

Pharmaceutical Price Controls and the Orphan Drug Megafund Model

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Dedicated to

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Rest in Peace, Dad

Abstract

The market for biomedical R&D suffers from underinvestment as a consequence of its scale, time horizon, and risk. The megafund has been introduced as a potential solution to this market failure via the provision of large-scale financing and a market for diversification, effectively serving to alleviate scale misalignment and improve the efficiency of biomedical capital markets. Orphan drugs are particularly suitable for portfolio financing due to pathological characteristics which increase the rate of regulatory approval and decrease the correlation between projects. Application of the megafund model to orphan drug development thus has the potential to mitigate information asymmetry problems in biomedical capital markets and stimulate R&D investment.

These predictions, however, are obscured by the increasingly probable scenario of government intervention. Empirical analyses suggest that price controls on pharmaceutical drugs would reduce R&D spending by lowering the expected returns to such investment. Thus, megafund financing and free-market intervention have competing effects on the equilibrium level of biomedical R&D investment. The following paper explores this relationship and the relative magnitude of each component. I begin by expanding the existing megafund theoretical framework to better represent the realities of orphan drug development. I then analyze the megafund's performance in statistical simulations under two price control regimes. I find that price controls do not materially influence the default rate on debt securities, but lead to a 25 – 70% decline in equity returns on average. The decline in performance is significantly larger under a fixed, multidimensional price control regime as opposed to a variable, unidimensional regime, and thus may carry implications for optimal drug pricing policy.

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Finally, to the men of Jenkins, the next bottle of Kirkland Prosecco is on me. It's been a hell of a run; here's to many, many more.

Table of Contents

1. Introduction	1
2. Literature Review	7
2.1 Research and Development Investment	7
2.2 Portfolio Financing – A Generalized Solution	9
2.2.1 Diversification and Portfolio Theory	9
2.2.2 Securitization	10
2.2.3 The Biomedical Megafund	12
2.2.4 The Orphan Drug Megafund	13
3. The Effect of Price Controls on Pharmaceutical R&D	15
4. Theoretical Integration of ODA Incentives	20
5. Price Control Simulations	29
5.1 Simulation Framework and Parameters	30
5.2 The Kassebaum/Metzenbaum Sales Trigger	34
5.3 The Orphan Drug Windfall Tax	36
6. Results	39
7. Discussion	42
8. Conclusion	44

1. Introduction

Capital markets channel savings and investment between individual investors (lenders) and firms, governments, etc. (borrowers) through the transaction of debt and equity instruments. The transfer of capital is essential for generating economic output and growth, and thus, capital markets are a vital component of any economy. A breadth of economic research has documented the prevalence of information asymmetry problems in capital markets. From a macroeconomic perspective, the primary consequence of information asymmetry within such markets is an inefficient allocation of capital.

Like all markets, biomedical capital markets, in which capital is allocated to drug research and development (R&D) projects, exhibit these same problems. Their magnitude, however, is amplified by the nature of drug development. Rising costs and lengthening development periods have increased the risks associated with drug development, contributing to a ‘productivity crisis in pharmaceutical R&D’ (Pammolli et al. 2011). Average pre-approval costs per new drug have risen to \$2.6 billion, while clinical development periods have stagnated between 6 – 8 years with a meager 12% approval rate (DiMasa et al. 2016, PhRMA 2015). Because of the investment size and associated uncertainty, information asymmetry problems are exacerbated in biomedical capital markets. These market imperfections increase the cost of external capital, which precludes some firms from participating in public capital markets. Ultimately, the result is an aggregate underinvestment in drug research and development.

While market interventions, such as the establishment of specialized investors, have served as piecemeal solutions, a market failure persists. This failure, specifically, is the misalignment of investment scale and consequent lack of diversification capacity.

Drug development requires significant upfront capital, and thus, it is difficult for any single investor to hold a portfolio of investments in drug development programs. Consequently, R&D underinvestment persists because investors are unable to sufficiently diversify the idiosyncratic risk associated with biomedical investment. Empirical evidence corroborates this claim. Approved new molecular entities (NMEs) have experienced average annual declines since the mid-1990s, with 22 approvals in 2016 marking a six-year low (Hirschler 2017). Lagging productivity has exerted downward pressure on market valuations, ultimately leading to capital outflows and the persistence of suboptimal investment levels.

Fernandez et al. (2012) propose a solution to this market failure in the form of a biomedical megafund. The megafund utilizes diversification and securitization to develop a portfolio-financed investment vehicle through which investors can spread idiosyncratic risk across numerous drug development programs. Further, the megafund provides large-scale financing to biomedical R&D, effectively serving to mediate scale mismatch, lower transaction costs, and improve the efficiency of biomedical capital markets.

Fagnan et al. (2014) specify the megafund framework to orphan drugs exclusively. Orphan drugs are developed to treat rare diseases and possess several characteristics that make them exceptionally suitable for the megafund model. Despite these characteristics, though, orphan drugs have not traditionally received significant R&D investment. Despite countless medical breakthroughs over the past century, hundreds of rare diseases still exist as ‘untreatable,’ which is largely a result of the privatization of drug development and the supply-demand framework that informs firms’ R&D decisions. Because resources for pharmaceutical R&D are scarce, decisions must be made to maximize profit opportunities. Thus, historically, disease severity and quantity afflicted have guided resource allocation:

the most serious diseases affecting the largest patient populations have received the greatest proportion of resources, and so on (Rhode 2000).

Rare diseases, meanwhile, are inherently characterized by limited patient populations and quantitatively limited demand, and thereby fail to provide sufficient incentives for R&D investment. Thus, rare diseases historically remained ‘orphaned’ because of their preclusion from R&D investment. While the behavior of firms was rational in this context, a perceived market failure had developed: absent additional economic and/or regulatory incentives, the pharmaceutical industry would continue to neglect rare diseases while more than five million afflicted Americans would continue to suffer inexorably (Rhode 2000). In response, the U.S. government intervened in the market, and in 1973, the Orphan Drug Act was signed into law.

The Orphan Drug Act (ODA) formally defines orphan drugs as ‘pharmaceutical treatments for diseases that affect fewer than 200,000 U.S. inhabitants’. The Act provides several financial incentives to encourage the development of orphan drugs, and by all accounts, it has been a powerful driver of drug development for rare, traditionally-neglected diseases. In the decade preceding the passage of the ODA, only ten orphan drugs were approved for use in the United States (Rhode 2000). Since then, more than 300 orphan drugs have been approved while an additional 2000 candidates have been granted orphan drug designations (Wellman-Labadie and Zhou 2010). Between 2000 and 2010, the compound annual growth rate (CAGR) of orphan drug approvals was ~10%, in contrast to a negative CAGR for non-orphan approvals over the same period (Meekings et al. 2010).

On the other hand, some ODA incentives have been condemned for enabling firms to engage in price gouging behaviors (Garber 1994). Commonly cited are the orphan drugs Cosmegon, Indocin I.V., and Acthar, which increased in price by 3,436%, 1,389%, and 1,310%, respectively, between 1998 and 2008 (Hemphill 2010). More recently, Marathon Pharmaceuticals became the exemplar for such behavior after placing an \$89,000 price tag on its newly approved muscular dystrophy drug. In addition to egregious prices, proponents of government intervention often cite the abuse of orphan drug status for a single drug across several disease indications. For example, as of 2008, only 4 of the 18 blockbuster drugs¹ solely approved as orphan drugs had a single therapeutic use. In this case, it is possible that initially unprofitable drugs reach ‘blockbuster status’ by treating multiple orphan disease niches, effectively increasing the drug’s patient population while preserving its monopoly pricing privileges (Wellman-Labadie and Zhou 2010). Although such examples are rare, they have contributed to a growing public perception of abuse and exploitation, and have thrust orphan drugs into the wider debate concerning drug pricing and healthcare provision.

In developed countries like the United States, the pharmaceutical industry is unique in that a third-party healthcare provider, such as a private health insurer or a government agency, directly pays for at least a fraction of the consumer’s prescription drug expenditures (Hemphill 2010). While the U.S. government pays for more than 40% of total healthcare expenditures, it does so through several uncoordinated programs, which impedes its ability to exert market power to negotiate prices. As such, both the public and private sectors act as price takers, and thus price consideration has not traditionally been a

¹ A blockbuster drug is defined as any pharmaceutical product which exceeds \$1 billion in annual sales.

priority in the U.S. pharmaceutical market (Garber 1994). Indeed, it is oft speculated that the pricing discretion granted to private drug developers and the U.S.'s status as a world leader in medical innovation share a causal relationship. As such, drugs have traditionally been considered 'priceless goods' to ensure the development of novel therapeutics and their dissemination to the masses (Maitland 2002).

Recent sociopolitical developments, however, contradict this perspective. Public rhetoric for government intervention has reached a crescendo in response to drug price increases and swelling healthcare expenditures. Pharmaceutical productivity has plummeted while drug price inflation has far outpaced the CPI. Average prices of brand-name drugs have increased by 164% since 2008. In 2015 alone, prescription drugs received an average price increase of 16.2% and aggregate U.S. drug spending rose by 5.2% (Express Scripts 2016). In response, public sentiment has shifted in favor of government intervention – a 2016 survey found that 78% of respondents favored drug price controls (Rau 2016).

Because orphan drugs tend to be among the most expensive, they have been inextricably entwined in discussions regarding the industry's pricing practices. Given the combination of perceived commercial and ethical abuse, shifting public sentiment against the pharmaceutical industry, and a Republican majority under the Donald Trump administration, government intervention is becoming increasingly likely. While any potential legislation would likely target drug prices more broadly, orphan drugs would be disproportionately affected because of their inherently high prices.

If the detrimental effects of price controls on R&D investment outweigh the incentives conferred by the ODA, government intervention could carry significant

ramifications for orphan drug development going forward. Such ramifications could extend to drug development more broadly if the costs of government intervention similarly outweigh the general benefits of portfolio financing. To explore this possibility and illustrate the long-run implications, I analyze the effects of government-imposed price controls on the megafund model. I begin by evaluating the effect of price controls on historical pharmaceutical R&D levels within several models. Secondly, I incorporate the financial incentives mandated by the ODA within an illustrative megafund model, something Fagnan et al. (2014) fail to do. I then use a mathematical example to demonstrate how the benefits of portfolio financing for orphan drugs may exceed those of non-orphan drugs. I continue this analysis by considering the impact of proposed price regulations within the megafund framework. Finally, I simulate the performance of an orphan drug megafund under the constraints of price controls. I find that the megafund proves resilient to a moderate level of price regulation. Price controls do not materially influence the megafund's default rate on debt securities, but lead to a 25 – 70% decline in equity returns on average. I conclude by considering the policy implications these results may carry.

The remainder of the paper is organized as follows. Chapter 2 establishes the financial theory underlying the megafund model. Chapter 3 analyzes the relationship between price controls and R&D investment. Chapter 4 expands the existing megafund framework to include ODA incentives. Chapter 5 outlines the price control simulations. Chapter 6 presents the results of those simulations. Chapter 7 discusses the findings and their implications. Chapter 8 concludes.

2. Literature Review

2.1 Research & Development Investment

Economic theory has long propagated the belief that innovation is difficult to finance in a perfectly competitive capital market. First proposed by Nelson (1959) and Arrow (1962), and summarized by Hall and Lerner (2009), economic theory argues that the knowledge produced by innovation is a non-rival good, and as such, the use of that information cannot be restricted by the firm undertaking the capital investment to produce it. Thus, the incentives for firms to invest are diminished, which ultimately generates a socially suboptimal equilibrium level of R&D investment.

Market interventions, such as the protection of intellectual property through patents, R&D tax incentives, government funding, etc., have successfully combatted these problems. For example, Bloom et al. (2001) found that a 10% R&D tax credit led to a 10% increase in long-run R&D investment, while Varsakelis (2001) found that patent protection is a universally strong determinant of R&D intensity.

However, Hall (2009) proposes an additional market failure contributing to R&D underinvestment: the ‘wedge’ between the cost of capital from external financing sources and the private rate of return required by the firm undertaking the project. It is possible that the external cost of capital, the minimum return required to compensate third party investors, exceeds the private rate of return, the internal rate of return (IRR) at which a project’s net present value (NPV) is equal to zero. Thus, some projects, despite possessing a positive NPV within a private financing structure, will not attract external investment. The underpinning to this ‘wedge’ derives from the traditional components of information asymmetry. In R&D markets, asymmetry between the researchers’ and the investors’

knowledge of the probability of success for a given project may contribute to the development of an orthodox Akerlof (1970) ‘lemons market’ in which adverse selection problems drive the least risky investments out of the market. Further, the separation of firm management and ownership, as is standard among modern industrial firms, may contribute to moral hazard and principal-agent problems.

Together, these asymmetry problems increase the cost of external capital, which precludes some firms from participating in public capital markets. This phenomenon has been supported empirically by analyzing the liquidity constraints of firms with respect to R&D investment. If innovative firms were financially constrained, Brown and Haegler (1997) argue, then their R&D expenditures should be highly correlated with fluctuations in internal finances. Indeed, findings from both Hall (1992) and Brown and Haegler (1997) exhibit a significant positive correlation between cash flows and R&D investment, particularly amongst innovative firms, suggesting that imperfect public markets may constrain firms to internal funding sources.

The aforementioned market failure is particularly acute for innovation-focused firms like those I consider. The private sector has developed a solution in the form of venture capital (VC), which are privately-managed capital funds specializing in equity investments in high-growth firms. The literature has exhaustively outlined venture capitalists’ potential to address information asymmetry problems via extensive screening, active monitoring, exit incentives, and investment staging (Hall 2009). Indeed, the success of the venture capital industry has been convincing. Bernstein et al. (2016) find that, on average, heavy VC involvement leads to a 3.1% increase in produced patents by portfolio companies and a 1.4% increase in the probability of a successful exit.

While venture capital successfully remediates the information asymmetry problems in many such capital markets, I argue that, due to the investment scale and management required for drug development, venture capital only serves to mitigate this market failure. Drug development is risky and requires investment upfront while the returns are unpredictable and volatile. Drug development, therefore, is perceived by investors to be among the riskiest sectors in the economy. Consequently, biomedical technology is treated differently by private sector investors like venture capitalists. Previous studies have documented the difference in selection criteria employed by VCs when considering a non-technology-based proposal vs. a technology-based proposal. For instance, UK venture capitalists require higher hurdle rates for technology-based proposals² (Lockett et al. 2002). Further, several VCs have been documented to exclude biotechnology proposals out of principle, citing regulatory difficulties, financing size, and exit uncertainty (Baeyens et al. 2006). Ultimately, these investment strategies have been justified, as life-sciences venture capital investments generated an average return of -1% between 2001 and 2010 (Fernandez et al. 2012). Such observations indicate that, despite venture capitalists' ability to mediate information asymmetry problems, underinvestment in drug development persists.

2.2 Portfolio Financing – A Generalized Solution

2.2.1 Diversification and Portfolio Theory

Before delving into the specifics of the megafund model, it is important to note the statistical principle on which it is built: diversification. Cecchetti and Schoenholtz (2015)

² The hurdle rate for an investment represents the potential return threshold beyond which a proposal is considered attractive.

outline the basic framework. Consider an equally weighted portfolio of n assets, the expected return remains the same regardless of the value of n : $E(P) = \sum_{i=1}^n w_i E(x_i)$. The variance of the portfolio's return, however, depends on the value of n :

$$Var(P) = \sum_{i=1}^n w_i^2 Var(x_i) + \sum_{i=1}^n \sum_{j=i+1}^n w_i w_j Cov(x_i, x_j)$$

Since we are considering an equally weighted portfolio, $w_i = w_j = 1/n$. If we define $\overline{\sigma_{ij}}$ as the average covariance among all assets within the portfolio, then:

$$Var(P) = \frac{1}{n} Var(x_i) + \frac{n-1}{n} \overline{\sigma_{ij}}$$

And thus, as the number of assets, n , increases: $\lim_{n \rightarrow \infty} Var(P) = \overline{\sigma_{ij}}$

This decomposition carries a powerful implication which is central to the megafund model: for portfolios holding many assets, the variance of the portfolio tends to converge to the average covariance between the assets. In the case of orphan drugs, the benefits of this implication may exceed that of the average asset. Orphan diseases tend to exhibit monogenic pathology, meaning they are caused by an anomaly in a single gene. As such, we can safely assume that the biological mechanisms utilized by their treatments will tend to be unrelated, and thus, that the covariance between orphan drug development programs is modest. Mathematically, this implies that as the as the number assets in the portfolio, n , increases, $Var(P)$ will unambiguously converge to a small value.

2.2.2 Securitization

Securitization uses financial engineering to transform an illiquid asset, such as a group of loans, into a security. The process typically involves two steps. First, the originator, the owner of the assets to be securitized, pools the assets and transfers them to an issuer, which often takes the form of a special purpose vehicle (SPV), an independent legal entity which is restricted from any activity beyond owning and servicing the

securitized assets (Jobst 2008). Second, the SPV finances its acquisition of the assets by issuing securities collateralized by the assets' cash flows (Fabozzi and Kothari 2008). The portfolio is often sliced into several tranches which are sold separately and correspond to different maturities or levels of risk (Jobst 2008). Securitization, therefore, provides financing to the originator while generating interest and principal payments for investors corresponding to their specific risk-reward preferences (Telpner 2003).

In the wake of the 2007 financial crisis, asset-backed securitization has experienced intense scrutiny. Several studies have documented the role of securitization in encouraging lax lending standards which contributed, in part, to the credit crisis (Drucker and Mayer 2008, Nadauld and Sherlund 2009, Keys et al. 2010). Provided responsible oversight and regulation, however, securitization offers benefits both for creditors and the wider economy.

Most importantly, securitization lowers the cost of borrowing. Securitization allows the separation of financial assets from the credit risk of the originator, and thus the resulting securities are often of a higher credit quality than the secured debt of the originator itself (Jobst 2008, Fabozzi and Kothari 2008). In addition, securitized assets are more liquid than the assets underlying them, and therefore carry less of a liquidity premium. For both reasons, securitization enables the movement of investment capital from debt markets to more efficient capital markets, resulting in lower funding costs (Jobst 2008). For instance, several studies have concluded that the securitization of residential mortgages has lowered the interest rates paid by borrowers (Jameson et al. 1990, Sirmans and Benjamin 1992).

Ultimately, securitization lowers the cost of credit and expands financial markets, both of which contribute to economic growth. Because of these benefits, the use of securitization has expanded to a plethora of financial assets, including student and auto loans, credit card receivables, litigation settlement payments, and cash flows from oil reserves (Iacobucci and Winter 2005). A particularly poignant example of securitization's expansion was the issuance of \$100 million of bonds by Yale University collateralized by a royalty interest and licensing agreement between the University and Bristol-Myers Squibb based on a pharmaceutical patent (Kramer and Patel, n.d.). Thus, the securitization of intellectual property like drug development programs is quite plausible. Indeed, the precedent has been set and reinforced many times over.

2.2.3 The Biomedical Megafund

The megafund model, as first proposed by Fernandez et al. (2012), is designed to couple diversification and securitization to reduce the cost of borrowing for drug developers and deliver large-scale financing to biomedical capital markets. The megafund consists of two interdependent components: (1) The creation of a diversified portfolio of drug development projects; and (2) The use of securitization to structure the portfolio's financing as a combination of equity and debt. In this case, Fernandez et al. (2012) propose the use of future cash flow securitization, in which financial interests in drug development projects and their associated intellectual property are used to collateralize debt instruments called Research-Backed Obligations (RBOs). The megafund, in this process, takes the form of a special purpose vehicle (SPV), an independent legal entity through which the assets are purchased and the securities are issued. The development of RBOs with attractive risk-reward profiles, though, necessitates scale. Diversification, in

turn, reduces portfolio risk to the extent that the megafund can raise funds by issuing both equity and debt. Finally, the size of the debt market relative to the equity market enables the megafund to raise capital at the scale necessary to achieve sufficient diversification. Thus, the two components share a complementary relationship.

Fernandez et al. (2012) use a dataset of 733 anti-cancer drugs which entered clinical trials between 1990 and 2011 to execute simulations that test the efficacy of the megafund model. The researchers complete two 7.5-year simulations: (1) a portfolio with \$5 billion of initial capital (2x leverage) consisting of 100 preclinical and 100 Phase I compounds; and (2) a portfolio with \$15 billion of initial capital (2.5x leverage) consisting of 100 Phase II compounds. In both cases, the financial structure of the portfolio consists of three components: (1) Equity; (2) a senior RBO tranche which pays a 5% annual coupon; and (3) a junior RBO tranche which pays an 8% annual coupon. The researchers find that the megafund is almost always profitable. Specifically, the megafund yields returns of 8.9 – 11.4% and 5 – 8% for equity investors and RBO investors, respectively, while the rate of full RBO payment exceeds 99%. In comparison, an all-equity megafund generates a comparable risk profile and yields average returns of only 7.2%.

2.2.4 The Orphan Drug Megafund

Fagnan et al. (2014) build on the results of Fernandez et al. (2012) by applying the megafund model to orphan drugs. In their own simulations, the researchers use a large-molecule drug data set to simulate a megafund of parallel tranche structure as Scenario 1 in Fernandez et al. (2012), but with only \$575 million in initial capital and a target portfolio of 10 – 20 projects. Consistent with previous analyses, the megafund yielded average

returns of 13.4% for equity investors, while the rate of full RBO payment again exceeded 99%.

These results carry a significant implication: an orphan drug megafund can achieve attractive returns with significantly less scale, which mitigates the operational challenges to the cancer megafund proposed by Fernandez et al. (2012). Fagnan et al. (2014) suggest multiple characteristics of orphan drugs which make them particularly suitable for portfolio financing and may explain the intuition behind their results. Firstly, orphan diseases are generally caused by individual genetic mutations (termed ‘monogenic pathology’) and act through unrelated biological mechanisms. Consequently, the pharmacological functions of orphan drugs tend to be unrelated, and thus, the success or failure of individual orphan drug development projects is unlikely to be correlated across diseases (Maher 2008). Further, again attributable to monogenic pathology, orphan drug development enjoys a significantly higher rate of success than that for more complex disease fields like neurodegeneration or oncology (Fagnan et al. 2014). Once the underlying genetic defect has been identified, the development of a targeted therapy is relatively straightforward. As such, the regulatory success rate of orphan compounds far exceeds that of non-orphan compounds. For drugs entering clinical testing between 2003 and 2011, the probability of FDA approval for orphan candidates was 23% while it was merely 15% for non-orphan candidates (Hay et al. 2014). Secondly, orphan drugs’ small patient populations are often compensated for large per-patient revenues. Therefore, orphan drugs tend to generate lifetime revenues comparable to those of non-orphan therapies. For example, between 2000 and 2010, the same percentage (29%) of newly approved orphan and non-orphan drugs achieved blockbuster status (Thomson Reuters

2012). Finally, orphan drug developers receive a host of financial and regulatory incentives as stipulated by the ODA, which are further discussed in Chapter 4.

3. The Effect of Price Controls on Pharmaceutical R&D

From an ethical perspective, the morally optimal pricing regime is that which relieves the most suffering and saves the most lives. This ethical framework is consistent with both Rawls' Difference Principle, in which the utility of society's worst-off is maximized, and Utilitarianism, in which society's sum utility is maximized (Maitland 2002). In such a society, any systematic exclusion from pharmaceutical care both violates the principles of fairness and results in a suboptimal level of utility (Hemphill 2010). Price regulation, Maitland (2002) argues, would oppose these ethical goals. Within a market economy, binding regulation of prices reduces investment in that industry or product. Because price controls would reduce expected returns, pharmaceutical R&D investment would decline, resulting in the development of fewer products – today's profits are tomorrow's drugs (Maitland 2002). Price regulation, though, may appear attractive myopically because its benefits are observed immediately while its costs are deferred. Such a situation can be represented graphically via an Access-Innovation Frontier, as shown in Figure 3.1.

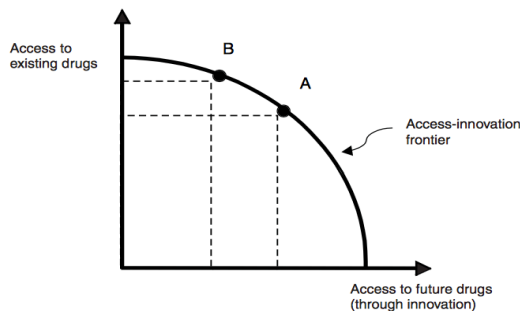


Figure 3.1
Access-Innovation Frontier
(Vernon and Golec 2008)

Even within a regulatory regime in which drug producers are forced to supply products below their average total cost, firms will continue to produce in the short-run

because most of their costs are sunk. In the long-run, however, firms will invest until the expected marginal efficiency of investment (MEI) is equal to the firm's marginal cost of capital (MCC). This market equilibrium can be visualized within a basic supply-demand framework, in which the downward sloping MEI curve represents the aggregation of the expected return for each individual project while the upward sloping MCC curve represents the supply price of investment funds at the margin (Vernon 2005). Expected profits and lagged cash flows are the principal determinants of firms' sales-to-R&D ratios (Grabowski and Vernon 2000, Scherer 2001, Lichtenberg 2001). Thus, price controls influence firm investment through two primary channels: (1) By reducing the firm's expected returns to R&D (Figure 3.2); and (2) By limiting the supply of capital, also referred to as a 'cash-flow effect' (Figure 3.3) (Vernon 2005).

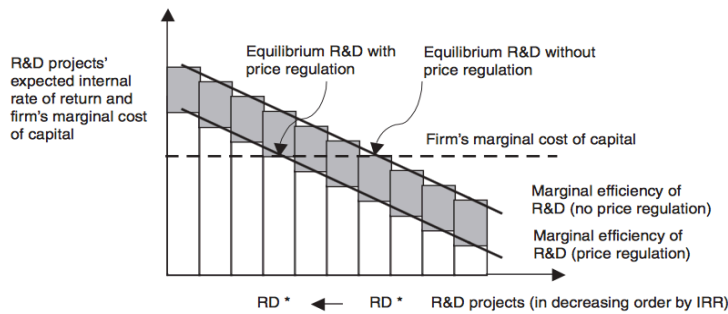
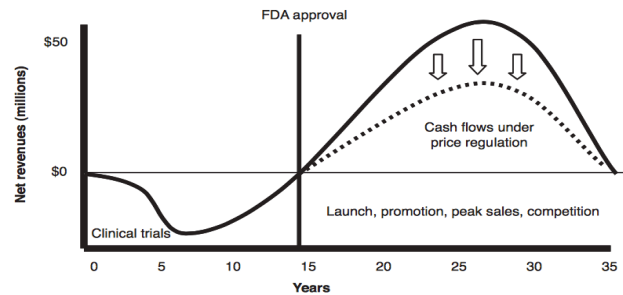


Figure 3.2
Price controls lower the expected returns to R&D, leading to a decline in equilibrium R&D investment (Vernon and Golec 2008)

Figure 3.3
Price controls restrain cash flows from any given approved drug, which limits the supply of internally-generated capital for R&D investment (Vernon and Golec 2008)



Ceteris paribus, price controls will reduce the expected profitability of any given investment project, resulting in a leftward shift in the MEI curve. Further, price controls will limit the lagged profitability of the firms themselves, and thus the supply of funds for

investment, either from internally generated cash flows or from external investors, will decline, generating a leftward shift in the MCC curve. Irrespective of which channel takes precedence, aggregate R&D investment declines unambiguously, as shown in Figure 3.4.

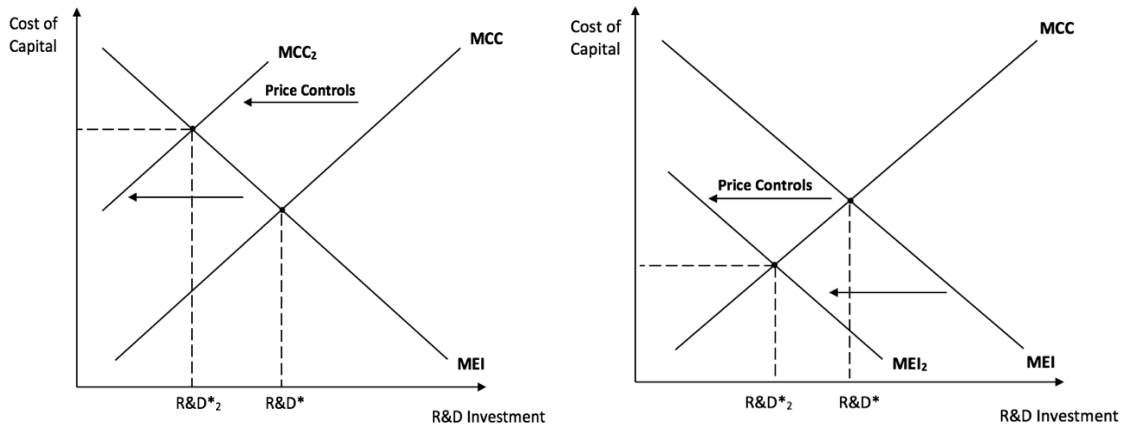


Figure 3.4

Price controls lead to a leftward shift in either the MEI or MCC curve, or, in the worst case, both (Author's Figures)

This equilibrium model has been substantiated by various models of pharmaceutical R&D investment. Simulations of an illustrative government-imposed price control regime from 1980 to 2001 indicated that R&D investment would have fallen by ~30%, ultimately resulting in ~350 new medicines going undeveloped, which is more than one-third of all new drugs brought to market over that period (Giaccotto et al. 2005). In the long run, a similar model suggests that a 10% decline in drug prices would cause a 5 – 6% decline in pharmaceutical innovation (Lichtenberg 2006).

These theoretical predictions have been buttressed empirically by analyzing several models in which price regulation has been threatened or enacted. Because of its regulatory system, empirical analyses have primarily focused on Europe as a model. Since the early 1980s, nearly all European Union countries have employed demand and supply-side mechanisms to regulate pharmaceutical prices. While there is significant regulatory heterogeneity across countries, most exert some form of direct price control, and most have

stated an identical objective: to limit pharmaceutical price inflation to the rate of overall consumer price inflation (Sood et al. 2009, Golec and Vernon 2010). According to this benchmark, the policies have been successful: EU real pharmaceutical prices did not increase between 1986 and 2004 (Golec and Vernon 2010). Moreover, EU prices are 20 – 40% lower than those in the U.S (Danzon and Furukawa 2008).

A strictly price-focused analysis, however, is superficial and fails to investigate the unintended consequences of regulation on firm profitability and R&D investment. Across nineteen OECD countries, direct price controls have reduced pharmaceutical company revenues by an average of 16.8%, which has contributed to an average difference of 4.9% in aggregate profitability between U.S. and EU firms (Sood et al. 2009, Golec and Vernon 2010). Firm profitability is positively correlated with R&D investment (Sherer 2001, Trushin 2011, Golec et al. 2010); and that relationship has held in this case. EU pharmaceutical R&D spending was 24% higher than that of the U.S. in 1986, but by 2004, following the widespread adoption of price controls, EU R&D spending trailed that of the U.S. by 14% (Vernon and Golec 2008). The implications of Europe's R&D paucity are self-evident: EU firms introduced twice as many new pharmaceutical products as U.S. firms between 1987 and 1991, but they introduced 20% fewer products between 2000 and 2004 (Vernon and Golec 2008). Eger and Mahlich (2014) further confirm these results with more recent data. The findings are consistent with the predicted cash-flow effect, in which a decline in firms' profitability constrains the supply of funds for investment, causing a leftward shift in the MCC curve and receding R&D investment.

Drug prices in the United States, on the other hand, have largely remained unregulated. However, the domestic pharmaceutical industry has not been entirely

immune from the threat of price controls. The most preeminent threat came in 1993 with the Clinton administration's proposed Health Security Act (HSA). Although the proposal was ultimately defeated in Congress, it has served as an experiment through which the response of U.S. pharmaceutical firms to potential regulation can be observed. Under the HSA, drug prices would have unambiguously declined in accordance with mandated formulary restrictions, rebate negotiations, and generic substitution (Ellison and Mullin 2001). Further, the Act would have established an Advisory Council on Breakthrough Drugs which would have had the authority to limit prices of newly developed pharmaceuticals (Kutyavina 2010).

Although it was never passed, the HSA introduced a credible threat of price controls within the U.S. market. In response, real pharmaceutical price inflation fell abruptly in 1993 and lingered near zero for several years thereafter (Golec and Vernon 2010). I have previously discussed the positive correlation between drug prices and overall financial performance. As such, one would expect firms and investors to integrate their revised expectations into investment decisions a priori; and indeed, this was the case. Expectations of firm profitability (using stock market valuations as a proxy) declined significantly: a sample of stock performance from 1993 to 1995 for 111 pharmaceutical and biotechnology companies revealed an average downturn of ~19% (Golec and Vernon 2010). The availability of external financing for biotechnology companies similarly faltered (Lerner et al. 2003). Consistent with the theoretical predictions made heretofore, aggregate pharmaceutical R&D investment declined in turn. Investment was 7.7% lower in 1994 than 1993; but tellingly, R&D spending quickly recovered in 1995 following the HSA's rejection (Golec and Vernon 2010). This observation suggests that the short-term

decline in investment derived from lower expected returns and restricted external financing, both of which are consistent with the market equilibrium detailed previously.

In summary, while there are multiple channels through which price controls influence firms' R&D investment decisions, they are unambiguously associated with declining R&D investment. Declining investment, in turn, results in a dearth of biomedical innovation and approved drugs. This reality carries significant implications not only for human population health but also for the financial feasibility of the orphan drug megafund, which is discussed hereafter.

4. Theoretical Integration of ODA Incentives

The Orphan Drug Act mandates five specific incentives to improve the economic viability of orphan drug development: (1) Minimum 7-year post-approval market exclusivity period; (2) Receipt of a 50% tax credit for clinical trial expenditures; (3) The award of NIH grant funding to some drug developers³; (4) FDA clinical trial protocol assistance; and (5) FDA application fee waivers. The ODA, however, remains unconsidered in the orphan drug megafund proposed by Fagnan et al. (2014). While such an approach may suffice for their purposes, a more accurate theoretical incorporation of ODA incentives is necessary for a comprehensive analysis of orphan drug megafund efficacy under the stress of price controls. As such, I integrate three of the five ODA market incentives into the illustrative megafund framework developed in Fernandez et al. (2012). The theoretical development begins by augmenting single-drug metrics, such as revenues and costs, and concludes by expanding the analysis to portfolio performance.

³ Currently, the ODA guarantees up to \$14 million in NIH funding per year. It is unclear how this amount may change given the Trump administration's decision to significantly reduce the NIH's budget. As such, I omit this incentive from the theoretical model.

Of the financial incentives mandated by the ODA, the guaranteed seven-year market exclusivity period is the most significant. In effect, this provision grants the drug developer monopoly privileges for seven years following the approval of an orphan drug. This exclusivity, however, differs in important ways from a traditional patent. Patent protection is often granted early in a drug candidate's life cycle and encompasses a wide variety of uses and indications. Moreover, patent protection for a given drug expires exactly twenty years from the date of issue, regardless of the drug's regulatory standing at the time. In contrast, market exclusivity under the ODA grants exclusive marketing rights for exactly seven years following approval, regardless of the drug's patent status. Further, market exclusivity only encompasses the indication for which the drug was approved and is conditional on the developer's ability to meet market demand (Rohde 2000). Consequently, it is possible for the market exclusivity period granted by the ODA to act concurrently or independently of a drug's patent protection period; an intricacy that warrants theoretical consideration.

Fernandez et al. (2012) assume a 10-year drug development period with post-approval generation of income X from year 10 to year 20⁴. For my purposes, however, the assumption of a fixed income-generating period is overly simplistic. As such, I propose the incorporation of a variable L which represents the residual patent exclusivity given a clinical trial and approval period of T_D for each drug. Thus, in the case of an approved orphan drug, the modified framework should account both for the unconditional 7-year market exclusivity granted by the FDA as well as any remaining post-approval patent

⁴ The twenty-year upper bound represents the maximum period of patent exclusivity.

exclusivity. This modification places a lower bound of seven on the market exclusivity for orphan drugs while allowing patent protection to extend that period up to twenty years.

In the existing framework, the present value of cash flows from an approved drug, given a cost of capital r and a marketing period of ten years, is:

$$Y_{10} = \frac{X}{r} \left(1 - \frac{1}{(1+r)^{10}} \right)$$

The incorporation of residual patent exclusivity in relation to monopoly privileges granted by the FDA augments this model as follows:

$$Y_L = \frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right)$$

where $L = 20 - T_D$ and is bound by $7 \leq L \leq 20$

Because the length of market exclusivity is a significant driver of lifetime cash flows, the consideration of variable periods of exclusivity amongst drugs is critical. As such, my framework better represents the reality for both orphan and non-orphan drugs.

Market exclusivity operates as a ‘pull’ incentive by generating market demand. The other primary mandates of the ODA, in contrast, act as ‘push’ incentives by reducing R&D costs (Grace and Kyle n.d.). The ODA’s push mechanisms are two-fold: (1) The Orphan Drug Tax Credit (ODTC); and (2) FDA Application Fee Waivers.

The ODTC provides a tax credit to drug developers equal to 50% of the cost of completed clinical trials. This tax credit can be applied immediately or carried forward for up to twenty years, which is a significant distinction, as orphan drug developers are often pre-revenue firms without existing tax liabilities (U.S. FDA 2016). Importantly, the ODTC is provided regardless of the drug’s regulatory outcome. As clinical trial costs often amount to hundreds of millions of dollars, the approval-independent nature of the ODTC serves to alleviate some of the risk of orphan drug development and lower the

effective cost of capital for developers (Ernst & Young 2015). Thus, considering the overall costs of development for orphan drugs necessitates the incorporation of the ODTC.

The final incentive provided by the ODA is the remittance of FDA application fees. Specifically, this provision mandates that the developer's application fee, as established by the Prescription Drug User Fee Act (PDUFA), is waived for any product which has received orphan drug designation. In 2016, the fee for a drug application totaled \$2,038,100 (U.S. FDA 2016). While, the fee waiver provision is far less significant than the ODTC, it is an important distinction between orphan and non-orphan drug candidates, and thus merits consideration in the theoretical framework.

To incorporate these incentives into the model, it seems intuitive to begin with the framework's measure of costs. However, because Fernandez et al. (2012) assume a pre-discounted cost metric, considering these incentives as sources of income avoids overcomplicating the model. Thus, I propose the integration of a variable F which represents both the variable tax credit and fixed fee waiver granted to the drug developer. The integration follows:

$$F = .5\alpha C + w \text{ where } \alpha = \frac{\text{clinical trial costs}}{\text{total development costs}} \text{ and } w = \text{fixed cost of FDA application fee}$$

In the existing framework, if C represents the present value cost of development associated with an approval, the total investment return, R_s , between $t=0$ and $t=10$ for a single approved drug is as follows:

$$Y_{10} = \frac{X}{r} \left(1 - \frac{1}{(1+r)^{10}} \right)$$

$$R_s = \frac{Y_{10}}{C} - 1 = \left[\frac{X}{rC} \left(1 - \frac{1}{(1+r)^{10}} \right) \right] - 1$$

In the orphan drug model, I incorporate F into lifetime income, Y_L , as follows. Importantly, because F is a one-time payment received prior to approval, I assume that it occurs at $t=0$, and thus, remove any need to discount.

$$Y_L = \frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) + F$$

$$R_s = \frac{Y_L}{c} - 1 = \frac{\left\{ \left[\frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) + F \right] \right\}}{c} - 1$$

Thus far, I have only incorporated ODA incentives into a single-drug framework. To fully consider the effects on megafund returns, it is essential to expand this development to the portfolio level. Because the financial incentives provided by the ODA directly increase a drug's income-generating potential, their incorporation will unambiguously increase the portfolio's returns. However, it is also imperative to consider how the incentives influence portfolio variance. The modified framework stands as follows:

Given a cost of capital r , the present-value of cash flows over the post-approval market exclusivity period L is represented by:

$$Y_L = \frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) + F$$

If C represents the present value cost of development associated with an approval, the total investment return, R_s , between $t=0$ and $t=L$ for a single approved drug is as follows:

$$R_s = \frac{Y_L}{c} - 1 = \frac{\left\{ \left[\frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) + F \right] \right\}}{c} - 1$$

For a single drug, development represents a Bernoulli trial, denoted I_i , in which the probability of drug approval/sale ($I_i = 1$) is equal to p and the probability of failure ($I_i = 0$) is

equal to $1-p$. Therefore, the rate of return, R , from $t=0$ to $t=L$ for one drug is a random variable given by:

$$R = \begin{cases} R_s & \text{with a probability of } p \\ -1 & \text{with a probability of } (1-p) \end{cases}$$

The mean and standard deviation for the return on one drug, R , then, are given by:

$$E(R) = p(1 + R_s) - 1$$

$$SD(R) = \sqrt{Var(R)} = (1 + R_s)\sqrt{p(1-p)}$$

When applied to a portfolio, R_p , of n independent⁵ and identical projects, we find:

$$R_p = \frac{Y_L \sum_{i=1}^n I_i}{nC} - 1 = \left[\frac{(1+R_s)}{n} \sum_{i=1}^n I_i \right] - 1$$

$$E(R_p) = p(1 + R_s) - 1$$

$$SD(R_p) = \sqrt{\frac{(1+R_s)^2}{n} p(1-p)} = (1 + R_s) \sqrt{\frac{p(1-p)}{n}} = \frac{Y_L}{C} \sqrt{\frac{p(1-p)}{n}}$$

While the portfolio's total asset return is paramount, because the megafund is also debt-financed, it is essential to consider its default probability. Doing so necessitates the probability distribution of drug failures/approvals, $\sum_{i=1}^n I_i$. I_i is a binomial random variable, thus its cumulative distribution function is:

$$\Pr(\sum_{i=1}^n I_i \leq k) = \sum_{j=0}^k \binom{n}{j} p^j (1-p)^{n-j}$$

Assuming a zero-coupon RBO at $t=0$ which pays Z upon maturity at $t=L$, the probability of default on that security then follows:

$$\Pr(Y_L \sum_{i=1}^n I_i < Z) = \Pr\left(\sum_{i=1}^n I_i < \frac{Z}{Y_L}\right) = \sum_{j=0}^{\lfloor \frac{Z}{Y_L} \rfloor - 1} \binom{n}{j} p^j (1-p)^{n-j}$$

⁵ Fernandez et al. (2012) assume insignificant covariance for simplicity. While this may not accurately represent reality, the simulations executed hereafter explicitly account for pair-wise correlation between projects.

By making some basic assumptions about the drug development process, the preceding framework can be used to illustrate the benefits of portfolio financing. The following examples follow the structure of those presented in Fernandez et al. (2012), but I extend them to consider the effects of ODA incentives. Consider a single drug with development costs (C) of \$200 million over a period of ten years. Assume the drug has a 5% chance of approval, and if approved, will generate net income of \$2 billion for the ten remaining years of its patent protection period. At a 10% cost of capital (r), the present value of the drug upon approval (Y_L) is \$12.3 billion. At that valuation, the implied compound annual rate of return over years 11 to 20 (L) is equal to $\left(\frac{\text{Expected Value}}{\text{Cost}}\right)^{\frac{1}{n}} - 1$, and thus, $\left(\frac{5\% * \$12.3}{\$0.2}\right)^{\frac{1}{10}} - 1 = 11.9\%$. The expected return may seem attractive on the surface, but the returns are largely dichotomous. While investors enjoy a 5% likelihood of earning 51% returns, they also have a 95% chance of returning -100%. The annualized standard deviation in this scenario is equal to 423.5%. Such an all-or-nothing risk-reward profile is unlikely to appeal to the overwhelming majority of investors, and is particularly unlikely to satisfy the criteria of investors with \$200 million in free capital. Indeed, this situation is indicative of the reality in drug development today.

Now consider a portfolio of investments in 150 such projects ($n=150$). As previously illustrated by portfolio theory, the expected rate of return is still 11.9%. The standard deviation, meanwhile, decreases by a factor of $\frac{1}{\sqrt{n}}$. Thus, while the annualized standard deviation of returns was 423.5% for a single investment, it is merely 34.6% $\left(\frac{423\%}{\sqrt{150}}\right)$ in the case of 150 investments.

This reduction in risk, though, comes at the cost of investment scale. Because each project has an independent development cost of \$200 million, the megafund requires \$30 billion of capital to finance 150 investments. At the same time, however, the risk reduction allows the megafund to issue financing via both debt and equity instruments. For example, if the megafund issued a total of \$24.6 billion (Z) of zero-coupon bonds, the default probability of those bonds would be the probability of less than two drugs earning approval, which is equal to 0.4%. Fernandez et al. (2012) note that this default rate is comparable to that of Aaa corporate bonds, and thus use the average yield on those securities to proxy for the yield on megafund bonds. The assumed yield of 3.85% on \$24.6 billion of ten-year securities implies a present value of \$16.8 billion, and thus the remaining \$13.2 billion would need to be financed via equity. In this case, the expected return on equity and standard deviation would be 21.5% and 78.9%, respectively. While the addition of leverage does inflate the risk-reward profile compared to the all-equity case, the risk associated with an investment in a megafund is significantly lower than that associated with an investment in a single drug development program.

Finally, consider a similar portfolio of 150 investments in orphan drug development programs. In this scenario, the ODA incentives (represented by F) increase the present value of any approved drug (Y_L). For simplicity, assume that clinical trial expenses comprise the entirety of development costs⁶. As noted previously, the FDA application fee totaled \$2,038,100 in 2016. Thus, F is equal to ~\$103 million, and Y_L increases to ~\$12.4 billion. Further, because orphan drugs enjoy higher rates of regulatory

⁶ In reality, total development costs include pre-clinical research expenses, to which the ODA tax credit does not apply. These costs, however, are typically minute in relation to clinical expenses.

success than non-orphan drugs, a 10% probability of success better represents the realities of orphan drug development.

Given these assumptions, an all-equity portfolio of 150 orphan drug investments would generate an expected compound annual rate of return of $\left(\frac{10\%*\$12.4}{\$0.2}\right)^{\frac{1}{10}} - 1 = 20\%$ with an annualized standard deviation of 48%. While the promise of higher returns does increase the portfolio's risk, the relative increase in expected returns exceeds that in expected standard deviation, implying that the overall risk-reward profile of an all-equity portfolio is generally more attractive for orphan drugs than non-orphan drugs. Further, assume that the megafund issued \$24.8 billion in zero-coupon bonds. Like before, the probability of default on those bonds is the probability of less than two drugs earning approval, which is equal to .0002%, 200x smaller than that in the non-orphan drug scenario. This value is consistent with (and in most cases, lower than) the default rates among the safest debt securities available, and largely results from the increased rate of regulatory success for orphan drugs.

The preceding analysis suggests that, *ceteris paribus*, ODA incentives serve to increase overall portfolio expectations and performance. This model, however, is illustrative and presents an overtly stylized exemplar of drug development. Further, the model assumes that the drug development programs comprising the portfolio are statistically independent. While this is convenient mathematically, it is unlikely to hold in practice. Thus, the framework presented in exposition may overstate the diversification benefits of portfolio financing (Fernandez et al. 2012). Pairwise correlation, while not considered here, is incorporated explicitly in the megafund simulations presented hereafter.

Irrespective of its simplifications, my modified framework successfully incorporates the financial incentives mandated by the Orphan Drug Act within the megafund model. While purely for illustrative purposes, the integration of these elements demonstrates the quantitative benefits of orphan drug development while adding qualitative depth to the model. The combination of these incentives, as well as the pathological characteristics mentioned previously, suggest that orphan drugs may be particularly apt for large-scale, portfolio financing. But, an important question remains: in the case of government-imposed price controls, is the orphan drug megafund still a viable solution to the suboptimal accessibility of capital for biomedical research? Can the benefits of portfolio financing outweigh the detriments of invariably-restrained returns? Ostensibly, the answers are ambiguous. The definitive resolution of these questions necessitates expanding this analysis beyond the illustrative. The remainder of this paper attempts to answer these questions analytically via the simulation of portfolio performance in price control scenarios.

5. Price Control Simulations

Within the wider drug pricing debate, the ODA has been the subject of extensive legislative dispute. For example, the act was amended in 1994, '95, and '98, all of which remain in place today, while countless further revisions have fallen short in Congress. The proffered restraints vary in their severity and structure, but generally fall within one of two silos: fixed, in which one specific restraint is applied to all relevant goods, and variable, in which the extent or type of control is dependent on a subset of traits specific to each good. As such, I consider a proposed orphan drug price control from each silo. I then use

statistical simulations to analyze the effects of each price control regime on the megafund's performance. Specific details regarding the simulations and price control policies follow.

5.1 Simulation Framework and Parameters

Following the structure of Fagnan et al. (2014), I simulate the performance of an orphan drug megafund under the pressure of price controls. These simulations embody a purely probabilistic model, and thus are independent of the illustrative framework presented previously. The model takes the form of a Discrete-Time Markov Process, a type of stochastic process in which the transition from state n to state $n+1$ is independent of the transition from $n-1$ to n . In other words, the past is conditionally independent of the future given the present state. Within the simulations completed here, and consistent with Fernandez et al. (2012), the Markov process takes the following form:

For each stage in the drug approval process, a vector of transition probabilities is generated which represents the probability that a drug candidate transitions from state n to state $n+1$ at any given time t . At each simulation period and for each drug candidate in the portfolio, a random number is generated and assigned from a uniform distribution. The value of this number is then compared to the probability vector to determine if the candidate transitions to the next state. This process continues through fourteen iterations for a total of fifteen simulation periods. Throughout the simulation, cash flow waterfall rules delineate the allocation of funds at each iteration. At the beginning of each period, proceeds from sales in the previous period are added to the portfolio's cash balance. That cash is then used, in order, for the following: payment of the megafund management fee, senior bond interest payments, senior bond principal payments, junior bond interest payments, and junior bond principal payments. If the sum of these liabilities exceeds the

current cash balance, the outstanding bonds default and the portfolio's assets are liquidated. If the megafund is not in default, a cash reserve is set aside for future debt payments, and any surplus cash is used to finance clinical trials for those compounds that have successfully transitioned. Once all outstanding bond payments have been satisfied, the assets are liquidated and the residual proceeds are allocated to the equity holders.

While the preceding description is a gross simplification, it suffices for my purposes. I encourage curious readers to refer to Fernandez et al. (2012) for further clarification.

I simulate the performance of a megafund with an initial capital of \$575 million which invests in sixteen orphan drug candidates. The fund is simulated under two distinct price control regimes, as described in subsequent chapters. In both cases, the fund's performance is simulated over fifteen consecutive six-month periods during which acquired drug candidates are either advanced to the next clinical stage, sold, or withdrawn. An equal number of pre-clinical and Phase I candidates are acquired with a projected liquidation following the completion of Phase II trials, but candidates can be sold beforehand to service outstanding RBO liabilities. To isolate the effects of price controls and ensure comparability between my results and those presented in Fagnan et al. (2014), unrelated parameters are left unchanged. In addition, a series of assumptions are made regarding the nature of the drug development process, including clinical trial costs and duration, phase transition probabilities, and drug valuations. These assumptions, as presented in Table 5.1, are discussed at length hereafter.

The drug development process consists of five stages: (1) Pre-clinical testing; (2) Phase I clinical trials; (3) Phase II; (4) Phase III; and (5) New Drug Application (NDA).

Timelines for this process were generated from the wider literature. Paul et al. (2010) provide pre-clinical timeline data across all drug classes. While these data are not specific to orphan drugs, the primary objective of pre-clinical testing is the verification of a drug's safety and toxicity profile, which should not vary significantly across drug classes. Clinical trial length, on the other hand, often differs for orphan drugs because trials must be structured to accommodate small, often dispersed, patient populations. Kaitin and DiMasi (2010) provide data for the average length of orphan drug trials from Phase I to NDA (5.9 years) and from NDA to regulatory decision (0.8 years). From there, the distribution of trial lengths by phase from Fernandez et al. (2012) is used to stratify the averages across the regulatory phases. The resulting timeline follows in Table 5.1.

The results of Paul et al. (2010) and Kaitin and DiMasi (2010) were also used to inform the success probabilities for each stage. Orphan drugs have proven to have higher rates of regulatory success in aggregate, but little has been done to isolate success probabilities by stage. As such, data for biologic drugs is used as an alternative. While this extrapolation is not perfect, biologics comprised 40% of approved orphan drugs in 2013, and thus serve as a reasonable proxy (Fagnan et al. 2014). The resulting success rates by stage can be found in Table 5.1. Compounding these values generates an overall approval probability of 0.218, or 21.8%, which is analogous to the results of Hay et al. (2014).

Clinical trial costs were similarly gleaned from previous analyses. Pre-clinical costs were taken from Paul et al. (2010), again under the assumption that pre-clinical development does not differ significantly between orphan and non-orphan drugs. Clinical costs were calculated by multiplying average trial sizes by estimates of per patient costs.

Orfali et al. (2012) report average clinical trial sizes for approved orphan drugs between 2001 and 2011. Using estimates of average costs per patient from Mathieu (2009), Fagnan et al. (2014) generate a distribution of costs by phase, as presented in Table 5.1.

Lastly, the simulations utilize a valuation matrix to assign drug candidates a present value at each stage of development. Assuming average annual revenues of \$200 million, per Thomson Reuters (2012), an average 11.7-year exclusivity period, per Seoane-Vazquez (2008), and a 10% cost of capital, per Harrington (2012), the present value of an approved orphan drug is ~\$2 billion. Fagnan et al. (2014) then reduce this value by 40% to account for marketing and selling expenses, yielding a final valuation of \$818 million per approved orphan drug. Finally, the average success rates discussed previously were used to calculate valuations corresponding to each development phase. The resulting valuations are shown in Table 5.1. In addition, the simulations assume a pairwise correlation of 20% amongst asset valuations, which was calculated from Bloomberg market data on the mean correlation of equity returns of small biopharmaceutical firms (Fernandez et al. 2012).

Within my simulations, it is through drug valuations that the implementation of price controls influence portfolio performance. Specific details regarding the controls and their dynamics are discussed below.

Table 5.1 – Base Case Parameters				
Phase	Trial Cost (\$ mil.)	Success Rate	Trial Duration (yrs.)	Valuation (\$ mil.)
Pre-Clinical	5	69%	1.00	7.1
Phase I	5	84%	1.66	27.6
Phase II	8	53%	2.09	75.6
Phase III	43	74%	2.15	321.5
NDA	-	96%	0.80	701.9
Approval	-	-	-	817.6

5.2 The Kassebaum/Metzenbaum Sales Trigger

The first orphan drug price control efforts were championed by Senators Nancy Kassebaum (R-KS) and Howard Metzenbaum (D-OH). Proposed to the 102nd Congress in 1991-92, the Kassebaum/Metzenbaum Initiative stipulated the implementation of a ‘sales trigger’ beyond which a drug would lose its market exclusivity privileges. The amendment guarantees market exclusivity for a period of two years, after which and for the following five years, it would be revoked if cumulative net sales surpassed a threshold of \$200 million (Garcia 2004). Cognizant of potential unintended consequences, more recent iterations of the legislation have tempered its injunctions. In the proposed amendments of 1993-94, the guaranteed period of exclusivity was extended to four years, with a potential three-year extension given demonstrated ‘limited commercial value’ (Waxman 1994). Additionally, proponents have argued that the sales trigger be set at \$200 million in annual sales (as opposed to cumulative sales) to reflect inflationary changes since the legislation was conceived. These efforts at modernization display the broad support behind the sales trigger approach, and as such, it is likely that prospective ODA reform would, at minimum, build off its ideology. For this reason, integration of the Kassebaum/Metzenbaum

Initiative is essential when considering the impact of price controls on the orphan drug megafund model. Rather than the original, I consider the diluted, modernized version is in the proceeding analysis, as it is more likely to garner bipartisan legislative support going forward.

Within the illustrative framework, the sales trigger manifests itself in two ways: (1) By imposing an upper bound on annual cash flows, X , such that $0 \leq X \leq 200,000$. For simplicity, I assume that $X=0$ following the loss of exclusivity; and (2) By expanding the lower bound of market exclusivity, L , from seven to four years. To discuss the repercussions of such an intervention, one must revisit the model developed previously:

Given a cost of capital, r , and a present value cost of development, C , the total investment return, R_s , between $t=0$ and $t=L$ for a single approved drug is as follows:

$$R_s = \frac{Y_L}{C} - 1 = \frac{\left\{ \left[\frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) \right] + F \right\}}{C} - 1$$

where X and Y_L are now bound such that $0 \leq X \leq 200,000$ and $4 \leq L \leq 20$

Thus, the mathematical structure of the illustrative model will not change, but its distribution will. By establishing an upper bound, the sales trigger approach will effectively restrain Y_L . This, in turn, will decrease the portfolio's mean return, R_p , and increase the number of successes ($I_i=1$) necessary to service its debt liability, Z . Meanwhile, expanding the range of market exclusivity, L , will increase the portfolio's variance. Thus, I expect that the implementation of a price trigger will adversely affect all three measures of portfolio performance. The magnitude of this effect, however, is harder to ascertain.

To do so, these restraints must be incorporated within the simulation's parameters. As noted previously, price controls operate via drug valuations. Because the valuations

generated in Fagnan et al. (2014) already assume annual revenues of \$200 million, the implementation of a sales trigger regime acts solely through a binding ceiling on a drug's exclusivity period. At an annual revenue of \$200 million, a drug would not satisfy the criteria to demonstrate a 'limited commercial potential,' and thus would not receive the conditional exclusivity extension. Consequently, its exclusivity period would effectively be bound at four years, which manifests itself in the drug's present value as follows:

$$PV = \sum_{n=0}^N \frac{X_n}{(1+i)^n} \text{ where } X_n = 200,000,000 \text{ and } N = 4$$

Assuming a 10% cost of capital, the resulting present value of an approved drug is ~\$380 million. In contrast to the \$818 million valuation used in Fagnan et al. (2014), this represents a 53% decline in value. The ultimate impact of this decline on overall portfolio performance is discussed in Chapter 6.

5.3 The Orphan Drug Windfall Tax

During the same Congressional session, Representative Fortney Stark (D-CA) first proposed the Orphan Drug Windfall Tax. Similarly meant to combat excessively profitable orphan drugs, the amendment proposed allowing developers to recoup twice the development cost of an orphan drug, after which all windfall profits, defined as the amount by which a drug's gross annual revenues exceed 125% of the drugs production costs, would be taxed at a rate of 75% for the remainder of the drug's market exclusivity period (Stark 1991). In addition, the bill proposed the expansion of the ODA's R&D tax credit incentives to include pre-clinical testing⁷ (Rin-Laures and Janofsky 1991). The bill, although ultimately defeated in Congress, was repurposed and re-proposed three times before its demise (Kim 2012).

⁷ The ODA currently mandates the provision of R&D tax credits only for clinical development costs.

Because it simultaneously extends one of the existing ODA incentives, the windfall tax proposal garnered support as a less severe alternative to the sales trigger approach. The two are not mutually exclusive, but rather, occupy different sides of the same coin. As such, the integration of a sales trigger regime within the megafund model necessitates a parallel consideration of the windfall tax. To do so, one must return to the equation for a drug's present value cash flows over its market exclusivity period, Y_L :

$$Y_L = \frac{X}{r} \left(1 - \frac{1}{(1+r)^L} \right) + F$$

Under the proposed windfall tax regulations, drug income is strictly controlled such that a drug's lifetime income is given by:

$$Y_L = 2C + 1.25 \sum_{n=0}^N P_n + .25(X_n - 1.25 \sum_{n=0}^N P_n)$$

where $P_n = \text{Production Costs in Year } n$

The directional effect of the windfall tax is difficult to decipher within the theoretical model because each of the terms in the equation above must be discounted to the present to generate a drug's ultimate valuation. The degree of discounting, moreover, will vary for each term and for each drug depending on the specific point at which Y_L exceeds twice the drugs development cost, $2C$. By using the assumptions made in Fagnan et al. (2014), however, I integrate the windfall tax into my simulations, through which it is possible to ascertain the regime's effects on the megafund's overall performance.

As discussed previously, the ODA grants a 50% tax credit for all clinical trial expenses, which the windfall tax further extends to pre-clinical expenses. Within the simulation, this effectively halves the cost of pre-clinical development to \$2.5 million, resulting in a total development cost of \$58.5 million. In contrast, drug valuations are adversely affected. Fagnan et al. (2014) assume annual revenues of \$200 million with a

profit margin of 60%, which implies an \$80 million per annum cost of goods sold (COGS) per approved drug. At this level, an approved drug's revenue exceeds twice its development cost (\$117 million) in the first year, after which, and for the remainder of the drug's exclusivity period, any revenue beyond \$100 million (125% of production costs, P_n) are taxed at a rate of 75%. The present value of the resulting stream of cash flows is given by:

$$PV = \frac{117}{1+r} + \frac{.25*(200-117)}{1+r} + \sum_{L=0}^L \frac{100}{(1+r)^L} + \sum_{L=0}^L \frac{.25*100}{(1+r)^L}$$

Thus, in the first year, the drug generates a net cash flow of \$137.75 million, followed by a net cash flow of \$125 million every year thereafter. In line with Fagnan et al. (2014), I assume a 10% discount rate, a market exclusivity period of 12 years, and a 40% marketing and selling write-down, which ultimately yields a present value of ~\$518 million per approved drug. The ultimate impact of this decline on portfolio performance is discussed in Chapter 6.

The relevant simulation parameters for each scenario are listed in full on the following page (Table 5.2).

Table 5.2 – Simulation Parameters			
Scenario	Base Case	Sales Trigger	Windfall Tax
Portfolio Structure			
Number of Compounds			
Preclinical	8	8	8
Phase I	8	8	8
Capital (\$ millions)			
Senior Tranche	86.25	86.25	86.25
Junior Tranche	115	115	115
Equity	373.75	373.75	373.75
Drug Dynamics			
Annual Revenue	200	200	200
Exclusivity Period (yrs.)	12	4	12
Valuation (\$ millions)	818	380	518

6. Results

The simulation results largely correspond to intuitive predictions: in both cases, the implementation of price controls significantly reduces the portfolio’s annualized return on equity (referred to as ROE hereafter). In the sales trigger scenario, the resulting ROE is 4.0%, representing a 70% decline from the base case returns. The decline is less severe in the windfall tax scenario, amounting to an ROE of 9.9%, a 26% drop.

Interestingly, under both price control scenarios, the megafund outperformed the base case in terms of debt fulfillment. While the RBO default probabilities in Fagnan et al. (2014) were 0.8 and 56 basis points for the senior and junior RBO tranches, respectively, they were <.01 and <30 bp under both price control scenarios. While the differences are not quantitatively material, this is a qualitatively unexpected result. I suspect that it may

be attributable to a rightward shift in the distribution for drug sale period. In the base case scenario, the ratio of drug candidates sold in Phase II vs. Phase III was ~1:2. The ratio rose to ~1:2.4 and ~1:2.6 in the sales trigger and windfall tax scenarios, respectively. This shift illustrates the cash flow pressure exerted by diminished drug valuation. Because the value of any given drug falls in a price control scenario, the megafund must increase its average investment horizon with the hope of liquidating drug candidates at larger, later valuations. The results suggest that, at the valuation parameters used here, this shift is consequential only for the equity tranche. However, one would expect that default risk is decreasing in valuation, and thus past a certain threshold valuation, the megafund's ability to service its debt liabilities would be materially influenced.

To test this theory, I execute the simulations using a valuation of \$100 million to proxy for extreme cash flow pressure. In this case, the default probabilities jumped to 10 and 660 basis points for the senior and junior tranches, respectively. Thus, the negligible default rates generated in the price control scenarios suggest that the RBO risk profiles are relatively insensitive to drug valuations.

The results are presented in Table 6.1. The table is comprised of three sections. The megafund's research impact refers to the number of compounds which were successfully advanced through clinical trials and sold in each drug development phase. The equity performance subheading contains a variety of performance metrics for the megafund's equity tranche. While the average annualized ROE is the preferred measure of performance, I also include a variety of probability measures for different ranges of ROE. Finally, the RBO performance subheading contains default the probability and expected loss, presented in basis points, for both the senior and junior RBO tranches.

Table 6.1 – Simulation Results			
Scenario	Base Case	Sales Trigger	Windfall Tax
Research Impact			
Number Sold in Phase II	2.3	2.0	1.9
Number Sold in Phase III	4.6	4.8	4.9
Equity Performance			
Average Annualized ROE	13.4%	4.0%	9.9%
Prob. (Equity = 0)	0.06%	0.3%	0.1%
Prob. (ROE < 0%)	13.1%	32.6%	14.7%
Prob. (ROE > 10%)	66.7%	29.1%	51.3%
Prob. (ROE > 25%)	18.4%	1.8%	6.6%
RBO Performance			
Senior Tranche			
Default Probability (bp)	0.8	< .01	< .01
Expected Loss (bp)	< .01	< .01	< .01
Junior Tranche			
Default Probability (bp)	56	30	10
Expected Loss (bp)	15	7.6	1.6

Figure 6.1 - Average Annualized ROE

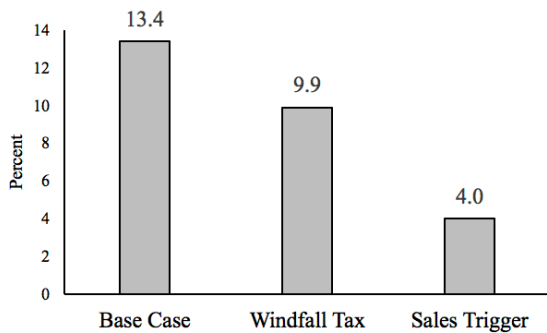


Figure 6.2 - Probability ROE < 0

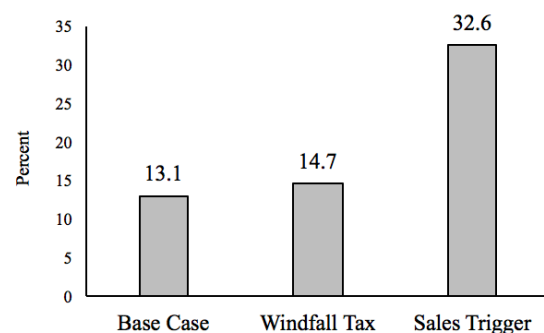


Figure 6.3 - Junior Tranche Default Probability

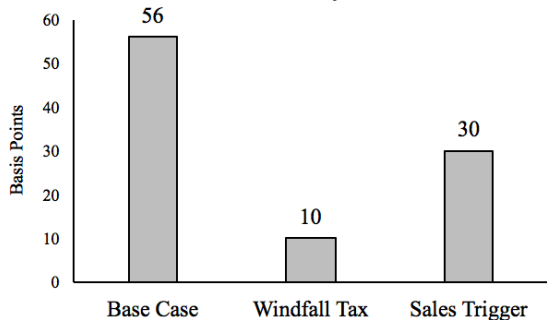
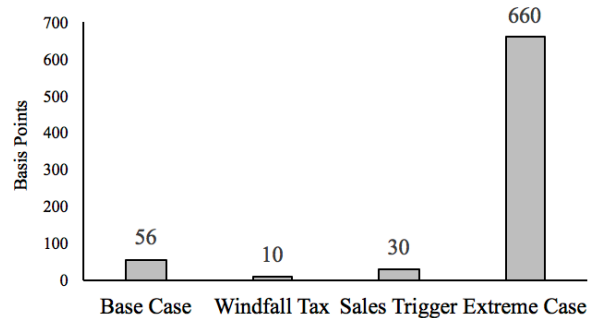


Figure 6.4 - Junior Tranche Default Probability



7. Discussion

The orphan drug megafund, by addressing information asymmetry problems and providing large-scale financing, increases the amount of loanable funds available for biomedical R&D, which may ultimately stimulate long-run medical innovation. My results suggest that price controls significantly obscure the feasibility of such a model. Interestingly, though, only in the sales trigger scenario do price controls implicate its feasibility entirely. It is likely that the megafund, under the downward pressure of a sales trigger price control regime, would fail to provide sufficient risk-adjusted returns to attract the scope of investment necessary for proper implementation. Conversely, in the windfall tax scenario, the megafund proved particularly resilient. At an annualized ROE of 9.9% and a 14.7% probability of a negative return, the megafund still offers a risk-reward profile comparable to many historically attractive equity instruments. For example, the geometric average return on the S&P 500 stock market index from 1928 – 2016 was 9.52% while the probability of a negative return was ~27% (Damodaran 2017).

These results, and in particular, the disparity between the megafund's performance across the two price control scenarios, carry implications which could inform policy decisions regarding drug prices. The most salient of these concern the differential merits of various price control structures. In general terms, the simulations measure the megafund's performance under both a multidimensional, fixed regime and a unidimensional, variable regime. The sales trigger represents a multidimensional, fixed price control, as it targets both drug profits and market exclusivity, and is implemented at a rigid threshold regardless of the circumstances. The windfall tax, in contrast, takes the

form of a unidimensional, variable price control, as it targets only drug profits, and its extent is dependent on a subset of traits specific to each drug.

The results here suggest that the economic incentives for drug development may be further restrained under a multidimensional, fixed price control regime as opposed to a unidimensional, variable regime. It seems intuitive that multidimensional restraints would be more distortionary than unidimensional controls. One would expect several simultaneous restraints to act multiplicatively, resulting in a significant reduction in commercial potential; and indeed, this is what my findings suggest. The second argument is less intuitive. It may be that variable price control regimes are more akin to case-by-case regulation, and grant the governing entity more flexibility to allow for moderate producer surplus while preventing exploitation.

In sum, the results suggest that, despite a marginal reduction in overall performance, the orphan drug megafund model proves resilient to a moderate level of price regulation, and thus may remain a solution to the suboptimal accessibility of capital for biomedical research despite government intervention. Importantly, though, megafund performance declines with increasing regulatory rigor. Such a finding illustrates the potential for extreme constraints to smother biomedical innovation, and suggests that, conditional on government intervention, a moderate, unidimensional price control regime may represent an optimal strategy.

While these considerations are imperative for a strictly financial discussion of drug pricing policy, my analysis does not address the welfare implications of price regulation and its various forms. On the surface, it seems that the megafund model could effectively address market failures in biomedical capital markets despite moderate price controls,

which may represent a Pareto improvement in net. Detailed welfare considerations are beyond the scope of this analysis, but should be an important concern in any market intervention strategy.

In addition, this paper fails to address a host of administrative challenges which must be overcome for the megafund model to be implemented. These challenges include, but are not limited to, the intellectual capacity of the biomedical research sector, secondary market liquidity for biopharmaceutical compounds, the megafund's ability to provide managerial and industry-specific expertise (à la venture capitalists), and the uncertainty associated with the potential repeal or restructuring of the Affordable Care Act. While these issues lie outside the realm of my analysis, I encourage interested readers to refer to Fernandez et al. (2012) for a more detailed discussion.

8. Conclusion

Financing drug development is a complex and imperfect process. Biomedical capital markets experience more severe information asymmetry problems than most capital markets, and are largely devoid of financial innovation to ameliorate such imperfections. The biomedical megafund, by providing large-scale financing and mediating scale misalignment, offers a potential solution to the suboptimal accessibility of capital for biomedical research. In this paper, I have shown that pharmaceutical price controls restrain the financial efficacy of this model. I have tailored and expanded the megafund theoretical framework to better represent the realities of orphan drug development. I have illustrated how the integration of ODA incentives suggests that orphan drugs may be particularly apt for portfolio financing. Finally, I have compared the performance of an

orphan drug megafund under the status quo to an identical megafund under two price control regimes.

My results indicate that megafund performance is relatively insensitive to moderate price controls, and thus may remain a solution to the suboptimal accessibility of capital for biomedical research despite government intervention. Further, they suggest that variable, unidimensional price controls may represent a financially optimal drug pricing policy with respect to the trade-off between managing drug expenditures and incentivizing R&D. Overly restrictive price controls, conversely, may exacerbate underinvestment in R&D and render financing alternatives like the megafund implausible.

These results, however, are merely suggestive rather than conclusive. The simulations rely on a host of assumptions about the drug development process and market. While I believe my assumptions are accurate and conservative, the pharmaceutical industry evolves in parallel with biomedical innovation, and thus the realities of drug development tomorrow may look different than they do today. Further, any implications for drug pricing policy are strictly financial, and do not encompass the welfare analyses which any proposal would necessitate.

Finally, it is important to note the precision of my analysis. The megafund is merely one of several alternative financing models, including Drug Royalty Investment Funds, ‘Regulated Investment’ Business Development Companies, and Health Care Loan Securitization, among others. Moreover, the price controls considered here are only two of an innumerable array. Indeed, the threat of price controls has contributed to the growing popularity of other pricing alternatives, including value-based and indication-specific pricing regimes. Regardless of the financing model and pricing structure used, it is a

foregone conclusion that the existing model of drug development and market pricing will be forced to evolve in the immediate future. As this paper illustrates, the balance between drug affordability and economic allure is tenuous, but optimizing this trade-off is paramount for ensuring both access and innovation. Straying too far in either direction may have grave consequences.

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