

ENABLING COMPETITION IN PHARMACEUTICAL MARKETS

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I. INTRODUCTION

The United States, unlike many other industrialized nations, does not regulate the price of pharmaceutical products directly. There are advantages to this approach. The U.S. generic market is one of the most dynamic and cost-effective in the world due to competition between manufacturers. The inventor of a socially valuable patented drug may charge high prices in the U.S. market, and the ensuing profit incentivizes innovation that benefits consumers. Subsequent competition between substitute therapies, even those on patent, can push down these prices over time. Generic entry after patent expiration pushes down prices even further. This form of price discipline, generated by market forces, rewards the attributes and efficacies that consumers want. For example, if a particular drug is differentiated from its competitors in a useful way, it will be able to command a higher price.

Prices that reflect value create exactly the incentives society desires for innovation. If the forces of competition are always strong, then the way for a pharmaceutical company to earn high profits is to invent a valuable treatment. If competitive forces weaken, then high prices for drugs may not reflect value but instead a lack of market discipline, sometimes exacerbated by regulations that enable or maintain high prices. When manufacturers can earn high profits by lobbying for regulations that weaken competition, or by developing mechanisms to sidestep competition, the system no longer incentivizes the invention of valuable drugs. Rather, it incentivizes firms to locate regulatory niches where they are safe from competition on the merits with rivals. The U.S. system performs well when competitive forces are strong, as this yields low prices for consumers as well as innovation that they value.

Weak competitive forces are more damaging to consumers in the pharmaceutical sector than some others. Patients in the U.S. are typically both insured and uninformed about therapeutic substitutes for the medications they take; thus, without effective rules and frameworks provided by the government, they face difficulty in creating market forces on their own. Without market pressures, drug makers may sell at arbitrarily high prices to insured consumers. Therefore, the policy environment in which those consumers shop is critical to maintaining effective price competition.

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Without a return to competitive conditions in this sector, expenditure will continue to grow. We are already hearing calls for regulation of pharmaceutical prices and seeing legislation that proposes price regulation.¹ It is very difficult to devise regulation that encourages innovation in a fast-changing industry. Regulators may be uninformed about valuable research, be captured by the industry, or lack the resources to keep up with changes in science or the cost of production.² Because innovation is hugely valuable to consumers, we are hesitant to recommend government regulation of pharmaceutical prices as a solution to the current problem of high and growing pharmaceutical expenditures.

The regulatory system in the U.S. is designed, in principle, to enable vigorous and effective competition that will bring down drug prices, particularly of any drug that faces a competitor or substitute. Over the last 10-15 years, however, industry participants have managed to disable many of these competitive mechanisms and create niches in which drugs can be sold with little to no competition. We argue in this paper that the first step toward bringing down pharmaceutical prices would simply be to fully apply the existing rules we already have. For example, speedy and effective entry of generic products, and financial incentives for consumers to choose treatments that have offered significant discounts are both part of the existing regulatory framework and result in lower prices. Both forces, however, have been greatly attenuated or stymied by the actions of pharmaceutical manufacturers. Enforcement of existing regulations that make markets more competitive will reduce pharmaceutical expenditures. The one type of market we will not address in this paper is the case of the patented, valuable medication that has no therapeutic substitutes because it represents a breakthrough in treatment. We refer the reader to the companion piece by Frank and Zeckhauser for a discussion of pricing when a drug faces no competition.³ We note that industry participants who benefit from the status quo may work against a return to competitive markets. If pharmaceutical firms and other market participants block policies that restore competition, then calls for more stringent regulation will re-appear and may well be successful.

In this paper, we outline three major barriers to effective competition in U.S. pharmaceutical markets. The first focus of the paper is on biologics, the fastest growing segment of drug spending. This category has seen price increases in double digits for a decade and now (along with specialty drugs) represents more than one third of total spending with only increases in sight. Moreover, because the science behind biologic treatments is newer, regulations that would enhance competition in the sector are less well developed. In particular, regulatory delays have left the United States without competitive biosimilars – biologic entrants analogous to generics – that create price competition. There are only two biosimilars on the market in the U.S. while there are more than twenty on the market in the EU. This delay in biosimilar entrance in the U.S. carries a hefty price tag. We also outline regulatory barriers that are likely to inhibit biosimilar competition even after FDA approval. These barriers have also been used by brands to prevent entrance of traditional generics, and include pay for delay schemes, abuse of orphan drug classifications, and REMS requirements meant to increase drug safety. These barriers have also slowed the market response to price hikes in small generic markets. In conjunction with the FDA's slow progress on biosimilar approval, these tactics have led to a decline in the fraction of pharmaceutical expenditure exposed to significant price competition.

1 On March 29, 2017, the Improving Access to Prescription Drugs Act was introduced in the Senate and the House, which, among other policy proposals, calls for Medicare to negotiate "fair prices" for prescription drugs, requires monitoring of price gouging by manufacturers, rebates from manufacturers to consumers, and shorter periods of marketing and data exclusivity for brand-name drugs. This legislation represents just the latest call for greater price regulation of drugs.

2 Jean-Jacques Laffont and Jean Tirole, *A Theory of Incentives in Procurement and Regulation* (Cambridge, Mass: MIT Press, 1993).

3 Richard Frank and Richard Zeckhauser, "Framework for Negotiation in Part D of Medicare," Hutchins Center Working Paper #28,

The second focus of the paper relates to the demand side imperfections of market participants. Pharmacy Benefit Managers (PBM), which are increasingly consolidated, may face agency problems that undermine their stated goal of bargaining for lower drug prices. PBMs may use rebates as a tool to increase profits by keeping a share of the high prices paid by patients who consume costly medication. Additionally, product hopping schemes instituted by brands and suboptimal Medicare reimbursement policies undermine patient incentives to substitute toward cheaper drugs. These problems are exacerbated by the ability of brands to provide kickbacks in the form of coupons, financial assistance, free meals, patient care, and other benefits designed to undo the financial incentives that exist in the marketplace and would otherwise steer demand to lower-priced alternatives. Insurers that negotiate low prices for a brand also give patients a low copay to steer them toward more cost-effective products, giving them higher market shares, but higher copays can be eliminated by competitors that provide financial assistance (e.g. coupons) to patients. These payments counteract the insurer's pricing incentives and lead the patient to consume the more expensive drug. In equilibrium, this results in higher prices on all drugs that consumers ultimately pay.

The third focus of this paper relates to older drug markets, where firms with small portfolios have recently instituted drastic price increases for essential drugs. This market also faces the potential for shortages and exit of competitors over time. After discussing these problems in some detail, we propose specific policies that would remedy or remove these barriers to competition, thereby lowering prices while incentivizing targeted innovation to the most valuable unmet medical needs.

II. MARKET TRENDS IN BIOLOGIC AND SPECIALTY DRUGS

Over the past two decades, pharmaceutical innovation has shifted from chemically-synthesized small molecule drugs toward more complex, bioengineered treatments grown from living tissue that are known as biologics. Biologics are often used to treat severe diseases that do not have effective small molecule treatments. The development of biologic medicines has represented a boon to many patients suffering from cancer, hepatitis, hemophilia, multiple sclerosis, autoimmune disorders such as rheumatoid arthritis, or inflammatory diseases such as Crohn's and ulcerative colitis. Many of these drugs impart high value to patients. Being able to sell at a high price while being protected from competition by a valid patent incentivizes manufacturers to innovate and produce high-value products. Recent hepatitis drugs, for example, have received negative press for the high prices that they carry, but they also represent some of the most innovative medical treatments in recent years, curing a disease that previously required a liver transplant. On the other hand, many drugs have high prices not justified by their value. This paper focuses on the incentives that enable the persistence of high prices when competing alternatives should drive down those prices.

The top thirty best-selling biologics, with licensure date, manufacturer, and corresponding indications, are listed in Table 1. Annual per-patient expenditure as measured by wholesale acquisition cost (WAC) demonstrates that biologics typically carry a high annual per-patient expenditure in the tens of thousands of dollars. Cheaper biologics, by this measure, tend to be insulins. Insulins are so widely used, however, that in aggregate, they are large contributors to pharmaceutical spending. Strikingly, although the biologics listed below carry a high price tag, many were licensed in the 1990s or early 2000s, suggesting that prices are high despite relevant patents having expired.

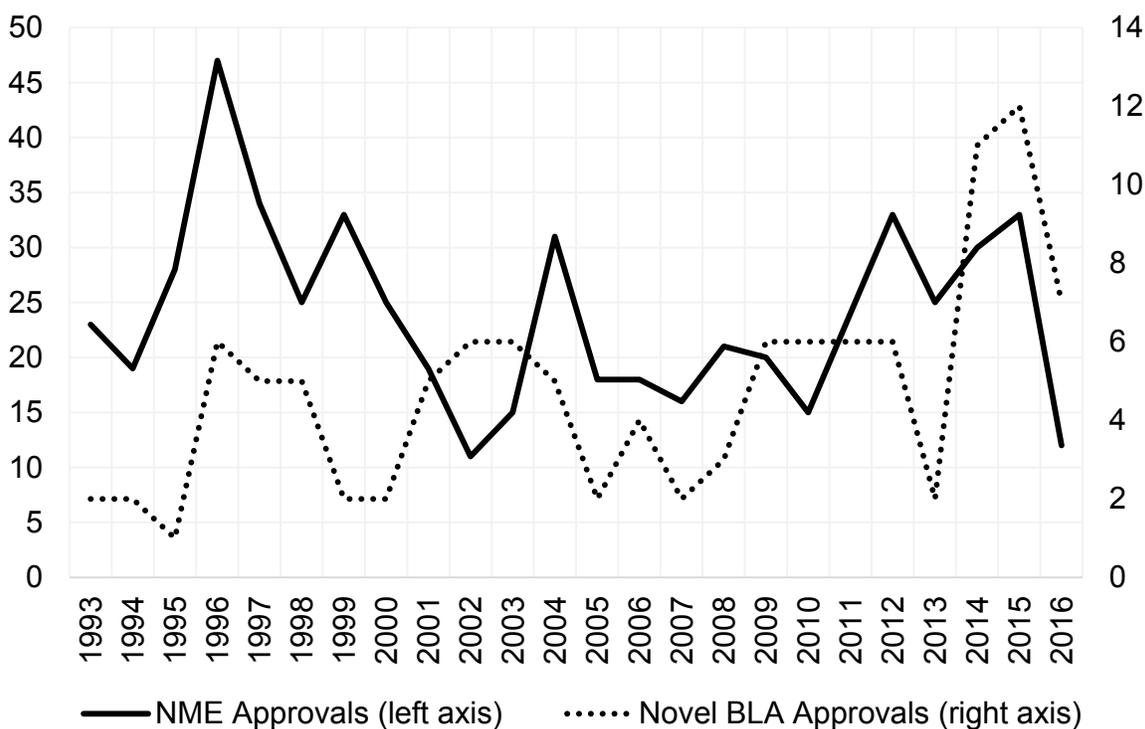
Table 1: Top 30 biologic drugs by sales

Proprietary name	Date of licensure	Innovator	2016 sales (US \$billion)	WAC (Annual per patient expenditure)	Common indications
<i>Humira</i>	Dec-02	Abbvie Inc	11.7	\$41,460 - \$48,372	Rheumatoid Arthritis, Crohn's disease, Ulcerative colitis
<i>Enbrel</i>	Nov-98	Amgen Corporation	7.1	\$41,468 - \$51,835	Rheumatoid Arthritis
<i>Remicade</i>	Aug-98	Johnson & Johnson	5.2	\$32,686	Rheumatoid Arthritis, Crohn's disease, Ulcerative colitis
<i>Neulasta</i>	Jan-02	Amgen Corporation	4.2	\$19,659	Cancer
<i>Rituxan</i>	Nov-97	Hoffmann-la Roche	3.7	\$29,916 - \$38,142	Cancer, Rheumatoid Arthritis
<i>Lantus</i>	Apr-00	Sanofi Aventis	3.6	\$2,982 - \$4,473	Diabetes
<i>Avastin</i>	Feb-04	Hoffmann-la Roche	3.1	\$91,572 - \$124,908	Cancer, Macular Degeneration
<i>Opdivo</i>	Dec-14	Bristol meyer squibb	2.7	\$30,090	Cancer
<i>Herceptin</i>	Sep-98	Hoffmann-la Roche	2.6	\$50,201	Breast Cancer
<i>Humalog</i>	Jun-96	Lilly	2.2	\$5,904	Diabetes
<i>Stelara</i>	Sep-09	Johnson & Johnson	2.2	\$25,655 - \$81,900	Psoriasis
<i>Novolog</i>	Jun-00	Novo Nordisk	2.1	\$3,065	Diabetes
<i>Tysabri</i>	Nov-04	Biogen Idec Corp	1.9	\$63,096	Crohn's Disease, Multiple Sclerosis
<i>Epogen/Procrit</i>	Jun-89	Amgen Corporation	1.7	\$13,128 - \$17,505	Anemia, Renal Failure, Cancer
<i>Lucentis</i>	Jun-06	Hoffmann-la Roche	1.5	\$14,000 - \$23,400	Macular Degeneration
<i>Orencia</i>	Dec-05	Bristol meyer squibb	1.5	\$33,054 - \$38,436	Rheumatoid Arthritis
<i>Xolair</i>	Jun-03	Hoffmann-la Roche	1.4	\$10,488-\$62,930	Rheumatoid Arthritis, Asthma
<i>Aranesp</i>	Sep-01	Amgen Corporation	1.1	-	Renal Failure
<i>Perjeta</i>	Jun-12	Hoffmann-la Roche	1.0	\$55,046	Anemia, Renal Failure, Cancer
<i>Xgeva</i>	Jun-10	Amgen Corporation	1.0	\$22,620	Osteoporosis, Bone Cancer
<i>Avonex</i>	May-96	Biogen Idec Corp	1.0	\$64,032	Multiple Sclerosis
<i>Levemir</i>	Jun-05	Novo Nordisk	1.0	\$3,228 - \$4,842	Diabetes
<i>Prolia</i>	Jun-10	Amgen Corporation	0.9	\$12,326	Osteoporosis, Bone Cancer
<i>Simponi</i>	Apr-09	Johnson & Johnson	0.9	\$41,997 - \$56,345	Rheumatoid Arthritis, Ulcerative Colitis
<i>Cimzia</i>	Apr-08	UCB	0.8	\$39,563	Rheumatoid Arthritis, Crohn's disease
<i>Neupogen</i>	Feb-91	Amgen Corporation	0.7	-	Cancer, HIV/AIDS
<i>Tarceva</i>	Nov-04	Hoffmann-la Roche	0.7	\$71,184 - \$80,508	Cancer
<i>Erbifutx</i>	Feb-04	Lilly	0.6	\$138,861	Cancer
<i>Synagis</i>	Jun-98	Astrazeneca Corp	0.5	\$35,571	Respiratory Syncytial Virus
<i>Cosentyx</i>	Jan-15	Novartis	0.4	\$54,840	Plaque Psoriasis, Psoriatic Arthritis

Source: All data except for prices sourced from "2016-2020 Roadmap: \$20 Bln Trophy with Pricing Challenge" (Morgan Stanley, November 14, 2016). Pricing data sourced from "High-Priced Drugs: Estimates of Annual Per-Patient Expenditures for 150 Specialty Medications," Report (AHIP, April 2016), <https://www.ahip.org/wp-content/uploads/2016/04/HighPriceDrugsReport.pdf>, and "Data Sample Shows January Brand Price Increases of ~6.2%, down ~180bps y/y" (Leerink Partner LLC Equity Research, January 17, 2017). WAC data for Aranesp and Neupogen not available.

The shift toward biologic sales in the United States is reflected by corresponding growth in R&D spend in the biotech industry and biologic approvals by the FDA. Whereas traditional drugs must file for FDA approval via a New Drug Application (NDA), most biologic drugs undergo a separate regulatory approval process known as a biologic license application (BLA).⁴ The growth in novel biologic license issuances compared to new molecular entities (NMEs), shown in Figure 1, demonstrates how the industry has shifted toward biologics, especially in recent years.

Figure 1: Biologic license approvals⁵



Source: John K. Jenkins, "CDER New Drug Review: 2016 Update," Presentation, (December 14, 2016), <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM533192.pdf>.

BROOKINGS

In the United States, biologics have grown from just 13% of pharmaceutical spending in 2006 to 27% in 2016 as shown in Figure 2 below.⁶

Although total pharmaceutical spending has been increasing rapidly, with 29% cumulative growth between 2011 and 2015, utilization has remained roughly constant, with only a 1% increase in units sold over the same period.⁷ This indicates that increased pharmaceutical spending can be attributed to increases in the price of the average bundle of drugs consumed, a shift caused both by price increases and consumption of more expensive drugs.

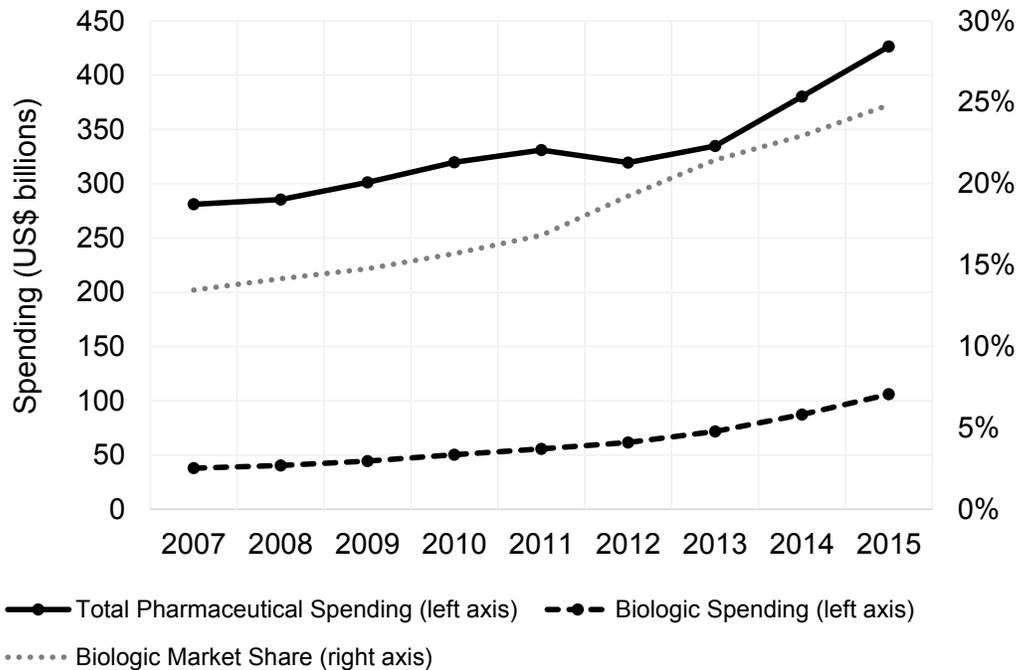
⁴ Some biologic drugs, such as insulin, continue to follow the traditional regulatory pathway.

⁵ Data excludes BLA approvals that do not contain a new active ingredient.

⁶ These statistics include biologic insulins as well as biologics that have been approved via a Biologic License Approval. This may somewhat understate true biologic spending as it does not include some vaccines and hormones that are neither insulins nor approved with a BLA.

⁷ "Global Pharmaceuticals, US, China, Japan and Europe: The Grand Tour of Drug Pricing, Reform, and Market Growth," Report (UBS Global Research, February 9, 2017). W. Price, I. I. Nicholson, and Arti K. Rai, "Manufacturing Barriers to Biologics Competition and Innovation," Iowa L. Rev. 101 (2015): 1023.

Figure 2: Pharmaceutical sales in the United States



Source: IMS data.

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Biologics are often classified as specialty drugs, a loosely defined category of high-priced medications that also includes small molecule drugs with special characteristics that increase expense.⁸ Specialty drug spending has grown at a much higher rate compared with spending on traditional drugs over the past 10 years as shown in Figure 3.⁹ One of the largest PBMs, Express Scripts, notes that in 2014, specialty drugs represented 32% of its spending but just 1% of prescriptions issued to its patients.¹⁰ Both units and prices of specialty drugs have grown in recent years. This cost is driven in part by the high price of biologic medicines compared with their small molecule counterparts. In 2007, the CEO of Express Scripts testified before Congress that the average daily cost of a biologic was more than 22 times the average daily cost of a small molecule drug.¹¹ That trend remains today.¹² Several biologics covered by Medicare Part B cost more than \$50,000 per beneficiary per year.¹³ Medicare Part D has also experienced massive spending increases on biologics in recent years, with spending rising from \$1.9 billion to \$3.5 billion between 2009 and 2012.¹⁴

8 Drugs requiring cold chain distribution or special monitoring by a healthcare professional (e.g., IV infusions) are also typically categorized as specialty drugs. Some drugs, however, are simply characterized as specialty drugs because they are expensive. One commonly used threshold to classify specialty drugs is if treatment exceeds ten thousand dollars in annual expenditure. "Specialty Drugs and Health Care Costs," Fact Sheet (The Pew Charitable Trusts, November 2015), http://www.pewtrusts.org/~media/assets/2015/11/specialty-drugs-and-health-care-costs_artfinal.pdf.

9 Not all biologic drugs are specialty drugs. Insulin, for example, is a biologic drug, but was originally approved under an NDA and so is typically classified as a traditional drug.

10 "U.S. Rx Spending Increased 13.1% in 2014." *Express Scripts*. Accessed March 6, 2017. <http://lab.express-scripts.com/lab/insights/industry-updates/us-rx-spending-increased-13-percent-in-2014>.

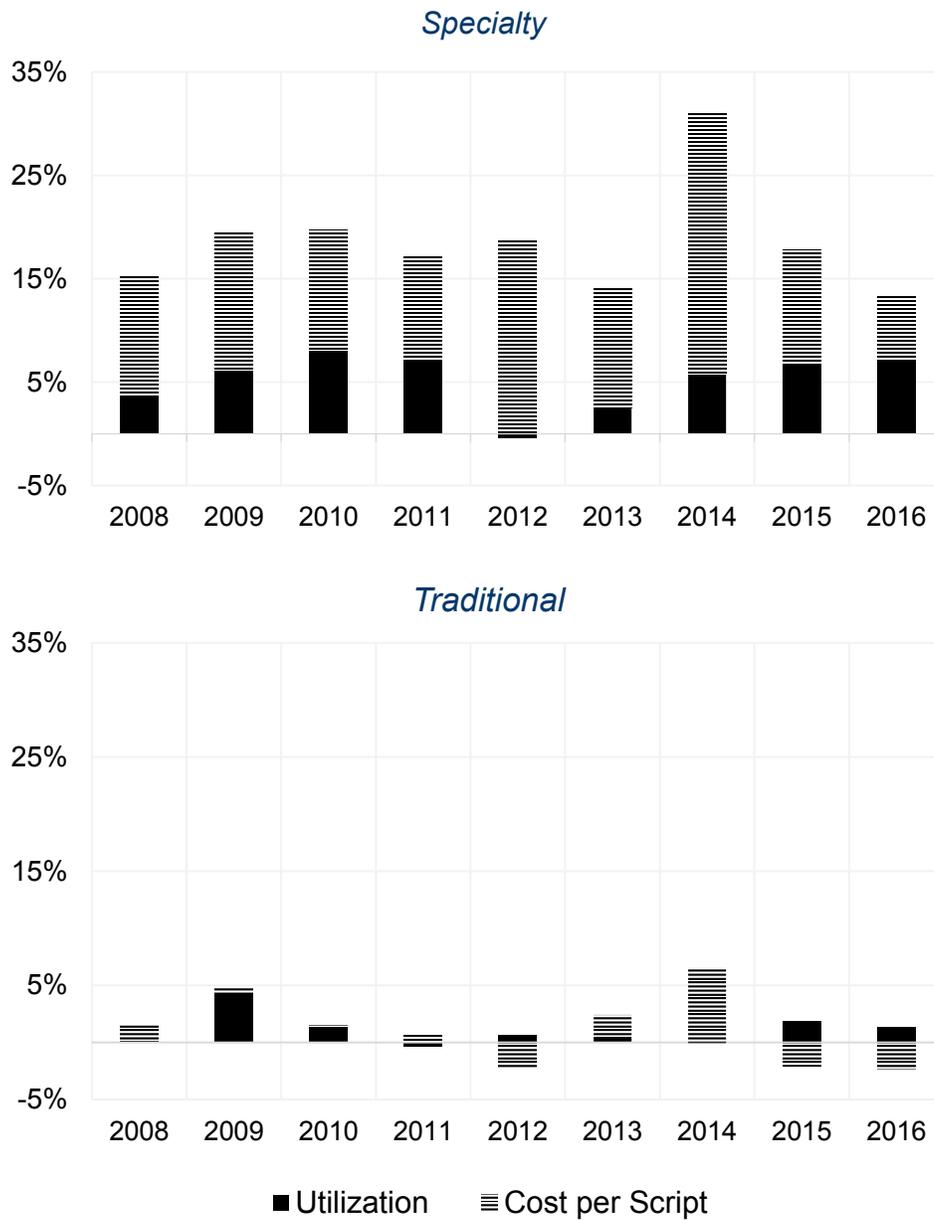
11 "Statement of Ed Weisbart, M.D., Chief Medical Officer, Express Scripts," Hearing Before the Subcommittee on Health of the Committee on Energy and Commerce, (May 2, 2007), <https://www.gpo.gov/fdsys/pkg/CHRG-110hrg40500/pdf/CHRG-110hrg40500.pdf>.

12 Erwin A. Blackstone and P. Fuhr Joseph, "The Economics of Biosimilars," *American Health & Drug Benefits* 6, no. 8 (2013): 469–78.

13 "Medicare Part B, Expenditures for New Drugs Concentrated among a Few Drugs, and Most Were Costly for Beneficiaries," Report to the Ranking Member, Committee on the Budget, House of Representatives (Government Accountability Office, October 2015), <http://www.gao.gov/assets/680/673304.pdf>. Table 4. See also Judith A. Johnson, "Biologics and Biosimilars: Background and Key Issues" (Congressional Research Service, September 7, 2016).

14 Surya C. Singh and Karen M. Bagnato, "The Economic Implications of Biosimilars," *The American Journal of Managed Care* 21, no. 16 Suppl (December 2015): 331–40.

Figure 3: Growth in traditional and specialty drug spending



Source: "Express Scripts Drug Trend Reports," (2008 - 2016). **BROOKINGS**

As will be explored in the following sections, there are numerous causes for the rise in U.S. pharmaceutical spending, two of which apply disproportionately to biologic and specialty drugs more broadly. First, regulatory barriers to competition are higher in biologic and specialty drug markets, resulting in fewer competitors and allowing manufacturers in the United States to increase prices above levels observed in other parts of the developed world, such as the European Union. Second, externalities and information asymmetries prevent consumers from optimally substituting toward cheaper equivalents because they do not typically bear the full cost of drug expenditures, and do not have the medical expertise or reliable information necessary to identify therapeutic equivalents. Pharmaceutical manufacturers further inhibit attempts to increase consumer price sensitivity by making side payments to insured consumers to

encourage consumption of particular products, distorting and undermining price mechanisms set by insurers to control costs. Because biologics are often very expensive, these demand-side distortions impose huge costs on the insurer and society.

III. REGULATORY BARRIERS TO COMPETITION

A patent for a novel and effective drug is of course a barrier to competition in the short run. This barrier is created by the government in order to generate incentives for innovation. The patent guarantees the inventor of the drug a limited monopoly over its sale, allowing inventors to earn a profit if their inventions are valuable. The potential to earn profits incentivizes the creation of new treatments for unmet medical needs. There is debate in the economics literature regarding the length of the optimal patent and whether the patent system on net increases or decreases innovation. This paper will not address those debates, but will take the current patent regime as given. Instead, we focus on the nature of competition among patented products and how quickly competition is restored upon patent expiration.

The Food and Drug Administration (FDA) controls entry into the market for both innovator and follow-on pharmaceutical treatments to ensure that they are safe and effective. Follow-on treatments typically enter the market after many years, well after the reference drug has demonstrated a history of safety and efficacy. Follow-on applicants have lower fixed costs of entry than the reference product because they do not have to prove the product is safe and effective, but only that their version of the product is bio-equivalent (or similar) and safe. Moreover, a follow-on entrant is likely to significantly intensify competition and erode the profits of the incumbent reference medication. Incumbents will thus have a financial incentive to influence regulation to make competitive entry harder, slower, or less effective. To the extent incumbents are effective at shifting the priorities of the FDA away from consumer welfare, regulations governing the entry of follow-on products form barriers to competition. In particular, the U.S. regulatory framework governing biologic follow-on entry has experienced numerous delays, and the guidance that has been issued has raised competitive concerns.

Other regulations promulgated by the FDA or Congress may limit competition in ways not foreseen by the writers of the regulation or legislation. Examples discussed below include orphan drug provisions, patent settlements with Hatch-Waxman, drug safety regulations (REMS), and formulary regulations. Finally, FDA approval delays of follow-on products may further inhibit competition.

III.1 Regulatory process for biosimilar entry

The regulatory framework governing small molecule drug competition comes from the Hatch-Waxman Act, which was passed by Congress and signed into law in 1984. The Hatch-Waxman Act attempted to strike a balance between innovation and provision in the market for pharmaceutical drugs by granting a period of patent exclusivity to manufacturers of novel drugs while at the same time lowering the regulatory barriers to generic entry by offering an abbreviated new drug approval process (ANDA).

Biologics, on the other hand, are approved by the FDA under the Public Health Service Act (PHSA).¹⁵ In 2010, Congress passed the Biologics Price Competition and Innovation Act (BPCIA) to encourage competition in biologic markets, amending the PHSA to establish an abbreviated regulatory pathway for FDA approval of follow-on biologics (i.e., biosimilars and interchangeable biosimilars) parallel to Hatch-Waxman's ANDA pathway for small molecule generics. Provisions of the BPCIA differ in some significant respects from those of the Hatch-Waxman Act because the technical methods used to show interchangeability between generics and small molecule reference drugs are not adequate for biologics, and because current methods are incapable of measuring exact differences among biologics due to their complexity.¹⁶

Under the BPCIA, a "biosimilar" product is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "there are no clinically meaningful differences between the biological product and the [FDA-licensed biological] reference product in terms of safety, purity, and potency of the product." The BPCIA requirements for an "interchangeable" biologic product are more stringent. An interchangeable biologic product is expected to produce the same clinical result as the FDA-licensed biological reference product in any given patient even if a patient switches to the interchangeable drug in the middle of a treatment regimen. Parallel to regulatory construction of varying degrees of therapeutic equivalency for generic drugs as either A-rated (automatically substitutable by the pharmacist) or B-rated (requiring additional steps by the pharmacists including a new prescription), the BPCIA directed the FDA to establish guidelines for manufacturers to prove drugs meet the standards of biosimilarity and interchangeability. Interchangeable products are meant to allow for automatic substitution by pharmacists without the consent of a physician.¹⁷

Although BPCIA was passed in 2010, final guidances for demonstrating biosimilarity were only made available beginning in early 2015, about the same time as the first biosimilar approval. This contrasts with regulations in the EU, which issued guidelines ten years prior and has experienced successful biosimilar entry. The first draft guidance for demonstration of interchangeability was made available only in January 2017, more than six years after the passage of the BPCIA, and final guidance is not expected until 2019, nearly nine years after the enactment of the original law.¹⁸ As a result, firms that are pursuing follow-on biologic applications face delay and uncertainty over how their applications may be received and evaluated by the FDA. Due to lack of guidance from the FDA, none of the biosimilars approved thus far have obtained interchangeable status, which would further promote price competition among biologics by allowing for

15 "Biologics Price Competition and Innovation Act of 2009," 42 U.S.C. § 262. Generally, the reference biologic is approved by the FDA with a full Biologics License Application pursuant to the requirements set forth under 42 U.S.C. § 262(a); whereas follow-on biologics are approved pursuant to the requirements set forth under 42 U.S.C. § 262(k).

16 Under Hatch-Waxman, generic applicants must provide "information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug," that the "route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug," and that the drug is "bioequivalent to the listed drug" Aaron S. Kesselheim and Jonathan J. Darrow, "Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era," *Yale J. Health Pol'y L. & Ethics* 15 (2015): 293.

17 Interchangeability is granted if a product is biosimilar and if it "...can be expected to produce the same clinical result as the reference product in any given patient..." and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

18 "Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022" (FDA, 2016), <https://www.fda.gov/downloads/forindustry/userfees/biosimilaruserfeeactbsufa/ucm521121.pdf>.

automatic pharmacist substitution toward cheaper biologics.¹⁹

The United States, known for having some of the world's highest drug prices, lags behind other developed countries in encouraging biosimilar entry. Although four biosimilars have been formally approved following the FDA's final guidance for demonstration of biosimilarity, at least twenty-two biosimilars have been approved in the EU, where the regulatory pathway for biosimilars has existed since 2005 and entrants since 2007.²⁰ The first biosimilar in the U.S., on the other hand, Novartis' Zarxio (filgrastim-sndz), was approved by the FDA only in March 2015 and offered for sale in the U.S. in September 2015 due to delays caused by patent litigation and the BPCIA patent resolution process.²¹

While this paper does not consider patent law, it will cover market exclusivity rights granted by regulators or the legislature. The BPCIA established that the FDA could not approve biosimilars that rely on the BLA of a reference product for at least 12 years after the approval of a reference biologic.²² This protection is known as "data exclusivity" and provides protection for branded products beyond that afforded by patents. The BPCIA also provided for a separate patent resolution mechanism. Both of these provisions were included over objections from the FTC, whose policy analysis concluded that no such period of additional data exclusivity, over and above patent exclusivity, was necessary to ensure innovation, and that the creation of an early patent resolution mechanism separate from the usual legal process would burden and delay entry of potential competitors.²³ Two of the four approved biosimilars in the United States have not been marketed due to ongoing patent litigation, and a third has entered at risk, with the potential for a considerable penalty if the court rules for the reference biologic.²⁴

Due to uncertainty regarding the biosimilar entry process, lack of approvals, and, more recently, delays caused by patent litigation, most innovator biologic products in the United States are effectively never exposed to competition from another maker of the treatment even after patent expiration. Although biosimilar entrants for some of the best-selling biologics appear to be close to market, lack of competition among many biologics with expired patents will likely extend into the foreseeable future unless there is reform of regulatory and reimbursement policies. In the absence of reform, the evidence indicates that prices of branded biologics will be high and rising indefinitely. The ability of biologic prices to persist beyond patent expiry contrasts greatly with the experience of small molecule branded drugs, which typically

19 Biosimilars that attain interchangeable equivalence with a branded biologic drug also gain a period of regulatory exclusivity as to any other interchangeable biosimilar similar to the first generic entrant under the Hatch-Waxman Act. The period of exclusivity is the earlier of (i) twelve months after the first commercial marketing of the interchangeable biosimilar, or (ii) eighteen months after a final court decision on patent litigation. Importantly, biosimilar interchangeable exclusivity expires 42 months after approval even if there is ongoing patent litigation, a provision discussed later in this paper under the context of pay for delay schemes that have emerged in the pharmaceutical industry in recent years.

20 Steinar Madsen, "From Biosimilar Approval to Biogenerics in Practice," Presentation (Norwegian Medicines Agency, December 2, 2016). Henry Grabowski, Rahul Guha, and Maria Salgado, "Biosimilar Competition: Lessons from Europe," *Nature Reviews Drug Discovery* 13, no. 2 (2014): 99–100.

21 For a discussion of the Amgen v. Sandoz BPCIA litigation from the beginning see e.g., "Solicitor General Urges SCOTUS to Take Up Sandoz and Amgen Petitions on the BPCIA's Notice and Patent Dance Provisions," *FDA Law Blog*, December 8, 2016, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/12/solicitor-general-urges-scotus-to-take-up-sandoz-and-amgen-petitions-on-the-bpcias-notice-and-patent.html; see also "The Demise of the BPCIA Patent Dance?," *FDA Law Blog*, March 2, 2017, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2017/03/the-demise-of-the-bpcia-patent-dance.html.

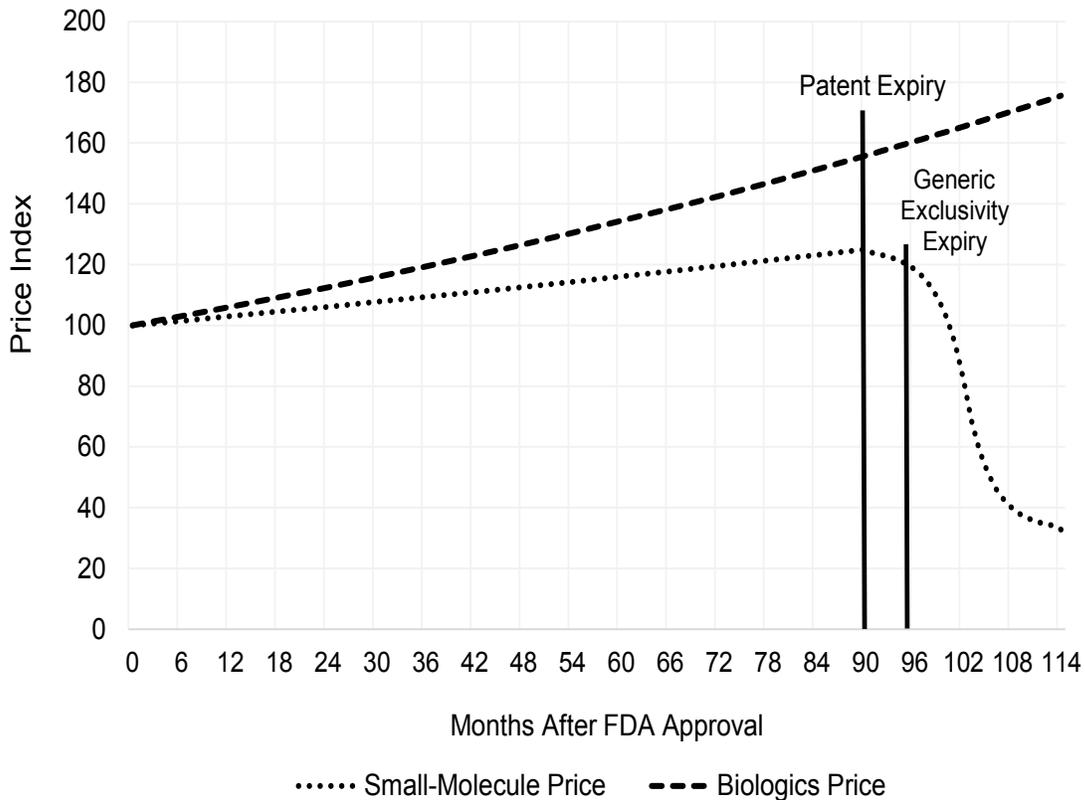
22 Recent legislation has been introduced suggesting a reduction in the data exclusivity period afforded to biologics after FDA approval from 12 years to 7 years. "The Improving Access to Affordable Prescription Drugs Act: A Different Tack on Exclusivity," *FDA Law Blog*, March 29, 2017, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2017/04/the-improving-access-to-affordable-prescription-drugs-act-a-different-tack-on-exclusivity.html.

23 "Emerging Health Care Issues: Follow-on Biologic Drug Competition" (FTC, June 2009), <https://www.ftc.gov/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report>.

24 "The Biosimilars Litigation Landscape For 2017," *Law360*, January 6, 2017, <https://www.law360.com/articles/878105/the-biosimilars-litigation-landscape-for-2017>.

experience drastic price declines after generic entry as demonstrated in Figure 4.

Figure 4: Patent cliff - Biologics vs. small molecule drugs



Note: This chart assumes a period of seven and a half years of patent exclusivity after FDA approval. The Hatch-Waxman Act guarantees a five year minimum exclusivity period, and Paragraph IV certifications allow for an additional 30-month stay. Average exclusivity periods are typically closer to twelve years. See Aaron S. Kesselheim and Jonathan J. Darrow, "Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era," Yale J. Health Pol'y L. & Ethics 15 (2015): 293. Chart assumes that generic prices decrease by 32% in the first 12 months and by 73% in the first 24 months following generic entry. See Ernst R. Berndt and Murray L. Aitken, "Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century after the 1984 Waxman-Hatch Legislation," International Journal of the Economics of Business 18, no. 2 (2011): 177–201.

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Finalizing regulatory rules and removing uncertainty surrounding the biosimilar entry process will only gain importance in the coming years. The three best-selling biologics – Humira, Enbrel, and Remicade – have experienced FDA-approved biosimilar entrants in 2016. Inflectra, the biosimilar for Remicade, entered the market at the end of 2016, whereas the others do not expect to begin selling until 2018 due to patent litigation, so prices are as of yet unchanged. Roughly 50% of biologic sales will go off-patent in the next four years, offering a major opportunity to control spending growth in the United States pharmaceutical market if biosimilars are incentivized to compete.²⁵ The large variation in biosimilar penetration rates across European countries seems to be caused by differences in buyer institutions.²⁶ This suggests that regulatory pathways must be developed in conjunction with cost-effective procurement methods. In the United States, this implies that insurers, including Medicare, must incentivize consumption of biosimilars if cost savings are to be realized. The savings in price reductions offered by biosimilars in Europe can exceed 50%, and recent advances in manufacturing that have lowered marginal costs suggest that the most competitive

25 Morgan Stanley estimates that around \$47 billion in biologics sales will face patent expiration in the next four years. "2016-2020 Roadmap: \$20 Bln Trophy with Pricing Challenge" (Morgan Stanley, November 14, 2016).

26 Fiona M. Scott Morton, Ariel Dora Stern, and Scott Stern, "The Impact of the Entry of Biosimilars: Evidence from Europe," Working Paper 16-141 (Harvard Business School, January 2017), http://www.hbs.edu/faculty/Publication%20Files/16-141_5daa4ccc-66c6-42e4-bcc3-b54cabb158b5.pdf.

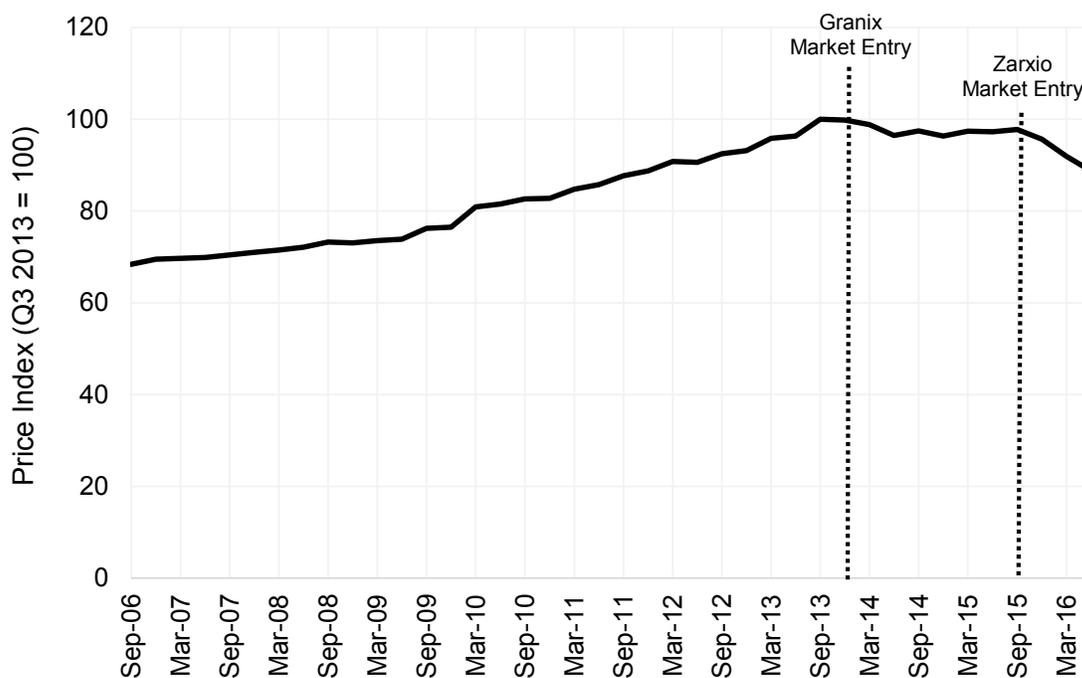
prices could drop yet further.²⁷ These savings are more substantial than initial forecasts of the potential savings from biosimilars prior to 2010, which generally estimated modest cost savings.²⁸

The great success the U.S. has had at containing the cost of drug treatments in the past (U.S. nominal expenditure on pharmaceuticals actually fell in 2012) has been largely driven by the entry of generics, vigorous competition in the generic market, and the efforts of insurers – where possible – to move substitute use of generics for branded products. If the U.S. is effectively without a functioning follow-on sector in the most expensive and fastest-growing segment of pharmaceutical expenditure, biologic drugs, there is little chance of expenditure growth slowing in the future, which will have predictable consequences for access.

III.2 Evidence of cost savings from the first biosimilar approval in the United States

The following chart shows the evolution of the average price of filgrastim, a biologic that first gained approval in 1991 under the brand name Neupogen. A follow-on variant of filgrastim, Granix, was approved by the FDA in August 2012 and entered the market in the final quarter of 2013. Note that Granix entered the way a standard branded drug would, using a costly BLA, even though it was not a new drug, but instead a version of filgrastim. Although Granix was not approved as a biosimilar, it did generate price competition, halting aggregate price growth for filgrastim. Zarxio, the first biosimilar approval in the United States, also a version of filgrastim, was approved in March 2015 and entered the market in the third quarter of 2015. Between the entrance of Zarxio into the filgrastim market and the second quarter of 2016, less than a year, the average price of filgrastim fell by about 11%.

Figure 5: Filgrastim price evolution



Source: IMS data.

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27 Madsen, "From Biosimilar Approval to Biogenerics in Practice."

28 Andrew W. Mulcahey, Zachary Predmore, and Soeren Mattke, "The Cost Savings Potential of Biosimilar Drugs in the United States" (The RAND Corporation), https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf.

Sales of Humira, Enbrel, and Remicade, the three biologics with the highest sales, totaled over \$20 billion in 2015. As mentioned, biosimilars were recently approved for all of these drugs, although market entry has been delayed due to patent litigation.²⁹ Assuming that these biosimilars can achieve similar competitive effects implies at least \$2.2 billion of dollars in annual consumer savings from these approvals alone. Allowing for greater price competition by finalizing interchangeability guidance could greatly increase this figure.

III.3 Biosimilar naming conventions hinder competitive comparisons

Although the FDA has made progress in developing a regulatory framework for biosimilar entry in recent years, there are indications that the agency may not be prioritizing efforts to increase access for consumers. As discussed, guidance for establishing interchangeability has still not been finalized seven years after the relevant law was passed, and the agency continues to debate the proper structure for scientific names in biologics despite calls to do so from many stakeholders. These choices and others indicate that the United States may be pursuing a path of regulation that limits rather than enables competition.

One regulatory guideline, recently finalized in January 2017, that has garnered support from the branded biologic manufacturers lobbying arm and opposition from the FTC and others requires differentiated naming standards for medications that have passed FDA hurdles to be sold as biosimilars. This regulation requires biosimilar manufacturers to affix a four-letter nonsensical suffix to the drug's scientific name to distinguish them from the reference product. For example, Zarxio is a branded reference product with the international scientific name of filgrastim. The first biosimilar for filgrastim was first approved as filgrastim-sndz and then redesignated as filgrastim-bflm.³⁰ Differentiated naming creates problems for bodies that administer directories of drugs, those who design formularies, and those who wish to sort available drugs to find out what alternative treatments are available. Although the ostensible reason for the suffix is that it will allow the agency to track adverse effects of particular strains of biologics, which vary at the batch level due to the differentiated nature of biologic production, it does not correspond to the batch of manufacture or provide any meaningful information to patients or providers. The FTC and the National Council for Prescription Drug Programs (NCPDP), a non-profit healthcare electronic standards group, have strenuously objected to the addition of nonsense suffixes to biosimilar names, noting that this argument fails to stand up to logical scrutiny.³¹

First, as demonstrated in the established European market over the past decade, adverse drug reactions among biosimilars are relatively low.³² Second, the naming convention applies the suffix to a corporation, not a manufacturing plant or specific batch. Corporations may contract to have a biosimilar manufactured by another approved maker, or may open a new plant, or a new line at an existing plant. None of these potentially medically significant changes would be captured by the suffix. Due to the highly heterogeneous nature of biologic production, any tracking of potential adverse events would have to examine more granular

29 Inflectra, the biosimilar for Remicade, entered at risk in November 2016.

30 "Nonproprietary Naming of Biological Products: Guidance for Industry" (FDA, January 2017), <https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf>. The FDA is still considering naming conventions for biosimilars that are deemed interchangeable.

31 Sue Sutter, "FDA's Burden Estimate on Biologic Naming Ignores Downstream Costs, Critics Say," Pink Sheet, February 16, 2017, <https://pink.pharmamedtechbi.com/PS120052/FDAs-Burden-Estimate-On-Biologic-Naming-Ignores-Downstream-Costs-Critics-Say>.

32 Paola M. Cutroneo et al., "Safety Profile of Biological Medicines as Compared with Non-Biologicals: An Analysis of the Italian Spontaneous Reporting System Database," *Drug Safety* 37, no. 11 (November 2014): 961–70.

details, such as the manufacturing facility and batch. More sophisticated tracking tools already exist for the purposes of pharmacovigilance, including National Drug Codes (NDC) used by pharmacies and hospitals to track pharmaceutical inventory; the suffix could even undermine existing systems that track product safety.³³ As one Express Scripts executive has noted, “[w]e could tell you the exact product in the hands of every patient because of the use of the NDC codes that are required for pharmacy reimbursement.”³⁴

The costs of implementing a differentiated nonsensical suffix are significant. First, differentiated naming standards may sow confusion among practitioners regarding the therapeutic equivalence of biosimilars and brands, thereby preventing efficient substitution, slowing biosimilar market penetration, and maintaining higher prices. Evidence from Europe suggests that the market share of biosimilars with differentiated names significantly trails the market share of biosimilars with identical names.³⁵ Second, this requirement would necessitate considerable expenditure to modify existing computer systems to incorporate naming differentiation at significant cost.³⁶ The FTC has expressed concern that buying organizations that fail to pay the costs of redesigning their systems will be unable to take advantage of increased competition from biosimilar entrants and therefore will pay higher prices than if naming were standardized, as is the case with generic drugs.³⁷

If consumers have trouble finding a competitive biosimilar entrant, that entrant must expect lower revenue than in a system where its scientific name is the same as its competitors. Lower revenue will cause fewer entrants in equilibrium, as entrants trade off the cost of entry with expected profits. Thus, a collection of small frictions in the market for biosimilar products will result in less expected entry and higher prices for consumers.

III.4 Orphan drug exclusivity hinders generic entry

The Orphan Drug Act of 1983 was passed by Congress to incentivize the development of drugs for treatment of rare diseases. Gaining orphan drug status bestows many benefits on a drug manufacturer, including market exclusivity, tax breaks, and reduced regulatory costs.³⁸ By some measures, the Orphan

33 Lee Ann Stember, “Comment from the National Council for Prescription Drug Programs NCPDP to OMB,” February 7, 2017, <https://www.regulations.gov/document?D=FDA-2013-D-1543-0189>; Elizabeth Jex, “Perspective on the Importance of Biosimilar Competition,” Presentation (2016 GPhA Biosimilars Council Conference, September 7, 2016).

34 “Comment of the Staff of the Federal Trade Commission in Response to a Request for Comments on Its Guidance for Industry on the “Nonproprietary Naming of Biological Products”” (FTC, October 27, 2015), https://www.ftc.gov/system/files/documents/advocacy_documents/ftc-staff-comment-submitted-food-drug-administration-response-fdas-request-comments-its-guidance/151028fdabiosimilar.pdf.

35 Jex, “Perspective on the Importance of Biosimilar Competition.”

36 The NCPDP has stated in its public comment filed with the FDA that the biologics naming directive “will require every segment of healthcare including, but not limited to, hospitals, payer, and providers to engage in thousands of hours of information technology redesign and reprogramming.” Consequently, they estimate that “direct implementation costs will be in the billions of dollars.” They also anticipate indirect costs to include drug price increases, adverse patient safety issues, drug shortages, and supply chain disruption. Stember, “Comment from the National Council for Prescription Drug Programs NCPDP to OMB.”

37 The naming guidance issued by the FDA departs from the international naming conventions that allow for cross-country standardization. The WHO assigns drugs an international nonproprietary name (INN) that is the same for brands and generics. Departure from this system could further hinder international price competition from imported drugs. While the WHO does recommend use a four-letter random identifier, known as a Biological Qualifier (BQ), it would be separated from the nonproprietary name in pharmacy databases. “Comment of the Staff of the Federal Trade Commission in Response to a Request for Comments on Its Guidance for Industry on the “Nonproprietary Naming of Biological Products”.”

38 Nicholas Bagley, “The Benefits and Costs of Promoting the Development of New Orphan Drugs,” Working Paper (University of Michigan Law School, February 12, 2017), <http://theincidentaleconomist.com/wordpress/wp-content/uploads/2017/02/2.12-orphan-drug.pdf>. Orphan drugs carry significant tax subsidies for drug manufacturers. Bagley notes that the U.S. Treasury estimates \$1.75 billion in foregone revenue in 2016 to subsidize orphan drug manufacturing.

Drug Act has been very successful at generating research and treatment for rare diseases. Over 50% of new drugs are approved for orphan populations, and over half of orphan approvals are first-in-class, indicating that no other treatment exists for the approved indication.³⁹

In recent years, however, it has become increasingly clear that drug manufacturers have found ways to gain orphan drug status in applications that do not adhere to the original intent of the law. Several of the most pressing concerns regarding orphan drugs relate to (i) orphan drugs exemptions from the 340B drug discount program; (ii) the ability of drug manufacturers to gain orphan status for pre-existing drugs; and (iii) the use of disease sub-types to maintain virtually permanent orphan status and delay generic entry. The exploitation of these imperfections in the Orphan Drug Act contribute to the high price of biologic drugs as over 60% of Orphan Drugs are biologics.⁴⁰

The 340B drug program was created in 1992, and requires that drug manufacturers provide discounted drugs to hospitals and clinics that serve poor communities. In return, manufacturers are included in Medicaid formularies, increasing demand for their product. More than 40% of hospitals in the United States are eligible to participate in the 340B program.⁴¹ Orphan drugs, however, are granted exclusion from the 340B program, preventing clinics from obtaining these drugs at discounted prices. Crucially, beginning in October 2015, a drug that has gained orphan status for treatment of one condition gains exclusion from the 340B program for all its sales.⁴² Since then, widely-used drugs can identify a small new use that qualifies as orphan, apply for that use, and, once approved, stop offering 340B discounts for all their sales. Humira, for example, is the best-selling medicine in the world, but has gained orphan drug status for treatment of pediatric Crohn's disease.^{43, 44}

Some prescription medicines obtain orphan status years after they originally gained FDA approval to treat a certain broad indication. Over time these medicines are prescribed "off-label" to treat other indications. Manufacturers can then run a clinical trial on a small off-label use, prove effectiveness, gain orphan status, and raise price significantly. 3,4-diaminopyrrolidine, a drug used to treat rare neuromuscular diseases for over thirty years, recently gained orphan drug status in the EU, causing its price to rise from \$1,600 to \$60,000 per year.⁴⁵ As noted by Bagley (2017), incentivizing further study of drugs that are already on the market but being prescribed off-label is socially valuable. However, it is generally less costly to study an existing safe drug than it is to invent an entirely new treatment for an unmet medical need and prove safety and effectiveness. This raises the question of whether the implicit subsidies and higher prices to consumers for to this category of orphan drugs might be greater than the social benefits.

39 Ibid.

40 Sinéad M Murphy, Araya Puwanant, and Robert C. Griggs, "Unintended Effects of Orphan Product Designation for Rare Neurological Diseases," *Annals of Neurology* 72, no. 4 (October 2012): 481–90.

41 U. S. Government Accountability Office, "Medicare Part B Drugs: Action Needed to Reduce Financial Incentives to Prescribe 340B Drugs at Participating Hospitals," no. GAO-15-442 (July 6, 2015), <http://www.gao.gov/products/GAO-15-442>.

42 Memorandum Opinion, *Pharmaceutical Research and Manufacturers of America v. United States Department of Health and Human Services*, et al., No. 14–1685 (U.S. District Court for the District of Columbia October 14, 2015). https://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2014cv1685-29.

43 Sarah Jane Tribble and Sydney Lupkin, "Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies," *Kaiser Health News*, January 17, 2017, <http://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/>.

44 Kaiser Health News provides a database of orphan drugs, classified by whether they are approved only for treatment of an orphan condition, whether they were first approved for mass market use, and whether they have been approved to treat multiple orphan conditions. "Interactive: How Orphan Drugs Win The 'Monopoly' Game," *Kaiser Health News*, January 17, 2017, <http://khn.org/news/orphan-drugs-lookup-interactive/>.

45 Bagley, "The Benefits and Costs of Promoting the Development of New Orphan Drugs."

Another abuse of the Orphan Drug Act occurs when a disease has many subtypes, each of which may be used in succession to gain a virtually permanent orphan drug distinction.⁴⁶ Cancer drugs are particularly susceptible to this tactic, as a drug that is generally effective on cancers may also be shown to effectively treat more rare phenotypes or subtypes of cancer patients, as well as other rare indications. This allows drug manufacturers to apply for orphan drug status on one sub-population, and then later apply for a separate sub-population once the first period of exclusivity has expired. Bevacizumab, for example, is the active ingredient in Avastin, a biologic monoclonal antibody used to prevent tumor growth. This biologic has gained fourteen different orphan approvals, with the first approval occurring in 2003 and the latest approval occurring in 2016.⁴⁷ When an indication is designated as orphan, it receives 7 years of marketing exclusivity thus preventing generic entry. A generic may enter the non-orphan sub-market under the normal rules and sell to those populations. Once a generic is in the broader market, a physician may prescribe it for an orphan indication – since they are all the same molecule – but the generic may not list protected orphan indications on its label and reimburse for those indications may not always be available. The additional years of exclusivity in the orphan sub-population reduce expected market size for entering generics, therefore lowering entry on average, and contributing to higher drug prices.

III.5 Pay for delay

“Pay for delay” or “reverse payment” settlement cases have been commonplace in the pharmaceutical industry. Such cases involve settlements to patent litigation in which a brand-name drug manufacturer compensates a potential generic entrant in exchange for an agreement to stay out of the market for a period of time. In *FTC v. Actavis Inc.*, a landmark decision from 2013, the Supreme Court ruled that these patent settlements are subject to antitrust enforcement under a rule of reason analysis.⁴⁸

Typically, a settlement in patent litigation cases involves payment of a royalty from an infringing generic manufacturer of the reference branded drug who also owns or controls a patent covering that invention. Edlin et al. (2015) note that such agreements are economically beneficial since they allow for sharing of information and tend to increase industry output.⁴⁹ “Reverse payments” are payments in the other direction, from the brand to the generic, which are generated by the following incentives. The brand faces the loss of its entire monopoly profit for the rest of the patent term should the patent be found invalid. Importantly, even if the generic were to win the patent case and enter, it would earn much less profit than the brand could. Therefore, the brand can offer to share its monopoly profit with the generic in exchange for the generic settling the patent litigation and agreeing to stay out of the market. The generic is better off because it is sharing the brand’s profit; the brand is better off because its patent remains in force so its profit is not entirely lost; and consumers are worse off because they are denied the lower prices that result from generic entry. This is why reverse payment settlements that involve no licensing have been called a “naked market division agreement.”⁵⁰ Edlin et al. discuss a simple test to determine whether a reverse payment settlement is likely to be anticompetitive. If a brand pays more than the prospective litigation costs to a potential generic entrant, and if the generic firm delays market entry, then one can reasonably infer that such behavior is anticompetitive.

46 Ibid.

47 “Orphan Drug Designations and Approvals,” <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>.

48 Federal Trade Commission v. Actavis, Inc., et al., 570 U.S. ____ (2013).

49 Aaron Edlin, Scott Hemphill, Herbert Hovenkamp, and Carl Shapiro, “The Actavis Inference: Theory and Practice,” *Rutgers UL Rev.* 67 (2015): 585.

50 Ibid. at p. 587.

Notably, the regulatory framework governing traditional pharmaceuticals exacerbates the anticompetitive harm created by pay for delay settlements because regulatory hurdles are often linked with patent resolution. Hatch-Waxman grants a 180-day period of exclusivity to the first generic applicant approved by the FDA from the date of production. Therefore, in the case of multiple potential generic entrants, payment to delay entry by the first generic firm to gain approval who has filed a paragraph IV certification to the patents listed by the reference product serves as an effective block on other generic entrants.⁵¹ The economic incentives for these agreements are high, as it is more profitable for two firms to share monopoly profits than to compete and earn oligopoly or competitive profits.⁵² The Supreme Court's Actavis decision vindicated the FTC's enforcement against these contracts and has deterred some subsequent pay for delay agreements.⁵³ However, innovative new forms of contracting between brand and generic continue to appear and the agency continues to litigate against those it determines are anticompetitive.

The applicability of Actavis to similar agreements in the biologics industry remains an open question. For example, the regulatory framework governing biologics, BPCIA, creates similar regulations to Hatch-Waxman that may incentivize pay for delay in biologics. BPCIA grants exclusivity for interchangeable follow-on biologics. The regulation differs from Hatch-Waxman in making the exclusivity provision granted to interchangeable biologics expire after 42 months regardless of whether the competitor decides to produce.⁵⁴ However, even in the case of biosimilars that do not obtain the interchangeable designation, i.e. when no exclusivity period exists, pay for delay could prevent a brand's patents from becoming invalidated, increasing legal hurdles for a third biosimilar entrant. Thus, although there appear to be fewer incentives for pay for delay schemes in the biologics industry compared to traditional pharmaceuticals, it is certainly possible that companies might pursue such schemes in the face of potential competition from biosimilars.⁵⁵

III.6 REMS status makes biosimilar and generic entry more costly and slower

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA). One piece of the legislation grants the FDA authority to require that manufacturers of dangerous drugs enhance the safety of drug provision by implementing Risk Evaluation and Mitigation Strategies (REMS). The specific form of REMS depends on the drug under evaluation. Some drugs subject to REMS may simply require a communication plan to indicate the potential risks of a drug to providers. Other REMS requirements are more stringent, and implement restrictions on the distribution of a drug. For example, some drugs may require that health care professionals monitor drug usage or that pharmacies sign up patients to a central register to track usage. These more stringent requirements linked to drug distribution are referred to as Elements to Assure Safe Use (ETASU).⁵⁶ Today, over 40% of new FDA approvals are subject to REMS, a majority of which restrict distribution.⁵⁷

51 Typically, an agreement will stipulate that the generic can enter before contemplated in the agreement in the event that any other generic enters the market (an "acceleration clause").

52 Edlin, Hemphill, Hovenkamp, and Shapiro, "The Actavis Inference."

53 "FTC Report on Drug Patent Settlements Shows Potential Pay-for-Delay Deals Decreased Substantially in the First Year Since Supreme Court's Actavis Decision," *FTC*, January 13, 2016, <https://www.ftc.gov/news-events/press-releases/2016/01/ftc-report-drug-patent-settlements-shows-potential-pay-delay>.

54 Darren S. Tucker and Gregory F. Wells, "Emerging Competition Issues Involving Follow-On Biologics," SSRN Scholarly Paper (Rochester, NY: Social Science Research Network, 2014), <https://papers.ssrn.com/abstract=2536969>.

55 Ibid.

56 "A Brief Overview of Risk and Evaluation Strategies (REMS)," Presentation (FDA), <https://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf>.

57 "Statement of Beth Zelnick Kaufman" (Senate Judiciary Subcommittee on Antitrust, Competition, Policy, and Consumer Rights, June 21, 2016), <https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Zelnick-Kaufman%20Testimony.pdf>.

Drug manufacturers have recently exploited REMS as a tool to deter generic entry by claiming that distribution restrictions allow them decline to sell the branded drug to generic manufacturers. There have been various lawsuits between generic manufacturers and brands over sample withholding.⁵⁸ Generic and biosimilar potential entrants require samples of a reference drug in order to perform testing and prove bioequivalence of their follow-on product. Without small quantities of the branded drug, the generic is unable to successfully complete an ANDA or follow-on BLA. Brands have taken the position that when their products are subject to REMS, it is too dangerous to sell to any entity who is not a patient with a prescription, thus effectively preventing generic entry.

In an amicus brief for a 2013 case involving the withholding of a drug sample from several generic manufacturers, the FTC noted that the regulatory process for generic approval ceases to function without availability of a sample of a branded drug to prove bioequivalence.⁵⁹ Estimates suggest that REMS abuse could cost consumers \$5.4 billion annually.⁶⁰ The abuse of REMS restrictions occurs despite language included in the FDAAA specifically meant to prevent such behavior because the statute includes no enforcement mechanism or penalty for violation.

Another way that drug manufacturers abuse the FDAAA legislation relates to a provision that allows manufacturers to patent their REMS programs, creating yet another barrier to generic entry. For example, thalidomide is a leprosy treatment that was originally developed in the 1950s. The drug is primarily produced by Celgene. Because it can cause birth defects, Celgene developed a distribution system to ensure that the drug would be restricted for patients who might be adversely affected – and Celgene patented that system. When a generic manufacturer attempted to enter the market in 2007 and use the existing REMS system, Celgene sued, claiming patent infringement of the REMS program. The generic manufacturer eventually withdrew its generic application in 2010.⁶¹

This issue has the potential to be very costly going forward. Physicians do not want to learn to use and subscribe to a different REMS system for each generic entrant of a molecule. They will tend to continue to use the drug that's accessible through the REMS system with which they are already familiar, likely that of the incumbent. Incumbent brands will therefore be able to reduce competitors' sales by creating proprietary REMS systems and refusing to share them with generic or biosimilar entrants.

REMS abuse has the potential to affect biologic drugs as well as small molecule generics. Both Hatch-Waxman and the BPCIA require that follow-on manufacturers obtain drug samples from brands in order to demonstrate bioequivalence or similarity.⁶² According to the FDA, 17 biologic drugs implement REMS, 10 of which restrict distribution.⁶³ As biologic patents expire in the coming years, biotech companies may resort to sample restriction or proprietary REMS systems as a way to prevent or delay biosimilar entry. According to

58 Examples include *Lannet v. Celgene* (2008), *Actelion v. Apotex* (2012), and *Accord v. Acorda* (2013). Darren S. Tucker, Gregory F. Wells, and Margaret E. Sheer, "REMS: The Next Pharmaceutical Enforcement Priority?," SSRN Scholarly Paper (Rochester, NY: Social Science Research Network, 2014), <https://papers.ssrn.com/abstract=2410950>.

59 Brief for the FTC as Amicus Curiae in *Actelion Pharmaceuticals Ltd., et al. v. Apotex Inc., et al.*, No. 14- cv-2094.

60 Alex Brill, "Lost Prescription Drug Savings from Use of REMS Programs to Delay Generic Market Entry" (Matrix Global Advisors, July 2014), http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

61 Ameet Sarpatwari, Jerry Avorn, and Aaron S. Kesselheim, "Using a Drug-Safety Tool to Prevent Competition," *New England Journal of Medicine* 370, no. 16 (April 17, 2014): 1476–78.

62 Tucker and Wells, "Emerging Competition Issues Involving Follow-On Biologics."

63 "Approved Risk Evaluation and Mitigation Strategies (REMS)," FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/>.

one study, delayed biosimilar entry from restricted access would result in approximately \$140 million in lost savings for every \$1 billion in biologics sales.⁶⁴

III.7 Formulary regulations can limit competition

Insurers use formularies as a bargaining tool to control the cost of drugs covered under their plans. An insurer typically must include drugs from all classes in its plan, but it does not need to include *all drugs* within a class – and therefore can threaten to exclude one. The threat of exclusion, and the resulting loss of sales, may induce a manufacturer to lower its price in order to be retained on the formulary. If several branded products treat the same condition, the insurer can threaten to move its volume to the product that offers to sell on the best terms. In this way, formularies stimulate price competition between on-patent branded products. In fact, Duggan and Scott Morton (2010) show that formularies are more effective at reducing drug prices than competition in markets populated by uninsured consumers. Even though uninsured consumers bear the full price of a drug and should therefore be sensitive to prices, they have no option but to continue to pay high prices because they cannot threaten to move their volume to a competitor.⁶⁵

The federal government requires Part D insurers to include all drugs in the “protected classes,” including many types of cancer, in their formularies.⁶⁶ A Part D insurer cannot threaten to exclude any drug in a protected class, and the manufacturers of those drugs know this. An insurer can still use some mechanisms to move demand such as differential copayments and step therapy, but overall it has much less bargaining power. A manufacturer that knows the buyer must purchase its product has a strong bargaining position and an incentive to increase drug prices and refuse to offer discounts.⁶⁷

Moreover, these manufacturers can take advantage of the fact that the insurer is purchasing a bundle of drugs to include in the insurance product. Besanko, Dranove, and Garthwaite (2016) develop a model where insurance is a bundle of drug treatments, some of which are competitively-priced generic products and others are patent-protected brands with prices reflecting market power.⁶⁸ Because of the generics in the bundle, the cost of insurance is lower than the sum of expected consumer valuations of all the drugs. A new entrant can take advantage of this surplus by charging more than the value of its patented product as long as the insurer must include it in the bundle. This is because the total cost of the bundle (now higher due to the new product) is still below its total value due to the included generics; the new brand “steals” some of the surplus created by generics when it sets a high price.⁶⁹ Required bundling enables the manufacturer’s strategy of pricing its product above value. If insurers could refuse to buy the new product, the manufacturer would face no sales when it charged a price above the drug’s value. The launch price of the new drug would have to decline until the drug was attractive. Besanko et al. shows that the

64 Brill, “Lost Prescription Drug Savings from Use of REMS Programs to Delay Generic Market Entry.”

65 Mark Duggan and Fiona M. Scott Morton, “The Effect of Medicare Part D on Pharmaceutical Prices and Utilization,” *American Economic Review* 100, no. 1 (March 2010): 590–607.

66 The protected classes are antiretrovirals, antidepressants, antipsychotics, anticonvulsants, immunosuppressants, and antineoplastics. Ibid.

67 CMS attempted to remove formulary restrictions in 2014, but this action was blocked by the pharmaceutical lobby. Katie Thomas and Robert Pear, “Plan to Limit Some Drugs in Medicare Is Criticized,” *The New York Times*, February 21, 2014, <https://www.nytimes.com/2014/02/22/business/plan-to-alter-medicare-drug-coverage-draws-strong-opposition.html>.

68 David Besanko, David Dranove, and Craig Garthwaite, “Insurance and the High Prices of Pharmaceuticals,” Working Paper (National Bureau of Economic Research, June 2016), <http://www.nber.org/papers/w22353>.

69 The authors apply their model to investigate the rise in the price of drugs in certain protected classes following the passage of Medicare Part D, finding evidence that the legislation allowed manufacturers of certain oncological drugs to raise prices above the estimated value of a quality-adjusted life year.

exact design of formulary rules – or bundles – and what can be omitted can have a large effect on price competition and the level of prices.

This effect is stronger when the manufacturer has a small market share because it does not internalize the impact of its higher prices on the cost of insurance. The decline in concentration in the pharmaceutical industry and the purchase of small manufacturers by financial entrants may be contributing to high prices via this incentive. Besanko et al. provide insight into the recent growth in drug prices, especially among oncological drugs and legacy drugs that have market power due to competitor exit, e.g. Turing pharmaceuticals, Valeant, and Mallinckrodt. They find that small firms are more likely to take advantage of market power to price drugs well above marginal cost. This feature is discussed in more depth in Section 5.2.

III.8 Any approval delays will reduce competition

FDA approval is the most basic and important entry barrier for small molecule drugs. Thus, it should always be an area of policy focus. The statistics on approval times are difficult to interpret because the applicant firm determines the quality of the ANDA. Short approval times may indicate that firms are submitting complete and correct applications and receiving quick approvals, and long approval times may indicate that deserving applications are being delayed unnecessarily by the agency. Alternatively, long approval times may indicate that firms are submitting low-quality applications many years before they want to enter for the purposes of utilizing FDA review and advice to improve their applications until they are successful. Whereas delays caused by agency inaction represent a costly entry barrier, delays caused by deficiencies in firm applications do not reflect any regulatory barrier to entry, although it may not be a good use of government resources.

One area where FDA approval procedures may be a barrier is that of combination products and products sold in a delivery mechanism. The standards for showing bioequivalence for these products is less clear and is established on a case by case basis, making approvals much slower. With the rise of many medicines like epinephrine and insulin that are delivered with a device, this ad hoc approval process is becoming more costly for consumers.

IV. IMPERFECTIONS IN CONSUMER BEHAVIOR

Consumers of pharmaceutical products must respond to price and quality differences among competitors to maintain and stimulate competition. These consumers comprise both patients who consume the drug, but seldom choose it, as well as agents who choose the drug, such as PBMs and physicians. The choices of these agents are critical. For example, if they do not respond to lower prices offered by a rival selling a close substitute, then that rival may have trouble generating sales and gaining market share. If the rival firm's low price results in no additional sales, it will have no incentive to lower price in the first place. Firms in this setting will keep margins high on their existing inertial consumers rather than competing on price. Thus, the behavior of consumers is critical to well-functioning markets of any kind, including pharmaceutical markets.⁷⁰

70 Kate Ho, Joseph Hogan, and Fiona Scott Morton, "The Impact of Consumer Inattention on Insurer Pricing in the Medicare Part D Program," *RAND Journal of Economics* Forthcoming (2017). for an application to consumers' choice of Medicare Part D plans as well as Judith A. Chevalier and Fiona M. Scott Morton, "State Casket Sales Restrictions: A Pointless Undertaking?," *The Journal of Law and Economics* 51, no. 1 (2008): 1–23. regarding consumer choice of funeral services.

IV.1 Consolidation in the PBM market

Demand from perfectly informed and incentivized consumers will generate competition among substitute treatments. However, in pharmaceutical markets, final consumers are generally both uninformed and insured. The institutional innovation that improves the elasticity of demand in buying pharmaceuticals is the PBM. The PBM, as already described above, is informed and elastic because its formulary committee has the ability to negotiate for lower prices in exchange for market share.

An important question is whether the PBM is, in fact, a good agent for the final consumer. There has been significant change in the PBM market structure in the last 25 years. In the early 1990s, pharmaceutical manufacturers acquired a number PBMs.⁷¹ The FTC closely scrutinized these transactions, requiring consent agreements to ensure that vertically integrated PBMs would not lessen competition by favoring drugs produced by their owners. These acquisitions were later spun off into independent entities in the late 1990s and early 2000s. More recently, multiple business models have emerged, with independent PBMs (Express Scripts), integration with pharmacies (CVS Caremark and RiteAid), and integration with insurers (UnitedHealth and OptumRx).⁷² Currently, just three firms (CVS Caremark, OptumRx, and Express Scripts) control between 80 and 85 percent of the prescription benefit covered lives in the U.S. market.⁷³ The most recent PBM merger, between UnitedHealth (owner of OptumRx) and Catamaran, occurred in July 2015. These firms formed the third and fourth largest PBMs at the time.

When the medical insurer is vertically integrated into the PBM there are likely to be some consumer benefits. First, the combined insurer will choose treatments that are cost effective overall, e.g. an expensive drug that reduces hospital admissions and saves expenditure on net. Second, there is no double-marginalization or bargaining friction between the insurer and the PBM. Lastly, such an integrated entity may be more able to take capitation or other incentives to reduce expenditure. When the PBM is integrated into a pharmaceutical manufacturer there is the concern that the PBM might disfavor medically appropriate treatments sold by rivals. When the PBM is vertically integrated into the pharmacy network, other competitive concerns may arise depending on the level of concentration on both sides.⁷⁴ Although PBM consolidation will increase bargaining power and drive down drug prices to some degree simply because of the increased size of the PBM, the reduction in competition caused by consolidation may create offsetting incentives for higher prices. We will return to this problem below.

IV.2 Rebates combined with imperfect competition may increase drug prices

Rebates are a source of price competition. They are percentage discounts used by manufacturers to gain market share from PBM enrollees. Rebates are paid after market shares are realized by the PBM and sometimes have a performance component (the higher the drug's share the higher the rebate). The

71 These transactions include Merck-Medco in 1993, Eli Lilly-PCS Health Systems in 1994, and SmithKline Beechum-Diversified Pharmaceutical Services also in 1994. Brian S. Feldman, "Big Pharmacies Are Dismantling the Industry That Keeps US Drug Costs Even Sort-of under Control," *Quartz*, <https://qz.com/636823/big-pharmacies-are-dismantling-the-industry-that-keeps-us-drug-costs-even-sort-of-under-control/>.

72 "OptumRx, Catamaran Complete Combination," July 23, 2015, <https://www.optum.com/about/news/optumrx-catamaran-complete-combination.html>.

73 Jessica Wapner, "Understanding the Hidden Villain of Big Pharma: Pharmacy Benefit Managers," *Newsweek*, March 17, 2017, <http://www.newsweek.com/big-pharma-villain-pbm-569980>.

74 As is usual with exclusive dealing, when both upstream and downstream markets are unconcentrated and competitive, harm is unlikely. On the other hand, if there were only one retail pharmacy network with market power, rival PBMs would be concerned that they would be foreclosed from using that network to distribute drugs to enrollees.

contract between the plan sponsor and the PBM is often based on the invoice price of each drug claim and administrative fees, but does not include the rebates. This is partially because, ex ante, their level is unknown, and partly because this practice incentivizes the PBM to bargain for larger rebates. In a perfectly competitive PBM industry, the savings represented by the rebates would be passed through to plan sponsors in administrative fees or invoice discounts or another dimension of the contract. For example, a PBM could offer a plan sponsor a lower invoice price for drugs that in total was equivalent to expected rebates. However, if the PBM market is not perfectly competitive, this pass through may be incomplete. If the value of rebates is not fully returned to customers, then PBMs will seek higher rebates because they can keep a share of them. What should be the equivalent of a high rebate, namely a lower price, is disfavored by the PBM in this setting. The low price is visible and therefore fully passed through to the plan sponsor, earning the PBM no profit. This was the story told by the executives of EpiPen.⁷⁵ In their telling, PBMs prefer an agreement with a high list price, \$600 for EpiPen, and a large rebate, to one with no rebate and a lower price. This behavior would create drug price inflation.⁷⁶

Complex payment structures may provide incentives for PBMs to keep list prices high, despite rebates, because the PBM has the ability to make the rebate increase smaller than the price increase, and keep the net gain. However, the strategy works only if the final consumer does not respond to the higher prices and move to a rival PBM; this might occur if plan sponsors were uninformed, had inelastic demand for insurance, or if imperfect competition limited plan sponsor choice among competing PBMs. There may be settings that allow the PBM to earn monopoly rents by withholding savings from consumers that would otherwise pass through in the form of lower premiums or prices.

Investors have suggested that infighting between drug manufacturers, insurers, and PBMs has caught the eye of regulators and consumer advocacy groups, threatening shared profits that would otherwise be disbursed to consumers. Recently, a health care reporter for the Wall Street Journal, citing the “investor’s perspective,” suggested that “the three sides should just keep quiet and do everything they can to preserve their very profitable relationship.... Clearly, the opaque system of a high sticker price and unseen rebates and discounts in place works well for industry, even though consumers are the losers.”⁷⁷

A second incentive for high prices lies in the fact that if manufacturers set higher drug prices and rebates are in percentage terms, the profits earned by the PBM will rise even though nothing else about the situation has changed at all.⁷⁸

Rebates themselves are never made public because they reflect the competitive advantage of both the PBM and the brand’s manufacturer. Neither wants to reveal to competitors how well it is doing, nor the lowest (highest) price it is willing to accept (pay). This confidentiality likely assists PBMs in bargaining for lower net prices, and it allows PBMs to reward very elastic consumers with lower prices. Thus, requiring

75 One Gilead executive noted “‘If we just lowered the cost of Sovaldi from \$85,000 to \$50,000, every payer would rip up our contract,’ said Jim Meyers, executive vice president of worldwide commercial operations, in an interview with Bloomberg News.” Caroline Chen and Robert Langreth, “Gilead Executive Says Pharmacy Benefit Managers Keep Prices High,” *Bloomberg*, March 3, 2017, <https://www.bloomberg.com/news/articles/2017-03-03/gilead-executive-says-pharmacy-benefit-managers-keep-prices-high>.

76 Joseph Walker, “Drugmakers Point Finger at Middlemen for Rising Drug Prices,” *Wall Street Journal*, October 3, 2016, sec. Business, <http://www.wsj.com/articles/drugmakers-point-finger-at-middlemen-for-rising-drug-prices-1475443336>.

77 Charley Grant, “The Blame Game on Drug Prices Is Getting Dangerous,” *Wall Street Journal*, April 9, 2017, sec. Markets, <https://www.wsj.com/articles/the-blame-game-on-drug-prices-is-getting-dangerous-1491758834>.

78 Choice in accounting methods makes assessment of the industry’s economic margins difficult.

rebates to be made public or transparent is likely to lead to higher drug prices. However, the difficulty a buyer has in knowing even a simple aggregate, such as the total magnitude of its rebates, may help PBMs soften price competition. Further study is needed to assess whether the incentives in the PBM industry are aligned with consumer benefit.

IV.3 Product hopping

Despite the well-established regulatory framework governing the generic market, pharmaceutical manufacturers continue to exploit aspects of the market to limit effective generic competition. One issue of current concern to many observers is known as “product hopping” or “evergreening.” This occurs when a branded manufacturer obtains a new NDA or BLA approval for a variant of its product (for example, capsules instead of the existing tablets, an extended release version, or a new delivery device). The branded manufacturer releases the new product and markets it heavily, convincing physicians to switch their patients to the reformulated product. After a period of time, the patent expires and an inexpensive generic or biosimilar version of the first-generation drug or biologic arrives on the market. By that time, a large fraction of consumers have been moved to the second generation product which is not A-rated or interchangeable with the previous first generation. Thus, when prescriptions for the second generation product are submitted to the pharmacist, that patient cannot be switched to the lower priced generic or biosimilar automatically without a new prescription from the physician.⁷⁹ Estimates suggest that automatic substitution at the pharmacy is a critical element of the generic drug savings that has saved consumers hundreds of billions of dollars per year.⁸⁰ This product hopping strategy slows the market penetration of generic or biosimilar versions of the older product.

The result of the situation is that consumers pay higher prices. In addition, the generic market is much smaller, which discourages entry. In some cases, the brand withdraws the old product instead of promoting the new product, so called “hard switching;” in that situation consumers have no choice but to take the new product if they want to continue with the same treatment approach.

The welfare impact of this strategy depends on the improvement in quality between the first and second generation medicines. One might imagine a case where the two were nearly the same and there was no functional difference for the consumer. One might also imagine a case where the new version delivers substantial benefits to some consumers. In regular markets, the price increase that accompanies, for example, a new flavor of ice cream or an improved laundry detergent would be geared to its value because consumers would not otherwise purchase the new product. In these types of markets antitrust authorities do not spend enforcement resources evaluating whether an innovation is beneficial to consumers; the market will answer that question. In pharmaceutical markets, agents for the consumer – the PBM and the physician – are imperfect. The physician is swayed by advertising to change prescriptions without internalizing the price difference that the consumer must pay. The PBM does not act to switch consumers back to the cheaper product perhaps because it does not have control over the physician to do so, and

⁷⁹ Because laws governing automatic substitution are typically linked to a technical FDA determination of therapeutic equivalence that is specific to dosage and form, such manufacturing changes prevent automatic substitution of generics by pharmacists. State pharmacy laws and FDA regulations governing therapeutic equivalency and automatic substitution govern under what conditions pharmacists may dispense any A or B rated version of a drug/biologic

⁸⁰ Brief for the FTC as Amicus Curiae in *Mylan Pharmaceuticals, Inc. v. Warner-Chilcott PLC, et al.*, No. 2:12-cv-03824-PD.

perhaps because it receives a rebate on the new product (a share of the monopoly rent captured by the new product's maker through the inaction of the PBM).

The difference in cost-sensitivity to drug prices can often be seen where total medical costs and the prescription costs are managed by the same entity. For example, an HMO that is the residual claimant on healthcare expenses will switch all prescriptions to the product with the best net performance profile (whether new or old) because it is both prescriber (controlling prescription choice) and insurer (with financial incentive for low costs) and is therefore a good agent for the consumer. When the end user has both full price and efficacy information, as well as total health cost responsibility, that purchaser shops optimally, whether through a perfect agent or as a consumer herself. When the purchaser chooses optimally, we are back in the setting of the laundry detergent example above, namely, the consumer purchases when the incremental innovation is more valuable than the price increase. Useless or low value innovations will gain no sales in a marketplace populated by careful shoppers.

It is logical that biopharmaceutical innovation ranges from breakthrough cures to incremental improvements, e.g. an extended release, and that these small incremental improvements may have value for all, or a subset of, consumers. What is needed is a market test that a product without value will fail. Unfortunately, a significant fraction of U.S. pharmaceutical consumers do not switch in response to price and quality incentives, mainly due to problems of agency and information asymmetry. Taking this into account, drug manufacturers can introduce small changes to drugs that have no therapeutic benefit, thereby preventing automatic substitution and taking advantage of PBMs and other middle men that either cannot or choose not to switch consumers.

The FTC has pursued cases in this area on the theory that the manufacturer's promotion of its new product necessarily reduces the market available for the generic and therefore lessens competition and consumer welfare. The economic literature has pointed out that promotional behavior on thin-to-nonexistent technological grounds is common – for example, it is true of makers of bottled water – and it is not clear that consumer welfare is lower as a result of that kind of innovation.⁸¹ Antitrust plaintiffs have had more success in settings where the brand has removed its own product from the market so that consumers have fewer choices. In the Mylan case, the defendant introduced a delayed-release version of a drug used to treat acne and withdrew the old version from the market.⁸² The withdrawal caused all consumers to switch to the new product, rather than only those whose physicians thought they would benefit. This modification allegedly added no therapeutic benefit, and the brand did not permit the market to judge by allowing competition between the new and old versions. The FTC alleged that the withdrawal provided a de facto barrier to competition from Mylan's generic drug.⁸³ A similar case involving a reformulation from instant release to extended release for the blockbuster Alzheimer's drug Namenda resulted in an injunction granted by a federal judge that prevented Allergan, the manufacturer, from switching drug formulations.⁸⁴ The case was dropped after it was determined that the injunction successfully prevented the alleged anticompetitive behavior.

81 Dennis W. Carlton, Frederic A. Flyer, and Yoad Shefi, "A Critical Evaluation of the FTC's Theory of Product Hopping as a Way to Promote Competition," 2016, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2808822.

82 Brief for the FTC as Amicus Curiae in Mylan Pharmaceuticals, Inc. v. Warner-Chilcott PLC, et al.

83 Ibid.

84 "A.G. Schneiderman Announces Resolution Of Lawsuit That Protected Alzheimer's Patients From Anticompetitive Tactic Aimed At Maintaining Higher Drug Prices," *New York State Attorney General*, <https://ag.ny.gov/press-release/ag-schneiderman-announces-resolution-lawsuit-protected-alzheimer%E2%80%99s-patients>.

Product hopping strategies may already be beginning to appear in biologic markets facing biosimilar competition. For example, Amgen developed an extended release version for Neupogen (filgrastim), called Neulasta (pegfilgrastim) and has moved \$4 billion of sales to this extended release version before the biosimilar to Neupogen, Sandoz' Zarxio (filgrastim-sndz) reached the market. On the eve of biosimilar competition, Neupogen has sales of less than \$1 billion.⁸⁵

IV.4 Incentives for price competition in Medicare

Medicare Part B covers outpatient care for Medicare enrollees. Pharmaceutical spending in Medicare Part B disproportionately uses specialty and biologic drugs, as these are often injectable or infused treatments that must be applied under the treatment of a physician in an outpatient setting. According to MedPAC, the independent payment advisory committee for Medicare, biologics represent 9 of the 10 highest expenditure products in Medicare Part B.⁸⁶

IV.4.1 Consolidation in the PBM market

Currently, Medicare assigns substitute drugs a category within the Healthcare Common Procedure Coding System – this is commonly referred to as a J-Code. Medicare reimburses physicians based on the Average Sales Price (ASP) for drugs within a given J-Code, with a 6 percent additional margin.⁸⁷ For J-Codes that include multiple close substitutes, this system incentivizes physicians to choose cheaper drugs since they receive the same reimbursement for any drug included in the J-Code. However, for biologic drugs, this reimbursement system fails to create price competition. Under current CMS policy, each biologic product with competing biosimilars has two J-Codes, one for the brand and another for its biosimilars. Separating the J-Codes of biosimilars and biologics means the physician does not gain financially from purchasing and delivering the less expensive treatment.

While CMS biologic reimbursement policy has had little effect on spending thus far due to the paucity of biosimilars on the market, it could represent a major lost opportunity for Medicare to reduce pharmaceutical spending as biosimilars enter the market in the coming years. MedPAC has recommended that CMS modify its reimbursement policy to group biosimilars and reference biologics within the same code. If this does not happen, physicians are likely to simply carry on prescribing the reference product regardless of possibly significant savings from biosimilars. At a minimum, CMS should include interchangeable biologics within the same J-Code as reference biologics to encourage price competition.

IV.4.2 Least costly alternative reference pricing

A report by the Health and Human Services Office of Inspector General (OIG) on prostate cancer treatments indicates that reimbursement using Least Costly Alternatives (LCAs), a more restrictive reimbursement policy, can lead to lower prices.⁸⁸ LCA reimburses providers for the price of the least costly

85 IMS Data.

86 "Report to the Congress, Medicare and the Health Care Delivery System," Report (Medicare Payment Advisory Commission, June 2016), <http://www.medpac.gov/docs/default-source/reports/june-2016-report-to-the-congress-medicare-and-the-health-care-delivery-system.pdf?sfvrsn=0>.

87 This margin was reduced to 4.3% due to the federal sequester.

88 See Daniel R. Levinson, "Least Costly Alternatives: Impact on Prostate Cancer Drugs Covered Under Medicare Part B," Report (Department of Health and Human Services, Office of Inspector General, November 2012).

treatment in a basket of substitute drugs. Between 1995 and 2010, payment for prostate cancer drugs in Medicare Part B was priced based on reference payments for least costly alternatives (LCAs), incentivizing physicians to choose the cheapest available treatment. The prostate example is different than most drugs under Medicare Part B, which are reimbursed based on the average sales price for a treatment class as outlined previously. Interestingly, in April 2010, LCA policies were discontinued due to a court ruling. The OIG report finds that costs increased by about 13% due to the removal of reference pricing. LCA pricing is an attractive cost-reducing policy when drugs are close substitutes, as is the case with many small molecule treatments.

IV.4.3 Medicare Part D coverage gap

Medicare Part D includes prescription drug coverage for treatments that do not need physician administration. Under current policy, patients must bear high out-of-pocket costs once they have reached a certain level of spending on prescription drugs. This is commonly referred to as the “coverage gap” or the “donut hole.” When patients enter the coverage gap, regulations set patient copays of biologics and biosimilars at the same level. However, beneficiaries will typically reach the out-of-pocket limit more quickly by using the reference biologic.⁸⁹ Thus, patients enrolled in Medicare Part D will face lower out of pocket costs by consuming the more expensive substitute, perversely raising program expenditure. Although the coverage gap will be closed by 2020, current policy fails to incentivize consumption of cheaper biosimilars.

IV.5 Kickbacks

Although insurers have some ability to control prices through formulary exclusion, as discussed in Section 3.7, they also implement contractual incentives to shift patients toward cheaper alternatives. For example, a co-payment might be \$15 for a generic prescription, \$30 for a preferred brand, and a \$60 for a non-preferred brand. This copayment structure is also known as tiering, and may be especially important to control costs in classes of drugs that have therapeutic substitutes. The idea of the increasing payments is to incentivize the patient to consume products lower down (cheaper) on the tier. The pharmacist can often inform the patient that there is a cheaper brand than the one her physician prescribed, and this may shift some demand to the preferred drug.

Recent evidence shows that drug manufacturers use various techniques to make side payments to patients in order to undo the incentives described above, and thereby shift consumption toward more expensive branded drugs. These side payments can take the form of coupons, in-kind benefits provided under the guise of marketing, or charitable assistance programs. Such practices are particularly extensive in orphan drug populations with high per-patient expenditure, such as hemophilia, that are often treated with biologics. Insurance companies cannot typically monitor for these kickbacks, and therefore cannot condition manufacturer payments on the existence or size of patient side payments.⁹⁰ In addition, by driving the effective price borne by patients to zero, manufacturers can encourage over-consumption of their drug, increasing costs for insurers and driving up premiums.

89 Rachel Schmidt and Shinobu Suzuki, “Biosimilars in Medicare Part D,” Presentation (MedPAC, October 7, 2016), http://www.medpac.gov/docs/default-source/meeting-materials/biosimilarsinmedicarepartd_oct16_pres_sec.pdf?sfvrsn=0.

90 Insurers could theoretically ban kickbacks by writing a contract with manufacturers to prevent such behavior. Informational constraints, however, prevent insurers from monitoring side payments to patients, making enforcement of such clauses costly.

IV.5.1 Coupon cards

Pharmaceutical manufacturers have devised a clever strategy to combat the price competition induced by tiering. They issue “coupon cards” that can be swiped at the pharmacy and pay exactly the difference between either the generic and the brand (\$15 in our example above) or the preferred and non-preferred brands (\$30 in our example above), depending upon which product’s out of pocket price the brand wants to match. The card leaves the consumer paying the lower out of pocket price that belongs to the inexpensive drug the PBM favors – even if she consumes the expensive drug. This scheme completely undoes the financial incentive created by the PBM to incentivize consumption of the cheaper product. While the manufacturer of the expensive product pays the difference in patient co-pay through the coupon card, that is usually much smaller than the difference in the full costs of the competing products. Thus, the insurer ends up paying much more, the consumer’s payment is unchanged, and the manufacturer comes out ahead. The practice blocks the ability of the PBM to create price competition among drugs in return for shifting share, which therefore raises negotiated prices and the cost of prescription drug insurance.⁹¹

Dafny, Ody, and Schmitt (2016) undertake an empirical examination of coupon cards. They find that drug manufacturers often issue coupons to consumers that reduce out of pocket costs.⁹² They show that the use of coupon cards reduces the ability of generic drugs to penetrate markets dominated by a brand-name drug.⁹³ By reducing the cost borne by patients, coupons allow the brand to capture a larger market share and thereby raise prescription drug expenditure. The practice has grown in recent years. Between 2007 and 2010, the percentage of branded drugs offering a copayment coupon grew from under 30% to over 50%.⁹⁴ Importantly, coupons do not generate cost savings for PBMs – who reimburse pharmacies at full price – instead, they undermine the PBM’s efforts to move demand to more cost-effective treatments. Dafny et al. take advantage of legislation passed in Massachusetts banning the use of coupons by insurers to quantify the competitive effects of couponing. They compare drug penetration between New Hampshire and Massachusetts based on insurance claims data, finding that coupons are associated with slower generic market penetration and higher prices. They suggest that coupons may have increased retail spending by billions of dollars over a two-and-a-half-year period, and increased brand utilization by up to 60%.⁹⁵

Coupons are banned in the Medicare and Medicaid programs as it is considered a violation of anti-kickback statues and raise costs to the government; however, these programs encounter problems monitoring the use of coupons by patients.⁹⁶

IV.5.2 Patient services

Pharmaceutical companies that offer treatments for high-cost diseases often use extensive marketing to convince patients to choose treatments. They offer gifts, financial incentives, and in-kind benefits to

91 “Kaléo Announces US Availability and Pricing to Patients of Auvi-Q Auto-Injector,” *PR Newswire*, January 19, 2017, <http://www.multivu.com/players/English/7981051-auvi-q-epinephrine-auto-injector-access-and-availability-launch/>.

92 Leemore Dafny, Christopher Ody, and Matthew Schmitt, “When Discounts Raise Costs: The Effect of Copay Coupons on Generic Utilization,” Working Paper (National Bureau of Economic Research, 2016), <http://www.nber.org/papers/w22745>.

93 Ibid.

94 Ibid. Figure 1.

95 The authors’ sample uses data gathered between June 2007 and December 2009.

96 “Manufacturer Safeguards May Not Prevent Copayment Coupon Use for Part D Drugs” (Department of Health and Human Services, Office of Inspector General, September 2014), <https://oig.hhs.gov/oei/reports/oei-05-12-00540.pdf>.

target potential customers.⁹⁷ Sometimes drug manufacturers directly employ high-value patients, such as hemophiliacs, at substantial pay.⁹⁸ As customers themselves, they also generate substantial profits directly by filling prescriptions through their employer. Moreover, because hemophilia is a genetic disease, many of the relatives of these employees are also customers of the same firm. These employees market drugs to patients by taking them to dinner and extending other in-kind benefits such as expense-paid vacations. Rather than competing on the basis of price and quality, such a manufacturer is compensating insured consumers with a fraction of its profits in exchange for their purchases of its brand. As in the case of couponing, in-kind payments to patients, whether through employment or under the guise of marketing, can eliminate the effectiveness of price mechanisms in insurance contracts, distorting consumer choice toward expensive products.

IV.5.3 Patient assistance programs

A number of charitable programs exist that are ostensibly designed to help low-income patients purchase prescription drugs. “Patient Assistance Programs” (PAPs) are now widespread, having grown from 378 million dollars in 2001 to about seven billion dollars in 2014. Frerick (2016) reviews corporate giving trends from 1992 to 2014, finding that pharmaceutical companies assist patients through two channels.⁹⁹ They give in-kind donations of medication to their own foundations, manufacturer-owned PAPs, that then distribute medications for free to patients. They also give money as charitable contributions to independent PAPs that *support the purchase of their own drugs*.

Independent PAPs are particularly problematic when it comes to tiering, a mechanism used to shift patients toward cheaper therapeutic substitutes. In these settings, donations can function in a manner similar to coupons, reducing a patient’s share of costs while insurers still pay the manufacturer their share of the full, undiscounted price. The independent PAP, often targeted to a particular disease, accepts donations from manufacturers who make medications that treat the disease. If PAPs tend to spend donations on the manufacturer’s product, then the donation will generate a financial return. Below we reproduce a table from one independent Patient Assistance Program that describes this mechanism and shows how manufacturers can profit from “charitable” giving.¹⁰⁰ The donated funds are sheltered from taxation, therefore the corporation enlists taxpayer dollars to fund its own marketing effort. Furthermore, such a scheme encourages manufacturers to set high prices because the insurer is effectively inelastic and the patient becomes inelastic when the manufacturer pays her co-payment. Thus, there is no loss of volume associated with setting a very high price. Patient assistance programs have calculated the potential profits from a corporation’s “charitable giving.” As shown in Table 2, one PAP provides a realistic example of a drug with 25% market share for which donations would generate a “charitable margin” of 60%.

97 Philip Kucab, Katelyn Dow Stepanyan, and Adriane Fugh-Berman, “Direct-to-Consumer Marketing to People with Hemophilia,” *PLOS Medicine* 13, no. 6 (June 14, 2016): e1001996.

98 Andrew Pollack, “Hemophilia Patient or Drug Seller? Dual Role Creates Ethical Quandary,” *The New York Times*, January 13, 2016, <https://www.nytimes.com/2016/01/14/business/hemophilia-patient-or-drug-seller-dual-role-creates-ethical-quandary.html>.

99 “The Cloak of Social Responsibility: Pharmaceutical Corporate Charity,” *Tax Notes* 153, no. 9 (2016): 1151–64.

100 The Academy of Managed Care Pharmacy (AMCP), a pharmacy interest group, has a report published on their website from a PAP that teaches drug manufacturers how to profit from charitable activity:

Every pharmaceutical manufacturer in the United States should contemplate the value of patient assistance programs (PAPs). If you haven’t, then you have missed one of the most significant opportunities to assist patients, promote patient advocacy, and **potentially increase revenues for your organization**.

“A Guide to Patient Assistance Programs” (Chronic Disease Fund, Inc., October 2006), <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=12585>.

Table 2: Charitable margin¹⁰¹

1	Charitable contribution	\$10,000,000
2	Charity overhead	20%
3	Net contribution	\$8,000,000
4	Market share	25%
5	Subsidized patient revenue	\$2,000,000
6	Insurer cost share	88%
7	Revenue	\$16,000,000
8	Charitable margin	60%

Source: Adapted from "A Guide to Patient Assistance Programs" (Chronic Disease Fund, Inc., October 2006), <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=12585>.

BROOKINGS

The other type of patient assistance, the manufacturer PAP, may also serve to raise prices and inhibit generic entry. In addition to promoting a positive brand image, donations of medical inventory qualify for a provision known as an enhanced deduction that allows manufacturers to deduct the cost of a drug plus one half of the difference between the fair market value and the cost.¹⁰² Because branded drugs typically carry a low marginal cost and high market value, the tax code incentivizes large in-kind contributions of pharmaceuticals. The donated medications can then be used to begin a consumer on a course of treatment that will require later purchases of the medication at commercial prices. The incremental consumers who begin and stay on the brand because of the donated medication are consumers that are not available to the generic entrant. Those consumers are also rendered less elastic, which encourages higher brand prices. The benefits to patients from these donations may not be very sizeable when compared to the cost to taxpayers in reduced tax receipts, higher prices, and less generic entry.

Frerick notes that pharmaceutical companies are some of the only firms that regularly reach the maximum corporate charitable deduction of 10 percent of income. Furthermore, he finds that manufacturers doubled charitable giving between 2007 and 2009, directly after the implementation of Medicare Part D, which increased pharmaceutical demand. As of 2014, PAPs represent 10 of the 15 largest charitable foundations in the United States by total giving with many such organizations seeing larger total giving than more well-known foundations such as the Ford Foundation.

Although there are clear benefits to incentivizing donations of expensive drugs to the poor, policy makers should be wary of provisions that effectively allow pharmaceutical companies to stimulate demand for their own product at taxpayers' expense, limit market size for lower-cost generic entrants, and raise prices.

101 This example assumes a \$10 million dollar charitable donation. If the charity has 20% overhead and the firm has 25% market share for the charity's intended market, then patients will spend \$2 million on the firm's product. Assuming that the patient's copay is 12.5% of the drug's WAC, this will generate \$16 million in revenue for the firm, for a "charitable margin" of 60%. If the drug's market share were 16%, then the firm would generate 0 profit from the donation.

102 Roger Colinvaux, "Enforcing the Enhanced Charitable Deduction: Improved Reporting on the Form 8283" (Urban Institute, December 2012), <http://www.urban.org/sites/default/files/publication/23211/412727-Enforcing-the-Enhanced-Charitable-Deduction-Improved-Reporting-on-the-Form--.PDF>.

Table 3: Largest foundations by total giving

Rank	Foundation	Total giving	PAP
1	Bill & Melinda Gates Foundation	\$3,439,671,894	
2	Silicon Valley Community Foundation	\$956,834,000	
3	The Abbvie Patient Assistance Foundation	\$853,356,401	✓
4	The Bristol-Myers Squibb Patient Assistance Foundation	\$811,433,684	✓
5	Johnson & Johnson Patient Assistance Foundation, Inc.	\$711,632,110	✓
6	Merck Patient Assistance Program, Inc.	\$686,800,564	✓
7	Genentech Access To Care Foundation	\$680,278,040	✓
8	Pfizer Patient Assistance Foundation, Inc.	\$668,050,404	✓
9	GlaxoSmithCline Patient Access Programs Foundation	\$625,427,284	✓
10	The Atlantic Philanthropies	\$521,711,000	
11	Ford Foundation	\$518,380,000	
12	Lilly Cares Foundation, Inc.	\$503,299,479	✓
13	Sanofi Foundation for North America	\$485,359,572	✓
14	Novartis Patient Assistance Foundation, Inc.	\$456,825,176	✓
15	The Susan Thompson Buffet Foundation	\$416,440,853	

Source: "Fiscal Totals of the 50 Largest Foundations in the U.S. by Total Giving, 2014,"

The Foundation Center, <http://data.foundationcenter.org/#/foundations/all/nationwide/top:giving/list/2014>.

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V. MARKET FAILURES IN OLD DRUG MARKETS

V.1 Consolidation in the PBM market can create an incentive for higher prices

The section above introduced the idea that imperfect competition in the PBM market might cause higher prices for pharmaceutical products. To the extent that recent consolidation has lessened competition among PBMs, this could be a contributing factor to higher U.S. drug prices. The less competitive pressure a PBM feels to pass through the savings it can extract from manufacturers, the more of those rents it retains. When a PBM can share in the market rents of the pharmaceutical manufacturers, both have incentives to establish higher prices.

V.2 Firms with smaller portfolios may set higher prices

As discussed in Section 3.7, Besanko et al. develop a model of drug pricing in the presence of formulary restrictions.¹⁰³ Surprisingly, they find the incentive to overcharge for restricted products and free-ride on an insurance bundle is stronger for smaller firms.¹⁰⁴ The authors argue that the effect they identify is particularly important for small firms, especially if those firms are owned by short-run profit-maximizing owners.¹⁰⁵ In particular, small firms with portfolios of one or two drugs are more likely to set high prices for drugs because they do not take into account negative externalities of their price on the portfolio of drugs

¹⁰³ Besanko, Dranove, and Garthwaite, "Insurance and the High Prices of Pharmaceuticals."

¹⁰⁴ This is a variant of the Cournot complements problem.

¹⁰⁵ E.g. hedge funds or financial investors such as Shkreli.

covered by insurance. Conversely, large firms are more likely to price drugs moderately due to caution about the negative effect of higher prices on demand for the rest of their portfolio. This suggests that there may be several significant forces driving recent growth in pharmaceutical prices: recent declines in concentration (e.g. portfolio size) in the pharmaceutical industry (firms with a top 10 drug have seen average market share decline from 6.7% in 1998 to 4.6% in 2013), financial investors in smaller firms, and formulary restrictions limiting insurer bargaining power.

This observation is quite consistent with recent high-profile cases, e.g. the drastic increase in the price of the generic drug Daraprim by Turing Pharmaceuticals. Daraprim is a drug for which patent expiration occurred many years ago, but which obtained market power due to exit of other approved makers of that molecule. Hedge funds and financial investors realized that consumers' elasticity of demand was close to zero, purchased the manufacturer, and drastically raised price. When a product comprises such a small share of expenditure, it may take PBMs and other buyers a long time to notice such price increases and organize a response, e.g., changing the formulary placement of the drug so that it obtains fewer prescriptions. However, in some of these cases, a manufacturer's price increases are so large that the product could lose 90% of sales and still be more profitable after the price increase.¹⁰⁶ The owner who has raised price in this way may face reputational consequences (e.g., Congressional hearings such as those experienced by EpiPen).

A final reason to take note of the recent growth in small pharmaceutical manufacturers relates to firm incentives to respond to political pressure. Large drug manufacturers are clearly aware of the possibility that profitability could be negatively impacted by price regulation. They may take into account potential reactions from consumers and politicians and therefore constrain the prices of drugs below what short-run elasticity of demand would indicate. The implicit threat of price regulation is more costly for manufacturers with a large drug portfolio whose commercial interest may be measured over a longer term than a hedge fund enjoying an exorbitant return of a single drug for a few years.

V.3 Shortages lead to temporary high prices

Drug shortages can occur for various reasons, but the primary factors causing shortages involve raw material supply disruptions and issues involving quality control at manufacturing sites.¹⁰⁷ Shortages disproportionately affect markets in which patents have expired. These products have thin margins because they are homogeneous generic drugs. When buyers are willing to switch to another seller for a small price decrease, then manufacturers may underinvest in fixed costs such as training, cleaning, and safety. It may rationally choose not to invest, even taking into account a greater likelihood of FDA inspection failures and shortages. Exacerbating the problem further, manufacturers of drugs facing a competitive pricing environment want to fully utilize capacity in order to keep costs as low as possible. If an applicant does not have enough demand for a product to be efficient, it may outsource production to a contract manufacturer that can combine several sources of demand into a quantity that fully utilizes a

106 Turing Pharmaceuticals, for example, increased the price of Daraprim by over 5,000%, implying that the strategy would be profitable even if it were to sell a small fraction of units sold prior to the increase.

107 Janet Woodcock and Marta Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages.," *Clinical Pharmacology & Therapeutics* 93, no. 2 (2013), <https://www.ncbi.nlm.nih.gov/pubmed/23337525>.

production line. Moreover, if the drug has small sales to begin with then it may be produced by a single, or very few, factories. In these cases, there is no excess capacity to call into use when a rival is shut down, resulting in shortages. Lack of manufacturing redundancy makes prices in these markets shoot up when there is a shortage.

Drug shortages occur most commonly in injectable drugs that involve complex manufacturing techniques; 72% of reported shortages between 2011 and 2015 involved injectable medications.¹⁰⁸ Injectables are commonly used in emergency room settings, thus drug shortages tend to reduce the quality of emergency care, forcing doctors to modify regimens – typically turning to a much more expensive branded injectable – according to drug availability.¹⁰⁹

One possible explanation of drug shortages in generic markets relates to firms' choices regarding production capacity and manufacturing quality. Woodcock and Wosinska (2013) argue that the shortage problems in the U.S. were caused by underinvestment in quality.¹¹⁰ Kim and Scott Morton (2015) make a similar argument, showing that in markets with high prices and inelastic demand, characteristics that are common in markets for patented drugs, firms will not invest in excess capacity that would solve potential manufacturing interruptions.¹¹¹ Price declines, e.g. due to the expiration of patent protection, may cause firms to remove capacity buffers, making shortages more widespread. According to HHS, there were an unusually large number of patent expirations between 2008 and 2010, coinciding with the peak in drug shortages that occurred in 2011, when 251 new drug shortages were reported to the FDA.^{112,113} In such a setting, a shortage of supply naturally leads to higher prices for the remaining firms' output. These higher prices are due to temporary market power on the part of the remaining generic firms, a market power they earned because their factory did not fail an inspection. Such financial rewards could be desirable to encourage investments in safety and quality.

In 2012, Congress passed the Food and Drug Safety and Innovation Act (FDASIA), requiring companies to notify the FDA in the case of potential supply disruptions.¹¹⁴ Since the legislation was passed, drug shortages have declined dramatically, as shown in Figure 6.

108 "Drug Shortages - Frequently Asked Questions about Drug Shortages," FDA, December 2016, <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>

109 Michelle Andrews, "Shortages of Essential Emergency Care Drugs Increase, Study Finds," Kaiser Health News, May 3, 2016, <http://khn.org/news/shortages-of-essential-emergency-care-drugs-increase-study-finds/>.

110 Woodcock and Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages."

111 Sang-hyun Kim and Fiona Scott Morton, "A Model of Generic Drug Shortages: Supply Disruptions, Demand Substitution, and Price Control," 2015, <http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.707.5899>.

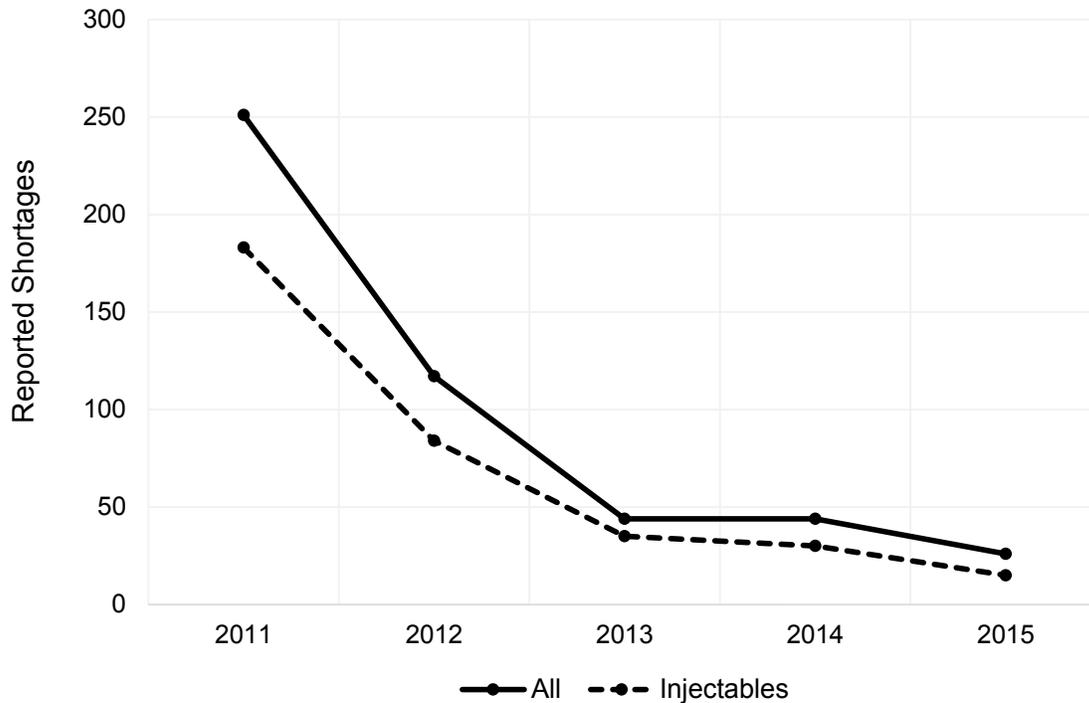
112 Ibid.

113 "Drug Shortages - Frequently Asked Questions about Drug Shortages."

114 "Fact Sheet: Drug Products in Shortage in the United States," FDA, January 29, 2016, <https://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentsToTheFDCAAct/FDASIA/ucm313121.htm>. Specifically, the law allows the FDA to:

1. Require manufacturers of medically important drugs to notify the FDA of permanent discontinuance or temporary interruption of manufacturing
2. Extend the early notification requirement to biologic drugs
3. Inform the public of manufacturers who fail to comply with drug shortage requirements
4. Establish a task force to develop a strategic plan on drug shortages to Congress

Figure 6: Drug shortages reported to the FDA



Source: "Drug Shortages - Frequently Asked Questions about Drug Shortages," FDA, December 2016, <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>.

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Despite the dramatic reduction in drug shortages, problems continue to affect patients, especially in emergency room settings, leading to overall higher expenditures.¹¹⁵ Additionally, the large number of patent expirations that occurred prior to 2010 in traditional generic categories may occur again soon. As mentioned in Section III.1, a large number of biologics will face patent expiry in the coming years, leading to the possibility that the industry will again lack capacity buffers and face drug shortages.

V.4 Exit from generic markets can cause high prices

Some of the most publicly controversial drug price increases have taken place in markets with expired patents. There are two primary causes for this trend. First, a branded product generally launches at the price the firm plans to maintain over time, so there is no need for a large price increase after launch. Generic drug prices are determined in a market context where supply and demand fluctuate and so prices fluctuate also. This is not usually a problem as long as the price changes are generated by competitive forces. An exception is a generic drug in a market that shrinks over time to be quite small. Only one manufacturer can be sustained in that setting, which generates a monopoly that allows the manufacturer to increase price above production cost. These price increases can be substantial for drugs that do not have substitutes. Second, reformulation of legacy generic drugs reintroduces market exclusivity and creates barriers to generic entry.

In September 2015, Turing Pharmaceuticals increased the price of the drug Daraprim from \$13.50 to \$750 per tablet. Pyrimethamine, the active ingredient in Daraprim, was discovered in 1952, and was originally

115 Michelle Andrews, "Shortages of Essential Emergency Care Drugs Increase, Study Finds."

used to treat malaria. The drug is still used to treat several parasitic diseases, as well as HIV/AIDS in combination with other drugs. The market for Daraprim is small, with only 8,000 to 12,000 prescriptions filled annually.¹¹⁶ Although there are no IP barriers preventing other generic firms from entering the market, Turing used a REMS restricted distribution system to prevent potential generic entrants from obtaining supply of Daraprim needed to perform the necessary bioequivalency trials. The fact that Turing used the REMS strategy suggests that it was worried about entry of rival generics. However, there are generic drug markets that are simply too small to sustain a second generic. Such a generic is a natural monopoly and may be able to increase price greatly without attracting entry. For a more detailed discussion of this issue, see the companion paper to this piece by Bollyky and Kesselheim.¹¹⁷

Another example of a legacy drug that has caused public outrage is EpiPen, an injectable drug produced by the generic manufacturer Mylan. The price of EpiPen increased by 400 percent since 2007, the year that Mylan acquired EpiPen.¹¹⁸ EpiPen is a reformulation of an old drug that uses a patented autoinjector, which allows non-professionals to inject the medication quickly and safely. Competitors to EpiPen have faced product recalls and issues obtaining FDA approval for their competing injection devices.¹¹⁹ This might indicate that EpiPen's high price is an appropriate return to its patented and unique injector. On the other hand, there is a tension between imitating a reference product like EpiPen without imitating its injector. If the generic must be bioequivalent to the branded reference product, and the drug itself is an old generic, that seems to imply that the generic product must infringe the delivery device.¹²⁰ The FDA does not have clear guidelines for generic applicants in this area.

Evzio, an autoinjector for naloxone, used to treat opioid overdose, experienced similarly dramatic price increases in recent years amid rising demand.¹²¹ The patents on these products apply to the delivery mechanism. As with product hopping, if these product reformulations have increased the safety of administration (perhaps, for example, allowing self-administration rather than physician administration), they could be valuable. If, on the other hand, an imperfect prescribing agent chooses the latest expensive insulin injector instead of an equivalent, cheaper treatment, then costs are higher and the patient does not benefit by the amount of the higher costs. Here again the PBM could help generate lower prices by steering demand to the lower cost insulin formulation.

The benefits of reformulation vary across different types of drugs and technologies depending on medical needs and existing substitutes. In the case of Evzio, the use of an autoinjector allows for safe treatment of opioid overdose by non-physicians, potentially saving the lives of patients that cannot get immediate access to medical care. In other cases, such as insulin reformulation, it is not clear that there are significant benefits when compared to previous iterations of the drug.¹²²

116 "A Generic Pill's Price Just Went up \$700. Why Doesn't Another Company Create a Competitor?," Vox, September 22, 2015, <http://www.vox.com/2015/9/22/9373557/daraprim-competitor-turing>

117 Thomas Bollyky and Aaron Kesselheim, "Can Importation Address High Generic Drug Prices?," Hutchins Center Working Paper #29.

118 Rita Rubin, "EpiPen Price Hike Comes under Scrutiny," *The Lancet* 388, no. 10051 (September 24, 2016): 1266.

119 "Why the \$600 EpiPen Costs \$69 in Britain," *Bloomberg*, September 29, 2016,

<https://www.bloomberg.com/news/articles/2016-09-29/epipen-s-69-cost-in-britain-shows-other-extreme-of-drug-pricing-itnvgvam>.

120 Brief for the FTC as Amicus Curiae in Actelion Pharmaceuticals Ltd., et al. v. Apotex Inc., et al.

121 Ravi Gupta, Nilay D. Shah, and Joseph S. Ross, "The Rising Price of Naloxone - Risks to Efforts to Stem Overdose Deaths," *The New England Journal of Medicine* 375, no. 23 (December 8, 2016): 2213–15.

122 Jing Luo, Aaron S. Kesselheim, Jeremy Greene, and Kasia J. Lipska, "Strategies to Improve the Affordability of Insulin in the USA," *The*

VI. OVERVIEW OF PROPOSED LEGISLATION

As legislators have become aware of shortcomings in the current regulatory framework, they have made numerous attempts to close loopholes and implement measures to increase competition. Table 4 summarizes some of the recent federal measures that have been introduced in Congress and whether they have been passed into law. Despite bipartisan support for many of these bills, most have stalled in Congress or died in committee. This outcome is not surprising if one considers the potential profit loss due to lower prices that pharmaceutical manufacturers would likely experience if these bills became law. Standard economic theory would suggest the intensity of lobbying against a reform is related to firms' expected losses from the reform – so effective legislation in this area may be unlikely. Congress continues to push for pharmaceutical reform, and we support many of these attempts at reform. Given the reality of the situation, however, policy solutions to the problems described in this paper may also come from state-level legislation and regulatory enforcement from the executive branch. For this reason the policy section below discusses legislative solutions at the federal and state level, as well as non-legislative options that may be pursued by federal agencies.

Table 4: Drug price legislation introduced by Congress¹²³

Category	Federal legislative action	Passed into law	Date introduced	Sponsors
Biosimilar Approval	Biologic Price Competition and Innovation Act (BPCIA)	✓	September 17, 2009	5 cosponsors (bipartisan)
Orphan Drugs	Closing Loopholes for Orphan Drugs Act	✗	September 27, 2016	Reps. Welch (D) and Griffith (R)
REMS	CREATES Act	✗	June 14, 2016	4 cosponsors (bipartisan)
Pay for Delay	Preserve Access to Affordable Generics Act	✗	September 9, 2015	Sens. Klobuchar (D) and Grassley (R)
FDA Approval Lag	Prescription Drug Affordability Act	✗	September 10, 2015	Sens. Sanders (D) and Franken (D)"
PBM Consolidation	21st Century Cures Act	✓	January 6, 2015	7 cosponsors (bipartisan)
Drug Shortages	SAVINGS Act	✗	September 22, 2016	Sen. Cotton (R)
Biosimilar Approval	HR 1038	✗	February 14, 2017	18 cosponsors (bipartisan)

Source: "Library of Congress," <https://www.congress.gov/>.

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VII. POLICY RECOMMENDATIONS

VII.1 Encouraging biosimilar and genetic entry

FDA approval

In our view, the single most valuable policy change in this area would be the approval of more biosimilars to compete with off-patent biologics. The FDA should put more emphasis and agency resources into approving the existing queue of biosimilar applicants. The U.S. has only two biosimilars on the market, lagging far behind the EU, which has more than twenty. Meanwhile, biologic spending continues to grow at double digit rates. The potential for savings from competition in innovator biologics is enormous and will

Lancet. Diabetes & Endocrinology 5, no. 3 (March 2017): 158–59.

123 The original Biologics Price Competition and Innovation Act was introduced in 2007 with 5 cosponsors. The bill was ultimately passed without Republican support as part of the Affordable Care Act in 2010.

improve patient access to these important medicines. Large consumer benefits justify increased agency effort to approve entry of biosimilar applicants in a timely fashion. The FDA should also quickly establish an interchangeable biosimilar standard and prioritize interchangeable approvals, which will further improve biosimilar market penetration.

A number of other FDA regulations can be improved to increase competition in the biologics sector. The FDA should immediately begin the process of changing its regulations so that the reference biologic and all follow-on products share the same USAN and INN root name, as is done in other countries. Regulations concerning the geographic location of samples for testing may be loosened to allow sourcing from EU, the location with the most competitive producers of biosimilars.

Orphan drugs

Reforming the orphan drug system in the U.S. is best done with legislation to modify the Orphan Drug Act. The reward for studying an existing drug should be less than the reward given for discovering a new and useful drug. Legislation should impose limits on the overall time period that a single drug can claim market exclusivity for various orphan drug designations.

Pay for delay

The FTC should continue its vigilance in this area. The arrival and importance of biosimilars gives manufacturers more incentives to find a way to delay the arrival of competition. Continuing antitrust litigation by the FTC will be an important component of deterring anticompetitive behavior. Congress should include incentives for manufacturers to avoid pay for delay schemes by including penalties such as termination of exclusivity for brands and loss of first filer status for generics who engage in settlements that include any terms other than the date of generic entry.¹²⁴

REMS abuse

Voluntary REMS allows a manufacturer to create an entry barrier even if a drug's patents have expired. This tactic should be prohibited by the FDA or legislation. Another way incumbents can deter generic entry and reduce their share is by excluding them from existing REMS systems. The FDA should devise a way in which the incumbent and the entrant can share a REMS system. Possible solutions include mandatory interconnection or common standards. Alternatively, the FDA could require the incumbent to grant access to proprietary REMS systems to any follow-on products. This will be an issue for biosimilars as well as small molecule drugs, so it will only grow in importance over time.

The FTC should pursue antitrust cases against brands that engage in exclusionary behavior with a REMS tool rather than competing on the merits. These cases would be analogous to the successful pay for delay cases also brought by the FTC. As in pay for delay, the FTC would argue that the incumbent brand that refuses to sell samples of its product to the entering generic is illegally attempting to maintain its monopoly.

¹²⁴ These incentives were included as part of a larger piece of legislation recently introduced in Congress, "The Improving Access to Affordable Prescription Drugs Act."

Approval delays

ANDA approval times continue to be important for competition in the generic sector. It is difficult to interpret FDA approval time statistics because applicant manufacturers may submit a low-quality application years in advance, planning multiple revisions with the help of the FDA. There is little the agency can do about that problem. One possible strategy is for the FDA to work to establish a reputation for quickly approving high quality ANDAs. This will reward firms that invest in submitting complete, excellent applications. Submitting high quality ANDAs would grant firms a path by which they could enter the market quickly.

Approval times for combination products and products delivered inside a device continue to be longer than others. The FDA should create more guidelines and certainty for applicants in this area, and clarify whether a generic entrant must use the same device as the reference product; patented delivery devices may effectively eliminate generic entrants. If generic entrants may use different delivery devices, the FDA should clarify those standards.

Because approval delays suffer from endogeneity in firm choices over timing and quality, as well as agency choices of effort and resources, they require constant monitoring. As a first step, the FDA should release the Orange Book and other already public data in usable form (e.g. a spreadsheet not a PDF) so that academics, policy analysts, and other government agencies can measure agency outcomes. Monitoring should also include the establishment of an annual public FDA report on competitive conditions in the pharmaceutical sector. Such a report should give approval times for biosimilars and generics and list and analyze competitive conditions in all combination drug markets, all drugs delivered in patented devices, and all products with two or fewer firms marketing the drug and at least one expired patent. This will isolate the problematic markets for focus. The FDA should release the underlying data to the FTC for additional analysis. After time for that analysis, representatives of both agencies should testify together at an annual Congressional hearing on competitiveness of pharmaceutical markets and barriers to entry.

Formulary restrictions

Simulating price competition among pharmaceuticals requires that consumers shift their purchases in response to price. If consumers are elastic then manufacturers have an incentive to lower prices to attract them. If consumers do not respond to price at all, then manufacturers will set higher prices as there is no downside loss of customers.

CMS should relax the definition of the Part D protected classes and other formulary regulations to give plans more flexibility to shift demand. It is critical that CMS require fulsome availability of treatments so that plans do not use this flexibility to design inadequate formularies that in turn discourage the sick from enrolling in their plan. Such cream skimming is inefficient and destroys healthcare markets. However, a regulation that requires formularies to be able to treat all enrollees adequately, no matter how sick, but gives flexibility to the plan to figure out how to do that given the set of products on the market and clinical evidence, would enhance price competition. CMS attempted to move in this direction in 2013 and retreated in the face of objections from the pharmaceutical industry, but this effort should be continued.

VII.2 Incentivizing optimal consumer behavior

PBM consolidation and competition

There is a legitimate open question as to whether PBMs act as effective agents of consumers in the purchase of pharmaceutical products and, secondly, whether agency imperfections lead to higher pharmaceutical expenditures. The FTC has authority to carry out industry studies under the 6(b) provision of the FTC Act. It should use this authority to investigate several questions about the PBM industry. These include whether PBMs act as good buying agents for final consumers and whether and how much they contribute to higher pharmaceutical prices and expenditures. In addition, the study could cover the competitiveness of the PBM industry in general. The answers to the first questions may reveal that increased competition in that sector would be very valuable to consumers. The FTC's enforcement staff should continue to observe the sector to ensure that no exclusionary behavior is occurring, and that any proposed mergers, even of smaller competitors, are scrutinized for anticompetitive impact.

The FTC could determine whether contracts that require PBMs to return rebates directly to plan sponsors might give PBMs incentives that result in lower drug prices. For example, as discussed above in the product hopping section, the problem that arises when a new product is introduced is that demand does not shift back to the generic product when it enters the market. Instead, patients continue to consume the expensive new product. The new product's share is partly determined by the effort of the PBM in shifting patients between products. If the new product maker obtains a high share because of PBM inaction, the PBM can bargain for a share of those profits in the form of a rebate. (The PBM gets paid for inaction that benefits a manufacturer.) If the PBM is not exposed to sufficient competition it may be able to retain a share of those profits rather than giving them to final consumers. In this setting, the PBM may not want patients to move back to the generic, even though they would save money by doing so, because it benefits directly when they consume the brand. In this way, the hidden rebate allows for a higher price – and higher prices of pharmaceuticals in general – because the plan sponsor cannot observe and counteract the poor incentives. However, if the plan sponsor were to receive the rebate directly, then the PBM would not directly gain from consumption of the new product. In an imperfectly competitive environment, a simpler contract between the plan sponsor and the PBM could enhance competition.

The advantage to this type of policy over revelation of each negotiated rebate is that rebates remain confidential. Only the plan sponsor sees them, so the PBM remains free to negotiate discounts for one customer that are different from another, or discounts that are different for one PBM than another. Confidential rebates likely lower drug prices. The FTC could encourage buyers, such as employers, to negotiate more pro-competitive contracts with PBMs or Congress could legislate the form of the contract.

Product hopping

Product hopping only has negative welfare consequences when consumer choice is imperfect. If the PBM market becomes more competitive through the reforms described above, this will remove the incentive for a manufacturer to introduce a new version of a medicine that brings a small or negligible consumer benefit. The FTC can use the antitrust laws to enforce against any clearly exclusionary hard switching or similar behavior.

Medicare reimbursement

In order for the government and commercial consumers to take advantage of any entry in the biosimilar pathway, procurement mechanisms must be adjusted. Many biologic drugs are administered under Medicare Part B in a physician's office. Current reimbursement rules do not incentivize physicians to prescribe cheaper biosimilars. CMS should follow MedPAC recommendations for reimbursement of Part B drugs so that biosimilars and the reference product are reimbursed under the same J-Code. This would stimulate price competition among biologic equivalents.

Likewise, the design of Medicare Part D, whether concerning expenditure in the donut hole or elsewhere, should incentivize patients to consume cheaper biosimilars. The current poor incentives should be corrected by CMS to shift patients toward cheaper therapies.

For drug categories where alternatives may be shown to be close substitutes, CMS should ask for legislative authority to use a least-costly alternative reference price instead of an average sales price. Congress should pass legislation that empowers CMS to use this tool more widely. Spending Medicare resources to pay vastly different prices for the same effective treatment is not a good use of government funds; providing physicians financial incentive to use the least costly alternative will lower prices.

A complement to reference pricing is to make the value of particular drugs more credible and public. While having a good understanding of value might raise the price that the most effective drugs can charge, it will lower prices for ineffective drugs. This aligns reward with value creation which is critical for consumer benefit. The FTC and insurers could combine efforts to give more prominence to entities like the Institute for Clinical and Economic Review that carry out comparative effectiveness studies.¹²⁵ Generating and spreading knowledge of cost effectiveness and comparative effectiveness would benefit consumers. More information about drugs' effectiveness and clinical options will enable insurers to be creative about formularies.

Anti-kickback enforcement

As a first step, all manufacturers should be required to submit detailed data to OIG and CMS on the amounts they spend on all patient assistance programs by drug, type of assistance, channel of assistance, and time period. OIG could be tasked with collecting and studying these data and producing a report estimating the impact of patient assistance programs. OIG should determine whether the use of any of these types of kickbacks raises prices to Medicaid and Medicare directly. In addition, OIG should determine

if these patient kickbacks affect commercial markets, thereby indirectly increasing government costs of pharmaceutical treatments. If these practices cause higher prices in the commercial market and raise the cost of a variety of federal and state healthcare programs, it would be clear that the taxpayer is adversely affected by kickbacks in general. State legislatures would be interested to know if patient kickbacks were raising the cost of drugs for the citizens of their states.

The FTC could also work against the use of coupon cards. For example, the FTC could encourage states to outlaw the use of coupon cards as Massachusetts did in 2012.¹²⁶ Any insurer that was the first to prohibit

¹²⁵ "ICER,"

¹²⁶ Dafny, Ody, and Schmitt, "When Discounts Raise Costs."

the use of a coupon card would likely upset consumers and lose market share. Yet the coupon cards cause higher prices for all consumers and are anticompetitive. Therefore, the FTC might work with states to ban the use of coupon cards in conjunction with a drug purchase under an insurance plan. Insurers in those states would benefit from lower utilization and lower prices, therefore the law might also include an annual cap on patient out of pocket spending on prescription drugs. Currently, a patient taking a drug with a \$100,000 list price and a 30% co-pay will obtain patient assistance from the manufacturer for her \$30,000 co-pay. This system leaves the manufacturer to collect \$70,000 from the insurer. Due to the patient assistance, the insurer's payment is roughly equal to the revenue of the manufacturer. Under a coupon ban-with-a-cap policy, the patient would pay the legislated limit on out of pocket costs (e.g. \$3,000) and the insurer would negotiate a payment to the manufacturer. This price could net out to be the same as before, e.g. \$67,000 from the insurer for a total of \$70,000. However, as described above, equilibrium prices would likely fall because insurers would now have the ability to shift patients to competing treatments, granting them bargaining power. Insurers would be able to switch a patient who does not face a co-payment of \$30,000 more easily.

Similarly, OIG should investigate the impact of practices such as hiring of patients as employees, gifts, free "wrap around services", and other similar practices. These have the same economic impact as the coupon card. They are likely to raise the price of the drug because the kickback makes the insured patients insensitive to the price the insurer must pay. These practices may also violate existing legal rules. As with coupon cards, the FTC could consider strategies to help states and insurers prohibit these practices.

Donations by manufacturers to foundations that purchase their own drugs likely push prices upward. The tax-deductibility of donations to independent foundations could be scrutinized by the IRS. An analysis similar to that from Frerick (2016) indicates that tax deductibility is only legitimate when purchase of the manufacturer's drug is only a small part of a foundation's activities. Using Table 2 as an example, if the chance that the manufacturer's drug is purchased by the foundation is below 16%, the donation would not be financially profitable – which is appropriate for a tax-deductible donation. IRS policy should be updated to specify that manufacturers claiming a tax deduction for donations must choose a foundation where market share is low enough to render the donation unremunerative. The IRS should require manufacturers to provide both OIG and the IRS with this calculation and the underlying data used to generate it annually.

Donations of medicine to patients should likewise be restricted. Since those donations may be used to prevent generic entrants, it is not clear why they should be subsidized by taxpayers. Congress should limit the tax deductibility of such donations to either zero or the cost of production of the drug.

CMS and FDA should adopt a rule that Patient Advocacy Programs must disclose their sources of funding when commenting to the FDA or other government bodies. Many PAPs are funded directly by pharmaceutical companies and may not represent neutral consumers.

VII.3 Market incentives for old drug markets

Small portfolios

The FTC should be encouraged to examine the impact of a pharmaceutical manufacturer's portfolio on the prices it sets. Firms with larger portfolios might set lower prices because they internalize the possibility of price regulation, or because they want their portfolio, when viewed as a bundle, to have a reasonable total price so that consumers continue to buy. If larger firms tend to set lower prices, the FTC could take this into account when performing merger analysis. Clearly, the FTC must continue to scrutinize merging pharmaceutical firms that sell therapeutic substitutes and may require divestitures. A merger that does not contain substitute products might be shown to create downward pricing pressure.

Shortages

The injectable shortage that arose five years ago seems to have largely subsided. However, if more biosimilars are approved in the near future, similar manufacturing issues may arise in that sector. Frequent FDA inspections of injectable facilities will create incentives for manufacturers to invest in cleanliness and safety.

Small market monopolies

The FDA could also reduce entry barriers in older generic markets by allowing generic imports in certain circumstances (see Bollyky and Kesselheim, Hutchins Center Working Paper #29, Forthcoming). When a product has lost patent protection and there is only one remaining manufacturer, consumers are potentially exposed to monopoly prices. If the sole maker of the drug chooses to raise price dramatically, buyers have no other source of supply. In this situation, the FDA could permit generic imports from a manufacturer that is approved in either the EU or Canada.¹²⁷ Wholesalers could source from these suppliers, creating competition in the United States. Indeed, the threat of such imports would likely prevent the sole U.S. supplier from raising price in the first place.

VIII. CONCLUSION

There are many promising policy and legislative changes that will create more competition in the pharmaceutical industry in the United States. Competition generates returns for innovative medicines while lowering the prices of drugs that lack value, have substitutes, or are generic commodity products. The biologic sector is especially critical to address at this time. It is growing fast and yet almost every product faces no meaningful competition, resulting in high and increasing prices. A competitive pharmaceutical marketplace has worked for the United States in the past and is a promising avenue for reducing pharmaceutical expenditures today.

¹²⁷ Note that this does not mean a U.S. buyer is entitled to purchase at a price negotiated by any other country. Rather, they can call the manufacturer, bargain, and legally import if they so desire.

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APPENDIX

A1: Regulatory barriers

Issue	Relevant institutions	Policy recommendation
Biosimilar regulatory framework	FDA	<ul style="list-style-type: none"> • Approve existing queue of biosimilars • Adopt interchangeable biosimilar standard • Use the same USAN/INN name for all versions of a biologic, following international standards
Orphan drug abuse	Congress	<ul style="list-style-type: none"> • Prioritize invention of new drugs over testing of existing drugs • Limit consecutive terms of exclusivity for a single medication
Pay for delay	FTC, Congress	<ul style="list-style-type: none"> • Enforce antitrust laws against anticompetitive pay for delay • Pass legislation to incentivize manufacturers to avoid pay for delay schemes (loss of exclusivity for brands and first filer status for generics)
REMS abuse	Congress, FTC, FDA	<ul style="list-style-type: none"> • Ban voluntary REMS (Congressional Hearing on March 22, 2017) • Require brands to sell samples of product to follow-on manufacturers at fair market value • Allow brands and generics to share REMS systems • Enforce antitrust laws to prevent anticompetitive use of REMS
Approval delays	FDA	<ul style="list-style-type: none"> • Improve guidelines for drug/device combination products • Improve public data availability to allow for public monitoring of agency outcomes • Establish annual report on competition in the pharmaceutical industry (with FTC)
Formulary restrictions	CMS, Congress	<ul style="list-style-type: none"> • Relax definition of Part D protected classes

BROOKINGS

A2: Imperfections in consumer behavior

Issue	Relevant institutions	Policy recommendation
PBM consolidation and rebates	FTC, Congress	<ul style="list-style-type: none"> Initiate FTC 6(b) study of the PBM industry to evaluate competition and whether contract form affects intensity of competition Create FTC recommendations and/or Congress to pass legislation based on FTC recommendations Enforce antitrust laws in PBM mergers
Product hopping	FTC	<ul style="list-style-type: none"> Enforce antitrust laws to deter anticompetitive use of product hopping
Medicare reimbursement	CMS, Congress	<ul style="list-style-type: none"> Incentivize providers to utilize cheaper therapies by including biologics and biosimilars within same J-Code for Medicare Part B reimbursement Incentivize providers to utilize cheaper therapies by reimbursing physicians using Least Cost Alternative methodologies, especially for drugs with close substitutes Ensure Part D cost-sharing incentivizes use of biosimilars Improve public evaluation of drug value, e.g. by elevating role of the Institute for Clinical and Economic Review
Kickbacks	Congress, states, FTC, OIG, IRS	<ul style="list-style-type: none"> Require manufacturers to disclose detailed data on all patient assistance programs to OIG Require manufacturers to disclose detailed data on returns on charitable contributions (monetary and inventory) to CMS and IRS Task OIG with studying collected data to determine the impact of anticompetitive kickbacks on government procurement costs and on commercial prices Remove tax deductions for charitable contributions that generate profit Encourage states to ban use of couponing for private insurance, perhaps in conjunction with annual out of pocket caps Ban patient services and in-kind benefits to high-value pharmaceutical patients Limit tax deductions for contributions of inventory from drug manufacturers

A3: Legacy drug markets

Issue	Relevant institutions	Policy recommendation
Consolidation in the PBM Industry	FTC	<ul style="list-style-type: none"> • See Section A2 above
Small Portfolios	FTC	<ul style="list-style-type: none"> • Examine impact of a pharmaceutical manufacturer's portfolio on price setting
Shortages	FDA	<ul style="list-style-type: none"> • Inspect manufacturers of essential drugs, injectable facilities prone to disruption
Small Market Monopolies	FDA, Congress	<ul style="list-style-type: none"> • Allow generic imports (see Bolyky and Kesselheim, Hutchins Center Working Paper #29, Forthcoming)

BROOKINGS

A4: Policy solutions by government institutions

Government institutions

Policy recommendation

- Approve existing queue of biosimilars
- Adopt interchangeable biosimilar standard
- Use same USA/INN name for all versions of a biologic, following international standards
- Allow brands and generics to share REMS systems
- Improve guidelines for drug/device combination products
- Improve public data availability to allow for public monitoring of agency outcomes
- Establish annual report on competition in the pharmaceutical industry (with FTC)
- Inspect manufacturers of essential drugs & injectable facilities prone to disruption

FDA

- Enforce antitrust laws against anticompetitive pay for delay, anticompetitive use of REMS, product hopping, and kickbacks
- Examine impact of a pharmaceutical manufacturer's portfolio on prices
- Initiate a 6(b) study of the PBM industry
- Recommend pro-competitive contract with PBM
- Enforce antitrust laws in PBM mergers

FTC

- Require manufacturers to disclose detailed data on charitable contributions (monetary and inventory)
- Share kickback data annually with HHS OIG for further study
- Remove tax-deductibility of profitable contributions, limits charitable contributions

IRS

- Use data collected by IRS and CMS to study the impact of anticompetitive kickbacks on government procurement costs and on commercial prices and generic entry
- Require manufacturers to disclose detailed data on all patient assistance programs for OIG to analyze impact and issue report

Health and Human Services OIG

- Incentivize providers to utilize cheaper therapies by including biologics and biosimilars within same J-Code for Medicare Part B reimbursement
- Incentivize providers to utilize cheaper therapies by reimbursing physicians using Least Cost Alternative methodologies in Part B, especially for drugs with close substitutes
- Ensure Part D cost-sharing incentivizes use of biosimilars (with Congress)
- Relax definition of Part D protected classes (with Congress)
- Improve public evaluation of drug value, e.g. by elevating role of the Institute for Clinical and Economic Review
- Require manufacturers to disclose detailed data on charitable contributions (monetary and inventory)

CMS

- Prioritize invention of new drugs over testing of existing drugs in Orphan Drug law
- Limit consecutive terms of exclusivity for a single medication in Orphan Drug law
- Ban voluntary REMS (Congressional Hearing on March 22, 2017)
- Force brands to sell samples of product to follow-on manufacturers at fair market value
- Relax definition of Part D protected classes (with CMS)
- Ask for recommendations from FTC and pass legislation implementing recommendations concerning PBM contract structures to ensure drug rebates benefit end consumer

Congress

- Ensure Part D cost-sharing incentivizes use of biosimilars (with CMS)
- Increase public evaluation of drug value, e.g. by elevating role of the Institute for Clinical and Economic Review
- Require manufacturers to disclose detailed data charitable contributions (monetary and inventory) to IRS
- Require manufacturers to disclose detailed data on all patient assistance programs to OIG
- Ban patient services and in-kind benefits to high-value pharmaceutical patients
- Remove tax deductions for charitable contributions that generate profit
- Limit tax deductions for contributions of inventory from drug manufacturers
- Allow generic imports (see Bollyky and Kesselheim, Hutchins Center Working Paper #29, Forthcoming)

A5: Policy issues by market structure

Market structure	Relevant issues
Patented brands with no substitutes	<ul style="list-style-type: none"> • Measuring drug value, see Frank and Zeckhauser (Hutchins Center Working Paper #28, Forthcoming)
Patented brands with therapeutic substitutes	<ul style="list-style-type: none"> • Formulary restrictions • PBM consolidation, distribution of rebates to consumers • Kickbacks • Medicare reimbursement policy
Off-patent with no current competitors and potential generic or biosimilar entrants	<ul style="list-style-type: none"> • REMS abuse, pay for delay, product hopping • Kickbacks, constraints on generic market entry • FDA approval of ANDAs (for small molecules and legacy biologics) biosimilars (for newer biologics) • FDA biologic naming, interchangeability guidance • Small portfolios and high prices • Shortages
Off-patent with generic or biosimilar competitors	<ul style="list-style-type: none"> • Product hopping • Kickbacks, constraints on generic market penetration • Medicare reimbursement policy • Exit from old markets
Patented brands with no substitutes	<ul style="list-style-type: none"> • Measuring drug value, see Frank and Zeckhauser (Hutchins Center Working Paper #28, forthcoming)

BROOKINGS