What Have We GAINed?

An Analysis of Federal Incentive Policies in the Orphan and Anti-Infective Drug Markets

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Abstract

The world faces a growing danger in the form of antibiotic resistance and a dwindling anti-infective pipeline. To help combat the threat, Congress passed legislation (the "GAIN Act") in 2012 that grants five years of additional exclusivity—or protection from competition from generic products—to drug applications that are designated as qualified infectious disease products (QIDPs). The exclusivity incentive is nearly a carbon copy of the hallmark design of the 1983 Orphan Drug Act, which was passed to spur development of treatments for rare diseases.

This thesis addresses the effectiveness of incentive policies in facilitating drug development in the orphan drug market for rare diseases and the anti-infective drug market. Using pricing data from Medicare Part D program and drug databases, the research develops frameworks for both the orphan and anti-infective markets and finds that the two markets vary widely across all measured categories. During the course of the past decade, anti-infectives became less of a priority in the development pipelines of the world's top pharmaceutical companies, and content analysis of earnings call transcripts reveals that industry executives do not seem to be discussing the new incentive. The results indicate that a new or augmented approach to anti-infectives may be needed. Instead of using exclusivity, the government should consider offering benefits that companies realize at the front end of the research and development pipeline as a means to increase drug development in the anti-infective drug market.

Central Questions

What has been the impact of offering additional exclusivity (i.e. extended patent protection) for the development of new drugs in the orphan and anti-infective markets? Should employing similar incentive policies in these markets be expected to produce equivalent results?

Introduction

The world faces a growing danger in the form of antibiotic resistance and a dwindling anti-infective pipeline. To help combat the threat, Congress passed the Generating Antibiotic Incentives Now (GAIN) provisions as part of the Food and Drug Administration Safety and Innovation Act in 2012 to stimulate research, development and commercialization of new anti-infective drugs. To incentivize companies to undertake this burden, the law grants five years of additional exclusivity—defined as protection from competition from generic products—as well as fast-track approval and priority review by the Food and Drug Administration (FDA) to drug applications that are designated as qualified infectious disease products (QIDPs). The exclusivity incentive is nearly a carbon copy of the hallmark design of the 1983 Orphan Drug Act, which was passed to spur development of treatments for rare diseases affecting fewer than 200,000 people in the United States.

Prior research has evaluated the efficacy of the Orphan Drug Act, but little has been written about the GAIN provisions, now in just their third year of existence. To date, the FDA has approved six QIDP-designated products, but those drugs had already been in the pipeline before the legislation was passed (Tomaras and Dunman). This paper seeks to determine whether Congress should expect the Gain Act to produce a new wave of novel anti-infectives in the next 10 years, using the 33-year history of the Orphan Drug Act as a comparison.

Literature Review

The Bayh-Dole Act of 1980 provided a major incentive for inventors conducting federally funded research discoveries—the ability to retain title to and eventually profit from the sale of products invented due to federal research dollars. Prior to this shift, discoveries subsidized by government grants were not put into commercial use because developers felt unprotected; only about 5% of government-owned patents were acted on by the private sector (Schacht 2009). After the law was enacted, university and industry collaboration soared, particularly in the field of drug discovery. Bayh-Dole laid the foundation for medical discovery in the United States, but other laws with additional incentives were deemed necessary by Congress to continue advancing medical progress and meet emerging public health needs.

Companies tend to pursue drug targets with high commercial potential, leaving many patients suffering from rare conditions with few if any treatment options. The 97th Congress identified this deficit as a public health issue, and passed the Orphan Drug Act in 1983 to address the gap. The Act provided three categories of incentives to pharmaceutical and biotechnology companies to invest in treatments for rare diseases. The bill defined a "rare disease" as one affecting 200,000 or fewer people in the United States ("Orphan Drug Act"). Under its provisions, companies that apply for and receive orphan drug designation from the Food and Drug Administration (FDA) are eligible for the following:

- Seven years of marketing exclusivity from the date of drug approval
- A tax credit covering up to 50% of the cost of clinical trials for the drug(s)
- Federal grants to support orphan drug research

Several other laws governing drug development policy have been passed since the Orphan Drug Act went into effect, but none have dramatically altered the terms of this legislation. This paper explores the impact of the Orphan Drug Act on the development of drugs to treat rare diseases and compares the orphan drug market's characteristics to characteristics of the anti-infective drug market, which includes antibiotics and treatments for bacterial, viral and fungal infections. The anti-infective market has experienced a shortage of new products, with just 12 new antibiotics approved since 2000 (Gupta). The growing threat of resistance has created a public health concern that commanded Congressional attention as early as 2012. A comparison of the two markets enables discussion of whether anti-infective drug development should benefit from the same type of incentives included in the Orphan Drug Act, some of which are currently included in the Generating Antibiotics Incentives Now (GAIN) provisions in the Federal Drug Administration Safety and Innovation Act of 2012 (from this point on referred to as the GAIN Act) that was signed into law by President Barack Obama in July of that year.

A. The Role of Government in Promoting Research and Development

The identification of a market failure invites the government to intervene in the market to attempt to resolve the problem. Without any government invention, the current level of research and development (R&D) undertaken by private firms in most fields would be less than socially optimal, because the development of new products is highly risky. Additionally, some of the benefit from creating successful new products accrues to society at large, not just to the company that made the upfront investment in the research (Feldman and Kelley 2006). Research and development therefore constitutes a positive production externality, and by definition will be undersupplied by the free market. An analysis of research and development in the United Kingdom estimated a private return to R&D of 7-14% of GDP and a social return of 30%,

meaning the private sector underinvested in new research by a factor of between two and four (Griffith 2000).

The government offers incentives to drug companies in an attempt to increase private investment in new research. These incentives take many forms, including tax breaks, research subsidies, government contracts and extensions of patent life; efficiency may be maximized in some cases if governments design policies aligning multiple types of incentives (Perez-Sebastian 2015). Government-funded R&D—typically subsidies or contracts—has been shown to increase private R&D; however, some researchers have expressed concern that these subsidies may crowd out private research. One study found that a moderate level of subsidy, around 15%, was most effective in stimulating private research and development when compared to more extreme policies in either direction (Guellec and Van Pottelsberghe de la Potterie 1997). Drug development incentives have incorporated several different types of incentives—as evident in the three tiers of the Orphan Drug Act described above—but among the most frequently discussed are policies involving intellectual property rights. Proponents argue that extended patent or exclusivity protection is needed to help insulate companies from the high cost and risk of investing in new drugs. However, critics point out that increased patent life allows companies to charge monopoly prices to the consumer (Silverman 2013). If a government incentive program includes the use of tax dollars to subsidize private research and development, and then a patient faces a high price because of other features of the government program, the patient is effectively paying for the same drug twice.

B. Impact of the Orphan Drug Act

At first glance, the Orphan Drug Act appears to have been remarkably successful. Between 1972-82, just 10 drugs were approved by the FDA to treat orphan diseases, while 325

approved products received orphan designation in the first 25 years after the law was passed (Haffner 2006). Pharmaceutical companies reacted swiftly to the legislation. By 1998, just 15 years after the law was passed, the number of orphan drugs had increased five-fold from 1979 levels, while the non-orphan drug pool grew less than two-fold (Lichtenberg and Waldfogel 2003).

However, attributing the growth of orphan drugs to the Orphan Drug Act alone would be misguided or, at least, fail to paint the full picture (Kesselheim 2010). Using descriptive statistics does not account for potential confounders, such as new developments in the industry, advancements in science and technology, the effects of other subsequent legislation and changes in macroeconomic conditions.

Several studies have assessed the impact of the Orphan Drug Act on measures beyond just the raw number of drugs approved to treat rare diseases. An inquiry into the law's effect on stimulating investment in research and development for rare conditions found that the Orphan Drug Act led to a 69% improvement in the number of annual clinical trials for "long-established rare diseases" (Yin 2008). With more clinical trials for rare diseases after the legislation passed, more orphan drug designations made it through the pipeline to FDA approval. The result was more treatment options for patients suffering from rare diseases. Thus, the Orphan Drug Act reduced the relationship between market size and the likelihood that patients with rare diseases had an available treatment for their conditions (Lichtenberg and Waldfogel 2003).

The influence of market size remains, however. There are 6,819 rare diseases recognized by the United States, and even after passage of the Orphan Drug Act, determining which diseases to pursue appears to remain primarily a question of potential profitability for drug companies rather than public health need (Seoane-Vazquez et al. 2008). One of the primary arguments for

the incentives in the Orphan Drug Act was the lack of market size—and therefore commercial opportunity—for rare diseases. With seven years of market exclusivity, advocates argued that pharmaceutical companies would be more willing to make an investment in a disease treatment with otherwise highly limited sales potential. Research indicates, however, that even within the subset of orphan drugs, companies prefer to target more prevalent conditions. Over the period from 1981 to 1994, rare diseases affecting between 100,000-200,000 people saw a greater increase in new clinical trials compared to all drugs than did rare diseases affecting fewer than 100,000 people (Yin 2008).

Orphan drugs are also stratified by therapeutic class, with oncology products accounting for nearly 33% of approved orphan drugs (Wellman-Labadie and Zhou 2010). Cancer drugs represented the top-grossing therapeutic category of drugs in 2013, so the decision to focus orphan research and development dollars on oncology is not surprising ("Top 10 Therapeutic") .

Conclusions regarding the Orphan Drug Act's impact on orphan drug pricing are less clear, owing largely to the wide range of observed data. The majority of orphan drugs did not generate significant revenues in comparison to non-orphans in the decade following passage of the law; both classes of drugs experienced peak sales 10 years after approval, and non-orphans enjoyed a mean sales edge of more than $100 million over orphan drugs at the peak sales point (Grabowski and Vernon 2000). This helps explain why the incentives in the law were necessary to promote investment. Duke University economists Henry Grabowski and John Vernon examined returns on pharmaceutical research and development for drugs approved between 1980-84 and later returned to re-examine the landscape for drugs approved between 1988-92. They found a significant skew in both study periods—a handful of drugs accounted for a majority of revenues—and the skew was larger in the second period, which they attributed in

part to the increase in orphan drugs in the drug pool (Grabowski and Vernon 2000). However, through various means, some orphan drugs overcame the constraints of their small domestic market sizes to become highly profitable; this will be discussed in the next section.

C. Shortcomings of the Orphan Drug Act

Although attitudes have changed, the Orphan Drug Act was not initially heralded as a success, even by those companies it was designed to help. A 1989 survey found that manufacturers wanted to see enhanced incentives for all three pillars of the Orphan Drug Act (Pal 1990). Specifically, a majority of survey respondents indicated that market exclusivity should be set at 10 years, companies should receive a tax credit covering 75% of the cost of clinical research and the federal assistance for clinical trial expenses should begin at $100,000 (Pal 1990). It is worth noting that Pal's survey population consisted of leaders from companies that had and those who had not invested in the development of an orphan drug. As members in the pharmaceutical industry, respondents certainly gave self-interested answers.

Although most literature seems to affirm that the Orphan Drug Act successfully produced an increase in the number of approved drugs for rare diseases, many have taken issue with the law's unintended consequences. To start with, the FDA may grant orphan designation for a particular line of research to multiple companies, but only the first company to get a drug approved under that designation receives the seven-year market exclusivity period (Bohrer and Prince 1998). In effect, this creates a high-stakes race to get the drug approved, and the loser is forced to sit on the sidelines while the winner enjoys the financial perks of the exclusivity. To make matters worse, for the first 15 years of the Act, the FDA did not reveal which company received the orphan designation status until a drug was approved. This potentially led companies to wastefully invest large amounts of money in the pursuit of the same drug, only to lose the

exclusivity pay-off if they lost the race to a competitor who simultaneously developed the treatment (Bohrer and Prince 1998). This problem has been addressed, at least in part, by the creation of a searchable FDA database of orphan drug designations (FDA). In addition, most biotechnology companies publicize their research projects in order to attract capital, meaning competitors become aware of their plans as well (Bohrer and Prince 1998).

Several orphan drugs have bucked the trend described by Grabowski and Vernon and gone on to become blockbusters. One analysis showed that 43 drugs with revenues larger than $1 billion had been assigned orphan designation, but only 18 of them were used solely for orphan drug treatment (Wellman-Labadie and Zhou 2010). This supports the notion that biotechnology and pharmaceutical companies may be gaming the system when it comes to the market exclusivity provided by the Orphan Drug Act. The alleged strategy is to narrow down a prospective drug's treatment population to the level required for orphan drug designation, then apply for additional non-orphan designations once the drug has FDA approval—and the seven years of orphan exclusivity. Alternatively, companies may be tacking on orphan designations to existing drugs after they have already been approved.

In one of the more famous cases, Genentech conceived of human growth hormone (hGH) as a treatment for children with hypopituitary dwarfism, but it wound up successfully treating several other growth disorders (Griffith 1996). In a more recent case, colchicine—used as a treatment for gout since before the FDA was created—was later granted an orphan designation for treatment of familial Mediterranean fever (FMF) after a review of existing data. The new product was rebranded as Colcrys and given exclusivity despite its already-understood benefits for FMF (Kesselheim and Solomon 2010). Mutual Pharmaceuticals, the makers of Colcrys, then filed to remove all other existing drugs containing colchicine from the shelves because they were

ostensibly in violation of the company's exclusivity, a move that court documents indicated would have increased the sticker price of a bottle of Colcrys from $9 to $485 (Mut. Pharm Co. v. Watson Pharm Inc., 2009). The cost of treatment used to be as little as 10 cents per pill; now, brand-name Colcrys sold for $6 per pill in January 2015, although a generic version of the colchicine formulation is now available (Allen, Gever 2015).

Not all blockbuster orphan drugs become profitable as a result of abuse of the system. AZT, the first drug shown to have any effect against AIDS, earned orphan drug approval in 1989, when the patient population was 45,000. Once it was shown to delay onset, AZT became a treatment option for 600,000 HIV+ Americans, with global market potential ballooning as well (Thomas 1989). The Orphan Drug Act did not have a mechanism to deal with orphan diseases that suddenly grew into conditions affecting much larger numbers of patients, but it was not for lack of foresight. Language that would have removed an orphan drug's market exclusivity once it reached a certain level of profitability was drafted by Senator Edward Kennedy (D-MA), but was not inserted into the final bill (Pal 1990). A different policy, recoupment—in which the government receives some compensation from the company for a profitable product that was developed using federal funds—was debated but omitted from the final version of the Bayh-Dole Act (Schacht 2009).

The European counterpart to the Orphan Drug Act includes a provision similar to the one proposed by Kennedy: a drug's exclusivity could be revoked if it becomes highly profitable. This provision has never been invoked. However, its presence may affect the number of drugs approved under the European law. Both the European version of the ODA and the Japanese Orphan Drug Act offer 10 years of market exclusivity, but the latter does not have a revocation provision, and has seen a greater number of drugs approved (Wellman-Labadie and Zhou 2010).

This suggests that the guaranteed protection of a seven-year exclusivity period has been critical to the development of orphan drugs in the United States.

The Orphan Drug Act has played an important role in spurring the supply side of the market for rare disease treatments, but it is not without flaws. This paper aims to a) trace and explain the success of the Orphan Drug Act across its 33-year history and b) evaluate whether the set of incentives laid out in the Orphan Drug Act would achieve positive results in spurring drug development if applied to the anti-infective drug market.

D. The Case for Intervention in the Anti-Infective Market

Similar to the rare disease market prior to passage of the Orphan Drug Act, the market for anti-infective drugs faces a major barrier to entry: low profitability. Unlike rare diseases, the hypothetical treatment population for anti-infectives is quite large, but successful short-term treatment with anti-infectives effectively reduces that population. According to IMS Health data, antibiotics alone constituted 6.4% of prescriptions written in the United States in 2013 but accounted for just 2.6% of prescription revenue (Outterson et al. 2015). It seems clear that companies are more likely to pursue therapeutic classes with chronic conditions that promise long-term use (Projan 2003).

The flight from anti-infectives comes at an inopportune time, as drug resistance is becoming more prevalent and new drug targets are proving ineffective (Outterson et al. 2015). The number of new antibacterial agents approved by FDA during the 1998-2002 period declined by 56% versus the 1983-1987 period. In 2004, just six of the 506 drugs listed in the developmental programs of the largest pharmaceutical and biotechnology companies were antibacterial agents (Spellberg 2004). However, the costs of not investing in new antibiotic drugs are huge: one estimate put the consequences of antibiotic resistance in the United States at tens

of thousands of deaths and $26 billion in additional healthcare costs each year (Forsyth 2013). The public health threat posed by resistant bacteria was enough to spur congressional action to facilitate increases in research and development in this field.

One reason investment dollars could be so scarce, beyond the intuitive explanation of low prices, is that developing antibiotics is riskier than the development of many other drug categories. One company reported needing 72 antibiotic candidates to produce one FDA-approved drug, while other drug categories only needed 15 candidates (2012). Given the low prices and limited period of use (and thus, low profit margins) of most anti-infective drugs and the high level of risk associated with these low-priced products, there are significant barriers to generating sufficient research and development in this market that are unlikely to be overcome without some carrot for companies to chase.

Projan concluded that, absent changes in incentives, the only way to make antibiotics attractive would be to charge high prices, which would alienate the public and/or third-party payers. Risk-adjusted net present value (rNPV)[1] data indicate that anti-infectives rank fifth in investment attractiveness out of five therapeutic classes studied with a rNPV of $100 million, well behind musculoskeletal ($1.15 billion), neurology ($720 million) and oncology ($300 million) projects and $60 million behind vaccines (Projan 2003). A counterargument asserts that basing investment decisions on NPV data is too narrowly focused on the short term—which it is, effectively by definition, since NPV calculations weigh costs and benefits in the present more heavily than costs and benefits in the future. If pharmaceutical companies develop new anti-infectives and market them globally, they could eradicate much of the infectious disease that

[1] rNPV allows for the valuation of projects with differing probabilities of success, taking the probability that a given outcome occurs (e.g., a drug passes through clinical trials and is approved for sale by the FDA) into account when determining the potential of the value. Because it is a probabilistic data point, it offers a better measurement than raw NPV data.

ravages developing countries. Success in that endeavor would extend global life expectancy tremendously, presumably expanding markets for drugs that treat chronic conditions (Nathan 2011).

The discussion of NPV analysis is interesting because that same logic would also apply to the exclusivity provision for orphan drugs under the Orphan Drug Act. The extra seven years of market exclusivity are heavily discounted, yet the FDA has seen an enormous increase in the number of drugs targeting and approved to treat rare diseases since the law was passed. One explanation for this could be that the early-year returns on an orphan drug are simply greater than the early-year returns for an antibiotic/anti-infective drug, so the NPV will be higher. One study found that if the relative risk-adjusted NPV (rNPV) for antibiotics was set at $100 million, the rNPV for vaccines would be $160 million, the rNPV for an anticancer drug would be $300 million and the rNPV for a musculoskeletal drug would be $1.1 billion (So and Shah 2014). This hierarchy indicates that antibiotics constitute a high-risk, low-reward investment, relative to other therapeutic categories.

However, although the poor relative rNPV of antibiotics could explain why investing in an orphan drug is more appealing, it does not explain why the exclusivity policy in the Orphan Drug Act would stimulate the desired response in the rare disease market, while the same policy in antibiotics would not. The gains from exclusivity under the Orphan Drug Act would also be discounted because the exclusivity does not take effect right away, and the extra two years—which differentiate the exclusivity provision of the seven-year provision Orphan Drug Act and the five-year counterpart in the GAIN Act—would be the two most heavily discounted because they are furthest from the present. As a result, it may be some of the other provisions embedded

in the Orphan Drug Act, not just the promise of extended exclusivity, that served as primary incentives for firms to invest in treating rare conditions.

E. The GAIN Act: A Brief Overview

In response to growing concerns about drug resistance, Congress passed the Generating Antibiotics Incentives Now (GAIN) provisions in 2012. The law borrows from the Orphan Drug Act, providing five years of market exclusivity to "qualifying infectious disease products" (QIDPs) meant to treat diseases like those caused by the ESKAPE pathogens—six families of infection-causing agents that are mounting the most serious therapeutic issues for doctors because of the resistance they have developed (Brown 2013). This incentive is added on top of any other exclusivity obtained by the drug, such as any remaining patent exclusivity, the seven-year period under the Orphan Drug Act, the five-year period for a New Chemical Entity (NCE) under the Hatch-Waxman Act (which revolutionized the generic drug industry) and the six-month period for pediatric drugs (Forsyth 2013).

In their recently published breakdown of the anti-infective drug sphere, Outterson et al. noted that four drugs already nearing FDA approval received this QIDP designation as an added bonus. Six drugs with the QIDP designation have been approved by the FDA since the designation was created via passage of the GAIN Act (FDA 2015). However, this is not an indication of the GAIN Act's success after just three years of existence. The companies that submitted these drugs to the FDA for review had done so prior to the law's enactment, meaning they did not expect to reap the benefit of any sort of incentive at the time of submission.

Some experts do not expect the GAIN Act to have a significant impact on anti-infective development in the next decade (Outterson et al. 2015). There are already concerns that the incentives in the act are not strong enough to persuade companies to invest in anti-infective

development (Forsyth 2013). Other criticisms of the law include the adverse effects of extending exclusivity on drug prices and healthcare costs. Since the extended exclusivity prevents generics from entering the market for five additional years, a company benefiting from the GAIN Act enjoys a monopoly on its anti-infective drug, which usually translates into higher prices for consumers (Forsyth 2013). However, this claim must be considered in the context of the point made earlier that anti-infectives and antibiotics tend to have lower prices than other therapeutic categories (despite the emergence of newer drugs with high prices such as the new crop of anti-hepatitis C agents).

Due to its youth, the GAIN Act has not yet been the subject of much rigorous empirical study. Prior research has focused on the potential costs and benefits of the policy and its potential impact. Analysis of general research and development—not pharmaceutical-specific—has asserted that there is a one-year lag before government incentive programs begin to show an effect on private investment in R&D (Guellec and Van Pottelsberghe de la Potterie 1997). As the GAIN Act surpasses the three-years threshold, this study evaluates the initial response to the law by the pharmaceutical industry.

F. How Literature Informs This Project

A review of the relevant literature reveals both similarities and differences between the orphan drug and anti-infective drug markets. Prior to passage of the Orphan Drug Act, the rare disease market was an underserved therapeutic area, just as today's anti-infective pipeline is running dry. However, anti-infectives have proven less lucrative than orphan drugs because of their limited cycle of use and lower prices. The passage of the GAIN Act in 2012 offers a chance to make another comparison between the two drug pools. The law incorporates a multi-year period of market exclusivity, the key incentive of the Orphan Drug Act. At just more than three

years old, the GAIN Act has not yet had a palpable effect on the number of new drugs approved. This paper investigates whether the law has helped refill the dwindling anti-infective drug pipeline and compares the orphan and anti-infective drug markets to determine whether or not Orphan Drug Act-style incentives are the best means to foster research and development investment in anti-infective products.

If significant differences exist between the orphan drug market and anti-infective/antibiotic markets, then the GAIN Act will likely not succeed in stimulating the resurgence of corporate interest in research and development in this sector as envisioned by Congress. This paper aims to parse out whether these differences exist and concludes by offering recommendations on how incentive policies for the anti-infective/anti-biotic market can be improved.

Hypotheses/Observable Implications

1. Academic researchers tend to support the idea that the Orphan Drug produced a dramatic increase in the number of available treatments for rare diseases. The number of drugs for rare diseases being pursued and eventually approved jumped tremendously following implementation of the ODA. Studies have shown that the correlation between the number of people afflicted by a condition decreased and their access to treatment improved after the Orphan Drug Act was passed, suggesting that the ODA did its job in stimulating new treatments for rare conditions.
2. If significant differences exist between the two drug markets, there should be disparities in several measurable characteristics of the drug markets, including: drug price and market size, the cost of drug development and resulting profit from commercialization,

demand for drugs and volume of consumption and treatment regimen. Other important differences that should be evaluated non-numerically are scientific/technological barriers to success and regulatory burdens.

3. If the differences between the two markets are substantial, pharmaceutical and biotechnology companies might not see sufficient reward to invest in the development of new anti-infectives. This claim can be evaluated by examining the number of drug applications (and to a lesser extent, drug approvals) in each market in the first three years following implementation of each market's respective law. The industry's response can also be revealed by analyzing comments from executives of biotechnology and pharmaceutical companies in official settings, searching for explicit mention of incentives and other constraints on the R&D process.

Research Design

Policy analysis methodology provides the foundation for separate investigations of both the orphan drug market and anti-infective drug market, followed by a comparison of their overlapping characteristics and significant differences. Incorporating multiple data sources—including database analysis; content analysis of conference call transcripts; and expert interviews—allows for an overarching comparative analysis of the drug markets, which informs policy recommendations for encouraging further drug development in the anti-infective market.

Examining the existing pool of academic literature is a critical and illuminating starting point for this research. There is a great deal of scholarship addressing the first portion of the research question: the general consensus among researchers is that the Orphan Drug Act has had a significant impact on the development of new drugs to treat rare diseases, although it is

interesting that most rigorous evaluations of the program were completed more than a decade ago. By contrast, most academic literature on the GAIN Act has been forward-looking, with the law's full impact anticipated after a few more years due to the lag time required to bring new drugs through the development pipeline to FDA approval. This policy analysis therefore contributes to the existing body of scholarship on drug development policy by bridging the gap between one widely studied law and one that is just beginning to attract interest.

Several pieces of descriptive data were gathered to contextualize the comparison between the two drug markets. In particular, market size, revenue potential (drug prices and demand) and the identity of the prominent companies producing drugs in each market established the framework for analysis and provide the earliest glimpse at the degree of similarity between the two markets. Compiling a snapshot of drug companies' research and development pipelines before and after implementation of the GAIN Act offered a revealing look at whether the law is achieving the success of the Orphan Drug Act in generating interest in developing anti-infective drugs, but must be evaluated in the context of external events. This initial analysis led to the crux of the research question: Should these drug markets operate under the same type of federal incentive structure?

Interviews with experts in the orphan drug and anti-infective markets offered valuable insight and comparative data points and informed the policy recommendations section of this paper, specifically the implications of the recommendations for the assorted stakeholders.

A. Data Collection

Using databases maintained by the FDA, all drug applications that have ever received orphan drug designation under the Orphan Drug Act were obtained. This data set contained 3,472 designations when downloaded on July 1, 2015, and included 495 total approved

indications for 401 unique drugs. Of those, 180 still had some amount of exclusivity remaining as of July 1, 2015; the analysis treated orphan drugs as an entire group, and then focused more specifically on "inactive orphans" (designations with expired exclusivity) and "active orphans" (designations with some exclusivity remaining).

A similar approach was pursued for all drug applications that have received qualified infectious disease product (QIDP) designation under the GAIN Act, but was curtailed by lack of government support.[2] Instead, the most complete list of QIDP designations possible was generated by searching for press releases on Google News. A third database, listing common anti-infective drugs, provides a more representative sample of the existing anti-infective market, not just drugs designated as QIDPs that have yet to be approved.

A critical factor in a drug company's decision to pursue development of a product is its potential for commercial success. Pricing and usage data (the number of patients and the prescriptions filled) for the approved drugs in each database mentioned above was collected from two different sources: the Center for Medicare and Medicaid Services (CMS) and GoodRx. CMS data for Medicare Part D—which covers prescription drugs—lists more than 3,400 drugs covered by the program in 2013, and includes the number of Medicare beneficiaries, the number of prescribers, the number of claims filed and the total cost to the program of each drug. Cross-referencing the approved drugs from the FDA orphan designation database and the newly generated anti-infective database with the CMS data produced a proxy for market size and market revenue for both the orphan and anti-infective spheres. A secondary analysis was performed using data from GoodRx—an online shopping tool that allows patients to compare

[2] The orphan drug designation database is readily available on the FDA's Access Data portal. The QIDP designation database is not readily accessible, and multiple formal FOIA requests to the FDA seeking information on QIDP-designated drug applications were denied.

pharmacy prices for prescription drugs—to gather pricing and dosage information about each of the listed drugs individually rather than in aggregate.

The examination of the existing drug pipeline for each drug market employed an approach similar to the method devised by Spellberg et al (2004). Their research involved visiting the websites of 15 prominent biotechnology and pharmaceutical companies and tabulating the therapeutic category of each new molecular entity (NME) in the firm's publicly available "in development" sections. Revisiting their approach with the world's largest 15 pharmaceutical companies (based on 2014 global sales figures) provides an indication of how, if at all, drug development trends have shifted in the decade since they performed their original analysis—and since passage of the GAIN Act.

Financial data and related information from an aggregate collection of sources provides context for the role of incentives in R&D decision-making. Transcripts of quarter-end and year-end conference calls for relevant companies were obtained from the Bloomberg terminal. Analyzing six quarters of transcript calls for the same 15 pharmaceutical companies discussed above allows for cross-comparison between what executives say and what their pipelines indicate about their R&D decisions. The six quarters analyzed are 2008 Q4, 2012 Q1, 2012 Q2, 2012 Q3, 2012 Q4 and 2015 Q1. These six sets of transcripts capture three distinct periods of time: well before passage of the GAIN Act; the entire of year of 2012, during which the GAIN Act became law; and three years removed from passage of the GAIN Act.

The Orphan Drug Act represented an important shift in drug development, while the GAIN Act could be potentially salient as well; examining the conversations between company executives and stock analysts offers a look at whether the change in anti-infective incentives moved the scale in a meaningful way among top pharmaceutical companies. Data describing the

amount of money these firms have historically spent on research and development will be obtained for the same time period using the SEC's Electronic Data Gathering, Analysis, and Retrieval system (EDGAR) to account for potential shifts due to the Great Recession and other macroeconomic events.

B. Data Analysis

The market size and drug cost information gathered from the databases and the analysis of the company pipelines at the start of the data-gathering process are presented descriptively as summary statistics. Rather than attempt to develop a regression formula for a company's R&D portfolio—the specifics of which undoubtedly vary from firm to firm—this information anchors the framework of the rest of the investigation with side-by-side comparisons of the two drug markets being studied. Aggregate financial data from the firms such as R&D expenditures are displayed as contextual information.

Content analysis was employed to evaluate the conference call transcripts and market research reports. Using NVivo, coding for key words such as "GAIN", "orphan", "antibiotic", "exclusivity" and "incentive," identified which company is speaking about a certain drug market—and how often. Those results were then cross-referenced with earlier findings of that company's participation in the orphan drug and anti-infective drug markets. In other words, how does a company's stated goals or concerns match with their research and development decisions, before and after the passage of the GAIN Act?

Analysis of the transcripts produced from interviews supplemented and emphasized findings from earlier pieces of the analysis, or offered alternative interpretations of the data. The transcripts were not subjected to content analysis on their own. Many interview questions focused on improvements to the system, particularly the anti-infective drug market; those

responses are incorporated into the discussion and recommendations section rather than the results section.

Results

A. Sizing the Orphan and Anti-Infective Markets

The Medicare Part D patient population for anti-infective drugs is more than three times that for orphan drugs, yet the program spent nearly $12 billion less on anti-infectives in 2013, or 11.2% of the program's total expenditure. Nearly 37 million Medicare beneficiaries filed claims for anti-infectives, or 10.9% of the total pool of 337 million beneficiaries. Among the 10.6 million beneficiaries who filed claims for orphan drugs, only 6.5 million of them (1.9% of the total) submitted claims for "active" orphan drugs, or orphan drugs still protected from generic competition by exclusivity.

Anti-infectives and orphan drugs are not mutually exclusive—898,219 Part D beneficiaries filed claims for a drug treating a rare, infectious disease. The drugs meeting both sets of criteria accounted for 0.1% of total claims filed and 0.5% of total drug costs (see Table 1).

Table 1: 2013 Medicare Part D Breakdown by Drug Type

Drug Market	Beneficiaries	Prescribers	Claims Filed	Drug Cost ($)
All Drug Types	337,522,201	78, 328,447	1,369,415,992	$103,704,226,748
Orphan Drugs	10,591,485	2,344,921	46,479,950	$15,815,696,986
Active Orphan Drugs	6,499,413	1,337,416	32,247,554	$9,230,336,347
Anti-Infective Drugs	36,845,342	7,555,844	58,476,727	$4,159,088,183
Dual Drugs	898,219	258,276	1,455,923	$467,201,136

Although they constitute just 309 of the 3,449 drugs covered by Medicare Part D in 2013, orphan drugs disproportionately affect costs for the Medicare program by a factor of 4.5. The nearly 46.5 million Medicare claims filed for orphan drugs account for 15.3% of total drug costs but just 3.4% of the total claims filed by Part D beneficiaries. Active orphan drugs exhibited the same disproportionate impact but the phenomenon was surprisingly less drastic. Patients enrolled in Medicare Part D filed 32.2 million claims for active orphan drugs (2.4% of the total), racking up a drug cost of $9.2 billion (8.9% of the total). By contrast, the program's spending for anti-infective drugs is in line with the total number of claims filed; the 58.5 million claims and $4.2 billion in drug costs constitute 4.3% of total claims and 4.0% of total drug costs.

B. Pricing the Orphan and Anti-Infective Markets

Of the 309 drugs in the 2013 Medicare Part D database with orphan indications from the FDA, 116 retained some amount of exclusivity at the time of this analysis. Anti-infectives accounted for another 251 drugs covered by Medicare, and 35 drugs were dually classified as

both an anti-infective and an orphan drug. All drug categories provided a wide range of patient populations and drug costs; to help mitigate the effect of outliers (i.e. ultra-expensive orphan drugs), the median figures for each group are summarized in Table 2.

Combining the median number of claims with the median drug cost produces a hypothetical drug for each drug category with the attributes of the median number of claims and the median drug cost. The cost per claim of each category's median drug is displayed in Table 2.

Table 2: Size and Revenues of the "Median" Drug

Drug Market	Number of Drugs	Median Number of Claims	Median Cost ($)	Cost Per Claim (of "Median Drug")
All Drugs	**3,449**	**2,945**	**$527,643.70**	**$179.17**
Orphan Drugs	**309**	**819**	**$2,617,818**	**$3,196.36**
Active Orphan Drugs	**116**	**1,228**	**$6,717,749**	**$5,470.48**
Anti-Infective Drugs	**251**	**3,476**	**$845,148.10**	**$243.14**
Dual Drugs	**35**	**1,651**	**$1,721,388**	**$1,042.63**

As expected, active orphan drugs had the highest median cost per claim ($5,470.48) because of their price protection. Despite the small market size discussed above, this figure allows orphan drugs to account for a disproportionately large share of total costs to the Medicare Part D program. The cost per claim of the "median" anti-infective drug was $243.14, smaller than the active orphan "median" drug by a factor of 22.5, reaffirming the appeal of orphan drugs over anti-infectives as a revenue-creating product.

However, the “median” anti-infective drug costs more on a per-claim basis than the overall “median” drug covered by Medicare Part D. This is notable because it suggests that although anti-infectives might not be as lucrative for pharmaceutical companies from a revenue-generating standpoint as orphan drugs or other preferred therapeutic categories such as oncology products, they still command a higher price point than other drugs covered by Medicare. The $243.14 figure will also likely rise in future years beyond 2013, thanks to the high prices charged by Gilead for its hepatitis C products, Sovaldi and Harvoni.

Snapshots of individual drugs within each category were generated using prescription cost and dosage data from GoodRx, an online pharmacy comparison tool. Comparing results across categories, the same picture emerges: Orphan drugs cost more than anti-infectives. Even drugs with inactive orphan designations (which are therefore subject to generic competition) command higher prices than anti-infectives. The average inactive orphan drug received $1,211.96 more than the average anti-infective drug; for active orphans, that differential ballooned to $5,123.06. After removing outliers skewed as high as $52,000 for a single orphan drug, active orphans retain a significant price advantage over inactive orphan drugs, which was expected because of their price insulation, as seen in Table 3.

Table 3: Analyzing Orphan and Anti-Infective Drugs at the Per-Unit Level

	Inactive Orphans			Active Orphans			Anti-Infectives		
	Cost of Drug ($)	**Cost per Unit ($)**	**Cost per Mg or mL ($)**	**Cost of Drug ($)**	**Cost per Unit ($)**	**Cost per Mg or mL ($)**	**Cost of Drug ($)**	**Cost per Unit ($)**	**Cost per Mg or mL ($)**
Mean	1,539	384.41	24.87	5,450.1	595.35	378.40	327.04	19.05	0.04
Median	586.50	107.49	0.87	5,192	212.57	3.87	118.41	6.41	.02
Std. Dev.	2,143.7	542.6	42.56	4,823.0	810.01	2,141.71	434.93	25.78	0.05
n	180	180	148	123	114	110	193	190	169

The price relationship between active orphans, inactive orphans and anti-infectives holds true across all data points. After controlling for the number of units in a prescription (i.e. number of pills, number of vials, etc.), active orphan drugs commanded a median price nearly double that of inactive drugs and 33 times higher than the unit price of the median anti-infective drug. Diving one level deeper, the median active orphan drug costs a patient $3.87 per milligram or milliliter, compared to $0.87/mg or mL for the average inactive orphan drug and $0.02/mg or mL for the average anti-infective. Based on patient population size and manufacturing costs, a company that knows it will earn $3.87 for each milligram of a substance produced in one therapeutic category compared to just two cents in another, faces a relatively easy investment decision, particularly because of the long timeline and high costs often associated with bringing anti-infectives from bench to bedside.

All three groups of drugs were highly volatile across the pricing categories, indicating that establishing an approximate revenue projection for an orphan or anti-infective drug could prove challenging. However, the analysis still shows conclusively that orphan drugs command

higher prices than anti-infectives, due in large part to the exclusivity provisions in place and the inelastic demand of patients with rare diseases. The next section of this policy analysis explores the potential effects of that pricing reality on firms' R&D investment decisions.

GoodRx listed prices for three of six drugs approved as QIDP-designated drugs under the GAIN Act. Both Dalvance and Orbactiv were priced at more than $1,000, and Cresemba was listed at $246.36. This suggests that QIDP-designated drugs may enjoy some level of price premium over regular anti-infectives, whether due to their exclusivity or the serious nature of the pathogens they are fighting against.

C. Analyzing the R&D Pipelines of Top Drug Companies

During the course of the past decade, anti-infectives have become less prevalent within the pipelines of the world's biggest drug companies, relative to oncology and other therapeutic categories. Table 4 shows the combined pipelines of the world's 15 largest pharmaceutical companies by 2014 sales (Novartis, Pfizer, Roche, Sanofi, Merck, Johnson & Johnson, GlaxoSmithKline, Gilead, Takeda, AbbVie, AstraZeneca, Amgen, Teva, Lilly and Bristol-Myers-Squibb) as of July 1, 2015, grouped by therapeutic category.

Table 4: The Pipelines of the World's 15 Largest Pharmaceutical Companies

	Therapeutic Category										
STAGE	Cardiovascular/ Metabolic/Renal	Immunology/Inflammation/ Dermatology/Respiratory	Neuroscience & Pain	Oncology	Vaccines	Biosimilars	Infectious Disease	Rare Diseases	Virology	Other	TOTAL
Phase I	25	48	24	111	11	1	11	7	1	14	253
Phase II	31	67	36	72	16	0	22	7	2	16	269
Phase III	23	45	19	85	12	10	15	7	1	14	231
Submission	7	12	6	16	8	1	5	1	3	7	66
Other	0	0	0	0	0	6	0	0	0	0	6
TOTAL	86	172	85	284	47	18	53	22	7	51	825
PERCENT	10.42%	20.85%	10.30%	34.42%	5.70%	2.18%	6.42%	2.67%	0.85%	6.18%	

Fifty-three of 825 (6.42%) drug indications in the pipeline target infectious diseases. A majority (62.3%) of those indications are currently in Phase I or Phase II clinical trials, which means that they are still several years from coming to market, if they survive the clinical trial phase. However, the large proportion of indications in the early stages of development also suggests that the anti-infective pipeline is no longer in danger of running dry in the near future.

Four other therapeutic categories account for a larger percentage of the overall pipeline: oncology (34.42%); immunology/inflammation/dermatology/respiratory (20.85%); cardiovascular/metabolic/renal (10.42%); and neuroscience and pain (10.3%). Vaccines and virology accounted for another 6.55% of the combined drug portfolio, mostly in the vaccine subcategory. Drugs specifically denoted as targeting "rare diseases" added another 22 indications to the pipeline, though some drugs classified within other therapeutic categories might overlap with the rare disease category as well.

In 2004, Spellberg et al. used similar methodology to evaluate the position of novel infectious disease treatments at large pharmaceutical companies. They found 31 new molecular entities (NMEs) targeting anti-infectives, or 9.8% of the 315 total NMEs. A new molecular entity is a drug with an active component that the FDA has never approved. As is currently the case, oncology was the most popular therapeutic category with 67 NMEs (21.3%). The most recent set of data accounts for both new NMEs and previously approved drugs seeking new indications because not all companies distinguished between the two when disclosing their pipelines, so a strict comparison is not possible. However, it appears that companies are putting a greater focus on finding drugs to treat cancer. Table 5 summarizes Spellberg et al.'s findings.

Table 5: Prevalence of New Molecular Entities by Therapeutic Category in 2004

Type of Agent	Number of NMEs	Percentage of total
Cancer	67	21.3%
Inflammation/pain	33	10.5%
Metabolic/Endocrine	34	10.8%
Pulmonary	32	10.2%
Anti-infective	31	9.8%
Neurological	24	7.6%
Vaccines	18	5.7%
Psychiatric	16	5.1%
Cardiac	15	4.8%
Hematologic	12	3.8%
Gastrointestinal	13	4.1%
Genitourinary	12	3.8%
Ocular	4	1.3%
Dermatological	4	1.3%
TOTAL	315	

D. Research and Development Costs

Since Spellberg et al. published their study in 2004, research and development expenditures have increased by an average of more than $2.3 billion and 71.9% in total R&D spending at the world's largest 15 pharmaceutical companies (see Graph 1 and Table 6). After controlling for inflation during the previous decade and presenting yearly R&D figures in terms of 2004 U.S. dollars, there is still a $1.2 billion increase in average R&D spending per company and a 37.2% increase in overall R&D spending at those companies, though R&D spending has declined in real-dollar terms since 2010 (see Graph 2 and Table 7).

These findings indicate that the fall in the share of anti-infective representation in the pipelines of the world's top pharmaceutical companies cannot be attributed to across-the-board declines in pharmaceutical R&D. Rather, the shift away from anti-infectives appears to be a systematic choice. Companies are ratcheting up spending in other areas at the expense of pursuing new anti-infective agents.

Graph 1: R&D Spending at the World's Largest Pharmaceutical Companies: 2004-2014

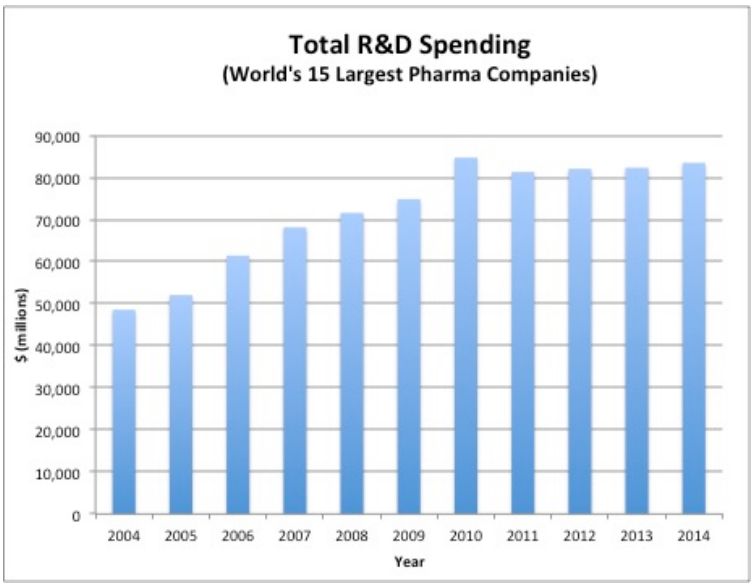


Table 6: Nominal R&D Spending at the World's Largest 15 Pharmaceutical Companies

Nominal R&D Spending (in millions of USD)
Among World's Largest 15 Pharma Co.

YEAR	AVERAGE	TOTAL
2004	3,237	48,554
2005	3,469	52,040
2006	4,094	61,413
2007	4,543	68,138
2008	4,772	71,574
2009	4,991	74,871
2010	5,649	84,733
2011	5,420	81,295
2012	5,471	82,058
2013	5,488	82,323
2014	5,565	83,474

Graph 2: R&D Spending at the World's Largest Pharmaceutical Companies (2004 USD)

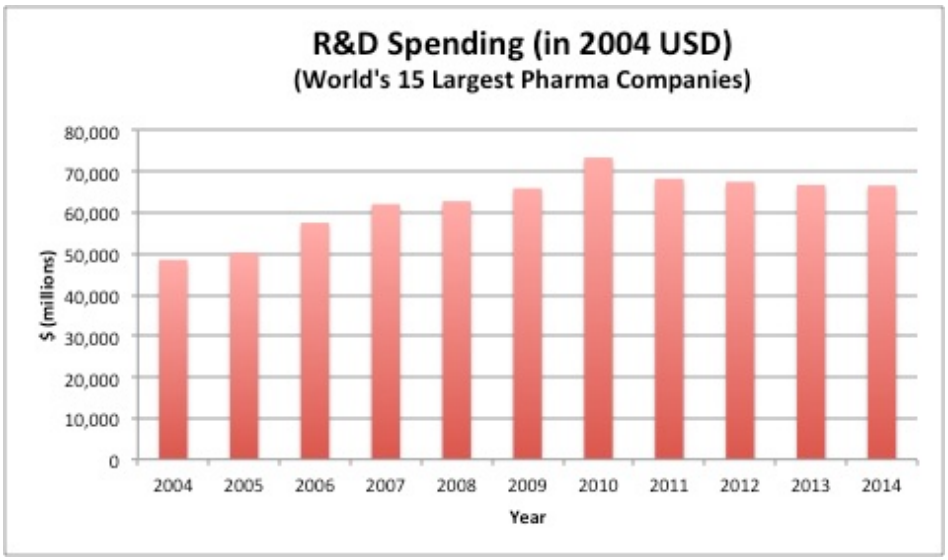


Table 7: R&D Spending at the World's Largest 15 Pharmaceutical Companies (2004 USD)

R&D Spending (in millions of 2004 USD)
Among World's Largest 15 Pharma Co.

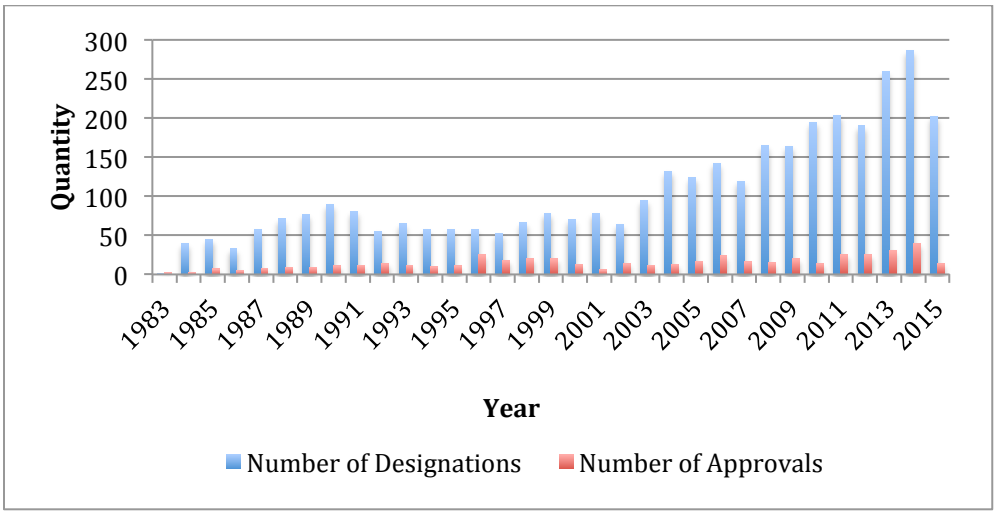
YEAR	AVERAGE	TOTAL
2004	3,237	48,554
2005	3,356	50,335
2006	3,836	57,545
2007	4,138	62,077
2008	4,186	62,797
2009	4,395	65,924
2010	4,894	73,404
2011	4,551	68,269
2012	4,501	67,514
2013	4,450	66,754
2014	4,440	66,607

E. Measuring the Response to the GAIN Act

In the three years following passage of the GAIN Act in July 2012, 43 drugs were designated as Qualified Infectious Disease Products (QIDPs), six of which were approved by the FDA. This response appears tepid compared to the reaction triggered by the passage of the Orphan Drug Act. In the three years following enactment, 85 compounds received orphan designations and 12 were approved by Jan. 1, 1986 (a total of 40 of those original 85 orphan designations eventually received the green light from the FDA).

However, as Graph 3 shows below, the initial response to the Orphan Drug Act was only a small part of the law's impact across four decades. The six years with the most orphan designations have all occurred since 2010. This could be because companies are looking to generate additional sources of revenue while incurring minimal costs. Finding a new indication for an already-existing orphan drug allows the company to save on the research costs (and high failure rate) of developing a new drug.

Graph 3: Impact of the Orphan Drug Act, January 1983-July 2015



F. The (Lack of) Impact of the GAIN Act on Corporate Communications with Investors

Analysis of 85 quarterly earnings call transcripts for the world's 15 largest pharmaceutical companies did not produce a single mention of the GAIN Act—"GAIN" (and its long-form title, "Generating Antibiotic Incentives Now") was the only search term that did not return any search results across the entire data set studied. Yet discussions of the roles of exclusivity and the government in the pharmaceutical companies' business—two key components of the GAIN Act—were the two most frequently mentioned key words by company executives (see Tables 8 and 9).

Table 8: Frequency of Keywords in Earnings Call Transcripts

		Key Word													
		Act	GAIN	economy	orphan	rare	federal	antibiotic	anti-infective	Congress	bacterial	infectious	exclusivity	incentive	immunology	government
Quarter	2008 Q4	2	0	21	1	0	4	1	2	3	1	5	16	1	9	31
	2012 Q1	1	0	1	1	5	3	1	2	2	0	5	30	1	8	18
	2012 Q2	3	0	1	0	2	2	1	1	0	0	3	42	2	8	44
	2012 Q3	1	0	5	1	0	6	0	0	1	1	5	38	0	6	28
	2012 Q4	8	0	6	0	4	6	2	1	4	1	0	37	1	16	19
	2015 Q2	0	0	4	4	6	1	4	2	2	1	5	26	0	20	13
	TOTAL	15	0	38	7	17	22	9	8	12	4	23	189	5	67	153

Table 9: Collections of Keywords in Earnings Call Transcripts

Category	Number of Mentions
GAIN Act	0
Government Impact	202
Antibiotic	44
Incentives	194
Economy	38
Immunology	67

Four keywords were selected to evaluate discussion of the anti-infective sphere during these calls. Company executives mentioned "infectious", "anti-infective", "bacterial" and

"antibiotic" a combined 44 times, but passage of the GAIN Act in 2012 did not correspond with a noticeable uptick in frequency of these keywords. Indeed, executives talked openly about their priorities, which often times did not include anti-infectives. AstraZeneca admitted in its fourth-quarter 2012 call that "Our priority is clearly going to be covering metabolism, oncology and respiratory inflammation. And to a lesser degree, anti-infectives." In April 2012, GlaxoSmithKline CEO Andrew Witty pinned the lack of interest in developing new anti-infective agents on low disease incidence: "I don't think anybody thinks that infectious disease agents have been beaten, and we're not going to see a return to growth in that marketplace. We are. It's just we've gone through what has been a prolonged cycle of relatively low disease."

Gilead, with its high-priced, highly effective duo of hepatitis C drugs, Sovaldi and Harvoni, was an exception among the firms, devoting much of its July 2015 earnings call to progress reports on those two anti-infective products. Executives mentioned Harvoni 29 times and Sovaldi 20 times, proving that is possible for successful anti-infective products to dominate a company's business model and agenda.

To continue the comparison between the two drug markets, the words "orphan" and "rare" were mentioned a combined 24 times. Unlike with anti-infectives, though, executives embraced the revenue-generating potential of these drugs, often citing opportunities for diversification into new indications. As Johnson & Johnson Chief Scientific Officer Paul Stoffels explained on October 16, 2012, a drug originally approved as a rare drug to treat Crohn's Disease "grew from an orphan indication to 16 different indications, and [the firm is] taking a similar approach to many of our products in other therapeutic areas. These products begin with targeted therapies in small indications and grow over time with expanding indications to be pipelines within a product."

The transcripts contained 189 mentions of the word "exclusivity," primarily in contexts relating to its effect on revenue potential for a particular drug or within a specific sector of the company's pipeline. For example, Bristol-Meyers-Squibb Chief Financial Officer Charles A. Bancroft noted in the company's Q1 2012 that "[W]e are coming to the end of the market exclusivity period for PLAVIX and AVAPRO in the U.S. and have lost exclusivity in Canada. During the quarter, sales for PLAVIX and AVAPRO were down 4% and 29%, respectively, driven in part by U.S. prescription trends."

The next quarter, AstraZeneca CFO Simon Lowth lamented that "Products with [loss] of exclusivity accounted for 15 percentage points of our 18% decline in second quarter revenue in constant currency terms." More recently, Pfizer CFO Frank D'Amelio noted in Pfizer's Q2 2015 that the company would absorb $3.4 billion in losses impact due to the expiration of product exclusivity.

The focus on exclusivity was widespread across the sample—the keyword appeared in the transcripts of every company except GlaxoSmithKline—but it seemed to be of particular significance to AstraZeneca, which accounted for 30.7% of total mentions (58). Although exclusivity was not mentioned within the framework of the GAIN Act, its importance as the most common keyword indicates that it is a primary concern for pharmaceutical companies, because of its importance in protecting firms from generic competition (and thus enabling higher prices and revenue collection). As such, it appears that the architects of the GAIN Act were smart to include extended exclusivity as one of the law's primary incentives. However, neither the exclusivity tied into the GAIN Act nor the GAIN Act itself were specifically mentioned during any of the earnings calls.

Beyond exclusivity—which can be implicitly assumed to be a function of prior government action—companies also repeatedly mentioned the role and effect of the government on their businesses. Surprisingly, many of the 153 mentions of "government" action at either the domestic or international level blamed governments for eating into profit margins. Abbott Executive Vice President Thomas C. Freyman hoped that "the government won't be quite as aggressive as we go forward," criticizing austerity measures in Europe. Other executives faulted governments around the world for downward pressure on prices, suppressing revenue. On the other hand, many companies made positive note of the U.S. federal tax credit for research and development, which created a $15 million benefit for Gilead in 2008.

For many companies, governments in emerging markets account for a significant fraction of sales. During its Q2 2015 call, Johnson & Johnson noted that "We're encouraged by the steps governments are taking to increase access to quality health care for their people and to also create and support a more innovation-friendly environment through designations that speed the review and approval of transformational products." Though not specifically mentioned, the GAIN Act is one such designation-driven, innovation-friendly attempt to spur additional R&D. The high number of mentions of government involvement during the earnings calls indicates acknowledgement on the part of pharmaceutical companies that government action is an important driver in their decision-making. Congress must now devise the appropriate incentives to drive those decisions toward increased R&D spending for anti-infectives.

The economy was another common talking point for company executives, particularly in the fourth quarter of 2008, when the world was still roiling in the midst of the financial crisis. Twenty-one mentions of the economy occur during this quarter's set of calls, or 55.3% of the total number of mentions. Unlike the other keywords, "economy" showed significant

fluctuations over time—companies did not mention it much during early 2012, but became concerned again by the end of 2012 and into 2015.

Discussion

The world's top 15 pharmaceutical companies acknowledge the role played by government in their business and the importance of drug exclusivity in driving bottom-line revenues and profits, but do not appear to have been swayed to action following passage of the GAIN Act in 2012. The GAIN Act itself was not mentioned in any of the transcripts analyzed, suggesting that the law and its myriad incentives have not materially affected the way these large companies approach anti-infective R&D.

The reactions of the pharmaceutical community to the Orphan Drug Act and GAIN Act are strikingly different. In the first three years following enactment of the Orphan Drug Act, 37 of the first 85 orphan drug designations were awarded to entities now under the control of the world's largest 15 pharmaceutical companies. Indeed, the success of orphan drugs has served as a catalyst for many of the acquisitions that have helped large companies like Roche and Johnson & Johnson diversify their portfolios. However, many of the orphan drug designations are not novel investments in newly developed drugs, but rather label expansions of pre-existing drugs (Schulman). Once again, the appeal of additional exclusivity is appealing to firms, and the barriers and clinical endpoints for approval as an orphan designation tend to be less burdensome, since the drug is treating a rare condition (Schulman). The market clearly responded to the Orphan Drug Act, but the amount of novel investment in new drugs is much less than Graph 3 indicates.

By contrast, only two of the 43 QIDP drug designations analyzed in this study can be traced to a top-15 pharmaceutical company—one project overseen by Merck and a joint effort between Entasis Therapeutics and AstraZeneca. The full list is broader, however; Tomaras and Dunman credit the FDA with designating 71 QIDP products as of March 26, 2015 (Tomaras and Dunman 2015). All QIDP designations should be examined to see if the trend holds, but drug discovery response to the GAIN Act appears to be driven primarily by smaller pharmaceutical and biotechnology firms, who often partner with these larger companies down the road as their products move toward FDA approval.

There are several additional reasons why large pharmaceutical companies may be avoiding—or even exiting—the antibiotic market, beyond the obvious price differences compared to orphan drugs. As opposed to orphan drugs—which are generally picked up from the pharmacy—antibiotics are frequently used in hospitals, which are very price-sensitive (Schulman). This helps explain the depressed cost of anti-infectives, because hospitals simply are not willing to pay more. In addition, the current system treats powerful new antibiotics as a form of insurance; when developed, they are often held in reserve for severe infections when patients do not respond to first-line treatments (Schulman). This adoption model makes it difficult for companies to start recouping their investment, because their product is held out of use so that resistance to it does not begin to develop; those research dollars may be better spent on other therapeutic categories like oncology, where it will be prescribed and used for a high price. Finally, treatment costs during the clinical trials process are greater than in other therapeutic categories because physicians cannot definitively confirm a specific bacterial infection for 48 hours; as a result, patients get randomized into a treatment during a clinical trial without researchers knowing for sure whether they qualify for the study (Schulman).

Considered independently, the incentives laid out in the GAIN Act appear unlikely to entice the hoped-for return of research and development dollars by large pharmaceutical companies, though the Act should still be afforded more time before a firm verdict is reached. Although the FDA has designated scores of products as QIDPs, the response has come nearly entirely from smaller pharmaceutical and biotechnology companies. Furthermore, the QIDP designations to date have clustered around one or two conditions—namely acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP)—creating a race to put a product in front of the FDA for approval.

Although that competition is healthy in promoting development of novel treatments for those conditions more swiftly, the disproportionate focus on ABSSSI and CABP comes with an opportunity cost, as other infectious diseases continue to go untreated. Small companies often struggle to attract capital to develop their projects, forcing them to pursue the quickest path to get to the market with a product and begin generating revenues (Schulman). This could explain the industry's current emphasis on ABSSSI and CABP treatments, as opposed to other conditions such as tuberculosis or MRSA. Future research could examine the cost and timeline for developing approved QIDP products compared to anti-infectives as a whole; if the GAIN Act is encouraging companies to pursue anti-infectives, but only those that are most cost- and time-effective to bring to market, then the law's incentives need to be rethought.

The GAIN incentives, based on those in the Orphan Drug Act of 1983, may not be appropriate for the anti-infective industry, given the significant differences found between the orphan and ant-infective markets. Of course, the presence of the seven years of extended exclusivity for orphan drugs is a driving factor behind many of those differences; however,

simply applying similar exclusivity provisions to QIDP-designated anti-infectives should not be expected to produce extreme price increases among those QIDP drugs.

The orphan drug patient population is by definition very small, and the number of patients who will take a specific orphan drug pales in comparison to the number of patients who will utilize a specific anti-infective. The small patient population in an orphan drug market enables a pharmaceutical company to significantly increase the price for that particular product without fear of a public relations disaster. Patient demand for the orphan drug tends to be continuous and highly inelastic—they need the drug to sustain their quality of life, regardless of its price. Conversely, anti-infectives have big patient populations who use the drugs for a short, finite period of time, rarely longer than six weeks (Schulman). The extended period of exclusivity under the GAIN Act would allow companies to set higher prices for their QIDP-approved drugs because of the lack of competition, but would be less palatable among the larger user base. Distinct differences in the market sizes and usage needs of patients in the orphan and anti-infective spheres will make it difficult for GAIN Act exclusivity incentives to mirror the success of the Orphan Drug Act.

The combination of these forces leads American healthcare consumers to seemingly irrational preferences: the market values treatments that improve a patient's quality of life without providing a cure (orphan drugs) more highly than life-saving treatments (anti-infective drugs). As a result, the large pharmaceutical companies who have tacked on orphan designations to existing drug labels receive an outsized return on their investment, while companies pursuing infectious diseases may struggle to reach a break-even point (Schulman). The Orphan Drug Act is a success in the number of drugs that have been brought to market for the treatment of rare

conditions; however, the price of exclusivity is paid again and again by patients (and their insurers) forced to deal with monopolistic pricing.

With all of this said, hepatitis C presents an interesting counterfactual for the anti-infective market. Gilead's breakthrough treatment, Sovaldi, has been wildly successful—with a 90 percent success rate—and immensely lucrative, selling for $84,000 per 12 weeks, or $1,000 per pill (Sanger-Katz). Its follow-on treatment, Harvoni, commanded an even higher price, ultimately leading to a U.S. Senate Finance Committee investigation into Gilead's pricing model for the drugs (Hiltzik). The cost of treatment prevented many patients from receiving it as insurers balked at the high prices. But the demand for Sovaldi and Harvoni remains huge, showing that, despite their short length of use, anti-infectives can become blockbuster drugs that deliver significant revenues to a company. Gilead's dynamic duo may just be an outlier, but their success will likely push other firms to try to replicate that magic (Schulman). If true, that may be good for the GAIN Act's goal of developing new anti-infective treatments, but it may not matter if prices begin to go through the roof.

In March, the Obama administration released its National Action Plan (NAP) for Combating Antibacterial Resistance, a program aimed primarily at developing measures for slowing resistance and improved methods of infection detection. The NAP should be complemented with a renewed federal commitment to basic scientific and medical research, where public funding dollars have been declining. If anti-infective agents are indeed a priority for the federal government, it should play a larger role in their development, not just adding exclusivity extensions to post-approval patent protection. Producing anti-infective products involves a long development timeframe, high costs and a high rate of failure; those current-period costs accrue a significantly larger weight in a firm's net present value calculation when

deciding whether or not to invest in basic research than a hypothetical, five-year exclusivity extension once a product is approved.

Rather than offer incentives at the end of the drug development tunnel, the government should entice pharmaceutical companies with upfront benefits to induce market entry. These incentives could take the form of subsidies, matching grants for R&D dollars earmarked specifically for anti-infective work or tax credits for new anti-infective discoveries made in a company's lab. Awarding incentives at the start of the development process provides tangible, immediate benefits for companies. In addition, these incentives would not give manufacturers an opportunity to use exclusivity to inflict painful price increases on consumers in the same way that the exclusivity provision of the Orphan Drug Act has adversely impacted price points for patients in that market. The Orphan Drug Act also included other provisions to help firms get projects off the ground with the tax credit for clinical trials and grants supporting orphan drug—the law's success is attributable to more than just the exclusivity provision, which bears responsibility for many problems, including today's high prices. The GAIN Act included a fast-track review process for QIDP drugs—another end-of-pipeline incentive—in addition to the five years of exclusivity; the government should instead look to place its policies at the front of the development process.

Alternatively, the federal government could move away from an exclusivity-based incentive model altogether. Rather than allow firms to charge high prices borne by patients and the Medicare program, the government could pay a sizable prize directly to a company that successfully gets an anti-infective product to the market. This would enable the firm to recoup some of its investment immediately and shift some of the high-price pain away from patients (Schulman). The FDA could also examine adjusting the regulatory hurdles it sets for firms. The

agency lowered its thresholds for anti-virals when the AIDS epidemic became a national and international crisis, and firm investment in anti-viral research and development has remained strong (Schulman).

Critics might argue that the federal government cannot afford such expenditures, particularly when most basic discoveries never materialize into an approved drug. However, President Obama proposed doubling the level of funding for preventing antibiotic resistance to $1.2 billion in his FY 2016 budget (Gupta). A crisis that is responsible for the deaths of 23,000 Americans each year deserves a strong response (Gupta).

Conclusion

Antibacterial resistance represents a dire threat to millions of people around the world, and the current pharmaceutical pipeline is not well equipped to provide doctors and patients with new treatments as resistance strengthens. Congress responded by enacting the GAIN Act in July 2012 to incentivize pharmaceutical companies to reinvest in bringing to market new anti-infective drugs that will target some of the more dangerous resistant strains. The GAIN Act incentives were modeled on those in the Orphan Drug Act of 1983. However, after three years, the incentives do not appear likely to foster the desired change on their own.

The orphan drug market and anti-infective markets are incompatible peers by nearly every measurable category. Anti-infective drugs have a much broader patient population, but sell for significantly lower per-unit prices than orphan drugs, which command high prices under pricing models while still enjoying protection from generic competition by patent exclusivity. Whereas orphan drugs are taken for a long period of time, anti-infectives serve their purpose

quickly and then are no longer needed; new anti-infectives may not even be deployed in order to retain them as insurance in the case of an epidemic or bacterial resistance. Once exclusivity expires, orphan drugs still bring in more revenue than anti-infectives, making anti-infectives a less attractive investment opportunity for pharmaceutical companies.

In the past decade, the pipeline has continued to dry; anti-infectives accounted for nearly 10% of new molecular entities under development by the world's top 15 pharmaceutical companies in 2004, but just 6.42% of sought-after indications in 2015. The GAIN Act does not appear to have done much to reverse this trend; content analysis of quarterly earnings calls finds that executives at the world's 15 largest pharmaceutical companies failed to mention the Act even once since its passage in July 2012. Although exclusivity and government action were high priorities for executives, this did not translate into the anti-infective sphere, indicating that anti-infective research and development remains an afterthought. As long as this continues, the GAIN Act cannot be considered successful and its incentives must be re-examined and reworked to change the status quo.

This paper has several important limitations. First, the timeframe needed to bring a drug from bench to bedside can be a decade or more, and this project is evaluating the initial impact of the GAIN Act just three years after its adoption. A comprehensive review of the Act's results should be undertaken after at least a decade, once companies have had more time to reallocate their financial resources and make the basic research discoveries that could lead to new anti-infective drugs. Second, the data used to perform the market sizing for both orphan and anti-infective drugs is taken from the Medicare Part D population—an elderly, sick population that is not illustrative of the entire U.S. patient population. Furthermore, the data gathered from GoodRx does not take into consideration the effects of insurance companies and rebates on the

profit levels each drug returns to its manufacturer. Finally, all data points on designations, prices, pipeline classifications and transcript analysis was manually generated, classified and coded, leaving open the possibility of human error.

Further research should apply Spellberg et al.'s methodology to smaller pharmaceutical and biotechnology companies, seeking to evaluate shifts in their pipelines over time in response to passage of the GAIN Act. Expanding this methodology to other companies where data is available is of particular importance because smaller firms appear to be taking the lead on new-infectives. Those firms eventually license late-stage production to larger companies. Targeting large pharmaceutical companies with the incentives in the GAIN Act seems to make sense because those firms can tap into their greater pool of resources to generate more anti-infective products. However, economies of scale will only work if the economics to invest make sense.

The GAIN Act has stimulated a drug development response among smaller companies, but new incentives may be necessary to push larger pharmaceutical companies to devote resources into R&D for anti-infectives. As long as the major players in the pharmaceutical industry continue to treat the current state of affairs as a "prolonged cycle of relatively low disease," the needs of patients suffering from infectious disease will continue to go unmet.

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Interviews

Schulman, Kevin. Professor of medicine, business administration and global health at the Duke University School of Medicine and associate director of the Duke Clinical Research Institute. In-person interview conducted on November 5, 2015.

Appendix A—List of Sample Interview Questions

- What changes, if any, have you noticed in the market environment since the GAIN Act was passed?
- Are the incentives in the GAIN Act sufficient to foster the development of the next crop of antibiotic drugs? Why or why not?
- In what ways are the orphan drug and anti-infective drug markets similar, and in what ways are they different?
- Why has the number of drugs for rare conditions increased so dramatically since passage of the Orphan Drug Act in 1983? What other factors beyond the incentives in that law, if any, have led to this increase?
- Beyond the incentives in the GAIN Act, how else should the U.S. government be promoting and incentivizing the development of new anti-infectives and antibiotics?
- Why is the antibiotic drug pipeline currently not an attractive area for research and development? What changes must be made to make it more attractive?
- Is additional market exclusivity a strong incentive in the orphan drug market? Is it a strong incentive in the anti-infective drug market?
- Are researchers hesitant about going into careers in antimicrobial research? If so, why, and how can this be changed?