

# The High Cost of Prescription Drugs in the United States

## Origins and Prospects for Reform

Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Ameet Sarpatwari, JD, PhD

**IMPORTANCE** The increasing cost of prescription drugs in the United States has become a source of concern for patients, prescribers, payers, and policy makers.

**OBJECTIVES** To review the origins and effects of high drug prices in the US market and to consider policy options that could contain the cost of prescription drugs.

**EVIDENCE** We reviewed the peer-reviewed medical and health policy literature from January 2005 to July 2016 for articles addressing the sources of drug prices in the United States, the justifications and consequences of high prices, and possible solutions.

**FINDINGS** Per capita prescription drug spending in the United States exceeds that in all other countries, largely driven by brand-name drug prices that have been increasing in recent years at rates far beyond the consumer price index. In 2013, per capita spending on prescription drugs was \$858 compared with an average of \$400 for 19 other industrialized nations. In the United States, prescription medications now comprise an estimated 17% of overall personal health care services. The most important factor that allows manufacturers to set high drug prices is market exclusivity, protected by monopoly rights awarded upon Food and Drug Administration approval and by patents. The availability of generic drugs after this exclusivity period is the main means of reducing prices in the United States, but access to them may be delayed by numerous business and legal strategies. The primary counterweight against excessive pricing during market exclusivity is the negotiating power of the payer, which is currently constrained by several factors, including the requirement that most government drug payment plans cover nearly all products. Another key contributor to drug spending is physician prescribing choices when comparable alternatives are available at different costs. Although prices are often justified by the high cost of drug development, there is no evidence of an association between research and development costs and prices; rather, prescription drugs are priced in the United States primarily on the basis of what the market will bear.

**CONCLUSIONS AND RELEVANCE** High drug prices are the result of the approach the United States has taken to granting government-protected monopolies to drug manufacturers, combined with coverage requirements imposed on government-funded drug benefits. The most realistic short-term strategies to address high prices include enforcing more stringent requirements for the award and extension of exclusivity rights; enhancing competition by ensuring timely generic drug availability; providing greater opportunities for meaningful price negotiation by governmental payers; generating more evidence about comparative cost-effectiveness of therapeutic alternatives; and more effectively educating patients, prescribers, payers, and policy makers about these choices.

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**Author Affiliations:** Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

**Corresponding Author:** Aaron S. Kesselheim, MD, JD, MPH, Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St, Ste 3030, Boston, MA 02120 ([akesselheim@partners.org](mailto:akesselheim@partners.org)).

The increasing cost of prescription drugs in the United States has become a source of growing concern for patients, prescribers, payers, and policy makers. After relatively modest growth after the expiration of patents on many widely used medications from 2010 to 2012, medication expenditures have begun to increase again, punctuated by several high-profile examples of very costly new agents and sharp increases in the prices of some older ones.<sup>1</sup> Between 2013 and 2015, net spending on prescription drugs increased approximately 20% in the United States,<sup>2</sup> outpacing a forecast 11% increase in aggregate health care expenditures.<sup>3</sup> Prescription medications now comprise an estimated 17% of total health care costs,<sup>4</sup> and prescription medication coverage constitutes 19% of employer-based insurance benefits.<sup>5</sup> Since the advent of the Medicare drug benefit in 2006, government entities have paid for approximately 40% of the nation's total retail prescription drug expenditure.<sup>6</sup> Certain expensive drug products are important clinical breakthroughs and may even be relatively cost-effective; others are merely costly, with prices that are difficult to justify in relation to their actual contributions to patient outcomes.

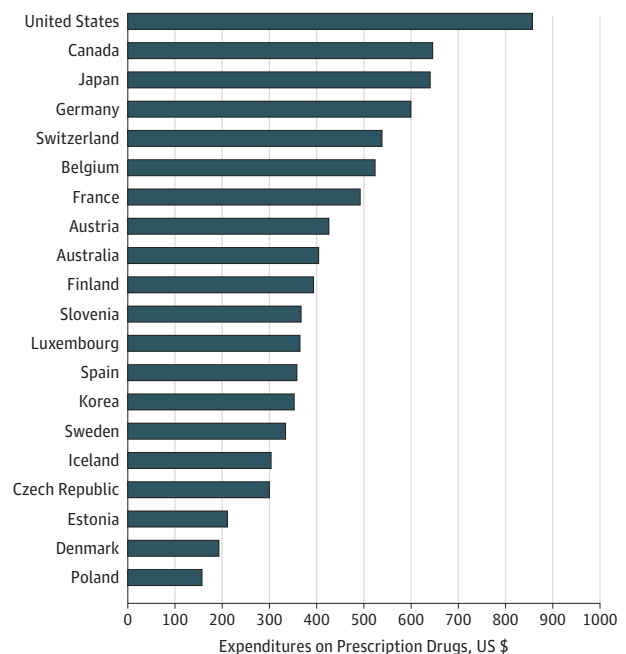
The United States has long spent more on prescription medications than other countries.<sup>7</sup> In 2013, per capita spending on prescription drugs was \$858 compared with an average of \$400 for 19 advanced industrialized nations (Figure 1).<sup>8</sup> List prices for the top 20 highest-revenue-grossing drugs were on average 3 times greater in the United States than the United Kingdom.<sup>9</sup> These disparities are reduced but remain substantial even after accounting for undisclosed discounts ("rebates") that manufacturers offer to US payers. In 2010, estimated average postrebate prices for medications were 10% to 15% higher in the United States than in Canada, France, and Germany (Table 1).<sup>11</sup>

In addition to their contribution to health care spending, increasing drug costs have important clinical implications. Because cost-containment efforts require patients to pay higher co-payments for their medications, such increases can reduce the affordability of prescribed regimens and thus patient adherence, leading to negative health outcomes.<sup>12</sup> However, some costly drugs may offer reasonable value. For example, sofosbuvir (Sovaldi) was found to be a cost-effective treatment of hepatitis C infection even at its 2013 launch price of \$84 000 per 12-week course in certain patient populations when viewed from a patient's lifetime horizon and a societal perspective.<sup>13</sup> Payers must pay for this treatment upfront, though, with health care benefits often accruing decades later

to a different payer. In 2014, state Medicaid programs spent an estimated \$1.1 billion (after discounts) on sofosbuvir,<sup>14</sup> usually with no additions to their budgets.

It is therefore important to understand what factors have contributed to recent medication price increases to lay the foundation for considering options to ensure that prescription drug expenditures are commensurate with their value, affordable within health budgets, and equitable for all parties involved in these complex transactions. We examined the origins and effect of drug prices in the US market and considered available policy options related to these payments. To do so, we reviewed literature published in peer-reviewed medical and health policy journals from January 2005 to July 2016, searching for rigorous empirical articles addressing the

Figure 1. Per Capita Spending on Prescription Pharmaceuticals



Data are derived from the Organisation for Economic Cooperation and Development (OECD), reflect expenditures in 2013 (or the nearest year), and include all countries for which values were reported. Data used with permission from OECD, *Health at a Glance 2015: OECD Indicators, 2015*.<sup>8</sup>

Table 1. Examples of Country-Specific Average Drug Prices for Top-Selling Drugs in 2015

Drug	Monthly Price, US \$		Canada	France	Germany
	United States				
	Nondiscounted Price	Estimated Discounted Price			
Adalimumab (Humira), 40 mg biweekly	3430.82	2504.50	1164.32	981.79	1749.26
Fluticasone/salmeterol (Advair), 250 µg, 50 µg daily	309.60	154.80	74.12	34.52	37.71
Insulin glargine (Lantus), 50 insulin units daily	372.75	186.38	67.00	46.60	60.90
Rosuvastatin (Crestor), 10 mg daily	216.00	86.40	32.10	19.80	40.50
Sitagliptin (Januvia), 100 mg daily	330.60	168.61	68.10	35.40	39.00
Sofosbuvir (Sovaldi), 400 mg daily	30 000.00	17 700.00	14 943.30	16 088.40	17 093.70
Trastuzumab (Herceptin), 450 mg every 3 wk	5593.47	4754.45		2527.97	3185.87

Source: Bloomberg Business report and SSR Health.<sup>10</sup>

determinants of drug prices in the United States, the justifications and consequences of these prices, and possible policy options.

### Brand-Name vs Generic Drugs

The primary reason for increasing drug spending is the high price of branded products protected by market exclusivity provisions granted by the US Patent and Trademark Office and the Food and Drug Administration (FDA) (Table 2). Although brand-name drugs comprise only 10% of all dispensed prescriptions in the United States, they account for 72% of drug spending.<sup>15</sup> Between 2008 and 2015, prices for the most commonly used brand-name drugs increased 164%, far in excess of the consumer price index (12%).<sup>16,17</sup> The annual cost of a growing number of “specialty drugs”—high-cost, often injectable biologic medications such as eculizumab (Soliris), pralatrexate (Foloty), and elosulfase alfa (Vimizim)—exceeds \$250 000 per patient.

Such high prices have historically been limited to brand-name drugs that treat rare conditions. For example, the price of alglucerase (Cerezyme), a treatment for Gaucher disease, was \$150 000 per patient per year when the drug was launched in 1991 (it is now \$300 000)<sup>18,19</sup>; the price of ivacaftor (Kalydeco), indicated for a small subset of patients with cystic fibrosis, is likewise currently approximately \$300 000 per patient per year. Both drugs are generally received for life. However, drugs that treat conditions affecting mil-

ions of individuals in the United States also now have high costs. For example, many new oncology drugs enter the market at a price exceeding \$100 000 per course of therapy.<sup>20</sup> Even the average price of insulin has increased 300% from 2002 to 2013.<sup>21</sup>

Although brand-name drugs account for the greatest increase in prescription drug expenditures, another area that has captured the attention of the public and of policy makers has been the sharp increase in the costs of some older generic drugs. In 2015, Turing Pharmaceuticals raised the price of pyrimethamine (Daraprim), a 63-year-old treatment for toxoplasmosis, by 5500%, from \$13.50 to \$750 a pill.<sup>22</sup> The company was able to set the high price despite the absence of any patent protection because no other competing manufacturer was licensed to market the drug in the United States. Significant increases in the prices of other older drugs include isoproterenol (2500%), nitroprusside (1700%), and digoxin (637%). Even though the prices of most generic drug products have remained stable between 2008 and 2015, those of almost 400 (approximately 2% of the sample investigated) increased by more than 1000%.<sup>23</sup>

### Sources of High Drug Prices in the United States

Drug prices are higher in the United States than in the rest of the industrialized world because, unlike that in nearly every other advanced nation, the US health care system allows manufacturers to set their own price for a given product.<sup>11</sup> In contrast, in countries with national health insurance systems, a delegated body negotiates drug prices or rejects coverage of products if the price demanded by the manufacturer is excessive in light of the benefit provided (Table 3); manufacturers may then decide to offer the drug at a lower price.<sup>24</sup> In England and Wales, for example, the National Institute for Health and Care Excellence considers whether a new drug passes a cost-utility threshold—usually between £20 000 and £30 000 (\$25 000-\$40 000) per quality-adjusted life-year added—before recommending it for coverage by the National Health Service.<sup>25</sup> Although prices can vary widely around the world<sup>26</sup> and have also increased faster than member states’ gross domestic products in recent years in Europe,<sup>27</sup> US drug prices per capita still substantially outpace those in other settings.<sup>10</sup>

Drug companies’ ability to maintain high prices in the United States is based on 2 market forces: protection from competition and negotiating power.

**Table 2. Key Terminology and Examples of Therapeutic Products**

Term	Definition	Examples
Brand-name drug	A medication usually sold by the original sponsor of the application for regulatory approval	Nexium, Crestor, Prilosec
Generic drug	A version of a brand-name small-molecule drug manufactured by a different supplier. Generic drugs can be certified as bioequivalent by the FDA and substituted for brand-name drugs by a pharmacist.	Omeprazole, simvastatin
Biologic drug	An often protein-based therapeutic product that is distinguished by its molecular complexity	Filgrastim, epoetin alfa
Specialty drug	A drug designated by a payer for special attention, often because of its high price, but also potentially because of the need for distinctive handling or particular patient monitoring	Sovaldi, Praluent, Soliris

Abbreviation: FDA, Food and Drug Administration.

**Table 3. Approaches to Drug Pricing in Selected Countries**

	Australia	Canada	Germany	United Kingdom
National organization	Pharmaceutical Benefits Advisory Committee	Patented Medicines Prices Review Board	Canadian Agency for Drugs and Technology in Healthcare	Federal Joint Committee or Institute for Quality and Efficiency in Healthcare
Remit	Public payers	All payers	Public payers except in Quebec (noncancer drugs)	All insurers
Review criteria	Comparative effectiveness, safety, and cost-effectiveness; projected usage and overall costs to the health care system	Therapeutic innovation; comparative pricing with respect to France, Germany, Italy, Sweden, United Kingdom, and United States	Comparative effectiveness, safety, and cost-effectiveness; patient experiences	Comparative benefit
Decision	Coverage (yes, no, limited)	Price reductions or rebates	Coverage	Price setting after first year on the market
Binding	Yes	Yes	No	Yes

### Competition in the Pharmaceutical Marketplace

The most important factor that allows manufacturers to set high drug prices for brand-name drugs is market exclusivity,<sup>28</sup> which arises from 2 forms of legal protection against competition. Together, these factors generate government-granted monopoly rights for a defined period. Initial regulatory exclusivity is awarded at FDA approval. New small-molecule drug products automatically earn a guaranteed period of 5 to 7 years before a generic competitor can be sold,<sup>29</sup> and new biologic drugs are protected from competition for 12 years.<sup>30</sup> The second type of market protection is patent-related exclusivity because manufacturers can receive patents lasting 20 years or more for their inventions.<sup>31</sup> The US Patent and Trademark Office issues this intellectual property right—originally written into the US Constitution to encourage innovation—for inventions that are “novel,” “useful,” and “non-obvious.”<sup>32</sup>

Although regulatory exclusivities often set a lower-bound duration for market exclusivity, the actual length of such exclusivity is most commonly dictated by patent time. Because initial patents protecting the active ingredient are usually obtained when a drug is first synthesized, and the clinical trial and FDA review process usually takes on average 6 to 8 years, only half of the patent period may be left by the drug approval date.<sup>33</sup> However, a company can apply to have this period extended by up to 5 years to account for the time spent during regulatory review and half the time in clinical trials (“patent term restoration”), to a maximum of 14 years.<sup>34</sup> In addition, sponsors can also earn 6 more months of market exclusivity by testing their products in children,<sup>35</sup> an incentive earned by more than 200 drugs since legislation created the pediatric exclusivity program in 1997.<sup>36</sup> Overall, the median length of postapproval market exclusivity is 12.5 years for widely used drugs (interquartile range, 8.5-14.8 years) and 14.5 years for highly innovative, first-in-class drugs (interquartile range, 13.3-15.8 years).<sup>37,38</sup>

During that exclusivity period, the availability of treatment alternatives might be expected to exert pressure to reduce the price of a drug.<sup>39</sup> For example, approximately a year after Gilead introduced sofosbuvir, AbbVie received approval for a 4-drug, direct-acting, antiviral regimen that achieved similar clinical response rates against the hepatitis C virus, leading some payers to negotiate sofosbuvir discounts of more than 40%.<sup>40</sup>

In practice, however, competition between 2 or more brand-name manufacturers selling drugs in the same class does not usually result in substantial price reductions.<sup>41</sup> For example, of the 8 cholesterol-lowering statins that the FDA has approved, 2 have until recently remained patented: rosuvastatin (Crestor) and pitavastatin (Livalo). Despite the similar performance of these drugs in decreasing low-density lipoprotein cholesterol to other off-patent statins,<sup>42</sup> the price of rosuvastatin increased 91% between 2007 and 2012, from \$112 to \$214 per prescription.<sup>43</sup> During the same time, the price of the comparably effective atorvastatin decreased from \$127 to \$26 per prescription owing to the expiration of its patent protection in 2011.<sup>44</sup> Similar effects have been observed for other drug classes.<sup>45</sup>

One factor that undermines competition among treatment alternatives is the separate roles of patients, prescribers, and payers: physicians write prescriptions, pharmacists sell medications, and patients or their insurers pay for them.<sup>46</sup> This separation has traditionally insulated physicians from knowing about drug prices or considering those prices in their clinical decision making<sup>47</sup> and can similarly

remove many patients with good drug coverage from considering the price of the medications they “purchase.”

The only form of competition that consistently and substantially decreases prescription drug prices occurs with the availability of generic drugs, which emerge after the monopoly period ends. With FDA approval, these products can be substituted for bioequivalent brand-name drugs by the pharmacist under state drug product selection laws. In states with less restrictive drug product selection laws, generic products comprise up to 90% of a drug's sales within a year after full generic entry.<sup>48</sup> Drug prices decline to approximately 55% of brand-name drug prices with 2 generic manufacturers making the product, 33% with 5 manufacturers, and 13% with 15 manufacturers.<sup>49</sup> In 2012, the US Government Accountability Office estimated that generic drugs accounted for approximately 86% of all filled prescriptions and saved the US health care system \$1 trillion during the previous decade.<sup>50</sup>

Entry of generic drugs into the market, however, is often delayed. For pharmaceutical manufacturers, “product life-cycle management” involves preventing generic competition and maintaining high prices by extending a drug's market exclusivity. This can be achieved by obtaining additional patents on other aspects of a drug, including its coating, salt moiety, formulation,<sup>51</sup> and method of administration.<sup>52,53</sup> In an example of this strategy, the manufacturer of the proton-pump inhibitor omeprazole (Prilosec) received an additional patent on the drug's *s*-isomer, despite the absence of any compelling pharmacologic difference. This led to the creation of esomeprazole (Nexium) as a newly branded product that was sold for \$4 a pill, a 600% markup over the over-the-counter version of omeprazole.<sup>54</sup>

Because permissive US Patent and Trademark Office standards for novelty or usefulness make it relatively easy to patent many nontherapeutic aspects of a drug, companies can strategically patent small changes and try to influence prescribers and patients to transition from one linked product to the next, sometimes discontinuing production of older versions of the drug. For their part, generic manufacturers have engaged in litigation with brand-name manufacturers that could lead to the patents being invalidated, but these suits are frequently settled.<sup>55</sup> Historically, brand-name manufacturers have offered substantial financial inducements as part of these settlements to generic manufacturers to delay or even abort generic introduction.<sup>48</sup> Settlements involving large cash transfers are called “pay for delay”; for example, in a patent challenge case related to the antibiotic ciprofloxacin (Cipro), the potential generic manufacturer received upfront and quarterly payments totaling \$398 million as part of the settlement and agreed to wait until patent expiration to market its product.<sup>56</sup>

Other factors affect the availability of generic versions of brand-name products.<sup>57</sup> Application backlogs at the FDA Office of Generic Drugs have meant delays of 3-4 years before a generic manufacturer can receive approval to make a drug not protected by any patents. After the 2012 FDA Safety and Innovation Act required user fees to be paid by generic drug manufacturers for such review, the FDA now reports being able to provide an initial response in approximately 15 months.<sup>58</sup> Some innovator companies have refused to provide the samples of their products needed for the potential generic manufacturers to conduct bioequivalence studies, slowing or blocking the process.<sup>59</sup> Direct competition

among biologic drugs has been rare because no pathway existed to facilitate entry of competing products. In 2010, the Biologics Price Competition and Innovation Act created the framework for such an expedited pathway for so-called follow-on biologics, versions of originator biologic drugs made by different manufacturers,<sup>60</sup> but has led to only 2 follow-on biologic approvals in the last 5 years.

Once generic access to the market has been achieved, the number of generic manufacturers for a particular small-molecule (nonbiologic) product depends on a variety of factors, including the availability of raw ingredients, mergers in the industry, and the relative attractiveness of a particular market. In the case of pyrimethamine, the small number of patients with toxoplasmosis in the United States did not attract other potential generic competitors, leaving Turing with a monopoly that it was able to exploit with a 50-fold price increase.

Notwithstanding high generic drug use rates, problems at the state level can diminish the capacity of generic drugs to help contain costs. Thirty states have drug product selection laws that allow but do not require pharmacists to perform generic substitution; in 26 states, pharmacists must secure patient consent before substituting a generic version of the same molecule.<sup>61</sup> The latter obligation was estimated to have cost Medicaid \$19.8 million in 2006 for simvastatin (Zocor) alone.<sup>62</sup> In addition, all states allow physicians to issue dispense-as-written prescriptions that pharmacists cannot substitute with a generic product, further contributing to hundreds of millions of dollars in spending on branded drugs for which generic versions are available.<sup>63</sup>

Even well-intentioned government policies can inadvertently reduce generic competition. In attempting to require formal approval of drugs predating the modern new drug review process initiated in the 1960s, the FDA made it possible for some companies to assert market exclusivity and demand high prices for once-inexpensive old drugs, including colchicine, which underwent a 5000% price increase.<sup>64</sup> Similarly, a government-mandated switch to chlorofluorocarbon-free inhalers for patients with asthma led to new, far costlier patented chlorofluorocarbon-free spray formulations, even though the constituent medications had been off patent for a long time.<sup>65,66</sup>

### The Role of Public and Private Payers

During a drug's market exclusivity period, the primary counterweight against excessive pricing is the negotiating power of the payer. Among public payers, Medicare covers approximately 40 million adults, most aged 65 years and older, for outpatient (Part D) and inpatient (Part B) drug costs.<sup>67</sup> Medicaid, the federal- and state-funded health insurance program for low-income individuals, covers prescription drug costs for another 72 million Americans.<sup>68</sup> Other public payers include the Veterans Health Administration, the Department of Defense health care system, state prison systems, and the federal employee health benefits program. In contrast, private payers provide insurance coverage to 177 million persons in the United States.<sup>69</sup> This is often accomplished through 3 large pharmaceutical benefits management companies: Express Scripts, Caremark, and UnitedHealthcare.<sup>70</sup> Approximately 29 million Americans have no public or private prescription drug coverage—a rate far higher than in nearly all other industrialized countries.<sup>71</sup>

Several features of the US marketplace constrain the ability of public and private payers to negotiate lower drug prices. Medicare, for example, accounts for 29% of the nation's prescription drug expenditure,<sup>72</sup> but federal law prevents it from leveraging its considerable purchasing power to secure lower drug prices while requiring it to provide broad coverage, including all products in some therapeutic categories, such as oncology. Based in part on considerable lobbying and arguments that government negotiating power could decrease revenues for the pharmaceutical industry,<sup>73</sup> Congress included a provision in the law that created the Medicare drug benefit program, prohibiting the Centers for Medicare & Medicaid Services from negotiating drug prices or from interfering with negotiations between individual Part D vendors and drug companies.<sup>74</sup> This made prescription drugs under Part D one of the few aspects of health care for which Centers for Medicare & Medicaid Services does not negotiate or set prices.

Similarly, state Medicaid programs are generally required by law to cover all FDA-approved drugs, even if a particular medication has alternatives that are safer, are more effective, or offer greater economic value. However, Medicaid is also entitled to receive a rebate of at least 23.1% of the average manufacturer price for most branded medications and is protected from price increases exceeding inflation.<sup>75,76</sup> In contrast, the Veterans Health Administration, which provides health care for veterans and their dependents,<sup>77</sup> is entitled to a rebate of at least 24% of the average price and also has broad authority to exclude products from its formulary. As a result, particularly for drugs for which formulary alternatives are available, it achieves additional discounts below what the Medicare drug program and state Medicaid plans pay.<sup>78-81</sup>

Similar issues affect the private sector. In the 1990s, prescription benefit management companies became prominent intermediaries whose role would be to help employers or insurers promote appropriate prescription drug use and decrease its cost. There have been some recent isolated examples in which pharmacy benefit managers have done so for specific drugs (most prominently for drugs treating hepatitis C or the pro-protein convertase subtilisin/kexin type 9 inhibitors to reduce cholesterol levels).<sup>82</sup> However, aggressive price negotiation is not the norm. This is not surprising because part of pharmacy benefit managers' annual fees are based on a given payer's spending on drugs. Although the details of such payments are rarely disclosed, when one of the largest pharmacy benefit managers became a publicly traded entity, it was obliged to disclose its business model, much of which depended on payments from drug makers for shifting market share to their products from others in its class.<sup>83</sup>

Even large, self-insured employers have avoided aggressive attempts to negotiate prices directly with drug suppliers or to curtail their formularies to avoid paying for prescriptions that are less cost-effective. A common reason for this reluctance is that because pharmacy benefits have traditionally comprised less than 15% of health care budgets, the organizational concern that could be caused by denying payment to an employee or retiree for a particular drug was seen as overwhelming the modest savings that could be realized. This may change as drug prices increase, particularly for widely used products, and as drug spending consumes a greater share of health budgets. As illustrated in Figure 2, the beginnings of such a trend appear present for retail spending on drugs (excluding hospital- or physician-administered products) for all major payers except the Veterans Health Administration.



## Justifications for High Drug Prices

The pharmaceutical industry has maintained that high drug prices reflect the research and development costs a company incurred to develop the drug, are necessary to pay for future research costs to develop new drugs, or both. It is true that industry often makes expensive investments in drug development and commercialization, particularly through late-stage clinical trials, which can be costly.<sup>84</sup> These assertions have been used to justify high prices on the grounds that if drug prices are constrained, the pipeline of new medications will be adversely affected. Some economic analyses favored by the pharmaceutical industry contend that it costs \$2.6 billion to develop a new drug that makes it to market.<sup>85</sup> However, the rigor of this widely cited number has been disputed.<sup>86,87</sup>

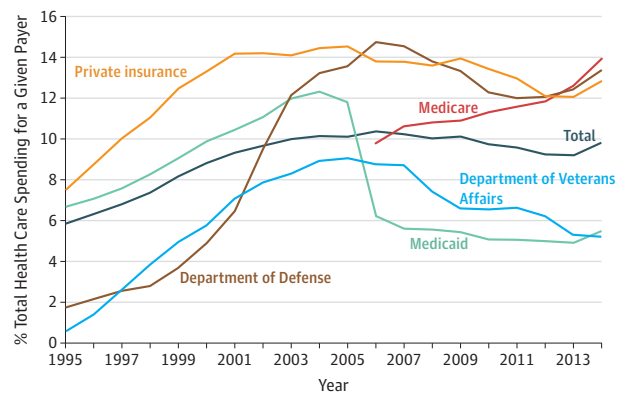
A number of factors weigh against these rationales for high drug prices. First, important innovation that leads to new drug products is often performed in academic institutions and supported by investment from public sources such as the National Institutes of Health. A recent analysis of the most transformative drugs of the last 25 years found that more than half of the 26 products or product classes identified had their origins in publicly funded research in such nonprofit centers.<sup>88</sup> Other analyses have highlighted the importance of small companies, many funded by venture capital.<sup>89,90</sup> These biotech startups frequently take early-stage drug development research that may have its origins in academic laboratories and continue it until the product and the company can be acquired by a large manufacturer, as occurred with sofosbuvir.

Arguments in defense of maintaining high drug prices to protect the strength of the drug industry misstate its vulnerability. The biotechnology and pharmaceutical sectors have for years been among the very best-performing sectors in the US economy. The proportion of revenue of large pharmaceutical companies that is invested in research and development is just 10% to 20% (Table 4); if only innovative product development is considered, that proportion is considerably lower.<sup>91</sup> The contention that high prescription drug spending in the United States is required to spur domestic innovation has not been borne out in several analyses.<sup>92</sup> A more relevant policy opportunity would be to address the stringency of congressional funding for the National Institutes of Health, such that its budget has barely kept up with inflation for most of the last de-

cade. Given the evidence of the central role played by publicly funded research in generating discoveries that lead to new therapeutic approaches, this is one obvious area of potential intervention to address concerns about threats to innovation in drug discovery.

Thus, there is little evidence of an association between research and development costs and drug prices<sup>93</sup>; rather, prescription drugs are priced in the United States primarily on the basis of what the market will bear. This explanation also helps to account for several high-profile case studies, including high-priced new branded products<sup>94</sup> and exorbitantly priced generic drugs described above.<sup>95</sup> In preparation for recent hearings on this topic, the US House Committee on Oversight and Government Reform subpoenaed internal correspondence from Turing and Valeant Pharmaceuticals, which had sharply increased the prices of older drugs the companies had acquired. The investigation revealed, for example, that Turing received “no pushback from payors” when it increased “Chenodal price 5x... [Thiola] price 21x... [and Daraprim] price 43x.”<sup>96</sup> Similarly, Gilead spent \$11 billion to purchase sofosbuvir from Pharmasset, a

Figure 2. Payer-Specific Retail Spending on Prescription Drugs Over Time in the United States



Data are derived from the Henry J. Kaiser Family Foundation and National Health Expenditure Accounts, official estimates of payer- and category-specific health care expenditures in the United States, published annually by the Centers for Medicare & Medicaid Services. Values incorporate estimated rebates. The reduction for Medicaid in 2006 reflects the adoption of much of these costs by the Medicare drug benefit program.

Table 4. Sales and Research and Development Expenditures of the 10 Largest Pharmaceutical Companies in 2014<sup>a</sup>

Ranking	Company	\$ (in Millions)		
		Total Sales	Research and Development	Research and Development, % Total Sales
1	Novartis	57 996	9943	17
2	Pfizer	49 605	8393	17
3	Sanofi	41 114	5873	14
4	Roche	48 039	10 015	21
5	Merck	42 237	7180	17
6	Johnson & Johnson <sup>b</sup>	74 331	8494	11
7	AstraZeneca	26 095	5579	21
8	GlaxoSmithKline	35 825	5372	15
9	Teva <sup>c</sup>	20 272	1488	7
10	Gilead	24 474	2854	12

<sup>a</sup> Sources: List secured from IMS Health. Sales and research and expenditure data compiled from company annual reports and 10-K filings with the Securities and Exchange Commission.

<sup>b</sup> IMS Health List-ranked companies specifically by pharmaceutical sales. However, because not all companies reported both sales and research and development costs specifically for pharmaceuticals, aggregate sales and research and developments costs were used.

<sup>c</sup> Teva principally manufactures generic drugs.

**Box. Possible Strategies to Limit the Effects of High Drug Prices****Federal**

**Patenting:** Limit secondary patents for trivial changes of a patented molecule (eg, heightening patenting standards to require showing enhanced safety or effectiveness over previously patented version of the molecule)

**Anticompetitive strategies:** Aggressively police anticompetitive business practices (eg, pay for delay, product hopping)

**Price negotiation:** Enable Medicare to negotiate drug prices for individual Part D plans and to exclude coverage for expensive products that add limited clinical benefit; experiment with value-based drug pricing and rational prescribing reimbursement models for Medicare

**Addressing extraordinary shortage or pricing problems:** Invoke “march-in” rights or government royalty-free license rights on excessively costly products that were developed in large part with government funding

**Generic drug policies:** Allocate greater resources at the FDA for reviewing generic drug applications to facilitate competition; in the event of a shortage of manufacturers, accelerate review of drug applications and authorize temporary drug importation from well-regulated pharmaceutical markets; mandate brand-name drug sample sharing with generic manufacturers

**Follow-on biologic policies:** Allocate greater resources to the FDA for reviewing follow-on biologic applications; promulgate product-specific guidance on demonstrating interchangeability; conduct rigorous postapproval surveillance of follow-on biologics to ensure the safety and effectiveness of these products

**State**

**Drug product selection laws:** Convert permissive generic substitution policies to mandatory substitution policies; eliminate patient consent requirements for generic substitution; limit “carve-outs” that make it more difficult to substitute in certain clinical categories (eg, antiepileptics, follow-on biologics)

**Price negotiation:** Test value-based drug pricing and rational prescribing reimbursement models for Medicaid

**Health Care Organizations**

**Price negotiation:** Develop value-based formularies and co-payment plans that encourage patients to make better choices but do not penalize them and hamper adherence

**Information dissemination:** Initiate academic detailing programs to market the best comparative evidence to prescribers and policy makers

small biotechnology firm that developed the drug, based in part on federally funded research led by an investigator at Emory University.<sup>97</sup> Gilead recouped almost all of this cost in the first year that sofosbuvir was on the market, recording sales of \$10.3 billion in 2014.<sup>98</sup> In December 2015, the US Senate Committee on Finance released a detailed report based on its access to internal company documents on Gilead’s strategies to maximize the prices it could charge for both that drug and its planned successor, which the company also owned.<sup>99</sup> In the current system for drug payment in the United States, few options exist to counter this approach.

Companies should of course be rewarded fairly for the research innovations they make that help generate new drug products and for their costly trial work that facilitates the assessment and

availability of new medications. But providing them with large incentives to do the opposite is counterproductive.

**Clinical Consequences of High Drug Prices**

The high cost of prescription drugs in the United States has clinical as well as economic consequences.<sup>100,101</sup> Even though more Americans have drug coverage as a result of the Medicare drug benefit plan and the Patient Protection and Affordable Care Act, cost-containment strategies in recent years have shifted an increasing share of drug expenses to patients.<sup>102</sup> Private insurers have increased deductibles<sup>103</sup> and most co-payments, and added a new payment tier for certain specialty drugs in which patients must pay coinsurance—often between 20% and 33% of the total drug price—rather than a simple co-payment.<sup>104</sup> Although such cost-shifting measures have helped “bend the cost curve” for employers and payers, they can reduce use of effective medications.<sup>105,106</sup> Almost a quarter of 648 respondents to a 2015 poll reported that they or another family member did not fill a prescription in the last year because of cost.<sup>107</sup> In other studies, patients who were prescribed a costly branded product rather than a more affordable generic alternative were found to adhere to their regimen less well than those receiving a similar generic drug<sup>12</sup> and to have worse health outcomes.<sup>108</sup> Nonadherence due to all causes has been estimated to contribute to \$105 billion in avoidable health care costs annually.<sup>109</sup>

In some cases, manufacturers have attempted to circumvent higher co-payments by providing patients with coupons that reimburse their out-of-pocket expenses.<sup>110</sup> Coupons can be useful for patients with no other option, but they leave the insurer obliged to pay the much larger amount of each prescription’s costs, thereby increasing health care spending. This approach has become common for branded drugs that have comparable but much less expensive alternatives.<sup>111</sup>

Faced with fixed health care budgets, states with higher drug costs for their Medicaid programs have had to reduce other services or increase health care eligibility requirements.<sup>112</sup> Several state Medicaid programs, for example, have imposed nonevidence-based policies to restrict sofosbuvir, including denying coverage to users of alcohol or other drugs.<sup>113,114</sup>

**Possible Solutions**

Various approaches have been proposed to mitigate the effects of increasing drug prices in the United States while still providing an adequate return on investment and maintaining incentives for meaningful innovation by pharmaceutical and biotechnology companies (Box).<sup>115,116</sup> These approaches include improving the competitiveness of the marketplace, enhancing government involvement in negotiating pharmaceutical prices, and providing more guidance for physicians and consumers in making medication use decisions.

**Improving Competition**

One possible strategy to contain drug costs would be better oversight of approaches used by manufacturers to extend market exclusivity. For example, changes in how the US Patent and Trademark Office interprets novelty and non-obviousness when issuing

patents could help avoid new secondary patents based on clinically irrelevant changes to active drug products. In recent years, a series of Supreme Court decisions have forced the US Patent and Trademark Office and federal courts to reconsider their previous permissive approach to the patentability of DNA sequences,<sup>117</sup> combination products,<sup>118</sup> diagnostic tests,<sup>119</sup> and business methods.<sup>120</sup> Re-examination of whether patents should be awarded to drug isomers or crystal structures should follow in cases in which there is no evidence of any clinical difference in drug effect. In India, current policy requires that a company proposing to patent a modification to a previously patented molecule show enhanced effectiveness.<sup>121</sup>

Better enforcement of existing laws and policies could also help contain drug costs. In 2013, the Supreme Court ruled that so-called pay-for-delay settlements with generic manufacturers could constitute an antitrust violation.<sup>122</sup> Nonetheless, numerous noncash-based settlements remain legal.<sup>123</sup> In one controversial case, Forest Laboratories introduced an extended-release version of its Alzheimer disease drug memantine (Namenda) shortly before the end of the market exclusivity period for the original product, which it then attempted to discontinue.<sup>124</sup> This "product hop" would have forced patients receiving the original drug to switch to the extended-release product before competition from generic products occurred. Litigation filed by the New York Attorney General helped undermine the strategy, averting an estimated \$6 billion dollars in increased Medicare drug spending.<sup>125</sup> Stronger government oversight of antitrust or inappropriate business practices intended to stifle competition can avert similar episodes. Greater rigor in this area could actually increase important innovation because it would require manufacturers to earn revenue from new medications that offer a clinical advantage, rather than from simply extending patent protection on existing products.

Another approach to reduce costs would be to decrease industry expenses. Reviews have pointed to the increasing expenditures for drug research and development, with the suggestion that steps be taken to make companies' investments more efficient.<sup>126</sup> A second area of spending that could be limited is in drug promotion, particularly related to direct-to-consumer advertising,<sup>127</sup> which is permitted only in the United States and New Zealand among high-income nations.<sup>128,129</sup> However, recent expansions of manufacturers' commercial speech rights under the First Amendment dim the prospects of legislative restrictions in this area and in fact could lead to an increase in promotional spending on marketing of products for non-FDA-approved ("off-label") indications.<sup>130</sup>

Increased attention to the generic drug marketplace is likewise needed.<sup>131</sup> Legislation recently proposed in Congress would forbid brand-name manufacturers from refusing to share samples of their products with generic drug manufacturers for necessary bioequivalence studies.<sup>132</sup> Dedication of greater resources to the Office of Generic Drugs in the first renewal of generic drug user fees expected in 2017 could further reduce application review times. In addition to addressing its backlog, the FDA has established an "express lane" for potential first generics that facilitates their prompt authorization.<sup>58</sup> To extend this progress, the FDA could be authorized to accelerate its review of new generic products and temporarily authorize large-scale imports from Canada, Europe, and other well-regulated pharmaceutical markets when the number of generic suppliers of a drug decreases below a critical level; this is currently permitted when the FDA identifies a shortage of a particular

drug.<sup>133</sup> Reciprocal recognition of generic products already approved by other stringent regulatory agencies (such as the European Medicines Agency) could make many well-manufactured medications available to the US market even before the current FDA approval backlog is fully addressed.

At the state level, laws permitting substitution of clinically similar drugs within the same class (ie, therapeutic as opposed to generic substitution) in carefully selected circumstances could also be an effective means of providing patients with the same clinical benefit at lower cost. For example, given data on the interchangeability of different proton-pump inhibitors or different versions of the same steroid cream, therapeutic substitution could allow patients prescribed a brand-name drug to receive a therapeutically equivalent generic drug in its place even if no exact generic equivalent is yet available.<sup>134</sup>

In the increasingly important area of biologic products, which account for a growing proportion of drug expenditures, enhanced competition from clinically equivalent follow-on biologic products could help reduce prices for originator biologic products that lack patents or other market exclusivities.<sup>135,136</sup> Price reductions caused by follow-on biologics are unlikely to reach the same levels as generic small-molecule drugs because the former are costlier to manufacture, and fewer companies have the capacity to develop them. Because most follow-on biologics will not be completely identical to the originator biologic, these products may also require greater investment in communication to encourage use by physicians when appropriate. Nonetheless, meaningful price reductions are still possible. The first follow-on biologic introduced into the US market in September 2015, a biosimilar version of the colony-stimulating factor filgrastim (Neupogen), offered a 15% discount on the originator's price.<sup>137</sup> In the European Union, in which 21 follow-on biologics are available,<sup>138</sup> the median price savings for biosimilar epoetin alfa (Epogen) is 35%, ranging from 6% to 79%, depending on the country and its price-negotiating power.<sup>139</sup> Further follow-on biologic approvals can be facilitated with greater guidance from the FDA about what levels of similarity will be required to obtain approval via the new Biologics Price Competition and Innovation Act pathway. A strong postmarket safety surveillance system could assess safety and effectiveness continually, particularly related to the possibility that patients will switch among different approved follow-on biologic products.

### Government Efforts to Reduce Drug Prices

In theory, the most effective way for a government to reduce drug prices would be for it to set them for the entire marketplace, as central governments do in countries such as Sweden,<sup>140</sup> or to engage in international reference pricing and set prices at levels similar to those of other countries. Taking such a step in the United States would have major marketplace ramifications and is not at present politically feasible, in part because of the power of the pharmaceutical lobby in Washington, DC.<sup>141</sup> Nonetheless, the US government can still take steps to help control excessive drug prices<sup>142,143</sup> by reassessing some existing unusual and overly permissive policies.

First, although the likelihood of legislative change is slim in the current political environment, Congress could authorize Medicare to negotiate the prices of drugs paid for by Medicare Part D plans, as it does for nearly all other goods and services. Such a change would require reorganization of the Medicare drug benefit, which



is currently managed through decentralized Part D plan administrators. Greater savings would be possible if Medicare and Medicaid had greater latitude in making clinically appropriate formulary choices, similar to the leverage the Veterans Health Administration drug program has. Medicare price reductions are likely to have effects on drug pricing in private markets, which tend to follow Centers for Medicare & Medicaid Services-set prices in other health services. The extent of such effects should be monitored to ensure that such choices are clinically reasonable and that prices for certain essential products do not decrease too far, as has occurred in some parts of the generic drug marketplace, leading to shortages. Centers for Medicare & Medicaid Services recently announced its intention to test various approaches to reducing prescription drug spending within the Medicare Part B program, which covers drugs administered in outpatient clinics or physicians' offices, such as altering payment levels according to the effectiveness for the purposes for which drugs are used (indication-specific pricing)<sup>144</sup> or reimbursing drugs offering comparable benefits at the level of the less costly agent (reference pricing).<sup>145-147</sup> This approach would also accomplish much toward reducing the large economic incentives provided through generous markups that encourage prescribers to use the costliest drugs.

A second way the government could help reduce prescription drug prices is by helping to generate and disseminate better information about the comparative clinical and economic value of drugs. In the United Kingdom, Germany, Australia, Canada, and several other countries, government-funded technology assessment activities provide support for comparative effectiveness studies and evaluate new products in light of comparative cost-effectiveness analysis.<sup>148</sup> The information thus generated could be used by government and private payers to help them respond to company-set prices, make determinations about formulary rules and exclusions, and educate physicians and patients about the value of medication choices.<sup>149</sup>

The Patient-Centered Outcomes Research Institute had been expected to serve in this role. It was hailed at its inception as a vehicle to promote robust comparative effectiveness research, but Congress precluded it from considering drug costs as a central focus of its work,<sup>150,151</sup> shifting instead to patient engagement and decision aids. The institute's reauthorization in 2019 will provide another opportunity to revisit its mission.<sup>152</sup>

In the meantime, patients, physicians, and payers can turn to non-governmental organizations, such as the Institute for Clinical and Economic Review,<sup>153</sup> *The Medical Letter*,<sup>154</sup> the Independent Drug Information Service,<sup>155</sup> Oregon's Drug Effectiveness Review Project,<sup>156</sup> and *Consumer Reports Best Buy Drugs*,<sup>157</sup> which provide information on value-based choices for select medications.<sup>158-160</sup> Other institutions, such as the American Society of Clinical Oncology and the Memorial Sloan Kettering Cancer Center, have organized approaches to establish value frameworks for cancer care.<sup>161,162</sup> The data generated by these groups can support lower drug prices by helping payers organize their formularies and negotiate appropriate rebates, as well as guide prescribers and patients toward more appropriate drug-use decisions.

Pharmaceutical manufacturers have also experimented with performance-based pricing programs, such as offering reimbursements for patients who do not respond to a particular drug therapy. For example, the manufacturers of the pro-protein convertase subtilisin/kexin type 9 inhibitor cholesterol-lowering drugs recently agreed to reimburse at least 1 private payer if low-density lipopro-

tein cholesterol-lowering outcomes did not reach the levels observed in clinical trials of these drugs.<sup>163</sup> It is too soon to know whether these pilot programs will have meaningful effects.<sup>164</sup>

In addition, pathways currently exist for the US government to intervene when prices for essential medicines are considered to be unreasonably high. One federal law allows the government to use patented products in exchange for reasonable and entire compensation,<sup>165</sup> similar to the government's eminent domain rights in regard to land. If applied to high-cost essential medicines, this law's invocation would allow the government to make a needed drug available widely at close to the cost of production while still providing manufacturers with adequate revenues tied to their amount of investment and risk of failure.<sup>166</sup> Another possibility is for the government to more actively invoke its royalty-free license or patent "march-in rights" for high-cost prescription drug products that were developed in part with governmental funding under the Bayh-Dole Act.<sup>167</sup> However, the US government has never implemented these existing rights and only once even indicated that it might do so—when the government sought to stockpile ciprofloxacin amid concern over widespread weaponized use of anthrax shortly after the September 11, 2001, terrorist attacks. The manufacturer of ciprofloxacin, Bayer, reportedly increased the drug's price during this added demand, and the government's threat to use the patented product anyway secured a 50% discount.<sup>168</sup> Opportunities to invoke march-in rights to address the unavailability or unaffordability of other drugs have been declined by National Institutes of Health; this option is also available only for drugs that have a clear link to federal funding on all of their FDA-listed patents.<sup>169</sup>

### Physician- and Patient-Level Solutions

Action by both physicians and patients can also play a role in containing excessive drug expenditures. Many physicians do not know the cost of the drugs that they prescribe<sup>47</sup> and do not discuss drug costs with patients.<sup>170</sup> Other practices such as writing dispense-as-written prescriptions to avoid generic drugs or using free samples of branded products left by pharmaceutical sales representatives also increase demand for costly products. More education about drug costs and value-based prescribing could be integrated into physicians' initial and continuing education; such information can also be provided through electronic medical record point-of-care reminders.

Academic detailing is an approach in which evidence-based information on appropriate prescribing is brought to physicians in their offices by specially trained noncommercial outreach educators, usually pharmacists or nurses.<sup>171</sup> This approach has been found to be effective in reducing suboptimal medication choices in a review of more than 60 randomized controlled trials<sup>172</sup> and is currently in place in several states and large health care systems.<sup>173</sup>

Another potential model to engage more physicians in considering the costs and value of the drugs they prescribe would be to integrate drug costs into their payment models.<sup>174,175</sup> The costs of prescription drugs are now largely separated from the costs of other health services. However, emerging health care systems such as accountable care organizations can provide an opportunity to link health services costs and drug costs so that physicians can be rewarded for prescribing drugs optimally. Such programs ought to focus exclusively on the quality of prescribing, not merely its cost; earlier experiments penalizing physicians for expensive prescribing

served merely to discourage their caring for patients with potentially costly diseases, such as cancer and AIDS.

Some market-oriented advocates of patient-level solutions have argued for shifting more of the costs of drugs to patients to make them more active consumers and ensure that they avoid drugs that do not provide adequate value. However, cost shifting can be highly problematic because patients often have insufficient information about the value of drugs to inform their decisions; such approaches also discriminate against sicker and poorer patients.<sup>176</sup> In contrast, programs that reduce patients' economic exposure to co-payments have been shown to improve adherence<sup>177</sup> and even patient outcomes.<sup>178</sup> Effective interventions will require greater attention to the clinical and ethical issues involved.

## Conclusions

High drug prices are the result of the increasing cost and complexity of drug development but also arise in large part from the

approach the United States has taken to the granting of government-protected monopolies to drug manufacturers, combined with restriction of price negotiation at a level not observed in other industrialized nations. Opportunities to address these problems include paying greater attention to potentially unjustified granting and extension of patent exclusivity, enhancing competition by ensuring timely generic drug availability, providing greater opportunities for price negotiation by governmental payers, generating more evidence about comparative cost-effectiveness of therapeutic alternatives, and actively educating physicians and patients about such choices to promote more value-based decision making. There is little evidence that such policies would hamper innovation, and they could even drive the development of more valuable new therapies rather than rewarding the persistence of older ones. Medications are the most common health care intervention and can have a major benefit on the health of individuals, as well as of populations, but unnecessarily high prices limit the ability of patients and health care systems to benefit fully from these vital products.

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