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Public Policy to Lower Prices and Deter Rent Seeking in Prescription Drug Markets

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Disclaimer

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Executive Summary

High drug prices are a top public concern among Americans today. The reasons that high drug prices can persist in off-patent, generic drug markets include the lack of competition and/or buyers' negotiating leverage. In the unique market for prescription drugs, the Food and Drug Administration (FDA) is a gatekeeper that limits competition as it attempts to maintain drug safety and efficacy. User fees charged to drugmakers are regressive, falling primarily on small drugmakers that would otherwise enter off-patent drug markets. Regulations to gain marketing approval are also burdensome and require years before firms can sell products to patients. Meanwhile, the United States government has avoided using monopsony power by directly negotiating prices with drugmakers, favoring broad drug choices over lower prices.

This paper reviews three leading policy counterfactuals that could reasonably be used to target high drug prices of often times old and small market drugs. An "economic pathway" is a novel concept that would add to the FDA's authority to target off-patent drugs, particularly those with no competitors. Reciprocal marketing approvals between countries is an emerging policy concept that offers substantial social benefits from trade of drugs already approved to be safe and effective. Direct price negotiation—a policy that has been discussed for years—would deliver substantial savings to public programs, but would likely reduce price competition due to market entry. Years of heavy regulation and mandates on off-patent, generic drug markets have created barriers to entry that far exceed those of America's trading partners. While reciprocal approvals would provide the most potential benefits, joining lower bound estimates of this policy with the economic pathway would yield net benefits equivalent to direct negotiation. Competition can continue to deliver savings to patients and taxpayers that are at least equivalent to direct government negotiation.

Introduction

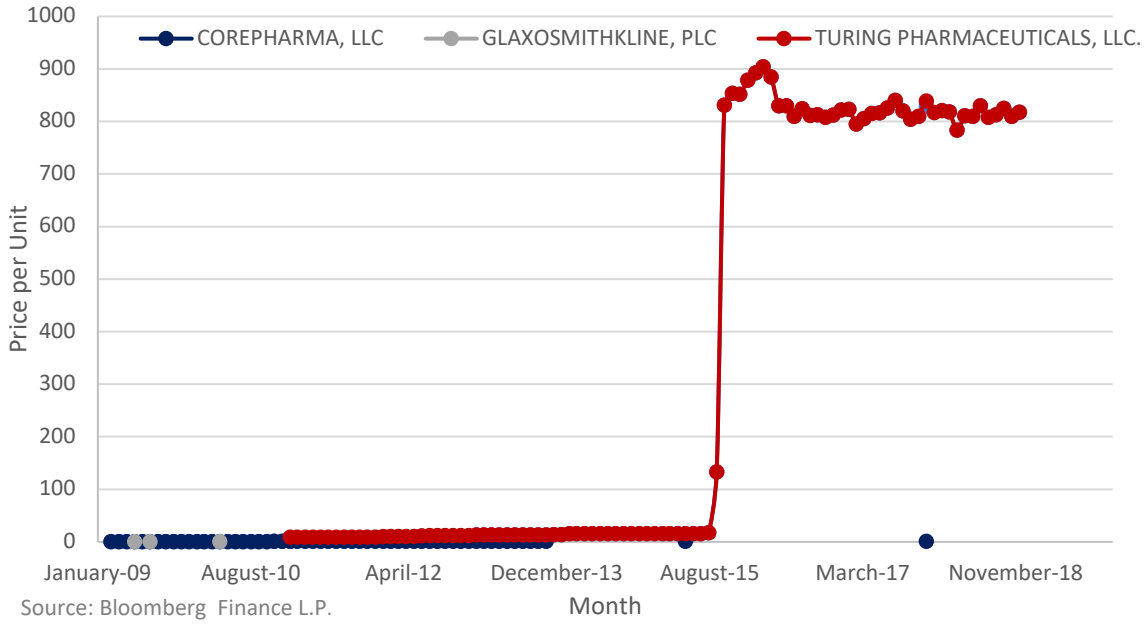
America is unique in the way that it uses markets to deliver prescription drugs to patients by favoring choice and allowing for competition to lower prices. Prescription drug markets provide significant social benefits, but a lack of competition can lead to market power and high prices. While innovators are awarded patents to encourage novel drug development, the off-patent generic drug market should have no monopoly power to earn economic rents. Over years of market regulation, barriers to entry have created highly concentrated markets for over half of the prescriptions sold in the country. The result is that generic drugmakers with no patent rights can raise prices without consequence.

The incidence of a high drug price falls largely on patients in the form of reduced access and on taxpayers through increased public expenditures. A panoply of cross-country comparisons and disease-specific evaluations imply that prescription drug spending results in improved health outcomes, quality of life, and longevity (Cremieux et al. 2007). By raising prices through monopoly power, generic drugmakers are crowding out public funds for other goods and services. Public policy should encourage scientists, financiers, and marketers to discover new therapies and bring them to market, rather than seek out economic rents for drugs that have been available for years.

Patients are increasingly buying off-patent generic drugs in these concentrated markets. Generic drug markets account for 90 percent of prescriptions sold, up from 72 percent in 2008 (IQVIA 2018). This is the result of generics being offered in 92 percent of drug markets and dispensed 97 percent of the time they are offered. The share of off-patent generic drugs with only one drugmaker remained around 40 percent from 2004 to 2016 (Berndt et al. 2011). Generics account for 23 percent of the $324 billion U.S. prescription drug market.

An infamous case of rapid price increases occurred in 2015 when Martin Shkreli, the CEO of Turing Pharmaceuticals, acquired the rights to Daraprim and increased the price by several hundred dollars overnight (Figure 1). Daraprim is a lifesaving drug first approved by the FDA in 1953 and is prescribed to treat toxoplasmosis, a disease from a common parasitic infection, which is also common among people with HIV-AIDS (Johnson 2017). The fact that the retail price remains above $800 per unit to this day with no competitors in sight suggests that the government policy for small market drugs is in need of a change. The General Accountability Office (GAO) recently identified a few hundred off-patent generic drugs—many of which were approved long ago and are sold to small patient populations—with prices doubling between 2010 to 2015 (GAO 2016).

Figure 1: Price per Retail Unit of Daraprim in the United States, 2009-18



Prices of generic and off-patent drugs in concentrated markets with few suppliers are higher in the United States than in comparable countries. Two primary mechanisms explain much of the price variation in drug markets: competition between drugmakers and leverage of the drug buyer in price

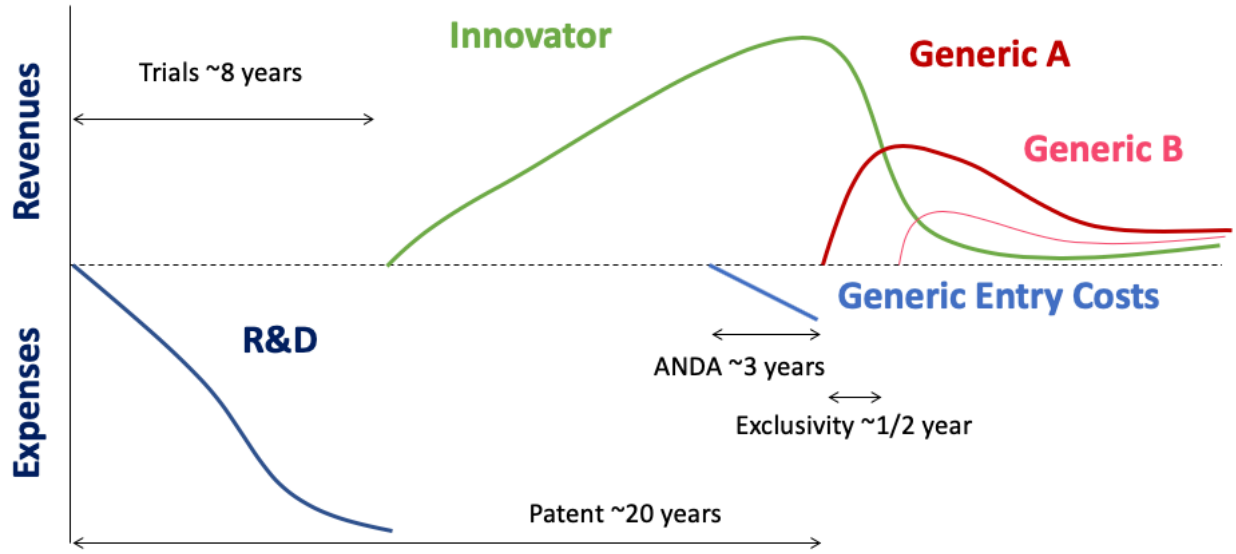
negotiations. This paper examines four policies to lower off-patent generic drug prices and attenuate drugmakers' ability earn economic rents.

Background and Literature Review

1. FDA Generic Drug Approval Process

The economics of the prescription drug market are unique in that there are high-fixed costs to research and development (R&D), low marginal costs of manufacturing, and significant government regulation to ensure the safety and efficacy of the products. While there is a vibrant debate over the precise cost of bringing an innovator drug to market, the cost estimates range from several hundred million dollars to a few billion dollars (ASPE 2016; DiMasi, Grabowski & Hansen 2016). These costs are high due to scientific uncertainty about the effect of new molecular entities on diseases as well as patient safety, which the government oversees through an extensive regulatory process. From clinical discovery to drug marketing, the process of bringing a new drug to market often takes a decade (DiMasi, Grabowski & Hansen 2016). As a result, the failure rate is high for companies deciding to bring a new drug to market, such that hundreds of attempts need to be made for every successful drug on the market. To encourage companies to invest in R&D, the United States government has established a patent system that grants monopoly rights to the innovator for 20 years (Figure 2). The prospect of considerable profits offered through the patent system is what encourages firms to invest in future research and development to discover new therapies.

Figure 2. The Economic Lifecycle of a Prescription Drug



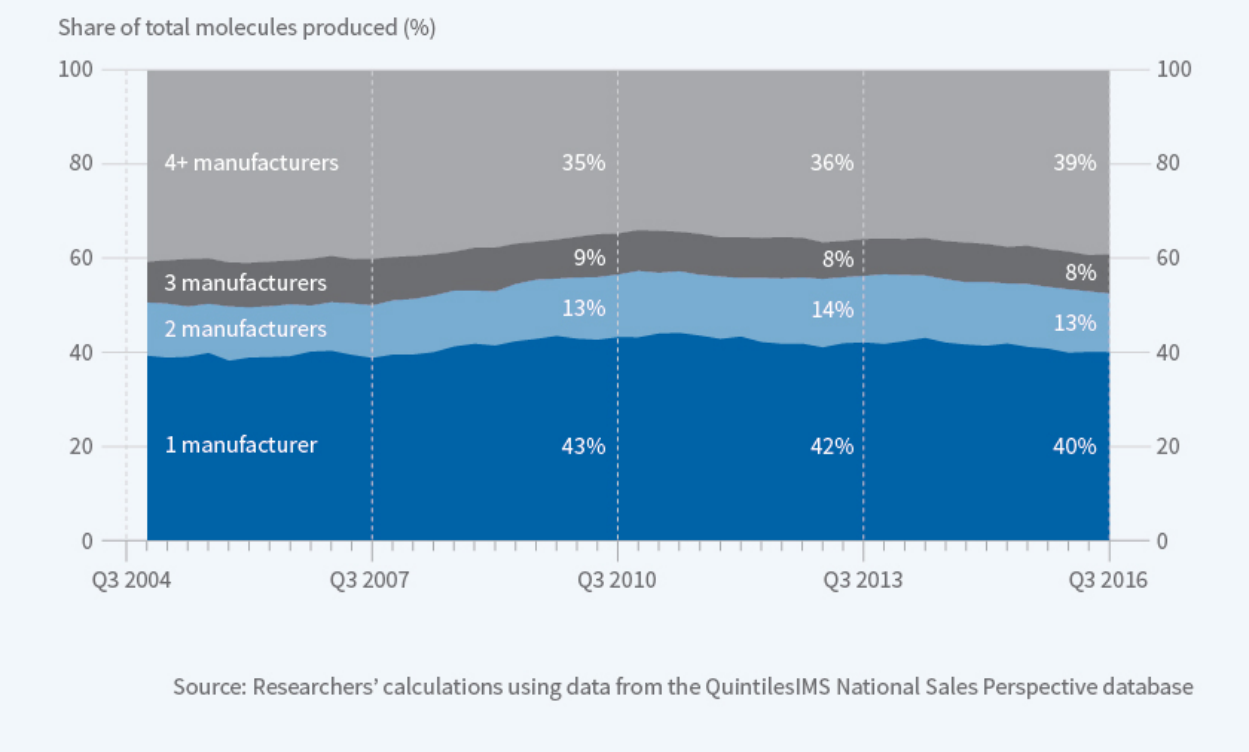
In 1984, the President signed off on the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (formally known as Drug Price Competition and Patent Term Restoration Act). The trade-off established by Hatch-Waxman created strong patent protections for new molecular entities while intending to create a vigorous market for generic drugs once the patent expired. After clinical trials and marketing approvals, patent protection typically provides for a dozen years of marketing and sales exclusivity, granting the equivalent of monopoly rights to innovators. The amendments established an approval pathway for generic drugmakers to submit an abbreviated new drug application (ANDA).

Once an innovator has earned economic profits and the drug patent expires, the framework of Hatch-Waxman encourages a generic drugmaker to apply to the Food and Drug Administration (FDA) for market entry after demonstrating that it can offer consumers a chemically equivalent drug. The first generic drugmaker with an ANDA approved by the FDA receives exclusivity as a generic supplier for 180 days.

The FDA has a dual mandate to ensure the safety and efficacy of all prescriptions sold in the United States (FDA 2015a). Patent expiry, however, does not always result in generic drug competitors due to small market size or low profits that do not justify the application fees and time required to apply for approval. When market size is substantial, there is vigorous price competition to gain market share and drug prices fall, often to pennies on the dollar of the brand name drugs (Caves et al. 1991). Generic drugmakers often decide not to enter small off-patent drug markets, however, due to barriers to entry and lower potential profits (Berndt et al. 2017). Off-patent drugmakers are increasingly preventing competitors from copying and marketing generic drugs through collusion and side payments to delay generic market entry (Towey 2013). This creates market settings where drugmakers have raised prices dramatically with no recourse from a competitor. In the United States, more than half of generic drugs exist in duopolistic markets, while 40 percent are monopolies (Berndt & Aitken 2011; Dave et al. 2017).

There were only several hundred drugmakers over the last decade selling about 2,000 unique molecules (Berndt & Aitken 2011). While brands make up a larger share of drug sales, generics have increased over time from 17 percent of sales in 2004 to 26 percent in 2016. Berndt and Aitken found suggestive evidence that the decreasing numbers of generic drugmakers is due to reduced market entry after the Affordable Care Act and GDUFA I (Figure 3).

Figure 3: Competition Among Generic Manufacturers, 2004-16



2. Generic Competition Lowers Drug Prices

The Cournot model of economic competition predicts that prices will fall substantially as only a few competitors enter an eventually oligopolistic market of homogenous goods because firms make simultaneous and independent decisions about quantity of production. The model assumes that firms are profit maximizing and not colluding. Early empirical evidence shows that market entry of generic drugmakers results in generic prices falling to only 17-25 percent of the original price within two years (Caves et al. 1991; Grabowski & Vernon 1992). Berndt and Aitken (2011) estimated that prices fell to six percent of patented prices after 24 months of generic entry. Assuming that these markets are perfectly competitive after dozens of entrants, these estimates imply a 16 percent marginal cost of production—or an 84 percent profit margin. This evidence also suggests that prices are not competitive after a few drugmakers enter the market. Caves et al (1991) found that the first three competitors would lead to substantial price declines that would

cut profit margins in half. Increasing to fifteen competitors, however, effectively eliminate economic profit, bringing the price down to marginal cost (Caves et al. 1991).

This literature is plagued by the endogenous selection of generic drugmakers more vigorously entering large markets where profits are more readily earned. Olson and Wendling (2013) used a feature of the 1984 Hatch-Waxman Act as an instrumental variable to account for endogenous entry of generic entrants and identify a causal effect. The Act allows the FDA to grant a 180-day marketing exclusivity period to a patent litigant, so that only one competitor can enter the market during that time. The study compares differences in entry and drug prices during the exclusivity period to those, measuring endogeneity. The selection effects are pronounced in drugs with large market sizes, but not an issue for drugs with small markets.

Further work explores the extent to which the threat of competition has an effect on drug prices. Gilbert (1989) used theoretical models to understand the effect of entrants' expected profits and pre-entry price of incumbents, but finds a wide range of potential competition from "extremely strong" to no ability to affect price. An empirical analysis of *potential* competition remains to identify whether an entrant into a drug market can lower the price just by threatening to compete, while controlling for endogeneity of entrants when estimating price effects.

To empirically test the effect of potential competition from generic drugmakers on the price of current drugs during and after sales exclusivity, Tenn and Wendling (2014) analyzed potential competition by exploiting Hatch-Waxman's 180-day marketing exclusivity feature. The authors use a difference-in-difference regression to identify differences in price changes between the treatment group assigned exclusivity and the control group not assigned exclusivity. They differentiate between actual competition and potential competition by observing markets where no

additional firms enter the market after the exclusivity period is over. In small drugs markets, incumbents reduce price by 19.4 percent as a strategic deterrent against potential competition. In large drug markets, potential competition does not lower price. Few firms will enter small drug markets due to limited profit potential, which suggests that price reductions just before the end of exclusivity are strategic deterrents to competition. Many firms will enter large drug markets, so the incumbents do not bother with strategic pricing. These results provide very specific answers to the authors' question, yielding a mixed result. This paper is important because it provides causal evidence that (1) generic drug entry lowers prices and (2) the threat of competition will lower prices as well.

In markets where firms manipulate prices, policymakers should consider encouraging entry, discouraging exit, or increasing threats to ensure that more markets are contestable. In the absence of fiat pricing, market competition is a necessary condition of lower drug prices. Even the best health plan or reimbursement model could not lower prices against a monopolist.

3. Buyer's Leverage to Negotiate Lowers Price

Many governments around the world use their monopsony buying power to make take-it-or-leave-it offers to drugmakers in an effort to keep costs down. To employ such negotiating power, a government must be prepared to walk away from a negotiation without an accepted offer and therefore make the drug unavailable to its citizens. This pricing regime exists in many countries with socialized health systems, where patients only have one health plan option unless they are wealthy.

Ganapati and McKinnin (2019) examined off-patent generic drug markets in the United States, the United Kingdom, Australia, Canada, and New Zealand in an effort to understand why prices vary

across countries for the same products. The United States pays prices that are 400 percent higher for off-patent drugs with no competitors, but lower prices when there are several suppliers in the market. Using a Nash bargaining model, the authors seek to explain price variation due to the number of competing drugmakers in the market and market power of the drug buyer. The model's identification strategy is to observe variation in the drug suppliers across international markets. This is a sound strategy so long as pricing is not dynamic such that prices today affect prices tomorrow. In the model's first stage, the determinants of price differences—market competition and buyer negotiating leverage—are identified, using observed variation in the number of drugmakers across international markets by molecule. The second stage yields differences in implied market entry costs, annually.

Danzon and Chao (2000) demonstrated that price negotiation and regulation limit the effect that generic competitors have on drug prices. They suggest that this is due to generic drugmakers rent seeking by introducing reformulations to earn higher prices or licensing to co-marketers rather than competing on price. Anis and Wen (1998) showed that price controls imposed in Canada were associated with price increases in existing drugs from 1987 to 1995.

4. Generic Drug User Fee Amendments

In 2012, the President signed the Food and Drug Administration Safety and Innovation Act (FDASIA), which included the Generic Drug User Fee Amendments (GDUFA I). The amendments allow the FDA to collect user fees from drugmakers for the work involved in reviewing applications and inspecting facilities (FDA 2018).[1] The legislation was partly a response to industry concerns that generic drug applications were burdensome and under FDA review for

[1] https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm.

excessive time periods. Congress designed GDUFA I to reduce application review times and regulatory uncertainty so that industry would focus on delivering more safe and efficacious generic drugs.

In 2017, the President signed the Food and Drug Administration Reauthorization Act (FDARA), which reauthorized GDUFA II for five years (FDA 2018). GDUFA is to be reauthorized every five years. The GDUFA II statute establishes a user fee revenue target of $493,600,000 annually adjusted each year for inflation (FDA 2018). GDUFA II made five primary changes: (1) delay the annual facility fee until an ANDA is approved; (2) charge only the Finished Dosage Form (FDF) fee to a facility that manufacturers Active Pharmaceutical Ingredients (API) and FDF; (3) charge a contracting fee (CMO) of manufacturers making FDF that do not hold an ANDA; (4) introduce annual holder program fee; and (5) eliminate Prior Approval Supplement fees—a charge for updating an application (Berndt et al 2017).

GDUFA II includes a fee schedule for generic drugmakers including application fees, drug master file (DMF) program fees, and facility fees. The generic drugmaker pays the application fee and drug master file fee upon submission of the first ANDA, which goes to fund the FDA's staff reviewing the application. The application typically references a Type II active prescription drug ingredient drug master file and this fee is paid once. Generic drug applicant program fees and facility fees are assessed annually.[2] The FDA assesses the annual program fee dependent on the number of approved ANDAs in a company's drug portfolio (see Table 1). A facility fee is assessed for each distinct facility where drug manufacturing takes place under the application, dependent

[2] https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm.

on location (domestic vs. foreign) and drug form. The intermediate drug form is called Active Pharmaceutical Ingredient (API) and final drug form is called Finished Dosage Form (FDF).

Table 1: GDUFA Fees

(Costs in Thousands)

Fee Type	FY 2018		FY 2019	
Facility Fees	**Domestic**	**Foreign**	**Domestic**	**Foreign**
Active Pharmaceutical Ingredient (API)	$45,367	$60,367	$44,226	$59,226
Finished Dosage Form (FDF)	$211,087	$226,087	$211,305	$226,305
Contract Manufacturing Organization (CMO)	$70,362	$85,362	$70,435	$85,435
ANDA Program Fees – Based upon the number of approved ANDAs held				
Large Portfolio (20 or more ANDAs)	$1,590,792		$1,862,167	
Medium Portfolio (6 – 19 ANDAs)	$636,317		$744,867	
Small Portfolio (5 or fewer ANDAs)	$159,079		$186,217	
Application Fees				
ANDA	$171,823		$178,799	
Type II DMF	$47,829		$55,013	

Source: FDA 2018a

GDUFA altered the funding structure to allocate more resources to the task of reviewing generic drugs. The amendments removed fees for receiving FDA approval in favor of upfront fees and eliminated first-time applicant or small business fee exemptions. While a majority of GDUFA fees are paid by foreign companies, only about 14 percent of GDUFA facility fees are paid by the top ten drugmakers holding almost half of approved ANDAs (Dong et al. 2017). While Congress considered the issue of first-time fee waivers, the FDA does not allow for first-time and small business fee waivers because a majority of generic drugmakers are small companies and the GDUFA fees are "orders of magnitude less than those in [the Prescription Drug User Fee Act]" (FDA 2018).

Table 2: Total Costs of the GDUFA Program

(Costs in Thousands)

Fiscal Year	Total Spent	Spent from Appropriations	Spent from GDUFA Fees	GDUFA Fee Percent	Approvals	Cost/Approval
2013	$266,884	$145,604	$121,280	45%	441	$605
2014	$387,081	$160,952	$226,129	58%	409	$946
2015	$452,705	$120,625	$332,080	73%	492	$920
2016	$493,951	$120,715	$373,236	76%	651	$759
2017	$533,807	$140,295	$393,512	74%	763	$700

Source: FDA FY 2017 GDUFA Financial Report

In FY 2017, GDUFA User Fees collected were $361 million, two thirds from facility fees and one third from application fees (Table 2). The new fee structure creates significant barriers to entry for new firms to enter the market, with $631,334 due in annual fees for a new drugmaker filing its first ANDA. The average approval time for ANDAs during 2018 was about three years (FDA 2018).[3] Given the application fee and approval delay, the drugmaker would need to earn $924,336 in the fourth year after operating costs just to break even on the application fees (see Appendix Table 1). This implies that the market must have at least $6.3 million in revenue if the drugmaker expects to share the market with two other competitors and at profit margins near 42 percent. Berndt and Aitken (2011) estimated that generic ANDA direct entry costs were in the range of $1-$5 million prior to GDFUA I.

Berndt, Conti, and Murphy (2018) found that generic manufacturing became more concentrated and foreign-owned from 2004 to 2016. The median number of drugmakers in a generic molecule market is only two, indicating that over half of these markets earn drugmakers significant economic rents. Using self-reported data by manufacturers mandated by FDA, the authors identify structural changes in U.S. generic drug markets since the passage of the Medicare Modernization

[3]https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm600678.htm

Act (MMA) of 2003 and find that the number of generic drugmakers has been decreasing due to more firm exits and less entry. The passage of GDUFA I is associated with 0.43 p.p. decrease in firm entry probability compared to the pre-MMA period (3.1 percent) and a 0.75 p.p. increase in the firm exit probability over the pre-MMA (1.5 percent).

Policy Options

1. An Economic Pathway for Generic Drug Approvals

One reason for high generic drug prices in concentrated markets may be higher implied costs of entry. The FDA could create a new "economic pathway" to approve generic drugs when companies price gouge. The Council of Economic Advisers proposed a policy option whereby the FDA would update its criteria for expedited ANDA review to prioritize the first or second application in a market with no generic drugs (CEA 2018). The vital elements of an economic pathway for generic drug approvals are (1) reducing the drug approval delay and (2) eliminating entry costs for potential drug manufacturers. To reduce the generic drug approval time down from a median 37 months, an official pathway could be designated with a dedicated FDA division to approve sole-source generic drugs. To reduce entry costs and encourage market entry, one option could be to rescind GDUFA application and facility fees for approval of generic drugs entering markets with fewer than five competitors. Reduced barriers to entry will increase competition among generic manufacturers and lower prices.

The FDA Reauthorization Act of 2017 (FDARA) already authorizes the FDA to assign a special designation upon request by an applicant when there is limited competition (i.e., only one approved generic). The FDA has made some regulatory changes to enhance price competition, recently announcing that it will open a communication pathway for drugmakers to enter with generic drugs,

list off-patent drugs, and prioritize review of off-patent sole source drugs. While these efforts have resulted in additional market entrants, these policies do not specifically address hundreds of drugs with small market sizes. Recent deliberations in Congress have also focused on the question of whether the FDA should have expedited review of ANDAs when a generic market has three or fewer manufacturers.[4]

2. Reciprocal International Marketing Approval

On July 19, 2018, the Secretary of Health and Human Services requested that an FDA working group examine ways to import prescription drugs from foreign nations in the event of a substantial price increase when the drug has no competitors, patents, or exclusivities.[5] While the United States has long considered drug importation as a policy option, concerns of importing harmful or low-quality prescription drugs has forestalled calls for such a shift in policy.

To mitigate drug safety and efficacy concerns, reducing non-tariff barriers to international trade through reciprocal off-patent drug approvals between the FDA and several foreign drug regulatory agencies in developed countries would increase gains from trade and enhance price competition through increased market size over multiple countries. Prior U.S. legislation has proposed countries that have comparable quality standards and publish information in the English language (Cruz 2015).[6] For example, if a drug is first approved by the European Union's European Medicines Agency (the equivalent of the US FDA), then the FDA would grant it generic drug approvals. Whereas drug importation proposals generally allow any business entity to export

[4] S.348 - Prescription Drug and Health Improvement Act of 2017. https://www.congress.gov/bill/115th-congress/senate-bill/348/text?r=72.
[5] https://www.hhs.gov/about/news/2018/07/19/hhs-secretary-azar-directs-fda-establish-working-group-drug-importation-address-price-spikes.html.
[6] EMA (European Union), HealthCanada (Canada), Therapeutic Goods Association (Australia), Medsafe (New Zealand), Swissmedic (Switzerland), Medicines Control Council (South Africa), and the Israel Health Ministry.

prescription drugs from an approved country, a policy of reciprocal marketing approval would restrict exporting entities to drug manufacturers approved by the FDA or an approved foreign drug regulator. Once a drugmaker is approved to market a generic drug in specified foreign countries, the drugmaker can inform the FDA and become approved to export to U.S. patients and businesses. Rather than waiting for FDA approval, this policy should reduce regulatory burdens by publishing a list of generic drugs and drugmakers approved for marketing throughout the international pact.

Former FDA Commissioner Scott Gottlieb proposed a Drug Competition Action Plan for the FDA to harmonize the generic approval process internationally (Gottlieb 2018). The FDA submitted a proposal for a global generic drug development application to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), an international association of regulatory authorities and industries. First, this would create a harmonized set of scientific standards for generic drug applications required by regulatory agencies. Second, the proposal would create a universal application program for drugmakers to use common elements of applications to multiple markets with the ultimate goal of supporting simultaneous fillings in member countries. Removing this non-tariff trade barrier would increase the size of markets that generic drugmakers can enter by combining multiple small markets into one, increasing firm entry and likely price competition. Harmonization could also reduce the fixed costs of generic drug development by allowing the use of one study required to demonstrate bioequivalence between branded and generic drugs across markets. The European Union has also signaled interest in a "mutual recognition agreement on pharmaceuticals and to reduce trade barriers" with the United States (European Commission 2016).

3. Direct Price Negotiation

A common proposal to curtail high drug prices is to allow the government to negotiate directly with drug companies. The Centers for Medicare and Medicaid Services would become the primary buyer of off-patent generic drugs in the United States for the elderly, disabled, and poor. Direct price negotiation would result in the monopsonistic pricing by the government that would give take-it-or-leave-it offers to generic drugmakers. Most developed countries have some form of fiat price controls in place to restrict the willingness to pay of consumers.

Methodology

This section identifies the means by which the proposed policies can lower prescription drug prices, decrease public expenditures, and reduce counterproductive rent seeking behavior by drugmakers. The primary criteria to evaluate policy counterfactuals will be a cost-benefit analysis where the benefit of reduced public expenditures will be weighed against costs to Medicaid. Changes in average drug prices and the number of generic drugmakers will be given as descriptive information that was used to generate estimates to public expenditures. Secondary consideration will be given to feasibility of the policy being enacted.

1. Cost-Benefit Analysis

To compare the policy counterfactuals, the cost-benefit analysis will focus on the Medicaid program for two reasons. First, drug market data is publicly available by molecule-dosage-form, which allows for precise estimates of competition and negotiation on drug price and total spending. Second, much of the literature on drug pricing analyzes the same dataset, allowing for the application of estimates to analyze the discussed policies. Table 3 summarizes national drug sales

and quantities by the number of drugmakers in the market.[7] Markets with five or fewer drugmakers represent 51 percent of sales to Medicaid, but only 26 percent of off-patent generic drugs. The drug sales are net of the 13 percent rebates required that drugmakers are mandated to pay Medicaid programs under the Affordable Care Act.

Table 3: Medicaid Off-Patent Generic Drugs, 2017

(In Thousands)

Drugmakers	Doses	Prescriptions	Sales ($)	$/Dose
1	257,998	7,114	919,319	3.6
2	306,888	7,715	331,637	1.1
3	579,408	12,896	1,052,759	1.8
4	1,313,802	30,574	1,120,182	0.9
5	2,011,558	46,264	976,936	0.5
6-10	8,960,672	216,521	2,749,777	0.3
11+	4,064,083	81,403	1,529,467	0.4
Total	17,494,410	402,487	8,680,077	0.5

Source: CMS 2019; Ganapati and McKibbin 2019

The average drug price ($/Dose) demonstrates the price premium that drugmakers with few competitors earn, compared with competitive markets (six or mores drugmakers) where drugs are priced near marginal cost. This data confirms theory and historical evidence that competition is effective at lowering prices, but this occurs primarily when many drugmakers enter larger markets. The median off-patent drug market in molecule-dosage-form on the Medicaid program had sales of approximately $15 million (2017) for sole-source drugs, which is larger than the median $10 million market size observed across all drugs (Ganapati & McKibbin 2019; Berndt et al. 2017).

The costs considered are the changes in FDA's revenues and outlays due to changed policies that require different levels of administrative burden to approve generic drug applications. Costs will

[7] The Affordable Care Act of 2010 mandated a 13 percent rebate off of the average manufacturers' price (AMP) for off-patent generics sold to Medicaid (Aitken et al. 2013).

be estimated using predicted changes in the number of generic drugmakers entering the U.S. market and the cost per approved ANDA (Table 2). Net benefits will be calculated as the change in public expenditures less the administrative costs of reviewing drug applications. For the direct price negotiation policy, administrative costs are assumed to be the present costs of the Centers for Medicare and Medicaid Services (CMS).

2. Feasibility

Consideration will be given to whether the policy can be accomplished through regulatory agreements, trade agreements, or legislation. To provide an *ex ante* assessment of feasibility, the historical probability of a policy becoming effective will be applied to the net benefits to generate an expected net benefit.

While the U.S. Constitution grants authority to Congress to regulate commerce, there are two exceptions in which the President has the authority to negotiate with industry: international trade agreements and FDA's user fee agreements (Berndt, Conti & Murphy 2018). The FDA negotiates with the pharmaceutical industry to establish user fees. Congress must then cast an up or down vote on the final fee schedule and the President must sign it. Both the 2012 and 2017 regulatory agreements were approved.

The Trade Promotion Authority (TPA) of 1974 gives the President guidance to negotiate international trade agreements (USTR 2019). The President must notify Congress 90 days before signing an agreement and then Congress has an up or down vote with no amendments to ratify it. Mansfield and Milner (2012) estimated survival functions of trade agreements and find that the probability of attaining ratification in Congress is 90 percent two years after it was signed by the

President. After this point the ratification can take several more years or it may not be attained as the composition of political power changes.

Volden and Wiseman (2011) calculated the likelihood of health legislation becoming law for Congress between 1972-2002. Only 1.58 percent (154 of 9,740 bills) of health bills successfully passed into law. Bills proposing regulation of drugs, devices, and labs became law 2.24 percent of the time (18 of 805), while prescription drug coverage and cost bills had a zero percent success rate. It is worth noting that the period from 2003 to the present has seen successful legislation to create Medicare Part D, the Affordable Care Act, and GDUFA.

Analysis

1. Economic Pathway

Ganapati and McKibbin (2019) estimated that the United States has implied market entry costs of $8.0 to $13.7 million in excess of the United Kingdom and Australia, respectively. These are the imputed fixed costs for entry into the United States, rather than global entry costs, that should be interpreted as the present discounted value of entry in excess of these other countries. Using a structural model that accounts for different use of buyer leverage and market competition, the estimated effect of eliminating these excess entry costs is a 31.8 percent reduction in average drug prices to Medicaid due to market entry. This implies estimate implies an entry cost elasticity of -0.66, such that eliminating all excess entry costs of $13.7 million would result in a 66.3% increase in off-patent drugmakers.

While the United States and Australia have historically had similar one-time generic drug application fees (Morgan, Yau & Lumpkin 2017), the former ($233,812) is now more than double

the Australian fee ($91,600) in 2019.[8] Australia has low annual facility fees (under $10,000) for inspections and licenses compared to the U.S. annual facility of $211,305 for domestic manufacturers and $226,305 for foreign manufacturers (TGA 2019; FDA 2019).[9] After U.S. facility fees increased by a compound average growth rate of 10 percent from 2013-2017, the number of facilities has been on the decline (Berndt, Conti & Murphy 2018).

Drugmakers assess the return on investment (profit over cost) of their potential portfolio of drugs prior to entering a drug market. By lowering the cost of market entry, the government can induce price competition in small and concentrated markets to increase consumer welfare. To illustrate the value of an economic pathway to a drugmaker, consider the median sole-source generic drug market in Medicaid with revenues of $15 million (Ganapati & McKibbin 2019). The drugmaker with the median 10 generic drugs in its portfolio will consider fixed costs of entry such as the one-time application fees, annual facility fees, and the time delay prior to marketing approval. A competitor entering this market will anticipate the effect of its entry on price as it gains market share. Ganapati and McKibbin (2019) estimated a supplier elasticity of -0.32, which suggests that moving from a monopoly to a duopoly—a 100 percent increase in drugmakers—will lower the Medicaid drug prices in these markets by 32 percent. While the present value of profits for the monopolist in the median off-patent market is $116.7 million, the duopolist would earn only $13 million due to price competition, $11.9 million in fixed entry costs and at least the same marginal costs as the incumbent.

[8] One-time ANDA ($178,799) and Drug Master File ($55,013) fees in 2019.
[9] GDUFA II changed the rules so that facilities making both Active Pharmaceutical Ingredient (API) and Finished Dosage Form (FDF) are only charged the FDF fees cited here.

Figure 4: Present Value of Faster Generic Approvals and Eliminating Facility Fees

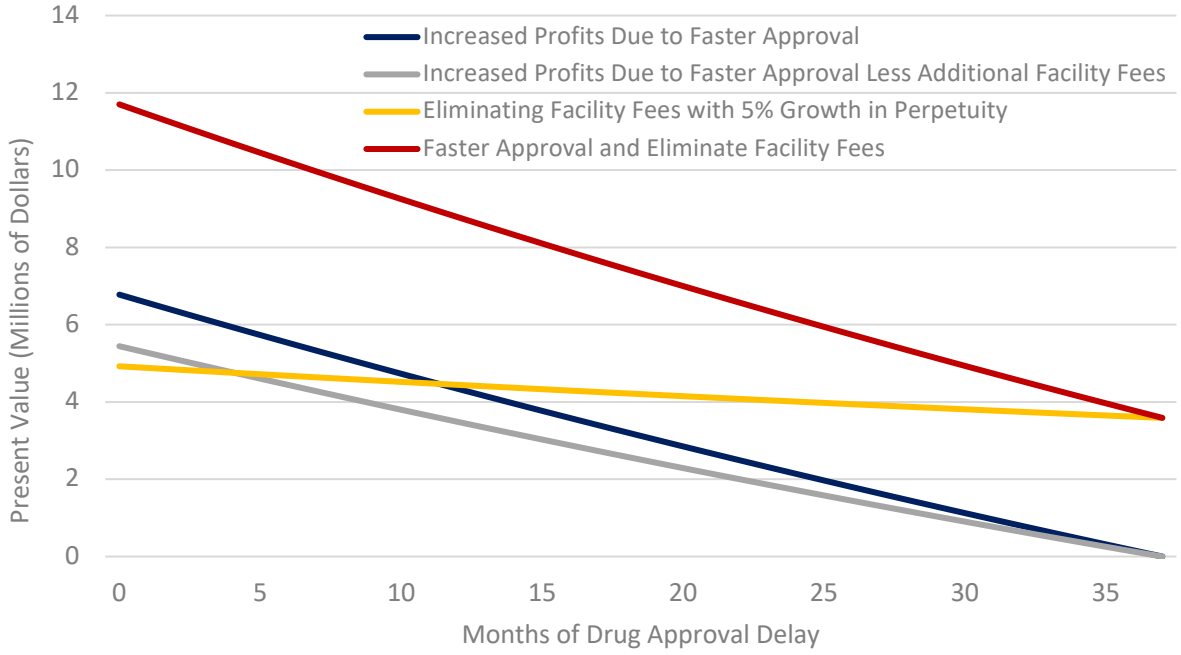


Figure 4 illustrates the present discounted value of facility fees and foregone profits during approval delay.[10] At the median 37-month approval delay, facility fees represent a present value of $3.6 million cost to entry, if firms assume that fees increase by five percent annually in perpetuity.[11] Eliminating the approval delay entirely is equivalent to a present value of $6.8 million. If faster approvals are achieved and fees remain, then the drugmaker would pay present value of $1.3 million in fees earning a maximum of $5.4 million. Eliminating facility fees and approvals within one month would reduce present value fixed costs by $11.7 million, 86 percent of the implied excess entry costs of the United States (Ganapati & McKibbin 2019). By also eliminating the application fees of $233,812, this policy would eliminate 87 percent of excess entry

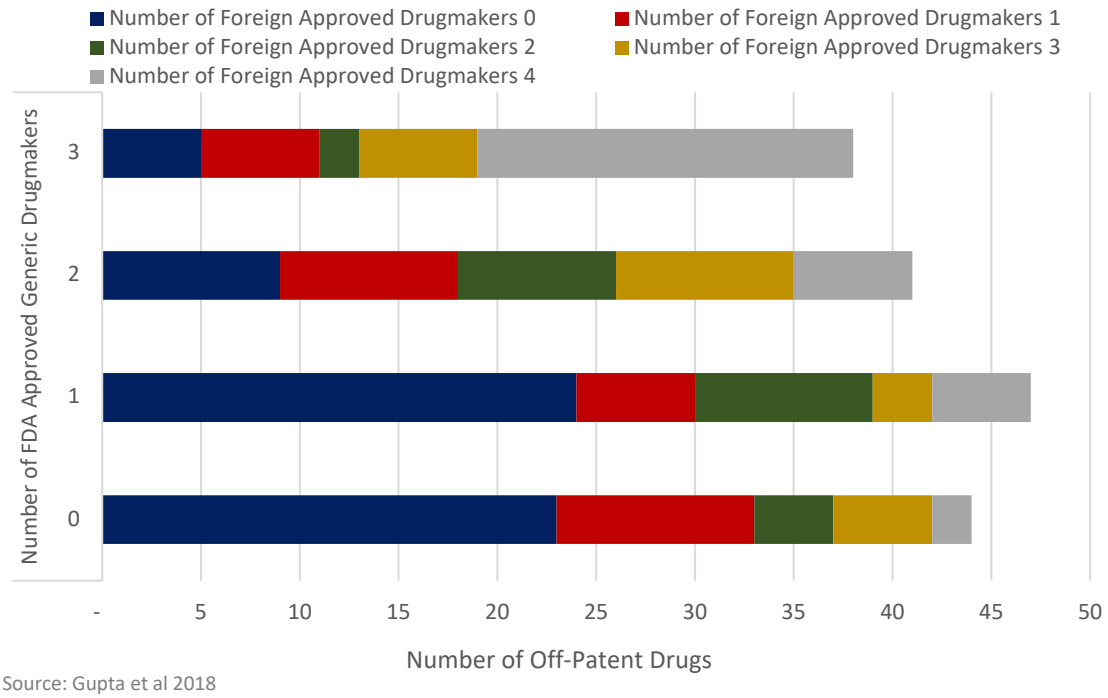
[10] Harrington (2012) uses a Fama-French model to estimate a 10.8 percent cost of capital for small pharmaceutical firms between 2001 and 2005. More recent estimates from 2006 to 2008 of 8 percent are not used here since the 2007 to 2009 recession likely affected cost of capital.
[11] Since GDUFA FDF fees increased by a compound annual growth rate of 10 percent from 2013-2017, but fees remained stable from 2018 to 2019, a 5 percent increase is the expected growth rate for a firm today.

costs. The remaining costs may be due to collusion or market expectations that user fees will increase at a faster annual rate. Using the Ganapati and McKibbin (2019) supplier elasticity, average drug price changes are estimated for using the share of excess costs reduced by the economic pathway. The effect of the economic pathway on the change in Medicaid spending is scaled likewise.

2. Reciprocal Marketing Approval

Ganapati and McKibbin (2019) estimate the effect of removing non-tariff barriers to trade and allowing for reciprocal drug approvals with four foreign countries: Australia, Canada, New Zealand, and the United Kingdom. Reciprocal marketing approvals in this small set of countries would induce an estimated 33 percent increase in the number of drugmakers in off-patent markets. This increased competition would lower average drug prices by 11.6 percent and total Medicaid drug spending by 7.8 percent. Gupta et al. (2018) examine drug approvals of off-patent drugs in the United States and seven foreign drug regulatory agencies in developed countries that have comparable quality standards and publish information in the English language: Australia, Canada, European Union, Israel, New Zealand, Switzerland, and South Africa. Similar country lists have been affirmed in recent proposed U.S. legislation to create international drug reciprocity (Cruz 2015).

Figure 5. Number of Off-Patent Drugmakers Approved by Foreign Regulators, with fewer than four FDA approved Off-Patent Drugmakers



Source: Gupta et al 2018

In an observational study, Gupta et al. (2018) identify tablet or capsule prescription drugs approved by the FDA that are off-patent and have up to three generic versions in the world. Of 170 such drugs, one quarter (44) had no FDA approved generics, but half of these (21) were already approved in one of the seven foreign regulators with equivalent standards (Figure 5). To estimate the effect of a wider reciprocal marketing approval regime with these seven regulators, I simulate the instant approval of these foreign drugmakers by summing the number of domestic and foreign firms. Domestic drugmakers of the 170 drugs totaled 287 in 2017. By adding drugmakers currently approved by foreign regulators would increase the number of drugmakers to 540, an 88 percent increase. The effect of competitors on Medicaid average drug prices and spending is scaled by the Ganapati and McKibbin (2019) estimates.

3. Direct Price Negotiation

To estimate the effect of direct price negotiation by the federal government on the number of off-patent generic drugmakers, estimates from a prior policy are used here. When the Affordable Care Act mandated a 13 percent rebate, Berndt et al 2017 estimate that the generic drugmaker exit rate increased by 0.82 p.p. up to 2.37 percent. To apply this estimate in the case of price negotiation, I scale this effect by Ganapati and McKibbin (2019) estimated average price decline of 33 percent to a 3.6 percent decline generic drugmakers. This assumes that branded drugmakers will not exit the market in anticipation of the government expanding negotiations into that market.

Ganapati and McKibbin (2019) simulate U.S. cost savings if the off-patent generic average price is adopted from five foreign markets that use government monopsony power to negotiate prices. In Medicaid, the average drug prices would fall by 33.3 percent and total drug spending would fall by -18.3 percent.

Results

The first panel of Table 4 reviews the estimated effects of the policies on the number of drugmakers, changes in Medicaid average drug prices, and changes in Medicaid drug spending. The second panel reports the societal benefits and costs of each policy intervention. Percent changes in Medicaid drug spending are converted to U.S. dollars by multiplying by Medicaid spending on off-patent drugs in 2017. The estimated changes in drugmakers is applied to the number of off-patent drugmakers in U.S. markets with less than four competitors (Gupta et al. 2018). The cost to society for these policies is that of reviewing more ANDAs as more competitors seek to enter the U.S. off-patent generic drug market. The average generic drug approval in 2017 cost $700,000 (Table 2).

Table 4: Outcomes Matrix

Policy	Share of Excess Entry Costs	Change in Drugmakers	Change in Average Price	Change in Medicaid Rx Spending
1. Economic Pathway	87.2%	57.8%	-12.2%	-8.7%
Eliminate Application Fee	1.7%	1.1%	-0.2%	-0.2%
Eliminate Facility Fees	36.0%	23.8%	-5.0%	-3.6%
Faster Approval	39.8%	26.4%	-5.6%	-4.0%
2. Reciprocal Approvals				
Australia, Canada, New Zealand and UK		33.1%	-10.6%	-7.8%
Australia, Canada, EU, Israel, New Zealand, Switzerland and South Africa		88.2%	-36.3%	-26.7%
3. Direct Negotiation		-3.6%	-33.3%	-18.3%

Policy	Medicaid Savings	Change in Drugmakers	ANDA Costs	Net Benefit
1. Economic Pathway	$757,520	166	$116,047	$641,473
Eliminate Application Fee	$14,841	3	$2,274	$12,568
Eliminate Facility Fees	$312,482	68	$47,870	$264,612
Faster Approval	$345,483	76	$52,926	$292,557
2. Reciprocal Approvals				
Australia, UK, New Zealand and Canada	$677,046	95	$66,512	$610,534
Australia, Canada, EU, Israel, New Zealand, Switzerland and South Africa	$2,318,588	253	$177,003	$2,141,585
3. Direct Negotiation	$1,588,454	-10	-$7,313	$1,595,767

Policy	Required Action	Probability of Policy Approval	Expected Benefit
1. Economic Pathway	Legislation	44.2%	$283,733
Eliminate Application Fee	Regulatory Agreement	100.0%	$12,568
Eliminate Facility Fees	Regulatory Agreement	100.0%	$264,612
Faster Approval	Legislation	2.2%	$6,553
2. Reciprocal Approvals			
Australia, UK, New Zealand and Canada	Trade Agreement	90.0%	$549,481
Australia, Canada, EU, Israel, New Zealand, Switzerland and South Africa	Trade Agreement	90.0%	$1,927,427
3. Direct Negotiation	Legislation	2.2%	$35,745

The net benefit is the Medicaid savings less the additional ANDA costs. While these policies are aimed at lowering prices in small off-patent markets, the benefits from reciprocal approvals and negotiation are derived from estimates on the overall market. This likely has a small effect because markets with five or more drugmakers generally have prices near marginal cost or where a government would negotiate. Since these policies would also benefit other public programs (e.g., Medicare) and patients who are privately insured or uninsured even more than the Medicaid program, this analysis should be considered a lower bound on benefits to society. This makes the cost-benefit analysis conservative in that it only considers benefits to the program that likely gets some of the best discounts on the market. The fact that these policies have such large net benefits suggests that national benefits would be substantial. The tradeoff in this analysis was to have precise estimates within one program rather national benefits.

Recommendation

Reciprocal marketing approvals provide substantial social benefits that far exceed the costs. By allowing foreign off-patent generic drugmakers to seamlessly enter the American drug market, Medicaid alone would save an estimated $669 million to $2.2 billion, depending on the number of foreign drug regulators that agree to harmonize standards and drug applications. While trade agreements with other countries are often signature political accomplishments, other countries stand to benefit even more by having American drugmakers entering their markets. If this policy recommendation is pursued through trade agreements, then it will have much domestic political support. The only reason that this policy would not exceed the net benefits of other alternatives is if the number of partner countries remains small.

Conclusion

There remains no reason to allow rent seeking by drugmakers of off-patent drugs. This paper reviews three leading policy counterfactuals that could reasonably be used to target high drug prices of often times old and small market drugs. The "economic pathway" is a novel concept that would add to the FDA's authority to target off-patent drugs, particularly those with no competitors. A key insight is that the annual user fees charged to drugmakers are a barrier to entry that is equivalent to the generic drug approval delay. Reciprocal marketing approvals between countries is an emerging policy concept that offers substantial social benefits from trade of drugs already approved to be safe and effective. Direct price negotiation—a policy that has been discussed for years—would deliver substantial savings to public programs, but would likely reduce price competition due to market entry. Years of heavy regulation and mandates on off-patent, generic drug markets have created barriers to entry that far exceed those of America's trading partners. Competition can continue to deliver savings to patients and taxpayers that are at least equivalent to direct government negotiation, and do it without the unintended consequences of a heavy hand.

Appendix

Table 1: Application Fees Over Time and Implied Market Size for Entry

	Years of Delay				
Scenario	0	1	2	3	4
Actual First ANDA Cost	$631,334	$694,467	$763,914	$840,306	$924,336
Market Sales Needed to Justify Generic Entry		$4,735,005	$5,208,506	$5,729,356	$6,302,292
Lower Hypothetical ANDA Cost	$100,000	$110,000	$121,000	$133,100	$146,410
Market Sales Needed to Justify Generic Entry		$750,000	$825,000	$907,500	$998,250

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