.

¹⁸ DiMasi et al., 2016.

¹⁹ DiMasi et al., 2012; Dickson and Gagnon, 2004; Paul et al., 2010.

²⁰ DiMasi et al., 2012; Dickson and Gagnon, 2004; Paul et al., 2010.

²¹ Researchers suggest that the increasing amount of time spent in clinical development is in part due to increasing regulatory requirements (DiMasi et al., 2012; Dickson and Gagnon, 2004; Paul et al., 2010). Additionally, trends in drug development are moving towards the treatment of chronic diseases that are more difficult to treat, and therefore have additional burdens during development (Dickson and Gagnon, 2004).

spent in clinical development also correlates with increased risk associated with pharmaceutical drug development.

2. Risk

Risk in the pharmaceutical industry should be thought of as the convergence of scientific risk, regulatory risk, and economic uncertainty.²² In the pharmaceutical industry, scientific risk is largely thought of as the risk that a NCE for which the firm has invested a significant amount may fail somewhere in the development process.²³ Drugs may fail during clinical trials if they fail to meet certain safety or efficacy targets; as such, success rates are a good proxy for risk.²⁴ Success rates vary significantly by trial stage, for reasons that will be discussed in more detail below. Scientific risk also includes the risk that a NCE may not gain enough market share once approved to recoup development costs.²⁵ One common example of this scenario is when a competitor develops a drug to treat the same indication faster.

Regulatory risks include any risks related to the FDA review and approval processes.²⁶ A significant regulatory risk is the uncertainty surrounding the time the FDA will take to review and approve a NDA once it has been submitted.²⁷ Unexpected regulatory delays can cause delays to product marketing and launches, costing the firm lost revenue tied to early drug sales. Another more serious, but less common, regulatory risk is the risk that a drug that has successfully undergone all stages of clinical trials still may not be approved for commercial sale by the FDA.²⁸

- (i) Success Rates

All scientific and regulatory risks become more significant as both time and money spent in development increases.²⁹ An accurate estimate of the cost of developing a new drug must reflect these scientific and regulatory risks. The first step in estimating the monetary costs inherently implied by scientific risk is determining the overall probability of clinical success (i.e. “the likelihood that a drug that enters clinical testing will eventually be approved”).³⁰ The overall probability of clinical success is calculated by finding the product of the phase transition probabilities (i.e. the probability that a drug in phase I trials advances to phase II trials, and so on and so forth) observed in a given sample of NCEs. DiMasi et al.’s most recent estimate of the overall probability of clinical success, or the probability that a drug entering phase I trials will reach FDA approval, was 11.83%.³¹ This estimate is much lower than that of their previous study, which yielded a success rate of 21.50%³², but is

²² Dickson and Gagnon, 2004; DiMasi et al., 2012.

²³ DiMasi et al., 2012.

²⁴ Dickson and Gagnon, 2004.

²⁵ DiMasi et al., 2012.

²⁶ DiMasi et al., 2012.

²⁷ Dickson and Gagnon, 2004; Morgan et al., 2011.

²⁸ Dickson and Gagnon, 2004.

²⁹ DiMasi et al., 2012; Morgan et al., 2011.

³⁰ Adams and Brantner, 2003.

³¹ DiMasi et al., 2012; 2016.

³² DiMasi et al., 2012.

consistent with several other recently published estimates.³³ Moreover, the decrease in success rates during the time period between DiMasi's studies is also consistent with longer historical trends showing clinical success rates decreasing over time.³⁴

Ceteris paribus, a decrease in overall clinical success rates will substantially increase the cost per approved new drug.³⁵ This is because a full estimate of the R & D cost of an approved NCE must also include the cost burden of R & D expenditures on failed drugs.³⁶ Lower success rates increase this burden. Conversely, an increase in overall clinical success rates would lead to a reduction in costs. DiMasi's 2002 study shows the cost per approved NCE could be reduced by up to 30% if the clinical success rate increased from approximately 20% to 33%.³⁷

Other studies have shown that the probability of clinical success varies based on firm size and strategy, as well as drug indication.³⁸ A 2001 DiMasi study on firm size presents evidence that indicates that larger firms have higher approval rates.³⁹ A separate Adams and Brantner study shows that a drug in phase III trials at one of the large, global pharmaceutical firms (i.e. "Big Pharma") has a 47% chance of gaining market approval, while a drug in phase III development at a smaller firm only has a 36% chance, all else being equal.⁴⁰

Regarding firm strategy, there is evidence to suggest that the increase in cost due to a decrease in overall success rates in recent studies is mitigated by firms abandoning failing drugs earlier in the R & D process.⁴¹ A comparison of the distribution of clinical failures in DiMasi's 2016 and 2012 studies corroborates this conclusion. Clinical failure rates in DiMasi's 2016 study were 45.9% (phase I), 43.5% (phase 2), and 10.6% (phase 3/ regulatory review) versus 36.9% (phase 1), 50.4% (phase 2), and 12.6% (phase 3) in 2012.⁴²

A 2001 DiMasi et al. study shows that success rates also vary significantly depending on therapeutic class.⁴³ More specifically, the study found the highest success rates for anti-biotics (28.1%) and the lowest success rates for central nervous system drugs (14.5%), antineoplastics (15.8%), and immunological drugs (15.4%). While these success rates have likely changed since the 2001 publication date, the results nonetheless show that indication is an important variable affecting the likelihood of success, and ultimately the cost, of an approved NCE.⁴⁴

The results of the 2001 DiMasi study, as well as a follow up 2004 study, offer evidence for the commonly made claim that the cost of R & D associated with an approved NCE are increasing because a growing portion of NCEs are being developed to treat chronic

³³ Paul et al., 2010; DiMasi et al., 2013; Hay et al., 2014.

³⁴ DiMasi and Graboski, 2013.

³⁵ Dickson and Gagnon, 2004; Morgan et al., 2011.

³⁶ DiMasi et al., 2012.

³⁷ DiMasi, 2002.

³⁸ Adams and Brantner, 2003; DiMasi and Grabowski, 2012.

³⁹ DiMasi et al., 2001.

⁴⁰ Adams and Brantner, 2003.

⁴¹ DiMasi et al., 2012; 2016; Morgan et al., 2011.

⁴² DiMasi et al., 2012; 2016.

⁴³ DiMasi et al., 2001.

⁴⁴ DiMasi et al., 2001.

diseases.⁴⁵ Relatively lower success rates in the CNS and immunological drug categories suggest that it may, in fact, be more difficult, and more expensive, to develop drugs for chronic diseases.⁴⁶

- (ii) Overall Risk and Economic Uncertainty

Overall, the effect of historical time and risk trends, increasing development times, lower clinical approval success rates, and increasingly complex clinical trials suggest that R & D costs have continued to increase in real terms.⁴⁷ The convergence of these trends result in significant overall risk for firms engaging in the R & D of NCEs.⁴⁸

However, the risks related to firms engaging in the development of new drugs are not purely internal. The pharmaceutical firms that comprise this project's sample are all publically traded, meaning that each is partially owned by stockholders (i.e. public investors). Thus, another important component of economic risk is the opportunity costs borne by investors investing in a pharmaceutical company, versus other less risky alternatives.⁴⁹

The financial burden of the opportunity cost is theoretically equivalent to the return on investment (ROI) that an investor will demand in order to accept the additional risks of investing in a given pharmaceutical firm.⁵⁰ Simply put, investors will expect higher returns as a reward for being willing to make a (relatively more) risky investment. In practice, the opportunity cost, or the risk of investing in drug R & D activity, is a firm's weighted average cost of capital (i.e. WACC or "discount rate"). In other words, a high weighted average cost of capital is associated with a higher risk stemming from a firm's operations.⁵¹

It should be noted that firms that operate multiple unique business segments (i.e. Johnson and Johnson®) may be viewed as less risky than other firms in the pharmaceutical industry because their diverse platform helps to protect against the consequences of economic losses in any individual business segment. In other words, the losses associated with a promising drug failing somewhere in the development process are offset by a landmark year in household product sales.

In addition to the effects of changes in scientific and regulatory risk, historical trends of increasing development times also influence the effects of WACC.⁵² More precisely, the WACC, or the effective opportunity cost, grows with increasing lag between when an investment is made, and when potential returns can be realized.

⁴⁵ DiMasi et al., 2001; 2004; 2012; Dickson and Gagnon, 2004.

⁴⁶ Many chronic conditions fall under either the CNS or immunological therapeutic category.

⁴⁷ DiMasi, 2012.

⁴⁸ Morgan et al., 2011; Dickson and Gagnon, 2004.

⁴⁹ DiMasi et al., 2012.

⁵⁰ Winegarden, 2014; DiMasi et al., 2012.

⁵¹ Investopedia. 2015.

⁵² DiMasi, 2012.

- (iii) A given firm's WACC, or opportunity cost, can be calculated using the equation:

$$\text{WACC} = \frac{E}{V} * R_e + \frac{D}{V} * R_d * (1 - T_c)$$

Where:

R_e = cost of equity

R_d = cost of debt

E = market value of the firm's equity

D = market value of the firm's debt

$V = E + D$ = total market value of the firm's financing (equity and debt)

E/V = percentage of financing that is equity

D/V = percentage of financing that is debt

T_c = corporate tax rate

Within the literature there is substantial variability regarding the appropriate discount rate – rates generally range from 9-12%.⁵³ However, based on relevant experience working in a prominent healthcare investment-banking group by one of the authors, we would argue that in practice, most companies in the space have a WACC no larger than 8%. Likewise, the NYU Stern School of Business also estimates the pharmaceutical industry's WACC at 7.72%.⁵⁴

An investor's opportunity cost has a significant impact on the fully capitalized cost of developing a NCE and insofar, the precise estimation of the WACC is crucial.⁵⁵ In two studies that attempted to estimate the fully capitalized cost of developing a NCE, a 1% difference in the WACC was responsible for a 13% difference in costs between studies.⁵⁶

Significant incursions of time from drug discovery to approval and high probabilities of failure during clinical trials (among other scientific and regulatory risks) create substantial economic risk for investors looking to invest in pharmaceutical firms.⁵⁷ Overall, the effect of risk and time trends on WACC, coupled with an increasing reliance on outside investors suggests that R & D costs have continued to increase in real terms.⁵⁸

3. The Effect of Competition on R & D Decisions

Competition in the pharmaceutical industry has a significant impact on the expected market returns for a newly approved drug, and thus a substantial effect on a firm's R & D decisions.⁵⁹ Firms are only willing to incur the substantial costs and risks associated with

⁵³ Adams and Brantner, 2003; 2010; DiMasi et al., 2009; 2012; 2016; Paul et al., 2010; Winegarden, 2014.

⁵⁴ NYU Stern, 2016.

⁵⁵ Fully capitalized costs, rather than out of pocket costs, should be considered as the total cost in order to account for the real costs firms must incur to attract investment.

⁵⁶ DiMasi et al., 2012.

⁵⁷ Dickson and Gagnon, 2004.

⁵⁸ DiMasi et al., 2012.

⁵⁹ Dickson and Gagnon, 2004; DiMasi et al., 2012.

developing a NCE if there is a reasonable expectation that a market will exist once a given product receives approval.⁶⁰ The market for an approved NCE is partially protected by the patenting process.

Patents are filed for in conjunction with the Investigatory New Drug (IND) application, prior to preclinical development. The period of patent protection begins when the patent is approved. Most pharmaceutical patents last for 20 years, though patent lengths vary.⁶¹ While patents do give drug makers exclusive rights to develop a specific molecular compound, patents don't protect firms from therapeutic competition.⁶² And eventually, once a patent expires, even the most successful name-brand drugs will lose significant market share to generic competitors.⁶³

- (i) Therapeutic Competition

While pharmaceutical patents protect against duplicating a patented compound's exact formula, more than one firm may be simultaneously developing drugs with similar therapeutic indications and mechanisms of action.⁶⁴ Take well-known Rheumatoid Arthritis drugs Enbrel and Humera, for example – Both drugs are patent protected, but still must compete with one another for market share. For another example, consider that multiple firms are currently developing molecular compounds to treat Hepatitis C. If more than one of these drugs gains market approval, it is possible that only one drug will gain significant enough market share to recuperate the R & D expenditures related to that drug. A recent analysis suggests that only 30% of all approved NCEs will ever recuperate all related R & D expenses, suggesting that therapeutic competition will continue to increase over time.⁶⁵

- (ii) Generic Competition

When a pharmaceutical patent expires, other firms can start producing generic equivalents of the brand-name drug. While development of the original NCE required a costly investment in knowledge and scientific discovery, the development of a generic drug is usually a fairly simple (and inexpensive) technical process of duplication.⁶⁶ Once a generic equivalent enters the market, the market share and returns on the brand-name original rapidly decrease.⁶⁷ Similarly, a study by Grabowski and Vernon shows that “after 42 months following generic entry for seven major drugs in 1989 to 1990, the average price was 34% of the brand price and generics had 71% of the market share.”⁶⁸ If this study was replicated today, the market share gained by generics would most certainly be higher as generic competition has intensified dramatically over the past 30 years.⁶⁹

⁶⁰ Dickson and Gagnon, 2004.

⁶¹ Winegarden, 2014; Dickson and Gagnon, 2004.

⁶² Dickson and Gagnon, 2004.

⁶³ DiMasi et al., 2012; Dickson and Gagnon, 2004.

⁶⁴ Dickson and Gagnon, 2004.

⁶⁵ Grabowski and Vernon, 2012; Klick and Wright, 2015.

⁶⁶ Dickson and Gagnon, 2004; Grabowski and Vernon, 2012.

⁶⁷ Dickson and Gagnon, 2004.

⁶⁸ Dickson and Gagnon, 2004; Grabowski and Vernon, 1996.

⁶⁹ Dickson and Gagnon, 2004.

- (iii) Competition Summary

Both therapeutic competition and generic competition drive firms' demand for constant streams of new innovative and strong development pipelines.⁷⁰ As competition increases, anticipation of decreasing market share and returns incentivizes firms to develop more drugs.⁷¹ While having more drugs in development at any given time would not clearly increase or decrease the cost of developing a single NCE alone, the trend of falling drug approval rates suggests that increased competition encourages firms to take on more aggressive and risky R & D strategies. This in turn puts upward pressure on the costs associated with developing a NCE and increases aggregate R & D expenditures.⁷²

4. Macroeconomic, Demographic, and Policy Factors Affecting R & D Funding

A full analysis of the factors affecting R & D expenditures must also consider the impact of macro-economic and demographic factors as well as public policy on business decisions.⁷³ While R & D expenditures are the product of R & D costs, these expenditures must also be considered as constrained by a predetermined R & D budget.⁷⁴

- (i) Demographic Factors

A growing demand for medicines means more revenue and more money flow into R & D.⁷⁵ Overall trends show pharmaceutical sales growing steadily. Year-on-year revenue growth was 7.8% in 2011.⁷⁶ Growing demand in both developed and developing countries fuel year-on-year growth.

General demographic trends contributing to growth include the increasing global population, and specifically the increasing elderly, sedentary, and obese populations. There is also a significant impact resulting from aging of the baby-boomer population.⁷⁷ Importantly, these trends may affect overall R & D spending, but it is unclear how they may affect the cost of developing a single NCE.

-(i) Policy Factors

Increased access to healthcare through programs like the Affordable Care Act (ACA) also increases the expected market size and revenues for the pharmaceutical industry. The ACA is especially important because the US is the largest market for prescription drugs, but the trend towards increased access (and thus expanding markets) is global.⁷⁸

The potential for future policies like legislating drug price-caps may also have an effect on R & D expenditure. In general, any government regulation around the pricing of prescription drugs has the potential to limit incentives for future R & D spending.⁷⁹ Similar

⁷⁰ DiMasi et al., 2012.

⁷¹ Dickson and Gagnon, 2004.

⁷² Dickson and Gagnon, 2004.

⁷³ Winegarden, 2014; Dickson and Gagnon, 2004.

⁷⁴ Dickson and Gagnon, 2004.

⁷⁵ PricewaterhouseCooper, 2012.

⁷⁶ PricewaterhouseCooper, 2012.

⁷⁷ PricewaterhouseCooper, 2012.

⁷⁸ PricewaterhouseCooper, 2012.

⁷⁹ Danzon, 2015.

to the relationship between demographic factors and R & D spending, these trends may affect overall R & D spending, but it is unclear how they affect the cost of developing a single NCE.

In summary, changing predictions of expected revenue growth can impact a firm's strategic R&D decisions, but due to a lack of literature on this specific topic, it is unclear how this trend manifests in the pharmaceutical industry. More broadly, studies have shown a strong relationship between expectations and decision-making.

5. CEO compensation, business strategy and firm decision-making

In order to incorporate an analysis of the media's claim that CEO compensation is to blame for high and rising drug prices, we searched the literature for evidence of links between executive pay and business strategy at pharmaceutical firms, but little empirical evidence exists. In general, researchers have noted that it is difficult to account for the effects of firm strategy on the cost of developing a new drug, and that doing so would represent a significant contribution to the literature.⁸⁰ While the literature on this topic is minimal, a related Offstein and Gnyawali study of U.S. pharmaceutical firms shows that CEO compensation is closely related to firm competitive aggressiveness in the pharmaceutical industry.⁸¹ More specifically, this study shows that higher executive compensation among CEOs at pharmaceutical firms is correlated with a higher volume and increased diversity of competitive moves undertaken by the firm.⁸² A second study by Balkin et al. of CEO compensation at high technology firms reiterates this finding, and further suggests that CEOs in high technology industries such as the pharmaceutical industry are rewarded for innovation-based projects rather than for financial outcomes, giving CEOs an obvious incentive to induce executives at these firms to take more risks⁸³. Together, these two studies advance the theory that CEO compensation may influence R & D expenditures at pharmaceutical firms.

Similar to CEO compensation, firm decision making is an important aspect of business strategy that is largely absent in the relevant body of literature. In a broad study of firm behavior, economists confirm that one of the guiding principles of macroeconomics is the influence of expectations on behavior.⁸⁴ Notably, the authors show that analysts' expectations of a firm's future earnings are measurably correlated to firm activity, including R & D.⁸⁵ The authors also acknowledge potential issues with reverse causality, and use additional tests to prove that the results are meaningful in the intended direction.⁸⁶

6. Key Studies

There are multiple conceptual models and measurement methods for estimating the costs of developing a new drug. These models have developed from the earliest studies

⁸⁰ Dickson and Gagnon, 2004; DiMasi et al., 2012.

⁸¹ Offstein and Gnyawali, 2005.

⁸² Offstein and Gnyawali, 2005.

⁸³ Balkin et al., 2000.

⁸⁴ Gennaioli et al., 2015.

⁸⁵ Gennaioli et al., 2015.

⁸⁶ Gennaioli et al., 2015.

attempting to estimate the cost of drug discovery.

The cost of creating new medicines has been a subject of academic interest, as well as an important public policy issue since at least the 1960's.⁸⁷ The first wave of academic articles on the topic were published partially in response to the passage of the 1962 "Drug-Efficacy Amendment" to the 1938 Food Drug, and Cosmetic Act, which legislated that drug companies must show significant evidence of efficacy, as well as safety.⁸⁸ Academic researchers, interested in how the new FDA regulations might affect the cost of developing drugs, began to study how certain variables related to R & D costs in the pharmaceutical industry.⁸⁹ These researchers used survey data from the 1950's and 1960's on multiple NCEs from single firms to estimate average drug costs.⁹⁰ Additionally, other researchers used publicly available aggregate data on R & D expenditures and approved NCEs to estimate drug costs.⁹¹ However, these early studies were flawed because they only considered the out-of-pocket costs for approved compounds, and neglected to include the cost of failed drugs or consider fixed or time costs, among other factors.⁹²

The first study that attempted to estimate the fully capitalized cost of developing a new drug, rather than the out-of-pocket costs estimated by prior studies, was published by Hansen in 1979. Hansen's methods relied on confidential survey data collected from major pharmaceutical companies regarding drugs in development and R & D expenditures by compound and trial phase.⁹³ In 1976, Hansen estimated that the average capitalized cost for a drug developed in the late 1960s and early 1970s was \$54 million.⁹⁴ The Hansen study is pivotal because it established a basic methodology to estimate the fully capitalized cost of developing a NCE that is still used today.⁹⁵

Joseph DiMasi, the director of economic analysis at the Tufts Center for the Study of Drug Development (CSDD), has extensively built on the work of Hansen.⁹⁶ The current Hansen/DiMasi methodology involves estimating the average total cost per marketable NCE using retrospective cost accounting with project-level data on "the costs, success rates and durations of each stage of clinical investigation."⁹⁷ All Hansen and DiMasi studies rely on data from the Tufts CSDD database, which is composed of extensive private survey responses regarding the costs of drug development.⁹⁸

While the private nature of the Tufts CSDD database presents a challenge to conforming this project's methodology to the literature, a second approach to estimating the cost of new drugs has been developed in a series of publications seeking to validate Hansen

⁸⁷ DiMasi et al., 2012.

⁸⁸ U.S. Federal Drug Administration & Michelle Meadows, 2006.

⁸⁹ Schnee, 1972; Mund, 1970; Bailey, 1972.

⁹⁰ Schnee, 1972.

⁹¹ Mund, 1970; Bailey, 1972.

⁹² DiMasi and Grabowski, 2012.

⁹³ Hansen, 1979.

⁹⁴ Hansen, 1979; DiMasi and Grabowski, 2012.

⁹⁵ DiMasi and Grabowski, 2012.

⁹⁶ DiMasi and Grabowski, 2012.

⁹⁷ S. Morgan et al., 2011, 6.

⁹⁸ Dickson and Gagnon, 2004.

and DiMasi’s results using public data and proprietary (but publically accessible) databases.⁹⁹

Adams and Brantner used econometric methods to model “firm-level research expenditure as a function of the number of drugs a firm had under development at various stages of clinical investigation.”¹⁰⁰ To verify their estimates of the timing and success rates of each phase of development, Adams and Brantner used data published by earlier Hansen and DiMasi studies.¹⁰¹ The results of the 2006 Adams and Brantner study validated the results of the 2003 DiMasi study, and suggested that Adams and Brantner’s use of public data provide a viable alternative to Hansen and DiMasi’s study methodology.¹⁰²

Later Adams and Brantner studies also controlled for a variety of firm-related and drug-related variables including firm size (proxied by the number of employees) and therapeutic category.¹⁰³

Taken together, the DiMasi et al. and Adams and Brantner studies show that R & D cost estimates have increased over time. Table 1 summarizes the results of the six most relevant studies on the cost of developing new drugs and the factors affecting R & D expenditures.

Table 1: Cost of Developing Drugs and R&D Expenditures

Study {year of publication}	{1991}	{2003}	{2007}	{2016}
DiMasi et. al.,	\$318 million year 2000 dollars	\$802 million year 2000 dollars	\$1.2 billion year 2005 dollars	\$2.9 billion year 2013 dollars
Adams and Brantner (matched with comparable DiMasi et. al.,)		\$868 million year 2000 dollars	\$1.2 billion year 2000 dollars	

Source: DiMasi et al., 2016

III. Methodology

Because this project is constrained by the requirement of using publicly available data, the Adams and Brantner methodology is modified to work within this limitation.

The data used in this project was gathered from the Bloomberg terminal’s proprietary database and annual audited financial reports from a sample of 11 global pharmaceutical companies between 2010 and 2016. Data was collected on each firm’s annual aggregate R & D expenditure, CEO compensation package, annual total revenue, annual pharmaceutical

⁹⁹ DiMasi and Grabowski, 2012; S. Morgan et al., 2011; Wiggins, 1987; Adams and Brantner 2006; Adams and Brantner 2010.

¹⁰⁰ S. Morgan et al., 2011, 6.

¹⁰¹ S. Morgan et al., 2011.

¹⁰² S. Morgan et al., 2011; DiMasi and Grabowski, 2012.

¹⁰³ Adams and Brantner, 2010.

revenue, price-to-earnings ratio, and employee headcount. Data was also collected on the number of phase II and phase III trials ongoing at a given firm in a given year, and on whether a given firm publically reported a clinical focus in oncological, central nervous system (CNS), or immunological drugs.

This study improves on previous work with a more current sample and by investigating the effects of CEO compensation and profitability. The effects of revenue, firm size, and the number of drugs in development have been similarly modeled in previous studies. The dependent variable for the model is LNRD, which is the log of R & D dollars as reported in a company's annual 10K report. The log of R & D dollars was used to capture non-linearity in the spending profiles of companies. The empirical specification and sample variable characteristics/definitions are as follows;

$$\text{LNRD}_{it} = \beta_0 + \beta_1 \text{LLNTREV}_{it} + \beta_2 \text{LNCEOCOMP}_{it} + \beta_3 \text{P2DRUG}_{it} + \beta_4 \text{P2DRUGSQ}_{it} + \beta_5 \text{P3DRUG}_{it} + \beta_6 \text{P3DRUGSQ}_{it} + \beta_7 \text{IMMUNO}_{it} + \beta_8 \text{PE}_{it} + \beta_9 \text{LNEMPLOYEE}_{it} + \text{Error}_{it}$$

Table 2. Summary Statistics

<i>Variable</i>	Effective Sample = 51	
	<i>Mean</i>	<i>SD</i>
LNRD	22.49202	0.447627
LLNTREV	24.3231	0.516345
LNCEOCOMP	16.33647	0.382784
P2DRUG	17.60784	10.05003
P2DRUGSQ	409.0588	415.2794
P3DRUG	14.80392	8.337912
P3DRUGSQ	287.3137	338.267
IMMUNO	0.5454545	0.502519
PE	21.00895	10.08586
LNEMPLOYEE	11.15945	0.538773

Variable Definitions

- **LNRD** = the log of annual R & D expenditures () as reported by firms in their 10K reports, lagged one year. Source: Firm 10K reports, taken from firm websites.
- **LLNTREV** = the log of annual pharmaceutical revenue (USD) as reported by firms in their 10K reports, lagged one year. Source: Firm 10K reports, taken from firm websites.
- **LNCEOCOMP** = log of IV estimated values for CEO compensation (USD), including bonuses and stock-related benefits. Estimated values were predicted by an IV regression of dividends paid on CEO compensation. Source: IV estimator, see Appendix 1 (Table 4) for more information.
- **P2DRUG** = number of drugs in phase II development in a given year, based on published pharmaceutical pipelines on December 31 of that year. Only new chemical entities are considered (rather than drugs that are in development as an improvement on an already improved compound) and drugs are attributed to originating firm (ignoring any licensing agreements) Source: Firm 10K reports and investor presentations, taken from firm websites.
- **P2DRUGSQ** = square term of the number of phase II drugs, see above for additional information.
- **P3DRUG** = number of drugs in phase III development in a given year, based on published pharmaceutical pipelines on December 31 of that year. Only new chemical entities are considered

(rather than drugs that are in development as an improvement on an already improved compound) and drugs are attributed to originating firm (ignoring any licensing agreements)
Source: Firm 10K reports and investor presentations, taken from firm websites.

- **P3DRUGSQ** = square term of the number of phase III drugs, see above for additional information.
- **IMMUNO** = dummy variable indicating whether or not a company specifically states immunological drugs as a focus area in investor presentations for a given year. Observations are coded 1 if they state immunology as a focus area, and zero otherwise. Source: Investor presentations, taken from firm websites.
- **PE** = forward-looking price-to-earnings ratio for a given firm in a given year. Source: Bloomberg terminal data.
- **LNEMPLOYEE** = number of employees at a given firm in a given year. Source: Bloomberg terminal data.
- **LNCEOCOMP** = log of CEO compensation packages (USD in millions), including salary, bonus, and market value of vested stock options. Source: Bloomberg intelligence data.
- **LNDIVPAID** = log of total dividends paid to shareholders in a given year. Source: Bloomberg intelligence data.

This sample data set is approximately representative of the larger set of companies that comprise “big pharma” (i.e. large, global pharmaceutical companies), since many of these companies have similar revenues, CEO compensation packages, and employee headcounts. The sample is comprised of observations from 11 companies over a 6-year period. However, the lagged revenue variable and a handful of missing observations reduce the sample size to 51 observations.

IV. Empirics and Discussion

The regression results are reported in table 3, below. The model is estimated using the ordinary least squares (OLS) and two-stage least squares regression techniques. The coefficients of the LLNTREV, LNCEOCOMPHAT, P2DRUG and P2DRUGSQ variables are significant at the 1% level, while the coefficient of the LNEMPLOYEE variable is significant at the 5% level.

Table 3. Regression Results

Dependent Variable: LNRD	
LLNTREV	0.591 (3.60)**
LNCEOCOMPHAT	0.467 (4.44)**
P2DRUG	0.029 (3.16)**
P2DRUGSQ	-0.001 (3.40)**
P3DRUG	0.022 (1.67)
P3DRUGSQ	-0.0003 (1.37)

IMMUNO	0.123 (1.78)
PE	0.003 (1.64)
LNEMPLOYEE	-0.339 (2.30)*
_cons	3.677 (1.48)
R^2	0.89
N	51

* $p < 0.05$; ** $p < 0.01$

1. The lagged revenue effect

As expected, the LLNTREV (i.e. the lagged log of total revenue) variable is significant at the 1% level. The coefficient of the LLNTREV variable suggests that the elasticity of R & D expenditures with respect to the previous year's annual aggregate revenues is relatively inelastic. Specifically, the model predicts that if the previous year's revenue increases by 1%, then R & D expenditures will increase by 0.591% in the current year, all else staying constant. A firm's decision to expend a certain amount of capital on R & D can be thought of as akin to an investment decision.¹⁰⁴ And while a pharmaceutical firm's investment decisions undoubtedly relies on multiple factors, one of these factors must logically be the financial constraint imposed by the firm's recent performance.¹⁰⁵ Thus, the statistically significant positive relationship between R&D expenditures and the previous year's revenues is consistent with our expectations and fits within the framework of the relevant economic theory.

2. CEO compensation

The LNCEOCOMP variable was included in the model to control for the effect of executive behavior. Because there is some concern that the LNCEOCOMP variable may suffer from possible endogeneity bias, the model utilizes an Instrumental Variable (IV) technique. Specifically, the variable LNDIVPAID (i.e. annual dividends paid out to shareholders of a given firm) is used as an instrument to nullify the endogeneity.¹⁰⁶ Accordingly, LNCEOCOMP_{HAT}, generated by the IV method, is substituted for LNCEOCOMP in our final model. Previous studies, such as Offstein and Gnyawali's study of CEO compensation and firm competitive behavior in the U.S. pharmaceutical industry, suggest that dividends paid is a fairly robust predictor of CEO compensation packages, and is unlikely to be correlated with our error term.¹⁰⁷

The LNCEOCOMP_{HAT} variable meets our directional expectations and is statistically significant at the 1% level. The coefficient of the LNCEOCOMP_{HAT} variable suggests that the

¹⁰⁴ Jekunen, 2014.

¹⁰⁵ Lewellen, 2014.

¹⁰⁶ See Appendix 1: IV results reported in Table 4.

¹⁰⁷ Offstein and Gnyawali, 2005.

elasticity of R & D expenditures with respect to CEO compensation is 0.467. These results indicate that a 1% increase in CEO compensation leads to a 0.467 percentage point increase in R & D spending. As such, this suggests that even when the effects of revenue, firm size (proxied with the LNEmployee variable), and the number of drugs in development are held constant, the effect of a CEO's compensation package on the costs associated with developing new drugs (i.e. R & D expenditure) is significant. It must be noted that to determine the validity of the claim that high CEO compensation packages are the culprit behind the high and rising price of prescription drugs is outside the scope of this analysis. However, the significance of this coefficient suggests that CEO compensation is not irrelevant to the drug development narrative, and certainly indicates the need for further research.

Another alternative explanation of the LNCEOCOMP coefficient is that a firm's CEO compensation package is an indicator of business strategies. In the same study of CEO compensation and firm competitive behavior in the U.S. pharmaceutical industry, the authors show that CEO compensation is positively related to firm competitiveness.¹⁰⁸ The authors argue that because firms in the pharmaceutical industry compete on scientific innovation and technological superiority, "a firm's human capital may prove instrumental in enabling firms to compete and achieve a competitive edge".¹⁰⁹ Thus it may be the case that firms with higher CEO compensation packages also have more aggressive business strategies, including higher risk drug development, and as a result, higher R & D expenditure.¹¹⁰

While further research must be completed to validate this alternative but highly likely explanation, this result should tentatively be seen as an important contribution to the existing literature. Many of the leading studies have noted its importance. Yet, in current models, there is an absence of the effects of business strategy on R & D expenditures.¹¹¹ If, as the Offstein and Gnyawali study suggests, CEO compensation is a strong predictor of firm competitive behavior, then this project provides a starting point for understanding the effects of business strategy on R & D expenditures in the pharmaceutical industry.

3. Phase II trials

Our results show that the P2DRUG and P2DRUGSQ variables meet our directional expectations and are statistically significant at the 1% level. The P2DRUG and P2DRUGSQ terms are included in the model to examine the marginal effect of an additional phase II trial on R & D expenditures. We hypothesize that there may be a point at which the inclusion of an additional phase II trial is no longer associated with an increasing amount of R & D spending. Please refer to Figure 2 in Appendix 1. As a result, we would expect to see a number of trials at which R & D spending reaches a maximum. From our empirical model, the partial effect of P2DRUG on LNRD is:

¹⁰⁸ Offstein and Gnyawali, 2005.

¹⁰⁹ Offstein and Gnyawali, 2005; 202.

¹¹⁰ Offstein and Gnyawali, 2005; 202.

¹¹¹ Dickson and Gagnon, 2004.

$$\frac{\delta \text{LNRD}}{\delta \text{P2DRUG}} = (0.029) + 2(-0.001) * \text{P2DRUG}$$

Based on the above equation, the R&D expenditures peak at 14.5 trials. The mean number of phase II trials is approximately 17 trials, indicating that the inflection point is less than the mean by over two trials.

4. Phase III trials

Our results show that the P3DRUG and P3DRUGSQ variables are not statistically significant at traditional levels. Like the P2DRUG and P2DRUGSQ terms, the P3DRUG and P3DRUGSQ terms are included in the model to examine the marginal effect of an additional phase III trial on R & D expenditures. Similarly, we hypothesize that there may be a point at which the inclusion of an additional phase III trial is no longer associated with an increasing amount of R & D spending. However, the lack of statistical significance leaves us unable to accept this hypothesis.

It is somewhat surprising that the P3DRUG and P3DRUGSQ coefficients are insignificant, even when tested together for joint significance. Phase III trials are often regarded as the longest, and most complicated phase of clinical development. Moreover, phase III trials require the most study participants, and the most rigorous results with regard to both efficacy and safety. It is possible that our result is indicative of more firms making ‘go or no-go’ decisions with potential drug candidates earlier in the development process.¹¹² This is to say that firms are weeding out ‘bad drugs’ (i.e. drugs that are less likely to reach market approval) before they reach the last, and most expensive phase of drug development.¹¹³

It is also possible that the lack of significance is the result of measurement error stemming from the imprecision of the data. The number of phase III trials was sourced from annual investor publications. It is possible that a given firm ran phase III trials in the time between publications (i.e. they began after one year’s publication, and ended prior to the next) and therefore went unreported. Because most phase III trials can run well over a year in length, and because companies have incentive to report having as many drugs in late stage development as possible, we believe that there is a relatively low probability of committing this type of counting error, but nonetheless acknowledge the possibility.¹¹⁴

5. Immunology drug development focus

The IMMUNO variable is a dummy variable used to isolate the effects of developing drugs in the immunology therapeutic category on firm R & D expenditures. Observations are coded “1” for firms who state that the field of immunology is a focus area in a given year’s investor publications, and “0” otherwise. Previous studies have shown that immunology

¹¹² Abrantes-Metz et al., 2004.

¹¹³ Abrantes-Metz et al., 2004.

¹¹⁴ This may have also been the case with phase II trials, although because companies often have more phase II trials than phase III trials at any given time, the effect of discounting would likely have less of an effect in our phase II results.

drugs, such as drugs to treat Rheumatoid Arthritis, are more costly to develop than drugs in other therapeutic categories.¹¹⁵ While the IMMUNO coefficient is not significant at traditional levels, we have a meaningful reason to believe that the coefficient should be positive, so we employ a one-sided t-test and find significance at the 10% level. The coefficient of the IMMUNO variable suggests that, on average, firms that focus on immunology-related drugs are associated with 13.1% higher R & D expenditures.¹¹⁶ The relatively weak level of significance is likely due to the imprecision of the measurement. A firm stating that immunology is a focus area does not necessarily imply they are devoting a certain portion of their resources to this therapeutic area. In addition, “focusing” on a specific therapeutic area may mean different things at different firms. Defining a more precise firm level variable to indicate therapeutic focus would be a valuable extension of this project.

6. Firm profitability

The PE variable (i.e. price-to-earnings ratio) was used to control for the effect of market expectations on R & D spending. The price-to-earnings (p/e) ratio is calculated as the market value per share divided by earnings-per-share (EPS). Theoretically, the p/e ratio describes how much investors are willing to pay per dollar of a given firm’s earnings.¹¹⁷ If a firm has a p/e ratio that is higher than the industry average, it means that analysts and investors are expecting major announcements, growth, or results over the next few months.^{118,119} For pharmaceutical firms with high p/e ratios, this usually means that the market is expecting great dividends from their development pipeline. Because we have reason to believe that expectations may influence R & D spending decisions, we expected that the PE coefficient would be positive.¹²⁰

While the estimated coefficient was positive, our results suggest that the PE coefficient is not statistically significant at traditional levels. Nonetheless, it is possible that the lack of statistical significance is in some way meaningful. While other studies have broadly shown that expectations play a significant role in firm R & D decisions, the pharmaceutical R & D process (described in section IV) is both extremely complex and at the same time hampered by a continuous process of trial and error. Thus, it may be that a range of other factors at play obscures the effect of market expectations.

7. The employee effect

The LNEMPLOYEE variable is statistically significant at the 5% level. The coefficient of the LNEMPLOYEE variable suggests that a 1% change in the number of employees leads

¹¹⁵ DiMasi, 1995; Dickson and Gagnon, 2004; DiMasi et al., 2010; Sertkaya, 2016.

¹¹⁶ Refer to the calculation presented in Appendix 1.

¹¹⁷ Investopedia, Accessed February 2017.

¹¹⁸ Gallant, Accessed February 2017; Damodaran, 2017.

¹¹⁹ The current estimate for the average p/e ratio in the pharmaceutical industry is 21.19.

Likewise, the average p/e ratio in our sample is 21.00, indicating that our sample is representative of the broader industry. These metrics should be used as a reference point for relative comparison, the absolute value itself is rather unimportant.

¹²⁰ Gennaioli, 2015.

to a 0.339% change in R & D expenditure in the opposite direction. Initially, our theoretical expectations for this coefficient were positive, as we believed employees would be a good proxy for firm size.¹²¹ However, as is outlined above, our results suggest that the number of employees at a given firm is negatively correlated with R & D expenditure. Because we have reason to believe that there may be economies of scale (i.e. certain advantages from being a larger firm) in drug development, this result is surprising.¹²² After significant thought and further research, we believe this may be the result of firms exercising basic cost-benefit analysis in the face of financial constraint. In other words, we believe the negative coefficient may represent firms choosing between hiring more employees and expending more on R & D. While this theory cannot be verified using the data available in this project, this result presents an interesting avenue for further research.

V. Conclusions and Policy Implications

Pharmaceutical companies liken their core mission to saving lives, but thanks to high and rising prescription drug prices, only the federal government ranks lower than the pharmaceutical industry in public perception, according to a recent Gallop poll.¹²³ While the media accuses pharmaceutical companies of price gouging, company spokespeople respond that high drug prices are the unfortunate, but unavoidable, price of innovation. Yet even after months of media battles, there is little empirical evidence in support of either argument.

The results of the model confirm our theoretical expectations, and suggest that R & D expenditures are affected by both clinical development costs and business strategy decisions (such as CEO compensation packages).

Notably, our model shows that a firm's previous year's revenue and CEO compensation package are positively correlated with R & D expenditures. Because there is reason to believe that CEO compensation packages are a strong indicator of a firm's competitiveness, and also that firm competitiveness is an important component of business strategy, it may be the case that firms with higher CEO compensation packages have more aggressive business strategies, including higher risk drug development, and as a result, higher R&D expenditures. Including a control for CEO compensation represents a significant contribution to the existing literature and should be expanded upon in future research.

Interestingly, our model suggests that the number of employees at a given firm is negatively correlated with R & D expenditures. We believe this to be the result of firms exercising basic cost-benefit analysis in the face of financial constraint. In other words, we believe the negative coefficient represents firms choosing between hiring more employees and expending more on R & D.

The number of drugs in phase II development is positively correlated with R & D expenditures for relatively small numbers of phase II drugs in development, and negatively correlated after a certain point. The same is true of phase III drugs in development, although

¹²¹ Adams and Brantner had previously used a 'number of employees' variable to control for firm size in a similar study.

¹²² DiMasi et al., 1995; Danzon et al., 2005.

¹²³ Gallop, 2016.

these results are not statistically significant at traditional levels.

Overall, our results suggest that, in the debate over high drug prices, there is likely some truth to both sides of the argument. The significance of the coefficient of the variable representing the number of phase II drugs in development suggests that the drug development process is a significant predictor of a firm's R & D expenditures. However, the significance of the CEO compensation coefficient also suggests that firm behavior is driving up R & D expenditures, and as a result, the cost of developing new drugs.

Policy-wise our results suggest that there is no straightforward approach to legislating R & D activity in order to curb high and rising prescription drug prices. It is well known that the major argument against enacting drug price ceilings is that it would lower a given firm's incentive to innovate. Following, our results show that capping CEO compensation may help to limit the rise of R & D expenditure, but even this alternative would likely have detrimental consequences for innovation. If CEO compensation is an indicator of firm strategy, this suggests that limiting CEO compensation could result in firms shifting their strategies towards developing less risky drugs. In practice, this could have major societal consequences, as it could deter firms from finding a cure for chronic conditions like diabetes or from developing a treatment for currently untreatable diseases such as Huntington's Disease, to provide two examples. In conclusion, more research must be done in order to understand the nuanced effects of business strategy on R & D decisions and expenditures. Only then will it be possible to take responsible legislative action to lower drug prices while avoiding the unintended hampering of innovation.

VI. Possible Extensions

There are a number of project extensions that may serve as a starting point for future research on the economics of pharmaceutical drug development. Based on the significance of the CEO compensation coefficient, it is evident that additional analysis should be undertaken to better understand the relationship between CEO compensation and R & D expenditures. The CEO compensation variable should be further explored as a proxy for business strategy. Clarifying the effect of business strategy on the cost of drug development would represent another significant advancement to the current literature.

Alternatively, the current model does not take into account the money that firms spend on lobbying or in political contributions. Some firms have claimed that one reason drug prices are so high is that they have spent a significant amount of money lobbying the government to pass initiatives that increase access to lifesaving treatments and medications.¹²⁴ This claim could be examined by adding a LOBBYINGSPEND variable to the current regression model using data from the Bloomberg Intelligence Database.

Finally, additional work could be done to re-examine which therapeutic categories are correlated with increased R & D spending, all else constant. A key improvement to the current methodology would involve redefining the therapeutic category dummy variables to more precisely capture the effect of specific drug types on expenditures.

¹²⁴ An example of one such firm is Mylan, the maker of the EpiPen.

Appendix 1:

- IV regression results

The following model is used to gain the IV estimation of the CEO compensation variable. This instrumental variable regression is used to nullify issues of endogeneity. In an OLS model, an endogenous variable is one that is correlated with the error term, meaning that it is determined within the system. The potential causes of endogeneity are omitted variable bias, simultaneous causality bias, and errors-in-variables bias. Specifically, we are concerned with simultaneous causality bias in regards to CEO compensation because we have reason to believe that the direction of causality between the two variables is ambiguous.

Dividends paid is used as an estimator for CEO compensation because relevant literature suggests that the annual dividends paid to shareholders are a good predictor of CEO compensation, and we have no reason to believe that they are highly correlated with R & D expenditure. The significance of the t-value confirms the validity of this claim. The model and results are as follows:

$$\text{LNCEOCOMP}_{it} = \beta_0 + \beta_1 \text{LN DIVPAID}_{it} + \text{Error}_{it}$$

Table 4. IV Result

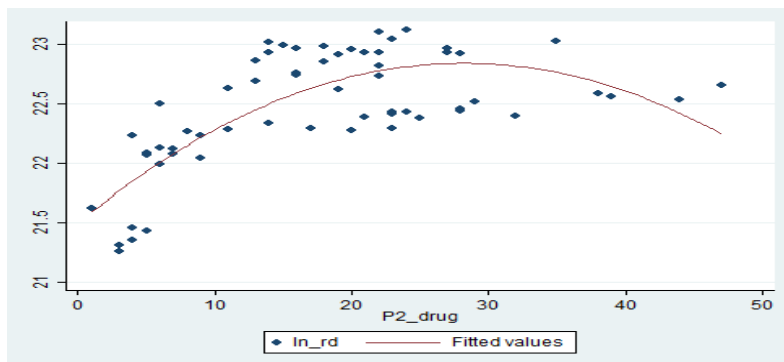
Dep. variable: LNCEOCOMP	
LNDIVPAID	0.681 (5.67)**
_cons	1.293 (0.49)
R^2	0.33
N	66

* $p < 0.05$; ** $p < 0.01$

- The effect of the IMMUNO (dummy) coefficient on R & D expenditures is calculated as follows:

$$\begin{aligned} & [e^{(\text{estimated coefficient})} - 1] \times 100\% \\ & [(e^{0.123} - 1) \times 100 = \mathbf{13.08\%}] \end{aligned}$$

- Figure 2: The quadratic relationship between the log of R & D expenditures and phase II trials



References

- Adams, Christopher and Van V Brantner. 2003. "New Drug Development: Estimating Entry from Human Clinical Trials." SSRN Scholarly Paper ID 428040. Rochester, NY: Social Science Research Network. <http://papers.ssrn.com/abstract=428040>.
- Adams, Christopher and Van V. Brantner. 2006. "Estimating The Cost Of New Drug Development: Is It Really \$802 Million?" *Health Affairs* 25 (2): 420–28. doi:10.1377/hlthaff.25.2.420.
- Adams, Christopher and Van V. Brantner. 2010. "Spending on New Drug Development." *Health Economics* 19 (2): 130–41. doi:10.1002/hec.1454.
- Arlington, Steve et al. 2012. "From Vision to Decision: Pharma 2020." Pharma2020. PricewaterhouseCoopers. <http://www.pwc.com/gx/en/industries/pharmaceuticals-life-sciences/pharma-2020/industry-strategies-trends-analysis.html>.
- Armour, Stephanie. 2015. "Lawmakers, Candidates Target High Drug Prices." *Wall Street Journal*, November 16, sec. Politics. <http://www.wsj.com/articles/lawmakers-candidates-target-high-drug-prices-1447635567>.
- Baber, William R., Surya N. Janakiraman, and Sok-Hyon Kang. 1996. "Investment Opportunities and the Structure of Executive Compensation." *Journal of Accounting and Economics* 21 (3): 297–318. doi:10.1016/0165-4101(96)00421-1.
- Baily, Martin Neil. 1972. "R & D Costs and Returns: The U.S. Pharmaceutical Industry." *Journal of Political Economy* 80 (1): 70–85.
- Balkin, David B., Gideon D. Markman, and Luis R. Gomez-Mejia. 2000. "Is CEO Pay in High-Technology Firms Related to Innovation?" *The Academy of Management Journal* 43 (6): 1118–29. doi:10.2307/1556340.
- Berndt, Ernst R., Adrian H. B. Gottschalk, and Matthew W. Strobeck. 2006. "Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA." *Innovation Policy and the Economy* 6: 91–121.
- Breeze, Penny, and Alan Brennan. 2015. "Valuing Trial Designs from a Pharmaceutical Perspective Using Value-Based Pricing." *Health Economics* 24 (11): 1468–82. doi:10.1002/%28ISSN%291099-1050/issues.
- Cardinal, Laura B. 2001. "Technological Innovation in the Pharmaceutical Industry: The Use of Organizational Control in Managing R & D." *Organization Science* 12 (1): 19–36. doi:10.1287/orsc.12.1.19.10119.

- Chen, Jie, and John A. Rizzo. 2010. "Who Pays for Drug Quality?" *Eastern Economic Journal* 36 (2): 239–54. doi:<http://www.palgrave-journals.com/eej/archive/>.
- Chit, A., M. Papadimitropoulos, M. Krahn, J. Parker, and P. Grootendorst. 2015. "The Opportunity Cost of Capital: Development of New Pharmaceuticals." *Inquiry (United States)* 52. doi:10.1177/0046958015584641.
- Chit, A., J. Parker, S.A. Halperin, M. Papadimitropoulos, M. Krahn, and P. Grootendorst. 2014. "Toward More Specific and Transparent R & D Costs: The Case of Seasonal Influenza Vaccines." *Vaccine* 32 (26): 3336–40. doi:10.1016/j.vaccine.2013.06.055.
- Clinch, Greg. 1991. "Employee Compensation and Firms' R & D Activity." *Journal of Accounting Research* 29 (1): 59–78. doi:10.2307/2491028.
- Comanor, William S., and Stuart O. Schweitzer. 2007. "Determinants of Drug Prices and Expenditures." *Managerial and Decision Economics* 28 (4/5): 357–70.
- Daemrlich, Arthur. 2003. "Invisible Monuments and the Costs of Pharmaceutical Regulation: Twenty-Five Years of Drug Lag Debate." *Pharmacy in History* 45 (1): 3–17.
- Damodara, Aswath. 2017. "PE Ratio by Sector (US)." NYU Stern. http://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/pedata.html
- Danzon, Patricia M., Sean Nicholson, and Nuno Sousa Pereira. 2005. "Productivity in Pharmaceutical–biotechnology R&D: The Role of Experience and Alliances." *Journal of Health Economics* 24 (2): 317–39. doi:10.1016/j.jhealeco.2004.09.006.
- Dechow, Patricia M., and Richard G. Sloan. 1991. "Executive Incentives and the Horizon Problem." *Journal of Accounting and Economics* 14 (1): 51–89. doi:10.1016/0167-7187(91)90058-S.
- Dickson, Michael, and Jean Paul Gagnon. 2004. "Key Factors in the Rising Cost of New Drug Discovery and Development." *Nature Reviews Drug Discovery* 3 (5): 417–29. doi:10.1038/nrd1382.
- DiMasi, J.A., Ronald W Hansen, Henry G Grabowski, and Louis Lasagna. 1991. "Cost of Innovation in the Pharmaceutical Industry." *Journal of Health Economics* 10 (2): 107–42. doi:10.1016/0167-6296(91)90001-4.
- DiMasi, Joseph A. 1995. "R & D Costs for New Drugs by Therapeutic Category. A Study of the US Pharmaceutical Industry." *PharmacoEconomics* 7 (2): 152–69.
- Dimasi, Joseph A., Henry G. Grabowski, and John Vernon. 1995. "R&DCosts, Innovative Output

and Firm Size in the Pharmaceutical Industry.” *International Journal of the Economics of Business* 2 (2): 201–19. doi:10.1080/758519309.

DiMasi, Joseph A. 2001. “Risks in New Drug Development: Approval Success Rates for Investigational Drugs.” *Clinical Pharmacology & Therapeutics* 69 (5): 297–307. doi:10.1067/mcp.2001.115446.

DiMasi, Joseph A, Ronald W Hansen, and Henry G Grabowski. 2003. “The Price of Innovation: New Estimates of Drug Development Costs.” *Journal of Health Economics* 22 (2): 151–85. doi:10.1016/S0167-6296(02)00126-1.

DiMasi, Joseph A., and Henry G. Grabowski. 2007a. “The Cost of Biopharmaceutical R&D: Is Biotech Different?” *Managerial and Decision Economics* 28 (4/5): 469–79.

DiMasi, Joseph A., 2007b. “Economics of New Oncology Drug Development.” *Journal of Clinical Oncology* 25 (2): 209–16. doi:10.1200/JCO.2006.09.0803.

DiMasi, J.A., R.W. Hansen, and H.G. Grabowski. 2008. “Misleading Congress about Drug Development: Reply.” *Journal of Health Politics, Policy and Law* 33 (2): 319–24. doi:10.1215/03616878-2007-063.

DiMasi, J.A. 2010. “Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs.” *Clinical Pharmacology and Therapeutics* 87 (3): 272–77.

DiMasi, J.A., and H.G. Grabowski. 2012. “R&DCosts and Returns to New Drug Development: A Review of the Evidence.” In *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*.

DiMasi, J.A., J M Reichert, L Feldman, and A Malins. 2013. “Clinical Approval Success Rates for Investigational Cancer Drugs.” *Clinical Pharmacology & Therapeutics* 94 (3): 329–35. doi:10.1038/clpt.2013.117.

DiMasi, J.A., H.G. Grabowski, and R.W. Hansen. 2015. “The Cost of Drug Development.” *The New England Journal of Medicine* 372 (20): 1972. doi:10.1056/NEJMc1504317.

DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. 2016. “Innovation in the Pharmaceutical Industry: New Estimates of R&DCosts.” *Journal of Health Economics* 47 (May): 20–33. doi:10.1016/j.jhealeco.2016.01.012.

Dubois, Pierre, Olivier de Mouzon, Fiona Scott-Morton, and Paul Seabright. 2015. “Market Size and Pharmaceutical Innovation.” *RAND Journal of Economics* 46 (4): 844–71. doi:10.1111/%28ISSN%291756-2171/issues.

- Feyzrakhmanova, Martina, and Constantin Gurdgiev. 2016. "Patents and R&D Expenditure Effects on Equity Returns in Pharmaceutical Industry." *Applied Economics Letters* 23 (4-6): 278–83. doi:<http://www.tandfonline.com/loi/rael20>.
- Fidelity. 2016. "Sectors & Industries Overview - U.S. Sectors." Accessed September 14. https://eresearch.fidelity.com/eresearch/markets_sectors/sectors/sectors_in_market.jhtml.
- Filson, Darren, Neal Masia, and Joseph Golec. 2007. "Effects of Profit-Reducing Policies on Firm Survival, Financial Performance, and New Drug Introductions in the Research-Based Pharmaceutical Industry [with Commentary]." *Managerial and Decision Economics* 28 (4/5): 329–55.
- Fuchs, Victor R. 2012. "Major Trends in the U.S. Health Economy since 1950." *New England Journal of Medicine* 366 (11): 973–77. doi:10.1056/NEJMp1200478.
- Gallant, Chris. Accessed February 2017. "Stocks with high P/E ratios can be overpriced. Is a stock with a lower P/E ratio always a better investment than a stock with a higher one?" Investopedia. <http://www.investopedia.com/ask/answers/05/lowperatiostocksbetterinvestments.asp>
- Gallop. 2016. "Restaurants Again Voted Most Popular U.S. Industry." *Gallup.com*. August 15. <http://www.gallup.com/poll/194570/restaurants-again-voted-popular-industry.aspx>.
- Gennaioli, Nicola, Yueran Ma, and Andrei Shleifer. 2015. "Expectations and Investment." Working Paper 21260. National Bureau of Economic Research. doi:10.3386/w21260.
- Grabowski, Henry, and John Vernon. 2012. "Longer Patents for Increased Generic Competition in the US." *PharmacoEconomics* 10 (2): 110–23. doi:10.2165/00019053-199600102-00017.
- Grossmann, Volker. 2013. "Do Cost-Sharing and Entry Deregulation Curb Pharmaceutical Innovation?" *Journal of Health Economics* 32 (5): 881–94. doi:<http://www.sciencedirect.com/science/journal/01676296>.
- Hansen, Ronald W. 1979. *The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes*. Center for the Study of Drug Development, Department of Pharmacology and Toxicology, University of Rochester Medical Center.
- Hay, Michael, David W. Thomas, John L. Craighead, Celia Economides, and Jesse Rosenthal. 2014. "Clinical Development Success Rates for Investigational Drugs." *Nature Biotechnology* 32

(1): 40–51. doi:10.1038/nbt.2786.

Healy, Paul M. 1985. “The Effect of Bonus Schemes on Accounting Decisions.” *Journal of Accounting and Economics* 7 (1): 85–107. doi:10.1016/0165-4101(85)90029-1.

Investopedia. Accessed February 2017. “P/E Ratio: Using the P/E Ratio.”
<http://www.investopedia.com/university/peratio/peratio2.asp>

Investopedia. 2015. “What does a high weighted average cost of capital (WACC) signify?”
Accessed January 2017. <http://www.investopedia.com/ask/answers/013015/what-does-high-weighted-average-cost-capital-wacc-signify.asp>

Jeon, Jieun, Suckchul Hong, Taeyong Yang, and Jay Y. Ohm. 2016. “How Technological Innovation Affects the Structure of an Industry: Entrepreneurship Evolution in the Biotechnology and Pharmaceutical Industry since 1980.” *Technology Analysis and Strategic Management* 28 (6): 733–54. doi:<http://www.tandfonline.com/loi/ctas20>.

Jorge Mestre-Ferrandiz, Jon Sussex, and Adrian Towse. 2012. “The R&DCost of a New Medicine.” London, United Kingdom: Office of Health Economics.
<https://www.ohe.org/publications/rd-cost-new-medicine>.

Kamuriwo, Dzidziso Samuel, and Charles Baden-Fuller. 2016. “Knowledge Integration Using Product R&DOutsourcing in Biotechnology.” *Research Policy* 45 (5): 1031–45.
doi:<http://www.sciencedirect.com/science/journal/00487333>.

Keehan, Sean P., John A. Poisal, Gigi A. Cuckler, Andrea M. Sisko, Sheila D. Smith, Andrew J. Madison, Devin A. Stone, Christian J. Wolfe, and Joseph M. Lizonitz. 2016. “National Health Expenditure Projections, 2015–25: Economy, Prices, And Aging Expected To Shape Spending And Enrollment.” *Health Affairs*, July, 10.1377/hlthaff.2016.0459.
doi:10.1377/hlthaff.2016.0459.

Kesselheim, Aaron S., Bo Wang, Jessica M. Franklin, and Jonathan J. Darrow. 2015. “Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study.” *BMJ* 351 (September): h4633. doi:10.1136/bmj.h4633.

Keyhani, Salomeh, Marie Diener-West, and Neil Powe. 2005. “Do Drug Prices Reflect Development Time and Government Investment?” *Medical Care* 43 (8): 753–62.

Klick, Jonathan, and Joshua D. Wright. 2015. “The Effect of Any Willing Provider and Freedom of Choice Laws on Prescription Drug Expenditures.” *American Law and Economics Review* 17 (1): 192–213. doi:<http://aler.oxfordjournals.org/content/by/year>.

Light, Donald W., and Joel Lexchin. 2005. “Foreign Free Riders And The High Price Of Us Medicines.” *BMJ: British Medical Journal* 331 (7522): 958–60.

- Light, Donald W, and Joel R Lexchin. 2012. "PHARMACEUTICAL R&D: What Do We Get for All That Money?" *BMJ: British Medical Journal* 345 (7869): 22–25.
- Light, D.W., and R. Warburton. 2011. "Demythologizing the High Costs of Pharmaceutical Research." *BioSocieties* 6 (1): 34–50. doi:10.1057/biosoc.2010.40.
- Loftus, Peter. 2016. "Faith-Based Investor Group Calls for Drugmakers to Be Transparent on Pricing." *Wall Street Journal*, October 24, sec. Business. <http://www.wsj.com/articles/faith-based-investor-group-calls-for-drugmakers-to-be-transparent-on-pricing-1477317600?mod=e2fb>.
- Morgan, Steve, Paul Grootendorst, Joel Lexchin, Colleen Cunningham, and Devon Greyson. 2011. "The Cost of Drug Development: A Systematic Review." *Health Policy* 100 (1): 4–17. doi:10.1016/j.healthpol.2010.12.002.
- Mullin, Rick, Chemical & Engineering News. 2016. "Cost to Develop New Pharmaceutical Drug Now Exceeds \$2.5B." *Scientific American*. Accessed September 15. <http://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/>.
- Mund, V.F. 1970. "The Return on Investment of the Innovative Pharmaceutical Firm." *The Economics of Drug Innovation*, 125–38.
- NYU Stern School of Business. 2016. "Cost of Capital." *Cost of Capital by Sector (U.S.)*. January. http://people.stern.nyu.edu/adamodar/New_Home_Page/datafile/wacc.htm.
- Offstein, Evan H., and Devi R. Gnyawali. 2005. "CEO Compensation and Firm Competitive Behavior: Empirical Evidence from the U.S. Pharmaceutical Industry." *Journal of Engineering and Technology Management* 22 (3): 201–25. doi:10.1016/j.jengtecman.2005.06.004.
- Paul, Steven M., Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht. 2010. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 9 (3): 203–14. doi:10.1038/nrd3078.
- Riggs, T Lynn. 2016. "R & D Costs for Drugs." *The Lancet* 363 (9404): 184. Accessed September 15. doi:10.1016/S0140-6736(03)15370-6.
- Roberts, Thomas G., Thomas J. Lynch, and Bruce A. Chabner. 2003. "The Phase III Trial in the Era of Targeted Therapy: Unraveling the 'Go or No Go' Decision." *Journal of Clinical Oncology* 21 (19): 3683–95. doi:10.1200/JCO.2003.01.204.

- Ronald W. Hansen. 1979. *The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effects of Proposed Regulatory Changes*. Rochester N.Y.: Center for the Study of Drug Development.
- Santerre, Rexford E. 2011. "National and International Tests of the New Drug Cost Offset Theory." *Southern Economic Journal* 77 (4): 1033–43.
doi:<http://journal.southerneconomic.org/loi/soec>.
- Schnee, Jerome E. 1972. "Development Cost: Determinants and Overruns." *The Journal of Business* 45 (3): 347–74.
- Stonebraker, Jeffrey S. 2002. "How Bayer Makes Decisions to Develop New Drugs." *Interfaces* 32 (6): 77–90.
- U.S. Congress, Office of Technology Assessment. 1993. *Pharmaceutical R&D: Costs, Risks, and Rewards*. OTA-H-522. U.S. Government Printing Office.
http://govinfo.library.unt.edu/ota/Ota_1/DATA/1993/9336.PDF.
- U.S. Federal Drug Administration, and Michelle Meadows. 2006. "Promoting Safe and Effective Drugs for 100 Years." *FDA Consumer Magazine*, February.
<http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/>.
- Vernon, John A., Joseph H. Golec, and Joseph A. Dimasi. 2010. "Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-Factor Model." *Health Economics* 19 (8): 1002–5. doi:10.1002/%28ISSN%291099-1050/issues.
- Wiggins, S.N. 1987. "The Cost of Developing a New Drug." Washington, DC: Pharmaceutical Manufacturers Association.
- Young, Bob, and Michael Surrusco. 2016. "Rx R&D Myths: The Case Against The Drug Industry's R&D Scare Card." *Public Citizen*. Accessed September 15.
<http://www.citizen.org/publications/publicationredirect.cfm?ID=7065>.