To Treat or To Cure: How Vertical Product Differentiation and Competition Affect Underinvestment in Pharmaceutical Drug Research and Development

Felix Tian-Hui Wu

December 6, 2021

Advisor: Professor Jun Ishii

Submitted to the Department of Economics at Amherst College in partial fulfillment of the requirements for the degree of Bachelor of Arts with honors

Abstract

The potential for drastic curative treatments of disease has expanded since the Human Genome Project, through breakthrough basic science like CRISPR and improved transcriptome and proteome characterization (Hofker et al. 2014). However, the development of actual treatment based on this science has been lacking (Hopkins et al. 2007). Arrow's creative destruction explains this lack of innovation as 'underinvestment' by firms as they maximize profits at the expense of overall social welfare. Monopoly firms avoid innovating because new treatments reduce profits from existing ones. On the other side, firms argue that developing these treatments involve fixed costs that far outweigh the additional surplus they generate.

My thesis evaluates these two competing claims by studying the interaction among competition, product differentiation, and fixed costs. Firms 'underinvest' when they avoid developing a treatment where the surplus generated is greater than the fixed cost to develop. Firms can develop an incremental treatment, a drastic treatment, or both. I first model this choice and competition between incumbent and entrant firms as a simultaneous game. Fixed costs for each treatment are added to show how their relative sizes shift preferred strategies for firms. I then show how a sequential version of the game can lead to underinvestment by the incumbent and change how surplus is allocated. I allow different fixed costs *between* firms to expand the set of conditions that produce underinvestment. Conventional market wisdom that competition leads to both treatments being developed can be undermined by first mover advantage and differences in fixed costs. Simply investing in one treatment can be enough for the incumbent to preempt rival firms and prevent them from entering. The results help investigate where interventions can be implemented to avoid underinvestment and maximize overall surplus.

JEL Classification: O32, I18, L13
Keywords: Vertical Differentiation, Pharmaceutical Research and Development, Fixed Costs

Acknowledgements

To Mr. Miller: Thank you for lighting the lamp and starting me down the path.

To Professor Durr and Professor Edwards: I am constantly in awe of the community you cultivate and will forever cherish being part of it. Thank you both for your honesty, advice, and support.

To Professor Reyes, the Not Director of the Honors Thesis Program: I was immensely fortunate to have taken my first economics course at Amherst with you. Thank you for encouraging my questioning of all things economics. Your mentorship, humor, and character are an inspiration. Amherst, the Department, and I are better because of you.

To Professor Ishii: I am so grateful for the energy, time, and care you have given me and this project. Your advising has taught me so much about what it means to do and think about economics. Thank you for asking for and expecting my best, even if I can't always get there. Thank you for just the right amount of rope.

To my thesis cohort and community - Cole and Martin, and the Fall 2021 Seminar: I cannot thank you enough for your support, comradery, and commiseration. I'll miss the co-working sessions and late-night conversations in Converse over Fun-Dip and Airheads.

To AMS, and to Jenkins: I wouldn't be here without you. Thank you for giving me reason to continue. Next one is on me.

To Maggie: Thank you for proof reading, helping me with math, sending me sources, and believing in me. You hold me with such care, and for that I am thankful. I couldn't have done it without you.

To Ma and Pa: Sorry this isn't a Biochem thesis (just kidding). You gave me your unwavering support when I was thankful for it and when I wasn't. I am who I am, where I am, because of you. I love you both.

Table of Contents

1 Introduction

To bring new drugs to market pharmaceutical firms must sink costs to either propel new chemical entities through clinical trials or purchase equivalent intellectual property throughout the phases of drug development. Firms face vertically differentiated options in this investment decision. A firm can choose to develop incremental updates to available treatment to slightly improve patient outcomes for a disease, or the firm can choose a riskier, harder path and develop a drastic treatment to cure a disease. The firm can also choose to take both paths. The key differences between the two treatments are the sizes of the fixed cost to develop them, and that patients value the drastic treatment more than the incremental treatment.

Underinvestment by firms is a failure to invest in a new treatment where the surplus generated by that treatment is greater than the fixed cost to develop it. Simply observing firm behavior gives limited insight into whether the market for treatment development in a particular therapeutic area is functioning optimally. A disease can go without any new treatments being developed because the fixed costs to do so outweigh the surplus generated. A disease could also go without new treatments being developed because firms are 'underinvesting' in development. Even if firms are observed developing new treatments, it is difficult to know whether there are innovations being left on the table. Underinvestment, while profit maximizing for individual firms, is viewed here as a market failure as 'better' treatments could still yield positive producer surplus. Underinvestment can also push market outcomes further away from the social efficiency where total surplus is not maximized, and the quantity of patients treated is lower than the optimal amount.

Firms must consider the behavior of potential competitors when deciding what fixed costs to sink in developing new drugs. Rival firms entering the market and developing substitute treatments have the potential to render a firm's investment in new treatment unprofitable where it otherwise would have been. However, this dynamic works in the reverse as well. A firm's development decisions impact the payoffs to potential entrants. This opens the door to strategic preempting behavior for incumbent and entrant firms.

I first model competition between an incumbent and entrant firm in a simultaneous game without fixed costs to examine the fundamental nuances of competition that produce underinvestment. Fixed costs are then added to show how their relative sizes shift preferred strategies for firms. I then show how a sequential game reinforces the production of underinvestment and changes how surplus is allocated in the market. Finally, I allow for different fixed costs *between* firms to further expand the set of conditions that result in underinvestment.

The results from the simultaneous model show that without fixed costs competition induces both treatments to be developed and there is no private underinvestment. However, a socially inefficient outcome may happen if a firm develops both treatments by themselves and only prices one affordably.

Firms can underinvest once fixed costs are added and if they are large enough to render single product oligopoly profits negative. Underinvestment occurs in the simultaneous game when the preferred strategy of firms is in no danger from competition.

Introducing sequential move and/or differences in fixed costs further expands the conditions under which such underinvestment might occur.

In a sequential game, fixed costs no longer need to be different between incumbent and entrant firms to produce underinvestment. A sequential game also allows the first mover to effectively block the decision set faced by following firms. Even where both incumbent and entrant firms face fixed costs such that both options are profitable individually and together, the first mover has the option to only choose one and underinvest. Depending on the relative value of treatments, the first mover can shift payoffs for entrants from monopoly or exclusive oligopoly to split oligopoly and render investment in treatment unprofitable. This result is especially significant because in a state of the world where three separate options are profitable for two competing firms, it is plausible for investment to occur only in the lowest value improvement.

Underinvestment also depends on the size of the market for a treatment, where an increase in the number of patients and the value those patients place on treatment allows all firms to see profits greater than fixed costs of treatment development.

The results indicate that regardless of the underlying competitive structures that allow underinvestment to persist, a simplified set of actions can realign market structure to produce proper investment. By subsidizing fixed costs such that single product oligopoly profits are non-negative and/or setting relative price controls for two-product monopolies, the government can move the market closer to efficient social and private investment.

2 Motivation

Morally, new drug development is an important part of improving patient welfare and keeping society happy and healthy. Pharmaceutical companies dominate the drug development landscape in the United States. Yet the pharmaceutical industry in the United States can look like a complicated set of contradictions. On one hand, pharmaceutical firms deliver effective and lifesaving treatments. The recent development of COVID-19 vaccines is an incredible example of industry's ability to create value for patients and firms. Bringing multiple highly potent treatments to market in less than a year is a credit to the scientific and manufacturing ability of the pharmaceutical industry.

On the other hand, pharmaceutical firms have a blemished reputation, with critics railing against runaway greed and exploitative price gouging. An ongoing billion-dollar lawsuit against Purdue Pharma L.P. for their deceptive marketing of highly addictive opioids (The United States Department of Justice 2020), protests by diabetic patients and families forced to ration insulin due to high prices (Hagan 2018), and 1000% overnight price hikes for decades-old drugs (Pollack 2015) all stand in stark contrast to what functional markets with properly aligned incentives producing socially efficient outcomes might look like.

Moreover, provision of care and access to pharmaceutical drugs are not solely dependent on patient need. They are also determined by complex interactions between patient health insurance providers (or lack thereof), hospitals, and doctors. These additional players muddy the connections between firms and patients, and between prices and profits.

To begin to make sense of this discordance, it is useful to examine what produces these conditions and why they are allowed to exist. In the U.S. the pharmaceutical industry is built on a bedrock of intellectual property rights. Knowledge produced by these firms is non-rival and non-excludable without government support. Drug patents and market exclusivity, given and enforced by the government, are intended to give firms temporary monopoly privileges to incentivize investment in innovation. Those monopoly conditions allow firms to escape competition and earn greater profits for their research efforts (Baker 2007). In a world without patent protection, a firm who shouldered the fixed cost to identify and bring a chemical entity through clinical trials could immediately be undercut by firms selling at marginal cost of production. Thus, the decision to invest in initial research would not be profit maximizing, and firms would choose not to innovate and bring new drugs to market. The pharmaceutical industry is unique when compared to other innovative industries because 'trade secrets' are not a viable option for protecting intellectual property. The Food and Drug Administration must review and verify data proving safety and efficacy tied to a unique chemical formulation or other innovation for a drug to be sold. Clearly, this practice protects the safety of patients and ensures reliability of drugs. It also means keeping data exclusively within the producing firm is likely impossible.

In theory, monopoly conditions allow pharmaceutical firms to charge prices sufficiently high above marginal costs to recoup innovation costs. Indeed, large innovation production costs are borne out in analysis. Estimated total out-of-pocket and capitalized R&D cost per new drug are $1.395 billion and $2.558 billion respectively (DiMasi et al. 2016), accounting for the development cost of numerous failed trials and chemical entities on top of the successful candidate. Classic Schumpeterian thinking reinforces the value of these monopoly conditions in

fostering firm innovation. Large incumbent firms could be more efficient than small firms when accessing capital, hold economies of scale in production, or even reduce likelihood of failure due to dominant market position (Baker 2007).

However, Kenneth Arrow identifies a disincentive that comes along with monopoly conditions. After monopoly firm's initial innovation, investing in subsequent innovations in the same marketplace may not be profit maximizing for the firm. If a firm already has a product under patent protection, a new product they introduce might fail to sufficiently expand the therapeutic area market and instead cannibalize revenue from the existing product offering (Baker 2007). This 'creative destruction' can direct an incumbent firm to rationally shift from engaging in R&D to erecting further barriers to entry to preserve current market power.

Given the serious ramifications of these government sponsored monopoly conditions, it is critical to examine where, and how they truly encourage innovative activity. The federal government already steps in to change incentives in multiple ways. By subsidizing the purchase of prescription drugs through Medicare and Medicaid, the government increases demand for drugs. The federal government also increases supply of new drugs and tries to account for market failures (CBO 2021). Already, several pharmaceutical specific legislative revisions that have been implemented. The Biologics Price Competition and Innovation Act (BPCIA) of 2009 gave special market exclusivity privileges and an abbreviated regulatory pathway to biologics because of their clinical and economic significance. The Orphan Drug Act of 1983 also afforded tax credits, grants, and fee waivers on top of market exclusivity to incentivize development of drugs for rare diseases with small populations. The Generating Antibiotics Incentives Now (GAIN) Act

of 2012 also used market exclusivity and expedited review status to combat the threat of antibiotic resistant "super bugs" (Grabowski et al. 2015). They, among others, are designed to induce pharmaceutical firms to innovate where market incentives create blind spots.

Many of the innovations that established pharmaceutical firms make are slight, add-on innovations. 65% of the new drugs produced by pharmaceutical firms[+] and approved by the FDA between 1998 and 2007 were classified as 'follow-on' innovations by the FDA's Center for Drug Evaluation and Research (Kneller 2010).

The rise of curative treatments throws an interesting twist into the decisions pharmaceutical firms face when developing new drugs. A curative treatment, from Wylie et al. 2019, is

> *"…a time-limited treatment that removes the symptoms of a disease through permanent (or semi-permanent) correction of the underlying condition. In contrast, a pill that a patient needs to take for the rest of their life to manage symptoms or disease progression is not curative."*

Already, there are almost a thousand potentially curative treatments currently in early-stage clinical trials, with the largest number (432) in Phase I trials (Wylie et al. 2019). The high value nature of curative treatments represents a drastic change for the revenues that firms currently receive for their drugs. This change complicates innovation incentives even further in the market for pharmaceutical drugs. Expanding on Arrow's logic, curative treatments produced by the

[+] Does not include drugs discovered by biotechnology firms or by universities, regardless of whether ownership of intellectual property is eventually transferred to pharmaceutical firms.

incumbent firm have the potential to foster both 'creative destruction' *and* 'curative destruction' whereby the total market size shrinks further due to cured patients.

3 Drug Development

The total market for pharmaceutical drugs is broad, spanning every imaginable disease or disorder and corresponding treatment. To understand research incentives, a useful market boundary is a single disease or disorder. Pharmaceutical firms develop their intellectual property for a specific application[*]. In a general case, the interaction between a firm's executive board setting strategic policy and the research director submitting proposals determines the firm's therapeutic and disease target selection (Knowles and Gromo 2003). Their research laboratories then work to identify biological mechanisms where intervention is beneficial and reasonable. This process depends on the work done by public academic research to continually build on the stock of scientific knowledge (Kneller 2010). After identification, useful chemical entities are screened out from libraries of millions of compounds. Research laboratories modify the drug candidates according to their targeted use to reduce potential negative side effects and improve effectiveness. During the modification phase, patent applications are also filed. Once granted, patents run for 20 years (U.S. Food and Drug Administration 2020), but clinical development timelines cut the effective exclusivity period by as much as 7 years (DiMasi et al. 2016). Specialty market exclusivity periods also have a similar cap on duration, from 180 days at the least to 7 years at the most (U.S. Food and Drug Administration 2020). Pharmaceutical firms are concerned with protecting the value of their investment before most of the cost of drug

[*] The same chemical entity may have multiple therapeutic uses, but each additional use requires a separate patent grant, clinical trials, and medical approval.

development is incurred during multi-phase clinical trials to prove safety and efficacy (Taylor 2015). Patents for a treatment create a first mover advantage. The first firm to develop a treatment and patent can market and sell the treatment before any other firm.

The initial market structure created by a patent for a disease treatment is a monopoly. Only one firm can market and sell a specific chemical entity and dosage until the patent expires. However, multiple firms can have different treatment offerings under patent for the same disease.

The global market for pharmaceutical drugs does not appear overly concentrated over the last few decades. Since the 1990s, the Herfindahl-Hirschman Index values for approvals of new chemical entities (DiMasi 2000) and market share (Richman et al. 2017) have remained beneath 500 and 750 respectively, under standards for a monopoly or oligopoly. However, the story changes within each specific therapeutic area. Between 70 and 80% of prescription drug revenues in the United States have gone to branded rather than generic drugs over the last 15 years (Mikulic 2020). Over a similar timeline, roughly 60% of identified conditions had 10 or fewer industry funded studies. An even higher percentage of conditions do not see any dominant pharmaceutical firms acting as trial sponsors, much less multiple dominant firms competing in the same therapeutic area (ClinicalTrials.gov 2021).

4 Model Set Up

For a particular disease, there is a mass **N** continuum of patients or 'potential customers' for some treatment. Patients can receive only one of two types of treatments. Patients can also only receive each treatment once. The **drastic (D)** option represents a curative treatment. The

incremental (I) option represents a palliative treatment. The N patients are uniformly distributed along [0,V] in the value they place on the drastic treatment. The patient's value for the incremental treatment is a proportion $\boldsymbol{\alpha \epsilon (0, 1)}$ of their value for the drastic treatment. In terms of product differentiation, the drastic and incremental treatment are vertically differentiated with the drastic treatment perceived as the higher quality good.

The indirect utility patients receive from a treatment is quasi-linear. For a patient with $\boldsymbol{\theta}$ value for the drastic treatment, their utility from purchase of the drastic treatment is $(\boldsymbol{\theta - P_D})$. $\boldsymbol{P_D}$ is the price of the drastic treatment in the market. For a purchase of the incremental treatment, their utility is $(\boldsymbol{\alpha\theta - P_I})$. $\boldsymbol{P_I}$ is the price of the incremental treatment in the market.

A patient is indifferent between a drastic treatment and an incremental treatment when the utility from each treatment is equal to the other.

$$\theta^* - P_D = \alpha\theta^* - P_I$$

$$\theta^* = \frac{P_D - P_I}{(1-\alpha)} \qquad (1)$$

θ^* is the value of the drastic treatment for a patient indifferent between the drastic and incremental treatment given prices P_I and P_D.

A patient is indifferent between the incremental treatment and receiving no treatment when the utility from the incremental treatment is equal to zero. A patient will only choose incremental treatment if utility is greater than zero:

$$\alpha\underline{\theta} - P_I > 0$$

$$\underline{\theta} > \frac{P_I}{\alpha} \tag{2}$$

A patient is indifferent between the drastic treatment and receiving no treatment when the utility from the drastic treatment is equal to zero. A patient will choose drastic treatment if utility is greater than zero:

$$\underline{\theta} - P_D > 0$$

$$\underline{\theta} > P_D \tag{3}$$

The proportion of patients distributed between treatments can be more easily understood graphically.

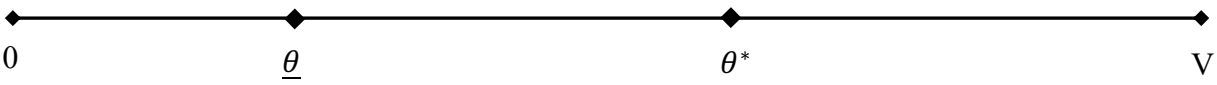

Figure 1. Proportion of patients that choose the drastic treatment, the incremental treatment, or no treatment. Between 0 and $\underline{\theta}$ patients choose no treatment. Between $\underline{\theta}$ and θ^* patients choose incremental treatment. Between θ^* and V patients choose drastic treatment. Indifference points are $\underline{\theta} = \frac{P_I}{\alpha}$ and $\theta^* = \frac{P_D - P_I}{(1-\alpha)}$.

In the market to provide treatment for the disease, an incumbent firm and a potential entrant firm are trying to decide which treatment or combination of treatments they should develop and sell. The firms also face identical, constant marginal costs of production ($\boldsymbol{c}$) for all treatments. Either firm can choose just a drastic or incremental treatment, or both treatments. The development decisions both firms make determines what market structure they operate in. There could be no market if both firms choose not to develop a treatment. There could be a drastic monopoly, or incremental monopoly, if only one firm develops only one treatment. There could be a single product oligopoly, where each firm develops only one treatment. There could be a two-product

oligopoly where one firm develops both treatments, and the other firm only develops one. Both firms could also develop the same treatment or treatments. Here they would be competing directly with each other in Bertrand's Paradox. Where both firms decide to develop identical treatments, and face the same marginal cost, any time a firm tries to charge patients a price above marginal cost the other firm can immediately undercut and take all of the higher priced firm's patients. The incumbent and entrant charge identical prices for the drastic treatment $\boldsymbol{P_D}$ and/or identical prices for the incremental treatment $\boldsymbol{P_I}$. The profits firms face in this case are zero assuming fixed costs are already sunk.

4.1 Drastic Monopoly

If only one firm chooses to provide only the drastic treatment, the market that firm faces is a drastic monopoly. There can be no other firms or other products in the market. The demand each firm would face as a monopoly for the drastic treatment given price (P_D) is:

$$Q_D = \frac{N}{V}\left(V - \underline{\theta}\right) \tag{4}$$

Another way to think about this demand is that $\frac{V-\underline{\theta}}{V}$ is the share of patients that choose to receive the drastic treatment, or the portion of [0,V] where the indirect utility from the drastic treatment is positive. The share of patients choosing the drastic treatment multiplied by the number of patients for the disease gives the demand for drastic.

Assuming research and development costs have already been sunk, the profit the firm faces is:

$$\pi_D = Q_D(P_D - c)$$

To maximize profits, the firm produces quantity ($\boldsymbol{Q_D^*}$) of the drastic treatment where marginal cost equals marginal revenue at price ($\boldsymbol{P_D^*}$).

$$P_D = \left(V - Q_D * \frac{V}{N}\right)$$

$$MR_D = V - 2Q_D * \frac{V}{N}$$

$$MC_D = c$$

$$c = V - 2Q_D * \frac{V}{N}$$

$$Q_D^* = \frac{N}{V}\left(\frac{V - c}{2}\right)$$

$$P_D^* = \left(\frac{V + c}{2}\right)$$

The maximized profit ($\boldsymbol{\pi_D^*}$) for the firm is:

$$\pi_D^* = \left(\frac{N}{V}\right)\frac{(V - c)^2}{2}$$

Importantly, when choosing the drastic treatment, the price, quantity, and profit a firm faces only depend on the value of N, V, and c. As the number of patients with a disease increases, the number of patients receiving treatment and the profit a firm receives increase as well. As the value patients place on treatment increase, the price of treatment and the profit a firm receives increase as well. However, as the cost of providing treatment increases, the price of treatment increases, the number of patients receiving treatment decreases, and the profit a firm receives decreases.

4.2 Incremental Monopoly

Similar to the drastic monopoly, if only one firm develops the incremental treatment, and only the incremental treatment, the firm is in an incremental monopoly. There can be no other firms or treatments in the market. The demand each firm would face as a monopoly for the incremental treatment given price (P_i) is:

$$Q_I = \frac{N}{V}\left(\alpha V - \frac{P_I}{\alpha}\right) \tag{5}$$

Assuming research and development costs have already been sunk, the profit the firm faces is:

$$\pi_I = Q_I(P_I - c)$$

To maximize profits, the firm produces quantity ($\boldsymbol{Q_I^*}$) of the drastic treatment where marginal cost equals marginal revenue at price ($\boldsymbol{P_I^*}$).

$$P_I = \left(\alpha V - \frac{V}{N}\alpha Q_I\right)$$

$$MR_I = \alpha V - 2\frac{V}{N}\alpha Q_I$$

$$MC_I = c$$

$$c = \alpha V - 2\frac{V}{N}\alpha Q_I$$

$$Q_I^* = \frac{N}{V}\left(\frac{\alpha V - c}{2\alpha}\right)$$

$$P_I^* = \left(\frac{\alpha V + c}{2}\right)$$

The maximized profit ($\boldsymbol{\pi_I^*}$) for the firm is:

$$\pi_I^* = \left(\frac{N}{V}\right)\frac{(\alpha V - c)^2}{4\alpha}$$

The same price, quantity, and profit relationships with N, V, and c hold for the incremental treatment option. A firm choosing the incremental treatment is also concerned with the relative value of the incremental compared to drastic treatment when determining price, quantity, and profit. As α increases, so do price, quantity, and profit. As α approaches 1 and the value of the incremental treatment approaches the value of the drastic treatment, price, quantity, and profit for the incremental treatment all approach those of the drastic treatment.

4.3 Two-Product Monopoly

If only one firm developed both treatments, they would be in a two-product monopoly. There are no other firms in the market. Assuming $\{\alpha, V, c\}$ such that $\theta^* > \underline{\theta}$, the demand for the drastic treatment given prices (P_D, P_I) is:

$$Q_D(P_D, P_I) = \begin{cases} 0 & if\ \theta^* > V \\ \frac{N}{V}(V - \theta^*) & if\ \theta^* \epsilon\ (0, V) \\ N & if\ \theta^* < 0 \end{cases} \qquad (6)$$

The demand for the incremental treatment given prices (P_D, P_I) is:

$$Q_I(P_I, P_D) = \begin{cases} 0 & if\ \underline{\theta} \leq 0 \\ \frac{N}{V}\left(\theta^* - \underline{\theta}\right) & if\ \underline{\theta} > 0 \end{cases} \qquad (7)$$

If a firm chooses to develop both the incremental and drastic treatments and assuming research and development costs have already been sunk, their profit is:

$$\pi_{Both} = \pi_D + \pi_I = \ Q_D(P_D - c) + Q_I(P_I - c)$$

The firm maximizes profits where the change in profits with respect to a change in P_d and P_i is zero.

$$\frac{d\pi_{Both}}{dP_D} = \frac{d\pi_D}{dP_D} + \frac{d\pi_I}{dP_D} = 0$$

$$\frac{d\pi_{Both}}{dP_I} = \frac{d\pi_D}{dP_I} + \frac{d\pi_I}{dP_I} = 0$$

Solving the first order conditions above gives a reaction curve for P_D^* that is a function of P_I and a reaction curve for P_I^* that is a function of P_D.

$$P_D^*(P_I) = \left(\frac{V(1-\alpha) + 2P_I}{2}\right)$$

$$P_I^*(P_D) = \left(\frac{2\alpha P_D + c(1-\alpha)}{2}\right)$$

Jointly solving the reaction curves by assuming P_I and P_D respectively gives the profit maximizing prices P_D^* and P_I^*.

$$P_D^* = \frac{V + c}{2}$$

$$P_I^* = \frac{\alpha V + c}{2}$$

The profit maximizing quantity of the drastic treatment for the firm in a two-product monopoly given P_D^* is:

$$Q_D^* = \frac{N}{2}$$

The profit maximizing quantity of the incremental treatment given P_I^* is:

$$Q_I^* = \frac{N}{V}\left(\frac{-c}{2\alpha}\right) = 0 \; where \; \theta^* > \frac{P_I}{\alpha}$$

The maximized profits for each treatment follow, given P_I^* and Q_I^*, P_D^* and Q_D^*:

$$\pi_D^* = \frac{N}{4}(V + c)$$

$$\pi_I^* = \frac{N}{4\alpha V}(c^2 - c\alpha V) = 0 \; where \; \theta^* > \frac{P_I}{\alpha}$$

The total maximized profit is simply the sum of the profits of both treatments:

$$\pi_B^* = \frac{N}{4\alpha V}(c^2 + \alpha V^2) = \frac{NV}{4} \; where \; \theta^* > \frac{P_I}{\alpha}$$

The profit maximizing strategy for a firm that developed both treatments is to set the relative price of the incremental treatment high enough that any patient is indifferent between two treatments and chooses the drastic treatment. No patients receive the incremental treatment, and all patients receive the drastic treatment, regardless of the relative value of the two treatments. The price of the drastic treatment does not change and is equivalent to the drastic monopoly. Only the price of the incremental treatment increases as α approaches 1 to maintain patient indifference between the two treatments. The quantity supplied of the drastic and incremental treatment also do not change with α. As before, the same general price, quantity, and profit relationships with N, V, and c hold for the drastic and incremental treatments. This result is driven by the assumption that marginal cost of production for the two treatments are identical. Intuitively, if a firm has one treatment that is perceived to be strictly greater than the other and marginal costs of production are the same, the firm would only want to sell the superior

treatment. The scope for profitable price discrimination is limited for the monopoly firm in this market. One would need to relax the assumption of identical marginal costs to make splitting the market between the two goods more attractive.

4.4 Single Product Oligopoly

If each firm chooses the one treatment opposite to their rival, the firms are in a single product oligopoly. Each firm faces either demand for drastic (Equation 6) or demand for incremental (Equation 7) depending on the treatment they choose. The firm that chooses the drastic treatment faces profit $\pi_D = Q_D(P_D - c)$ while the firm that chooses the incremental treatment faces profit $\pi_I = Q_I(P_I - c)$.

First order condition for the firm that chose the drastic treatment is $\frac{d\pi_D}{dP_D}\,|_{P_I} = 0$ and the first order condition for the firm that chose the incremental treatment is $\frac{d\pi_I}{dP_I}\,|_{P_D} = 0$.

Solving the first order conditions gives a reaction curve for P_D^* as a function of P_I, and a reaction curve for P_I^* as a function of P_D.

$$P_D^*(P_I) = \left(\frac{V(1-\alpha) + c + P_I}{2}\right)$$

$$P_I^*(P_D) = \left(\frac{\alpha P_D + c}{2}\right)$$

Jointly solving the reaction curves by assuming each firm individually maximizes profit with P_i and P_d gives the profit maximizing prices P_D^* and P_I^*.

$$P_D^* = \frac{2V(1-\alpha) + 3c}{(4-\alpha)}$$

$$P_I^* = \frac{\alpha V(1-\alpha) + \alpha c + 2c}{(4-\alpha)}$$

Profit maximizing quantity and the maximized profit for each treatment follow:

$$Q_D^* = \frac{N}{V}\left(\frac{2V-c}{4-\alpha}\right)$$

$$Q_I^* = \frac{N}{V}\left(\frac{\alpha V - 2c}{\alpha(4-\alpha)}\right)$$

$$\pi_D^* = \frac{N}{V(1-\alpha)(4-\alpha)^2}\left[4V^2 - 8\alpha V^2 + 4\alpha^2 V^2 - 4cV + 8\alpha cV - 4\alpha^2 cV + c^2 - 2\alpha c^2 + \alpha^2 c^2\right]$$

$$\pi_I^* = \frac{N}{\alpha V(1-\alpha)(4-\alpha)^2}\left(\alpha^2 V^2 - 2\alpha^3 V^2 + 8\alpha^2 cV - 4\alpha cV + \alpha^4 V^2 - 4\alpha^3 cV + 4\alpha^2 c^2 - 8\alpha c^2 + 4c^2\right)$$

The drastic treatment always yields greater profits than the incremental treatment. However, the drastic treatment profits decrease as the relative value of the incremental treatment increase. The incremental treatment profits increase until $\alpha = \frac{4}{7}$, then drop as α approaches 1. Similarly, the price of the drastic treatment is always greater than the incremental treatment, the price of the drastic treatment decreases as the relative value of the incremental treatment increases, and the price of the incremental treatment increases until $\alpha = 4 - 2\sqrt{3}$ or ≈ 0.54 then drops as α approaches 1. The number of patients receiving the drastic treatment is always greater than the number of patients receiving the incremental treatment. Interestingly, the number of patients

receiving each treatment increase as the relative value of the incremental treatment approaches that of the drastic treatment. As the two firms compete and the treatments become more similar, firms provide cheaper treatment at greater quantities. As before, the same general price, quantity, and profit relationships with N, V, and c hold for the drastic and incremental treatments.

4.5 Two-Product Oligopoly

If one firm chooses to develop both treatments, and the other only chooses to develop one treatment, the firms are in a two-product oligopoly. The firm that only develops one treatment, faces the same Bertrand's Paradox of price competition outlined in the Model Set Up. Price is equal to the marginal cost and profits are zero. This means the price for the treatment that both firms developed is equal to marginal cost. As such, the firm that developed both treatments does not face profits equivalent to the single product oligopoly because of this.

Note that if both firms choose to develop both treatments, they are competing in Bertrand's paradox for each treatment. In that case, price for the incremental and price for the drastic are both equal to marginal cost. All patients receive the drastic treatment because the treatments are priced the same and the drastic treatment is perceived to be strictly more valuable. Both firms earn no profit.

Where the incremental treatment is the treatment without direct competition, the firm producing both maximizes profit from both treatments given $P_D^* = c$. This gives a reaction curve of:

$$P_I^*(P_D = c) = \frac{2\alpha P_D^* + c(1-\alpha)}{2} = \frac{2\alpha c + c(1-\alpha)}{2}$$

This gives a profit maximizing price P_I^*.

$$P_I^*(P_D = c) = \frac{\alpha c + c}{2}$$

The profit maximizing quantity Q_I^*.

$$Q_I^* = \frac{N}{V}\left(\frac{\alpha c - c}{2\alpha(1-\alpha)}\right) = 0 \; where \; \theta^* > \frac{P_I}{\alpha}$$

The maximized profits given P_I^* and Q_I^* are π_I^*.

$$\pi_I^* = \frac{N}{V}\left(\frac{(\alpha c - c)^2}{4\alpha(1-\alpha)}\right) = 0 \; where \; \theta^* > \frac{P_I}{\alpha}$$

Intuitively, this result makes sense because of the greater perceived value of the drastic treatment. If the drastic treatment is being developed and sold where $P_D^* = c$, no patients would choose the incremental treatment as the incremental treatment would not be sold at a price below c. Profit and quantity go to zero and are strictly less than the single product oligopoly.

Where the drastic treatment is the treatment without direct competition, the firm producing both maximizes profit from both treatments given $P_I^* = c$. This reaction curve of:

$$P_D^*(P_I = c) = \frac{V(1-\alpha) + 2P_I}{2}$$

Gives a profit maximizing price P_D^*.

$$P_D^*(P_I = c) = \frac{V(1-\alpha) + 2c}{2}$$

The profit maximizing quantity Q_D^*.

$$Q_D^* = \frac{N}{2}$$

The maximized profits given P_D^* and Q_D^* are π_D^*.

$$\pi_D^* = \frac{NV(1-\alpha)}{4}$$

Profits from the drastic treatment in a two-product oligopoly are strictly less than the profits from the drastic treatment in a single product oligopoly. The intuition underlying this difference in profit between the single and two-product oligopolies is the lower price for the alternate treatment. The demand for the drastic treatment is more price elastic because of this lower price for the substitute treatment.

5 Results

From a social perspective, investment in a treatment should occur where the total surplus generated by a treatment is greater than the fixed cost required to develop it. With only one product, total surplus is the area beneath the demand curve above the marginal cost of production.

$$\int_c^V (x-c)\,dx \;\; where\; x = demand\; curve$$

For the drastic treatment this gives total surplus of $\frac{(V-c)^2}{2}$. For the incremental treatment, this gives total surplus of $\frac{\alpha\left(V-\frac{c}{\alpha}\right)^2}{2}$. For reasonable values of α, V, c:

$$\frac{(V-c)^2}{2} > \frac{\alpha\left(V-\frac{c}{\alpha}\right)^2}{2}$$

The socially efficient outcome is for the only the drastic treatment to be developed and sold at the marginal cost of production. All surplus in this case goes to the consumer and none goes to the producer, with total surplus maximized where price is equal to marginal cost. Having two treatments is not efficient because the drastic is perceived to be strictly better than the incremental *and* because they are assumed to have identical marginal costs of production. It could only make sense for the incremental treatment to be developed if it had a lower marginal cost. Underinvestment from the social perspective happens if the drastic treatment does not get developed. No treatment, or only the incremental treatment being developed fall into this category. Interestingly, the market could also overinvest in treatment if a firm develops both the incremental and drastic.

From a private perspective, investment in treatment should occur where producer surplus from a treatment is greater than the fixed cost required to develop it. As producer surplus is a sum of all firms, a firm profit maximizing and providing a single treatment is not necessarily privately efficient. There can still be a transfer of surplus from one firm to a rival if the rival enters with the opposite treatment and both firms yield positive profits. Whether the drastic or the incremental treatment are preferred depends on the size of the fixed cost associated with each treatment. The fixed cost to develop the incremental treatment must be lower than the fixed cost of the drastic for it to be the preferred option. However, the market can supply both treatments if the single product oligopoly profits are large enough for each firm to outweigh fixed costs. Underinvestment from a private perspective happens if a treatment has positive net surplus but firms do not develop the treatment.

The profit from each market structure type and treatment type help inform the preferred strategy for each firm in the payoff matrix for treatment development. Let us assume for now that the incumbent firm's existing intellectual property is expiring or has expired so that if it chooses not to develop any treatment it earns no profit. This is the case if there is sufficient generic competition after expiration. The payoff matrix without research and development costs is as follows:

		Entrant			
		Nothing	Incremental	Drastic	Incremental + Drastic
Incumbent	Nothing	$(0,\ 0)$	$(0, \pi_I^M)$	$(0, \pi_D^M)$	$(0,\ \pi_{Both}^M)$
	Incremental	$(\pi_I^M, 0)$	$(0,\ 0)$	$(\pi_I^O,\ \pi_D^O)$	$(0,\ \pi_B^{IID},)$
	Drastic	$(\pi_D^M, 0)$	(π_D^O, π_I^O)	$(0,\ 0)$	$(0, \pi_B^{IDD})$
	Incremental + Drastic	$(\pi_{Both}^M, 0)$	$(\pi_B^{IID}, 0)$	$(\pi_B^{IDD}, 0)$	$(0,\ 0)$

Table 1. Payoff matrix for an incumbent and entrant firm facing investment options in a drastic treatment, incremental treatment, both treatments, or no investment. Payoff matrix does not include fixed cost for developing treatments.

Let $\boldsymbol{\pi_I^M}$ be the profits from the incremental treatment in a monopoly. Let $\boldsymbol{\pi_D^M}$ be the profits from the drastic treatment in a monopoly. Let $\boldsymbol{\pi_{Both}^M}$ be the profits from the two-product monopoly. Let $\boldsymbol{\pi_I^O}$ and $\boldsymbol{\pi_D^O}$ be the profits from the incremental treatment and drastic treatment in a single oligopoly. Let $\boldsymbol{\pi_B^{IID}}$ be the profits from the drastic treatment in the two-product oligopoly. Let $\boldsymbol{\pi_B^{IDD}}$ be the profits from the incremental treatment in the two-product oligopoly. Without considering fixed costs, a firm will always prefer to be in a monopoly for the drastic treatment over a monopoly for the incremental treatment as $\boldsymbol{\pi_D^M} > \boldsymbol{\pi_I^M}$, $P_D > P_I$, $Q_D > Q_I$ for all α. A firm

is indifferent between a monopoly for the drastic treatment and a 2-product monopoly as $\pi_D^M = \pi_B^M$. In a single product oligopoly, a firm will always prefer to be the drastic option as $\boldsymbol{\pi_D^O > \pi_I^O}$ for all α. A firm will always prefer to be in the single product oligopoly over the two-product oligopoly for the drastic and incremental treatment as $\boldsymbol{\pi_D^O > \pi_B^{IID}}$ and $\boldsymbol{\pi_I^O > \pi_B^{IDD}}$ for all α. The price of the substitute treatment when it is developed by only one firm is larger than marginal cost of production. However, when the substitute is developed by both firms, they compete and undercut each other until the price is equal to marginal cost of production. The lower price of the substitute treatment in a two-product oligopoly hinders the profitability relative to the single product oligopoly.

Using the payoff matrix and relative profit values, the incumbent's best response strategy given some conjecture of the entrant's choice can be calculated. The same response strategies hold for the entrant in this baseline case, but the primary subject of interest is the behavior of the incumbent.

$$Best\ Response\ (conjecture, Nothing) = BR(Nothing) = \{Drastic\ or\ Both\}\ as\ \pi_D^M$$
$$= \pi_B^M > \pi_I^M > 0$$
$$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O > \pi_B^{IID} > 0$$
$$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O > \pi_B^{IDD} > 0$$
$$BR(Both) = \{Nothing\ or\ Incremental\ or\ Drastic\ or\ Both\}\ as\ all\ payoffs = 0$$

Note that from these best response strategies, four pure Nash equilibria can be found. If the incumbent chooses both because it expects the entrant to choose nothing, the entrant will choose nothing. This is a pure Nash equilibrium and applies for the case where the incumbent chooses

nothing as well. If the incumbent chooses drastic because it expects the entrant to choose incremental, the entrant will choose incremental. This is a pure Nash equilibrium and applies for the case where the incumbent chooses incremental as well.

Thus, if one firm supplies both treatments, the other firm supplies nothing, and vice versa. If one firm supplies the drastic treatment, the other firm supplies the incremental, and vice versa. Without fixed costs, both treatments are supplied. The distribution of surplus between incumbent and entrant firms differs across the equilibria. The distribution of surplus between firms and patients also differs across the equilibria. However, in all cases, equilibrium firm strategies result in both treatments being developed. This result aligns with prevailing market wisdom that competition induces both treatments to be developed.

There is no private underinvestment. The surplus from each treatment is greater than their development costs and both treatments are developed in each of the Nash equilibria. However, one firm developing both is less efficient from a social perspective than each firm choosing a different treatment to develop because the competition between firms drives the price of the drastic treatment closer to the marginal cost of production. This is also reflected in the higher number of patients treated in the single product oligopoly compared to the two-product monopoly.

5.1 With Identical Fixed Costs

Suppose instead firms face common research and development costs for the each of the treatments, drastic ($\boldsymbol{FC_D}$) and the incremental ($\boldsymbol{FC_I}$). These fixed costs play two roles in the model. First, they model the capital-intensive nature of research and development. Funding

clinical trials or purchasing external intellectual property can have significant costs. Second, the size of fixed costs can be used to incorporate the unpredictable nature of research and development. If a particular type of treatment is 'harder' or 'riskier' to develop, a firm could leverage more capital to fund additional clinical trials to achieve developmental success*. A firm looking to develop the 'hard' treatment anticipates this larger fixed cost in its preferred strategies. The payoff matrix with research and development costs is as follows:

		Entrant			
		Nothing	Incremental	Drastic	Incremental + Drastic
Incumbent	Nothing	$(0, 0)$	$(0, \pi_I^M - FC_I)$	$(0, \pi_D^M - FC_D)$	$(0,\ \pi_{Both}^M - (FC_I + FC_D))$
	Incremental	$(\pi_I^M - FC_I, 0)$	$(-FC_I,\ -FC_I)$	$(\pi_I^O - FC_I,\ \pi_D^O - FC_D)$	$(-FC_I,\ \pi_B^{IID} - (FC_I + FC_D))$
	Drastic	$(\pi_D^M - FC_D, 0)$	$(\pi_D^O - FC_D,\ \pi_I^O - FC_I))$	$(-FC_D,\ \ -FC_D)$	$(-FC_D, , \pi_B^{IDD} - (FC_I + FC_D))$
	Incremental + Drastic	$(\pi_{Both}^M - (FC_I + FC_D), 0)$	$(\pi_B^{IID} - (FC_I + FC_D), -FC_I)$	$(\pi_B^{IDD} - (FC_I + FC_D), -FC_D,)$	$(-(FC_I + FC_I),\ -(FC_I + FC_D))$

Table 2. Payoff matrix for an incumbent and entrant firm facing investment options in a drastic treatment, incremental treatment, both treatments, or no investment. Payoff matrix includes fixed cost for developing treatments.

*This abstracts away some of the complexity of uncertainty in investment, which is explored in (Reinganum 1983) and (Gilbert & Newbery 1982).

The relative size of the fixed cost difference between developing each treatment can change the best response strategies for each firm.

A firm would only choose to develop a drastic or incremental treatment if the fixed cost to develop the treatment is less than the producer surplus they receive from the market. If the surplus the firm extracts from the market in any scenario is enough to offset the fixed costs of development. For a drastic treatment, in monopoly $\pi_D^M - FC_D > 0$ for investment to occur and in a single product oligopoly $\pi_D^O - FC_D > 0$ for investment to occur. For an incremental treatment, in monopoly $\pi_I^M - FC_I > 0$ for investment to occur and in a single product oligopoly $\pi_I^O - FC_I > 0$ for investment to occur.

If the fixed cost to develop a treatment is greater than the surplus firms receive, they will not develop the treatment, and in the case of the entrant, will not enter. The Nash equilibrium is for both firms to develop no treatments.

Assuming $FC_D > 0$ and $FC_I > 0$, a firm would always prefer to be in a drastic monopoly over a 2-product monopoly as $\pi_D^M = \pi_B^M$ and $\pi_D^M - FC_D > \pi_B^M - FC_D - FC_I$.The best response strategies for the incumbent given some conjecture of the entrant's choice can be calculated. These best response strategies hold for the entrant.

$$BR(Nothing) = \left\{Incremental \frac{and}{or} Drastic \frac{and}{or} Nothing\right\} \text{ depending on whether } \pi_I^M - FC_I \text{ and } \pi_D^M - FC_D \text{ are both positive and which value is greater}$$

$$BR(Incremental) = \left\{Drastic \frac{and}{or} Nothing\right\} \text{ depending on whether } \pi_D^O - FC_D \text{ is positive}$$

$$BR(Drastic) = \left\{Incremental \frac{and}{or} \ Nothing\right\} \ depending \ on \ whether \ is \ \pi_I^O - FC_I \ positive$$

$$BR(Both) = \{Nothing\} \ as \ all \ other \ payoffs \ are \ negative$$

The importance of the relative size of fixed costs is that they can render the surplus from oligopoly treatments negative while still producing positive surplus from monopoly treatments. The cases of particular interest for understanding underinvestment compared to the general case are those dependent on (a) the relative value of the two treatments in monopoly where are each treatment yields positive profits and one is greater than the other, (b) whether drastic profits from a single product oligopoly are greater than zero, and (c) whether incremental profits from a single product oligopoly are greater than zero.

Where the drastic treatment is greater in (a), and (b) and (c) are negative, the best response strategies are:

$$BR(Nothing) = \{Drastic\} \ as \ \pi_D^M - FC_D > \ \pi_I^M - FC_I > 0$$

$$BR(Incremental) = \ \{Nothing\} \ as \ 0 > \pi_D^O - FC_D > \ \pi_B^{IID} - (FC_I + FC_D)$$

$$BR(Drastic) = \{Nothing\} \ as \ 0 > \pi_I^O - FC_I > \ \pi_B^{IDD} - (FC_I + FC_D)$$

$$BR(Both) = \{Nothing\} \ as \ all \ other \ payoffs \ are \ negative$$

The pure Nash equilibrium here is for one firm to choose the drastic treatment and the other to do nothing. From a private perspective, this could be considered underinvestment if developing both treatments in monopoly yields positive net surplus.

Where the drastic treatment is greater in (a), (b) is positive and (c) is negative, the best response strategies are:

$$BR(Nothing) = \{Drastic\} \ as \ \pi_D^M - FC_D > \ \pi_I^M - FC_I > 0$$

$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)\ and\ \pi_D^O - FC_D > 0$

$BR(Drastic) = \{Nothing\}\ as\ 0 > \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure Nash equilibrium here is for one firm to choose the drastic treatment and the other to do nothing. This produces the same private underinvestment as above.

Where the drastic treatment is greater in (a), (b) and (c) are positive, the best response strategies are:

$BR(Nothing) = \{Drastic\}\ as\ \pi_D^M - FC_D > \pi_I^M - FC_I > 0$

$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)\ and\ \pi_D^O - FC_D > 0$

$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)\ and\ \pi_I^O - FC_I > 0$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure Nash equilibria are for one firm to choose the drastic and the rival firm to choose the incremental, and vice versa. There is no underinvestment here as each treatment yields positive net surplus and both are developed. This result is also closer to social efficiency.

Where the incremental treatment is greater in (a), and (b) and (c) are negative, the best response strategies are:

$BR(Nothing) = \{Incremental\}\ as\ \pi_I^M - FC_I > \pi_B^M - (FC_I + FC_D), \pi_D^M - FC_D > 0$

$BR(Incremental) = \{Nothing\}\ as\ 0 > \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Nothing\}\ as\ 0 > \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure Nash equilibrium here is for one firm to choose the incremental treatment and the other to do nothing. From a private perspective, this could be considered underinvestment where developing both treatments in monopoly yields positive net surplus.

Where the incremental treatment is greater in (a), (b) is negative and (c) is positive, the best response strategies are:

$BR(Nothing) = \{Incremental\}\ as\ \pi_I^M - FC_I > \pi_B^M - (FC_I + FC_D), \pi_D^M - FC_D > 0$

$BR(Incremental) = \{Nothing\}\ as\ 0 > \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)\ and\ \pi_I^O - FC_I > 0$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure Nash equilibrium here is for one firm to choose the incremental treatment and the other to do nothing. This produces the same private underinvestment as above.

The previous two cases are critical when considering social efficiency because they demonstrate how only the lesser of the two treatment gets developed despite the better one being viable in the market. A social planner would want to develop only the drastic treatment, but instead the market develops only the incremental.

Where the incremental treatment is greater in (a), (b) and (c) are positive, the best response strategies are:

$BR(Nothing) = \{Incremental\}\ as\ \pi_I^M - FC_I > \pi_B^M - (FC_I + FC_D), \pi_D^M - FC_D > 0$

$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)\ and\ \pi_D^O - FC_D > 0$

$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)\ and\ \pi_I^O - FC_I > 0$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure Nash equilibria are for one firm to choose the drastic and the rival firm to choose the incremental, and vice versa. There is no underinvestment here as each treatment yields positive net surplus and both are developed.

In summary, the key insight from adding identical fixed costs is that underinvestment can occur where fixed costs are sufficiently large enough to render the single product oligopoly profits from treatment negative such that the preferred strategy of firms does not face the threat of competition. The fixed costs shift the Nash equilibria away from having both treatments developed in the baseline case to only developing one. If fixed costs are not sufficiently large to render single product oligopoly profits negative, the firms each choose a different treatment like in the general case. There is no underinvestment, and the market is closer to social efficiency than the monopoly cases. Additionally, fixed costs can explain general lack of investment by firms for treatment. If developing either treatment is rendered unprofitable by the fixed costs, and does not occur, there is no private underinvestment.

5.2 In a Sequential Game

Changing the simultaneous game to a sequential game adds nuance to firms underinvesting in treatments. Rather than the potential entrant and incumbent firm making the decision to invest in treatment at the same time, a sequential game allows a first mover to restrict payoffs for the follower. In the real world where firms are not restricted to single shot games, this is more representative of how investment decisions work. In addition to new drugs brought to market,

rival firms can observe the investment decisions of other firms through the clinical trials they are funding.

The sequential game does not change the Nash equilibria for the cases where the net surplus for each treatment is negative, or for where only one treatment has positive producer surplus. Where each treatment yields negative surplus for the firm, the pure Nash equilibrium is for both firms to choose no treatment. Where only the incremental treatment in monopoly yields positive producer surplus, the Nash equilibria is for one firm to develop the incremental treatment and for the other to do nothing. The same is true if the drastic treatment in monopoly is the treatment with positive producer surplus. The difference between the simultaneous and sequential game is the distribution of surplus between firms. The first mover can develop a treatment, prevent the rival firm from entering, and receive monopoly profits.

Underinvestment in the simultaneous model still holds, with additional cases of interest where preempting can change the best responses for firms. This is where firm profits in a single product oligopoly are sufficient to induce competition from the follower.

Suppose the value of FC_I and FC_D are such that $\pi_D^O - FC_D > 0 > \pi_I^O - FC_I$:

$BR(Nothing) = \{Drastic\}\ as\ \pi_D^M - FC_D > \pi_B^M - (FC_I + FC_D), \pi_I^M - FC_I > 0$

$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)\ and\ \pi_D^O - FC_D > 0$

$BR(Drastic) = \{Nothing\}\ as\ 0 > \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure strategy equilibrium here is for only one firm to develop the drastic treatment and for the other firm to do nothing. The first moving firm preempts the following firm, ensuring a drastic monopoly for itself. This can produce private underinvestment if developing both treatments gives positive producer surplus.

Suppose the value of FC_I and FC_D are such that $\pi_D^O - FC_D < 0 < \pi_I^O - FC_I$:

$BR(Nothing) = \{Incremental\}\ as\ \pi_I^M - FC_I > \pi_B^M - (FC_I + FC_D), \pi_D^M - FC_D > 0$

$BR(Incremental) = \{Nothing\}\ as\ 0 > \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D) > 0$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The pure strategy equilibrium here is for one firm to develop the incremental and for the other firm to do nothing. This result means there can be private underinvestment as above, but social underinvestment as well if the producer surplus to producing the drastic treatment in monopoly is positive.

Suppose the value of FC_I and FC_D are such that $\pi_D^O - FC_D > \pi_I^O - FC_I > 0$:

$BR(Nothing) = \{Drastic\}\ as\ \pi_D^M - FC_D > \pi_B^M - (FC_I + FC_D), \pi_I^M - FC_I > 0$

$BR(Incremental) = \{Drastic\}\ as\ \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)\ and\ \pi_D^O - FC_D > 0$

$BR(Drastic) = \{Incremental\}\ as\ 0 > \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

The preferred strategy for the first mover is to develop only the drastic treatment. However, the producer surplus from the incremental treatment in a single product oligopoly is positive, which means the follower will enter and push the monopoly profits to oligopoly profits. The first

moving firm would prefer to preempt this and produce both treatments in its first action if the additional cost to develop the incremental treatment is less than the loss of profit moving from drastic monopoly to drastic oligopoly.

$$\mathrm{FC_I} < \pi_{\mathrm{D}}^{\mathrm{M}} - \pi_{\mathrm{D}}^{\mathrm{O}}$$

If the fixed cost is higher than the loss of profit, the first moving firm chooses drastic, the follower produces incremental, and the market is in an oligopoly.

While traditionally having a two-product monopoly is advantageous for a firm as it allows them to price discriminate, in this model it instead serves as an investment to ensure monopoly power for the firm by preventing competition. The reason this preempting works in the sequential game and does not in the simultaneous game is because firms are making their threat of preemption concrete and credible.

As a critical final point, suppose the value of FC_I and FC_D are such that $\pi_D^M - FC_D > \pi_I^M - FC_I > \pi_I^O - FC_I > 0 > \pi_D^O - FC_D$:

$BR(Nothing) = \{Drastic\}\ as\ \pi_D^M - FC_D > \pi_B^M - (FC_I + FC_D), \pi_I^M - FC_I > 0$

$BR(Incremental) = \{Nothing\}\ as\ 0 > \pi_D^O - FC_D > \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Incremental\}\ as\ \pi_I^O - FC_I > \pi_B^{IDD} - (FC_I + FC_D)\ and\ \pi_I^O - FC_I > 0$

$BR(Both) = \{Nothing\}\ as\ all\ other\ payoffs\ are\ negative$

This case shows one of the worst-case scenarios for private and social underinvestment. Once again, the first mover would prefer to choose the drastic, but must worry about the follower entering and developing the incremental treatment. The first mover in this scenario has two

options for preempting. The first mover can decide to choose just the incremental treatment or develop both treatments. The preemption with both treatments is shown above. If the surplus the firm receives less fixed cost of development is greater than the drastic single product oligopoly *and* the two-product monopoly, the firm chooses that option. This is both a privately and socially inefficient outcome because a single 'worse' treatment can preempt other firms from entering. Moving to a sequential game adds new potential for private underinvestment from the simultaneous game and changes the distribution of treatments and where surplus is allocated in the market. Ultimately this affects social efficiency. Where previously in the simultaneous game firms might split treatment, the first mover can now preempt and develop one or both treatments to prevent rival firms from entering. If this is the case, private underinvestment can occur and moving away from a single product oligopoly brings the market further away from social efficiency. An incumbent could realistically move first due to sunk cost advantages, which makes the critical single product preemption a very real possibility.

5.3 Fixed Cost Differences Between Firms

Another story can be told if the fixed costs for a particular treatment vary between firms. An incumbent firm could have economies of scale in developing treatments or possess existing intellectual property that makes development cheaper. One potential example of this is if an incumbent firm does not have to worry about potential litigation costs because they own the IP where the entrant does or have a partnership with a public research institution that discovered a new chemical entity, mechanism, application.

The underinvestment shown in each step previously still hold. Now, the between firm difference in fixed costs adds even more possibility for the incumbent to underinvest as there is a chance that they need not to worry about competition.

As an example, suppose the value of FC_I and FC_D are such that $\pi_I^M - FC_I > \pi_D^M - FC_D > \pi_I^O - FC_I > 0 > \pi_D^O - FC_D$ for the incumbent but $0 > \pi_I^O - FC_I \; and \; 0 > \; \pi_D^O - FC_D$ for the entrant. The best responses for the incumbent are:

$BR(Nothing) = \{Incremental\} \; as \; \pi_I^M - FC_I > \; \pi_D^M - FC_D > 0$

$BR(Incremental) = \; \{Nothing\} \; as \; 0 > \pi_D^O - FC_D > \; \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Incremental\} \; as \; \pi_I^O - FC_I > \; \pi_B^{IDD} - (FC_I + FC_D) \; and \; \pi_I^O - FC_I > \; 0$

$BR(Both) = \{Nothing\} \; as \; all \; other \; payoffs \; are \; negative$

The best responses for the entrant are:

$BR(Nothing) = \{Incremental\} \; as \; \pi_I^M - FC_I > \; \pi_D^M - FC_D > 0$

$BR(Incremental) = \; \{Nothing\} \; as \; 0 > \pi_D^O - FC_D > \; \pi_B^{IID} - (FC_I + FC_D)$

$BR(Drastic) = \{Nothing\} \; as \; 0 > \pi_I^O - FC_I > \; \pi_B^{IDD} - (FC_I + FC_D)$

$BR(Both) = \{Nothing\} \; as \; all \; other \; payoffs \; are \; negative$

The pure Nash equilibria are for one firm to develop the incremental treatment and for the other firm to do nothing. In the sequential game, the incumbent will preempt and develop the incremental. This is private and social underinvestment on the part of the first moving firm because developing the drastic treatment and both treatments could still produce positive net surplus *for either firm* but does not occur. The first moving firm faces no threat of replacement or competition and does not need to develop both treatments.

Different fixed costs between firms also makes it so that the game does not need to be sequential for the incumbent to underinvest. If the other firm faces negative producer surplus from producing treatment in monopoly, the incumbent firm can simply do nothing or choose its maximized treatment without worrying about competition.

5.4 With an Existing Treatment

Now let us assume that the incumbent firm already has existing intellectual property because they developed the incremental treatment. We can treat this as if the firm chose to invest in the incremental option earlier, and now the sequential game is taking place in the middle of the incremental patent life. This means that the entrant would only be able to enter an oligopoly and never earn monopoly profits, and that the incumbent can't have pure monopoly profits for the drastic treatment.

		Entrant			
		Nothing	Incremental	Drastic	Incremental + Drastic
Incumbent	Existing Incremental Treatment	$(\pi_I^M, 0)$	$(0, -FC_I)$	$(\pi_I^O, \pi_D^O - FC_D)$	$(0, \pi_B^{IID} - (FC_I + FC_D))$
	Existing Incremental + Drastic	$(\pi_{Both}^M - FC_D, 0)$	$(\pi_B^{IID} - FC_D, -FC_i)$	$(\pi_B^{IDD} - FC_D, -FC_D)$	$(-FC_D, -(FC_I + FC_D))$

Table 3. Payoff matrix for an incumbent and entrant firm facing investment options where the incumbent has already developed an incremental treatment. Entrant can choose a drastic treatment, incremental treatment, both treatments, and no investment while the incumbent can choose an additional, drastic, treatment or nothing. Payoff matrix includes fixed cost for developing treatments.

If the "nothing" option where the incumbent firm does not invest in an additional drastic treatment yields the largest net surplus, the incumbent would prefer to remain there. However, the entrant will enter if the single product oligopoly profits from the drastic treatment are positive. Once more, the incumbent will preempt this if the loss of profit moving from the incremental monopoly to the incremental single product oligopoly is greater than the fixed cost of developing the drastic treatment.

$$\pi_{Both}^{M} - FC_D < 0 - \pi_I^M$$

If $\pi_D^O - FC_D < 0$ for the entrant, the incumbent has no need of preempting and can simply rely on its existing treatment.

Compared to the case where the incumbent does not have an existing treatment, this iteration of the model shows how firms have even less incentive to develop treatment when they already have a treatment in the market. Applied to the case where the incumbent firm already has an existing incremental treatment, the potential for underinvestment is still the same, but the observed behavior of the firm does change. Now, the firm can decide to do nothing if they face no threat of preemption, instead of having to develop at least one treatment. An easier way to think of this is that incumbent firms will be strategic in the timing of their treatment development and wait until their existing patents end before bringing new treatments to market.

6 Discussion

I have shown that in a baseline case without fixed costs, competition leads to the development of both a drastic and an incremental treatment, without underinvestment and potentially

approaching social efficiency. However, fixed costs, preemption in a sequential game, and differences in fixed costs together and separately derail those equilibria and allow firms to underinvest.

To prevent this underinvestment and reach a socially efficient outcome, the government can intervene in several ways. First, if the government and private firms had the same information about what research and development of new treatments required, the government could simply produce the drastic treatment themselves and give it to patients at the marginal cost of production to reach social efficiency. If the producer surplus for a private firm doing so would be positive, research and development costs for the government should be covered by taxes. The government would only need to produce the drastic treatment because it is perceived to be strictly better than the incremental option, the two treatments have identical marginal costs of production, and consumers can only be treated once. The government may choose to develop the incremental treatment, both treatments, or no treatments at all instead if the fixed cost of developing treatment are so great that it would be undesirable and inefficient.

However, firms may not have the same information that private firms do about what research opportunities are available, and the fixed cost required to develop them. Without an easy way to access the information firms have, social efficiency could represent an unrealistic first best goal.

For more feasible policy, the government could opt for a second option to reach private efficiency with an eye to social efficiency in the distribution of that private efficiency. Here, firms only develop treatment if the producer surplus they earn outweighs fixed costs of

development. The government instead should concern itself with whether the profits firms earn from the market outweigh fixed costs of development.

To resist underinvestment caused by fixed costs, preemption, and between firm differences and reach full private investment, the government should intervene by subsidizing fixed costs for developing treatments where a single firm can choose only one treatment to preempt other firms from entering the market. This induces firms to either choose both treatments or split the market with the entrant. When splitting the market, the drastic treatment does not have to make the incremental treatment useless from a private perspective because the firm that develops the incremental can extract some surplus from the drastic firm. Patients also benefit, and the market moves closer to social efficiency with this competition as prices for both treatments are held down, more patients can afford to and do get treated. If instead, one firm develops both treatments to protect its monopoly power, the government can step in and set price controls or take other antitrust actions to prevent the monopolist from pricing all incremental treatment out of the market.

7 Conclusion

Where the Orphan Drug Act and associated literature deals primarily with the issue of investment in research where fixed costs for all treatments are too large, my thesis shows primarily that a few simple assumptions can produce underinvestment in pharmaceutical research in development.

My work does not account for the possibility of collusion between firms as a contributing factor to underinvestment. The recommendation for government subsidies to increase the threat of competition indirectly addresses the possibility of collusion. Subsidies could make collusion no longer profit maximizing and push a firm on the margin into competition.

My work addresses a combination of social and private efficiency, and it is worth acknowledging a government may prefer to concern itself with only or primarily social efficiency. In a similar vein, my work does not suggest an avenue for patients who cannot afford treatment in the marketplace at or below oligopoly prices to receive care. Implied in the model is that expanding the patient pool for a treatment increases the N number of patients and potential profits firms can earn from developing treatment. Thus, expanding patients access to health insurance could have a twofold effect of addressing the shortcomings of access to care and improving the payoff of developing treatments in the market.

8 References

"7 Deadly Diseases the World Has (Almost) Eradicated." n.d. World Economic Forum. Accessed August 3, 2021. https://www.weforum.org/agenda/2017/05/7-deadly-diseases-the-world-has-almost-eradicated/.

Aghion, Philippe, and Jean Tirole. 1994. "The Management of Innovation." *Quarterly Journal of Economics* 109 (4): 1185–1209.

Arrow, Kenneth J. 1962. "Economic Welfare and the Allocation of Resources for Invention," 19.

Baker, Jonathan B. 2007. "Beyond Schumpeter vs. Arrow: How Antitrust Fosters Innovation." *Antitrust Law Journal* 74 (June): 35. https://doi.org/10.2139/ssrn.962261.

Berndt, Ernst R. 2002. "Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price." *Journal of Economic Perspectives* 16 (4): 45–66. https://doi.org/10.1257/089533002320950975.

Besanko, David, David Dranove, and Craig Garthwaite. 2016. "Insurance and the High Prices of Pharmaceuticals." https://www.nber.org/papers/w22353.

Brumley, James. 2017. "The 15 All-Time Best-Selling Prescription Drugs | Kiplinger." December 5, 2017. https://www.kiplinger.com/slideshow/investing/t027-s001-the-15-all-time-best-selling-prescription-drugs/index.html.

Carroll, Melissa. 2018. "Hepatitis C: The Evolution of Treatments." Healthline. March 9, 2018. https://www.healthline.com/health/hepatitis-c/evolution-of-treatments.

Chesbrough, H. 2002. "The Role of the Business Model in Capturing Value from Innovation: Evidence from Xerox Corporation's Technology Spin-off Companies." *Industrial and Corporate Change* 11 (3): 529–55. https://doi.org/10.1093/icc/11.3.529.

Chopra, Sameer S. 2003. "Industry Funding of Clinical Trials: Benefit or Bias?" *JAMA* 290 (1): 113. https://doi.org/10.1001/jama.290.1.113.

Contributor, Guest. n.d. "Finding Cures for Incurable Diseases." Accessed June 23, 2021. https://catalyst.phrma.org/finding-cures-for-incurable-diseases.

Del Deo, Adam, Yon Motskin, Lisa Nishimura, Stacey Offman, Jason Spingam-Koff, and Alex Gibney. 2018. *Dirty Money: Drug Short*. Documentary. Netflix. https://www.netflix.com/watch/80149535?trackId=200257859.

DiMasi, Joseph A. 2000. "New Drug Innovation and Pharmaceutical Industry Structure: Trends in the Output of Pharmaceutical Firms." *Drug Information Journal* 34 (4): 1169–94. https://doi.org/10.1177/009286150003400425.

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

"Exploring Companies' Manipulation of Pharma Patents." n.d. Accessed October 15, 2021. https://www.pharmaceutical-technology.com/features/pharma-patents-manpulation/.

"Federal Investment in Higher Education | U.S. Treasury Data Lab." 2019. 2019. https://datalab.usaspending.gov/colleges-and-universities/.

Fernald, K. D. S., H. P. G. Pennings, J. F. van den Bosch, H. R. Commandeur, and E. Claassen. 2017. "The Moderating Role of Absorptive Capacity and the Differential Effects of Acquisitions and Alliances on Big Pharma Firms' Innovation Performance." *PLOS ONE* 12 (2): e0172488. https://doi.org/10.1371/journal.pone.0172488.

"Formulary Management.Pdf." n.d. Accessed September 2, 2021. https://amcp.org/sites/default/files/2019-03/Formulary%20Management.pdf.

Garattini, Livio, and Anna Padula. 2018. "Pharmaceutical Pricing Conundrum: Time to Get Rid of It?" *European Journal of Health Economics* 19 (8): 1035–38.

Garthwaite, Craig. 2018. "The Economics of Drug Development: Pricing and Innovation in a Changing Market." *NBER Reporter* 2018 (3): 19.

Gebrekidan, Selam, and Matt Apuzzo. 2021. "Rich Countries Signed Away a Chance to Vaccinate the World." *The New York Times*, March 21, 2021, sec. World. https://www.nytimes.com/2021/03/21/world/vaccine-patents-us-eu.html.

Gilbert, Richard, and David Newbery. 1982. "Preemptive Patenting and the Persistence of Monopoly." *The American Economic Review* 72 (3): 514–26.

Glied, Sherry. 2003. "Health Care Costs: On the Rise Again." *Journal of Economic Perspectives* 17 (2): 125. https://doi.org/10.1257/089533003765888476.

Grabowski, Henry G., Joseph A. DiMasi, and Genia Long. 2015. "The Roles Of Patents And Research And Development Incentives In Biopharmaceutical Innovation." *HEALTH AFFAIRS* 34 (2): 302–10. https://doi.org/10.1377/hlthaff.2014.1047.

Gupta, Himanshu, Suresh Kumar, Saroj Kumar Roy, and R. S. Gaud. 2010. "Patent Protection Strategies." *Journal of Pharmacy and Bioallied Sciences* 2 (1): 2–7. https://doi.org/10.4103/0975-7406.62694.

Hagan, Allison. 2018. "Protesters at Sanofi in Cambridge Decry High Price of Insulin." Boston Globe. November 16, 2018. https://www.bostonglobe.com/business/2018/11/16/protesters-sanofi-cambridge-decry-high-price-insulin/MeEajamQHARWqDTQKXqPVL/story.html.

"Health Resources - Pharmaceutical Spending - OECD Data." 2019. OECD. 2019. http://data.oecd.org/healthres/pharmaceutical-spending.htm.

Hemphill, Thomas A. 2003. "Preemptive Patenting, Human Genomics, and the US Biotechnology Sector: Balancing Intellectual Property Rights with Societal Welfare." *Technology in Society* 25 (3): 337–49. https://doi.org/10.1016/S0160-791X(03)00050-2.

Higgins-Dunn, Noah. 2021. "The Top 15 Blockbuster Patent Expirations Coming This Decade." July 12, 2021. https://www.fiercepharma.com/special-report/top-15-blockbuster-patent-expirations-coming-decade.

Hofker, Marten, Jingyuan Fu, and Cisca Wijmenga. 2014. "The Genome Revolution and Its Role in Understanding Complex Diseases - ScienceDirect," October. https://www.sciencedirect.com/science/article/pii/S0925443914001306.

Hopkins, Michael M., Paul A. Martin, Paul Nightingale, Alison Kraft, and Surya Mahdi. 2007. "The Myth of the Biotech Revolution: An Assessment of Technological, Clinical and Organisational Change." *Research Policy*, Biotechnology: Its origins, organization, and outputs, 36 (4): 566–89. https://doi.org/10.1016/j.respol.2007.02.013.

Hoskins, Mike. 2016. "Historic Look at Insulin Prices and Access | DiabetesMine." Healthline. September 28, 2016. https://www.healthline.com/diabetesmine/history-of-insulin-costs.

"How Drug Life-Cycle Management Patent Strategies May Impact Formulary Management." n.d. AJMC. Accessed August 29, 2021. https://www.ajmc.com/view/a636-article.

Iglehart, Jk. 2001. "America's Love Affair with Medical Innovation." *HEALTH AFFAIRS* 20 (5): 6–7.

Information, National Center for Biotechnology, U. S. National Library of Medicine 8600 Rockville Pike, Bethesda MD, and 20894 Usa. 2015. "Cost Comparison Table for Drugs for Chronic Hepatitis C, Genotype 1." Text. Canadian Agency for Drugs and Technologies in Health. July 2015. https://www.ncbi.nlm.nih.gov/books/NBK362651/table/T33/.

Izaret, Jean-Manuel, Dave Matthews, and Mark Lubkeman. 2019. "Aligning Economic Incentives to Eradicate Diseases." BCG Global. January 7, 2019. https://www.bcg.com/publications/2019/aligning-economic-incentives-to-eradicate-diseases.

Jordan, Molly. 2016. "Redesigning the Orphan Drug Act: Examining the Government's Use of Subsidy and Exclusivity for Incentivizing Drug Development." Economics, Amherst, MA: Amherst College. https://www.amherst.edu/academiclife/departments/economics/z-economics/major-old/honors/theses/class-of-2016.

Kaitin, Kenneth I. 2011. "21st Century Bioinnovation: Academic-Industry Partnerships Are Increasingly Important in Biopharmaceutical Innovation." *Pharmaceutical Technology*, June 1, 2011.

Kamal, Rabah, Cynthia Cox, and Daniel McDermott. 2019. "What Are the Recent and Forecasted Trends in Prescription Drug Spending?" *Peterson-KFF Health System Tracker* (blog). February 20, 2019. https://www.healthsystemtracker.org/chart-collection/recent-forecasted-trends-prescription-drug-spending/.

"Killing Innovation in the Pharmaceutical Industry." n.d. London Business School. Accessed May 10, 2021. https://www.london.edu/think/iie-killing-innovation-in-the-pharmaceutical-industry.

Kim, Tae. 2018. "Goldman Sachs Asks in Biotech Research Report: 'Is Curing Patients a Sustainable Business Model?'" CNBC. April 11, 2018. https://www.cnbc.com/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html.

King, Anthony. 2019. "Building a Better Malaria Vaccine." *Nature* 575 (7784): S51–54. https://doi.org/10.1038/d41586-019-03639-5.

Kneller, Robert. 2010. "The Importance of New Companies for Drug Discovery: Origins of a Decade of New Drugs." *Nature Reviews Drug Discovery* 9 (11): 867–82. https://doi.org/10.1038/nrd3251.

Knowles, Jonathan, and Gianni Gromo. 2003. "Target Selection in Drug Discovery." *Nature Reviews Drug Discovery* 2 (1): 63–69. https://doi.org/10.1038/nrd986.

Komendant, Erik. 2018. “Pharmaceutical Patent Abuse: To Infinity and Beyond! | Association for Accessible Medicines.” Association for Accessible Medicines. 2018. https://accessiblemeds.org/resources/blog/pharmaceutical-patent-abuse-infinity-and-beyond.
Langreth, Robert. 2020. “Drug Prices QuickTake.” *Bloomberg.Com*, September 16, 2020. https://www.bloomberg.com/quicktake/drug-prices.
Ledford, Heidi. 2021. “Malaria Vaccine Shows Promise — Now Come Tougher Trials.” *Nature* 593 (7857): 17–17. https://doi.org/10.1038/d41586-021-01096-7.
Lee, Benita. 2020. “How Much Does Insulin Cost? Here’s How 27 Brands and Generics Compare.” GoodRx. November 6, 2020. https://www.goodrx.com/blog/how-much-does-insulin-cost-compare-brands/.
Light Donald W and Lexchin Joel R. 2012. “PHARMACEUTICAL R&D: What Do We Get for All That Money?” *BMJ: British Medical Journal* 345 (7869): 22–25.
Lowe, Derek and 2010. 2010. “Where Drugs Come From: The Numbers.” In the Pipeline. November 4, 2010. https://blogs.sciencemag.org/pipeline/archives/2010/11/04/where_drugs_come_from_the_numbers.
Luthra, Shefali. 2018. “‘Pharma Bro’ Shkreli Is In Prison, But Daraprim’s Price Is Still High.” *Kaiser Health News* (blog). May 4, 2018. https://khn.org/news/for-shame-pharma-bro-shkreli-is-in-prison-but-daraprims-price-is-still-high/.
Mikulic, Matej. 2020. “Brand vs Generic Prescription Revenue Share U.S. 2005-2019.” Statista. August 18, 2020. https://www.statista.com/statistics/205036/proportion-of-brand-to-generic-prescription-sales/.
Moser, Petra. 2013. “Patents and Innovation: Evidence from Economic History.” *Journal of Economic Perspectives* 27 (1): 23–44. https://doi.org/10.1257/jep.27.1.23.
“NDA Classification Codes.” n.d., 10.
“NIH Budget.” 2020. National Institutes of Health (NIH). June 29, 2020. https://www.nih.gov/about-nih/what-we-do/budget.
OECD. 2015. *Frascati Manual 2015: Guidelines for Collecting and Reporting Data on Research and Experimental Development*. The Measurement of Scientific, Technological and Innovation Activities. OECD. https://doi.org/10.1787/9789264239012-en.
Office, U. S. Government Accountability. n.d. “Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals.” Accessed October 12, 2021. https://www.gao.gov/products/gao-18-40.
“Open Innovation: The Answer to Slow Pharmaceutical Productivity.” n.d. Accessed June 17, 2021. https://www.europeanceo.com/business-and-management/open-innovation-the-answer-to-slow-pharmaceutical-productivity/.
“Opioid Manufacturer Purdue Pharma Pleads Guilty to Fraud and Kickback Conspiracies.” 2020. The United States Department of Justice. November 24, 2020. https://www.justice.gov/opa/pr/opioid-manufacturer-purdue-pharma-pleads-guilty-fraud-and-kickback-conspiracies.
Ornaghi, Carmine. 2009. “Mergers and Innovation in Big Pharma.” *International Journal of Industrial Organization* 27 (1): 70–79. https://doi.org/10.1016/j.ijindorg.2008.04.003.
Pagliarulo, Ned. 2018. “Gilead Forecasts Steep Slide in 2018 Hepatitis C Revenues.” BioPharma Dive. February 6, 2018. https://www.biopharmadive.com/news/gilead-hepatitis-c-revenues-slide-fourth-quarter-earnings/516494/.
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.
Pollack, Andrew. 2015. “Drug Goes From $13.50 a Tablet to $750, Overnight.” *The New York Times*, September 20, 2015, sec. Business. https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html.
“Prescription Drug Spending in U.S. 1960-2020.” n.d. Statista. Accessed April 12, 2021. https://www.statista.com/statistics/184914/prescription-drug-expenditures-in-the-us-since-1960/.
Priced Out of a Lifesaving Drug: Getting Answers on the Rising Cost of Insulin. 2019. Washington, D.C.
Reinganum, Jennifer. 1983. “Uncertain Innovation and the Persistence of Monopoly.” *The American Economic Review* 73 (4): 741–48.
Rena M. Conti and Frank S. David. 2020. “Public Research Funding and Pharmaceutical Prices: Do Americans Pay Twice for Drugs? [Version 1; Peer Review: 2 Approved].” *F1000Research* 9 (July). https://doi.org/10.12688/f1000research.24934.1.
“Research and Development in the Pharmaceutical Industry | Congressional Budget Office.” n.d. Accessed October 12, 2021. https://www.cbo.gov/publication/57126.

Research, Center for Drug Evaluation and. 2019. “Development & Approval Process | Drugs.” FDA. FDA. October 28, 2019. https://www.fda.gov/drugs/development-approval-process-drugs.
———. 2020. “Frequently Asked Questions on Patents and Exclusivity.” *FDA*, February. https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity.
Richman, Barak, Will Mitchell, Elena Vidal, and Kevin Schulman. 2017. “Pharmaceutical M&A Activity: Effects on Prices, Innovation, and Competition.” *Loyola University Chicago Law Journal* 48 (January): 787–819.
Richter, Salveen, Richard Yeh, Ross Weinreb, Ziyi Chen, Kevin Patel, and Alexana Astor. 2018. “Profiles in Innovation The Genome Revolution.” Equity Research. Goldman Sachs.
Scherer, F. M. 1993. “Pricing, Profits, and Technological Progress in the Pharmaceutical Industry.” *Journal of Economic Perspectives* 7 (3): 97–115.
“Search of: Industry - Results by Topic - ClinicalTrials.Gov.” n.d. Accessed August 31, 2021. https://clinicaltrials.gov/ct2/results/browse?fund=2&brwse=cond_alpha_all.
Sullivan, Thomas. 2018. “Pharmaceutical Development Slows Down In Search of New Products.” *Policy & Medicine* (blog). May 6, 2018. https://www.policymed.com/2012/10/pharmaceutical-development-slows-down-in-search-of-new-products.html.
Taylor, David. 2015. “The Pharmaceutical Industry and the Future of Drug Development.” In *Issues in Environmental Science and Technology*, edited by R E Hester and R M Harrison, 1–33. Cambridge: Royal Society of Chemistry. https://doi.org/10.1039/9781782622345-00001.
Teramae, Fumio, Tomohiro Makino, Shintaro Sengoku, Yeongjoo Lim, Takashi Natori, and Kota Kodama. 2020. “Research on Pharmaceutical Product Life Cycle Patterns for Sustainable Growth.” *SUSTAINABILITY* 12 (21): 8938. https://doi.org/10.3390/su12218938.
Thakor, Richard T., and Andrew W. Lo. 2020. “Competition and R&D Financing: Evidence from the Biopharmaceutical Industry.” SSRN Scholarly Paper ID 3754494. Rochester, NY: Social Science Research Network. https://doi.org/10.2139/ssrn.3754494.
Tranbarger, Cody. 2017. “Pharmaceutical Price Controls and the Orphan Drug Megafund Model.” Economics, Amherst, MA: Amherst College. https://www.amherst.edu/academiclife/departments/economics/z-economics/major-old/honors/theses/class-of-2017.
Walker, Joseph. 2015. “High Prices for Drugs Attacked at Meeting.” *The Wall Street Journal Eastern Edition*, June 1, 2015.
Wauthy, Xavier. 1996. “Quality Choice in Models of Vertical Differentiation.” *The Journal of Industrial Economics* XLIV (September). https://www.jstor.org/stable/2950501?seq=2#metadata_info_tab_contents.
Werble, Cole. 2017. “Formularies | Health Affairs Brief.” September 14, 2017. https://www.healthaffairs.org/do/10.1377/hpb20171409.000177/full/.
William D. Nordhaus. 1969. “An Economic Theory of Technological Change.” *The American Economic Review* 59 (2): 18–28.
Wylie, Craig, Rebecka Axelsson Wadman, Thomas Unger, Vikas Kharbanda, Ulrica Sehlstedt, and Satoshi Ohara. 2019. “Transforming Healthcare – How Curative Therapies Will Disrupt the Market.” Arthur D Little. September 10, 2019. https://www.adlittle.com/en/insights/prism/transforming-healthcare-how-curative-therapies-will-disrupt-the-market.