Journal of Economic Perspectives—Volume 39, Number 2—Spring 2025—Pages 53–78

Lessons for the United States from Pharmaceutical Regulation Abroad

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American politicians from across the ideological spectrum have found a rare point of agreement: US drug prices are too high, and the government should do something about it. Figure 1 presents the results of a study of drug prices in different countries, which finds that overall US pharmaceutical prices, and particularly prices of on-patent drugs, are several times higher than those in other high-income countries such as France, Germany, Japan, and the United Kingdom (Mulcahy, Schwam, and Lovejoy 2024). Such comparisons bolster the arguments of those advocating price controls or other government interventions in the United States.

Why are policies around drug prices necessary? In other words, why do most developed countries rarely leave drug pricing to "the market" without government intervention? In all countries, pharmaceutical markets operate under conditions that differ substantially from the assumptions behind a competitive market that would equilibrate supply and demand based on price. These conditions reflect information problems, the specificities of healthcare markets, and the cost structure of drug development.

First, pharmaceuticals are "credence goods": not only is their quality difficult for consumers to determine prior to consumption, but their effects are challenging to identify even after consumption. Regulation of entry, administered by the US Food and Drug Administration (FDA) and similar regulators like the European Medicines Agency (EMA), aims to reduce this information asymmetry. Consumers can be

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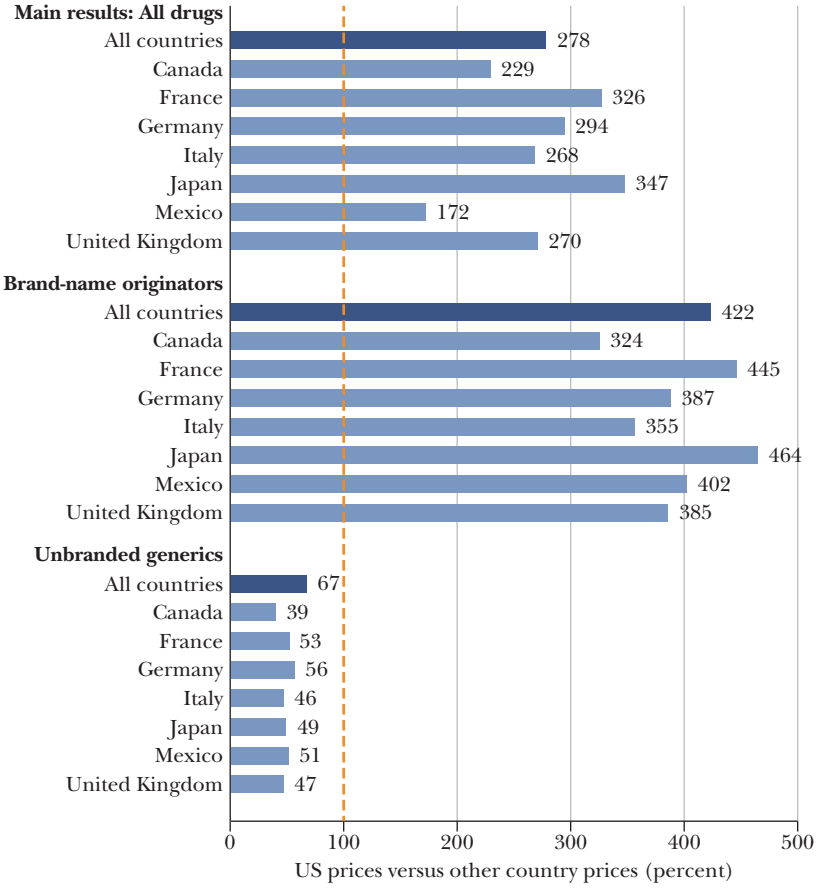
For supplementary materials such as appendices, datasets, and author disclosure statements, see the article page at https://doi.org/10.1257/jep.20241418. The author has received financial support from an interested party.

Figure 1
US Manufacturer Gross Prescription Drug Prices as a Percentage of Prices in Selected Other Countries, All Drugs, 2022



Source: Mulcahy, Schwam, and Lovejoy (2024).
Note: "All countries" refers to all 33 OECD comparison countries combined. Other countries' prices are set to 100. Biologics were excluded from unbranded generics. Only some presentations sold in each country contribute to bilateral comparisons. Brand-name originators and Unbranded generics reflect IQVIA's assignment of drug products in individual countries.

reasonably confident that the little pink pill they swallow is what it says on the label, and that clinical trials have demonstrated the safety and efficacy of the product. Absent such quality regulation, the market may shrink or collapse entirely (while manufacturers could signal quality through other means, such as brand name reputation or the use of certification by third parties, these would also likely raise costs and limit entry). A consequence of regulation, however, is that pharmaceutical markets do not have free entry—even as the structure of the industry has evolved with the entry of many smaller biotechnology and genomics firms.

Demonstrating quality to regulators requires the provision of detailed information from clinical trials as well as manufacturing processes. Development costs are very high for a new drug (DiMasi, Grabowski, and Hansen 2016). However, imitation of a drug whose safety and efficacy have been established is relatively easy, particularly if the detailed information provided to regulators is public. Innovators may not be able appropriate the benefits if rapid entry by competitors occurs. These conditions render investment in new drug development unattractive and explain a second intervention in pharmaceutical markets: patent protection and other forms of exclusivity. By shielding a new drug from direct competition for some period of time, these policies seek to encourage investment in innovation. But this regulatory protection is another reason that free entry does not exist in pharmaceuticals.

If we take entry regulation and patent protection as given, therefore, government intervention yields pharmaceutical markets that are not perfectly competitive. Few markets are, of course, but as a healthcare good, the purchase of pharmaceuticals takes place in a particular context. Specifically, many drugs are covered, at least in part, by health insurance.

Because patients with insurance do not face the true price of care, they may consume too much. Einav and Finkelstein (2018) provide an assessment of empirical studies of moral hazard and health insurance, and conclude that the evidence is consistent with moral hazard. This moral hazard increases costs for insurers, even when treatments are supplied in a perfectly competitive market, by increasing the quantity consumed. When suppliers have market power as a result of patents or other exclusivity, however, the problem is further aggravated. Facing patients with demand made less elastic by insurance, suppliers can set higher prices.

A further complication is that prescribers mediate demand for pharmaceuticals. Like many goods and services in healthcare, experts (usually physicians) are presumed to have better information on the appropriate treatment than the consumer (patient). For prescription drugs, the prescriber selects the drug and dosage. In Western countries, prescribers do not typically sell drugs to patients. They may not be aware of relative prices or be sensitive to them. This is partly by design: a stronger profit motive could introduce problematic agency issues (for evidence on this point, see Jacobson et al. 2006; Iizuka 2007). However, the separation of prescribing and dispensing drugs limits the price elasticity of prescribers, although there is evidence that prescribers do respond to information about price when it is made available (Epstein and Ketcham 2014).

Given all the informational difficulties and regulation in healthcare, prices determined in a market without price regulation may not provide an efficient outcome or profits that correctly incentivize innovation and provision. While regulations reduce asymmetric information, they do not eliminate it. Even if clinical trials provide an estimate of a drug's effectiveness on average, patients and physicians may have difficulty identifying the causal effect of a treatment on the individual. Placebo effects may play a role, for example, or other interventions or patient behaviors may be important. Physicians may not be well-informed about recent drug developments and innovations, or their clinical practices may evolve very slowly; this

can slow the adoption of therapeutically beneficial products (Kyle and Williams 2017). Advertising and marketing efforts may also influence demand, with ambiguous and heterogeneous effects (Leffler 1981; Azoulay 2002; David, Markowitz, and Richards-Shubik 2010; Ching and Ishihara 2012). Due to secret rebates and other factors that reduce transparency, the price of a pharmaceutical product may convey little information about its quality.

In summary, with regulatory barriers to entry, insurance, and prescribers without "skin in the game," conditions are ripe for very high prices on patented pharmaceuticals. This presents a budgetary challenge for payers who act as price-takers. They may respond by restricting access, with negative consequences for patient welfare. If pharmaceutical prices are unrelated to a drug's importance (that is, therapeutic value and effectiveness), the market is not sending appropriate signals for the direction of further investment (Kyle 2018).

Government intervention in pricing can, in theory, improve outcomes. The following sections discuss such interventions in more detail. The United States is an outlier among developed nations in having a more limited role of government in healthcare generally, and in pharmaceutical pricing specifically. While US drug prices are higher, spending on healthcare is also much greater in the United States. In addition, the sheer size of the US market gives its policies a greater role in global innovation incentives.

If a decentralized market has shortcomings, designing a well-functioning centralized market for pharmaceuticals poses numerous challenges. Some of these are common to other healthcare goods and services, like accounting for the opportunity cost of spending on drugs versus other treatments, or health versus other government programs. Administrative costs and the potential for gaming are also issues in setting reimbursement rates for procedures, office visits, and other areas. Numerous studies have examined strategic responses to regulated reimbursement rates, such as "upcoding" or a change in services provided (Dafny 2005; Fang and Gong 2017; Batty and Ippolito 2017). When these fees are vulnerable to manipulation by providers, they may be set at inefficient levels (Milcent 2021).

Other issues are more salient when intervening in pharmaceutical pricing than for most healthcare goods or services. Drug pricing is implicitly a tool of innovation policy. If innovation is not rewarded, we should expect lower levels of investment. Patents are ineffective policy instruments for pulling investment in innovation if prices are determined by maximizing only *static* welfare. The cost structure of pharmaceuticals is important here, because prices are usually determined after the costs of development have been incurred. If firms sell to monopsonistic purchasers, they are subject to hold-up. Purchasers then must commit to prices that exceed what is optimal in the short run. In addition to providing incentives for the level of innovation, prices must also provide information about the desired direction of innovation. That is, they should align social value and private rewards so that investors pursue innovation that is socially valuable.

Of course, measuring the social value of a pharmaceutical product is far from simple. The clinical trials required for market authorization by the US Food and

Drug Administration or its counterparts in other countries provide information about a drug's safety and efficacy under carefully controlled conditions; they do not, however, assess overall therapeutic value or social value more broadly. For example, a clinical trial may show that a cardiovascular treatment reduces heart attacks by 10 percent. But that does not tell us whether the treatment is more effective in an absolute sense than existing treatments, or whether it is more cost-effective, or whether that reduction leads to lower spending on emergency care or surgical interventions, or more productive days in employment. The market design for pharmaceutical price regulation must create incentives for the provision of this information, or incur the administrative costs of producing it.

Finally, unlike most services in healthcare, pharmaceuticals are globally traded products that are very similar across countries. The possibility of price arbitrage between markets may result in firms choosing to forgo smaller markets with low prices in order to preserve profits in large countries (Kyle 2007; Maini and Pammolli 2023). In addition, the innovation incentives created by any single country spill over to all other countries that might benefit from the results of that innovative effort. Small markets that account for a small share of global revenues may see little reason to create innovation incentives through paying high prices, as the private sector is unlikely to respond strongly to a small increase in expected revenues. Large markets like the United States, which do have the potential to shift innovation incentives through prices, are thus subject to free-riding (Grossman and Lai 2008). The inclusion of a minimum level of intellectual property protection in trade agreements seeks to limit that free-riding, but does not eliminate it if countries use price controls. These international externalities introduce an important complexity to market design.

The Landscape for Setting Drug Prices

Developed countries around the world have introduced an array of policies to control pharmaceutical prices. I focus here on those used for on-patent or branded drugs, although these have implications for the generic market as well. Some countries intervene directly in markets by setting a maximum price of a product, at any or all of the manufacturer, wholesale, or retail levels. Others allow manufacturers to set prices in response to government policies on coverage and reimbursement. Countries vary in how they evaluate products; for example, on an absolute or comparative basis, and in whether they consider only clinical characteristics or other factors, such as research and development costs or local production. I do not attempt a comprehensive survey here; useful summaries are provided by the Commonwealth Fund (2020) and the OECD (2008).

Types and Basis of Intervention

As monopsonist buyers in most countries, government payers have considerable sway over the price of drugs, but they have adopted different approaches. In

Table 1
Overview of Reimbursement and Pricing Regulations, Selected Countries

	Reimbursement decision			*Factors in price-setting*			
Country	*Timing*	*Economic considerations*	*Price regulation*	*Cost-plus*	*Therapeutic referencing*	*International benchmark*	*Profit regulation*
Australia	Before launch	Yes	Maximum ex-factor price	Yes	Yes		
France	Before launch	No	Maximum statutory price		Yes	Yes	
Germany	After launch	No	Statutory price negotiated after market entry		Yes	Yes	
Japan	Before launch	No	Reimbursement price		Yes		
United Kingdom	After launch	Yes	Not direct				Yes

Source: Paris and Belloni (2013).

some countries, prices are the result of a direct negotiation between the government and the manufacturer. Other countries take the manufacturer's price and decide whether the government will reimburse it. With either approach, governments use a variety of criteria to value a new drug; Table 1 provides an overview for several OECD countries.

Evaluation Criteria

Cost-based approaches. "Cost-plus" or "rate-of-return" regulations, like those once widespread in electricity markets, appeal to those who believe pharmaceutical firms earn excessive profits. The pharmaceutical industry itself uses the high costs of research and development as a justification for its pricing. Such policies can be applied at the product level, setting the price of a drug to its estimated development costs plus a mark-up, or at the firm or product portfolio level, in which the firm's overall rate of return is limited.

The UK Pharmaceutical Price Regulation Scheme (PPRS), now known as the Voluntary Scheme for Branded Medicines Pricing, is an example of rate-of-return regulation. In use since 1957, it is an agreement between the UK government and the "research-based pharmaceutical industry," members of the trade group Association of the British Pharmaceutical Industry (ABPI), and is renegotiated every five years. Participating manufacturers are subject to a maximum profit (currently 21 percent) allowed on their sales to the National Health Service (NHS); they also agree to limit growth in the total spending by the NHS on products covered by this scheme. Profits in excess of this cap are paid back to the NHS as rebates. Note that there is no minimum profit guarantee, and that the profit controls are assessed on a portfolio of products rather than drug-by-drug. Little empirical evidence exists on the effects of this policy. Borrell (1999) assesses outcomes through 1994, and concludes that the PPRS had little effect on prices. The ABPI (2014) documented a decline in the relative prices of branded drugs in the United Kingdom compared

to other countries between 2003 and 2011. Implications for the level and direction of research and development investment are even harder to identify because the UK market is a small percentage of global revenues.

Economists are generally skeptical of cost-plus or rate-of-return regulation in this context, particularly if applied to individual drugs rather than product portfolios. Cost-plus, in particular, risks rewarding research and development spending that may be inefficient. Firms are willing to spend more to develop products with higher expected revenues, and additional spending can result in a better clinical profile. However, more money spent on developing a product does not always yield greater therapeutic value, for the same reason that millions spent on producing a film does not guarantee either its commercial success or its artistic value. Setting a higher price for a drug that was expensive to develop but that has the same clinical effects as one with low development expenses both increases costs for the payer as well as distorting incentives. Rate-of-return regulation applied to a portfolio of products creates no incentive for firms to bring development costs down; these have increased substantially over time (DiMasi, Hansen, and Grabowski 2003; DiMasi, Grabowski, and Hansen 2016), potentially representing an important barrier to entry as well. With both cost-plus as well as rate-of-return regulation, price is not necessarily linked to therapeutic or social value. In the former case, as just discussed, development cost and therapeutic value may not be related. In the latter, if firms may freely price, the link with social value may be weakened due to market frictions discussed in the previous section.

A second concern is the need for detailed internal data from firms on their expenses in order to determine costs. The World Health Organization recommends against cost-plus regulation in its 2020 Guidelines mainly for implementation challenges, noting that the "[a]pplication of cost-plus pricing to medicines requires significant technical and human resources, particularly in obtaining and validating reliable estimates of component costs." The difficulty of estimating costs may be one reason that cost-plus policies are not widespread in developed countries. Recent calls for increased transparency in research and development spending, such as spending by product rather than the aggregate figures usually reported, target this difficulty. Rate-of-return policies at the firm level have a lower, but still important, information burden.

Value-based criteria. In recent years, the industry has advocated the adoption of "value-based" pricing, in which research and development and manufacturing costs play no role. Rather, in this approach, more valuable (therapeutically superior) products receive higher prices. Because a product may be more effective for certain patient populations, or may treat several diseases with varying effectiveness, a value-based price may differ for the same drug across therapeutic indication or patient subgroup, at least in theory.

There are at least two challenges to the implementation of value-based pricing. First, while it does not require information on research and development costs, it does require assessments of a drug's therapeutic value that go beyond what is

typically required for market authorization. These health technology assessments often include comparative studies, in which a trial tests a new product against other treatments available rather than a placebo. The clinical endpoints may differ, and these studies may exploit "real world evidence" to examine the use of a product outside the carefully controlled clinical trial setting. These assessments are often costly and time-consuming. While regulatory agencies have largely harmonized requirements for marketing authorization, there is less coordination across countries in designing health technology assessments, and this can lead to different conclusions about a drug's value. In part, that stems from the variation in standard of care or the importance of competing products, which are not the same in every country. Satisfying different demands for health technology assessments adds to the manufacturer's costs, although manufacturers may prefer a diversity of views on a drug's value if it allows them to price discriminate across countries. A second challenge is that if therapeutic superiority can be established, it still remains to determine how much a payer is willing to pay for that clinical improvement.

In France, the pricing and reimbursement process begins with an initial determination of whether a product is important enough to be reimbursed (its "service médical rendu" (SMR)) and its therapeutic advantages over existing treatments (ASMR or "amélioration de service médical rendu"). These assessments are officially independent of price; the ASMR is an input into subsequent price negotiations, which typically establish a price for a three-year period. Products judged to add therapeutic value are entitled to a price premium over competitors, while others must be priced at or below existing products. However, perhaps in anticipation of those negotiations, the body assigning ASMRs has historically judged very few products to add significant therapeutic value, and the revenues of products are only loosely related to their ASMR scores (Kyle 2018). Although a drug may have several ASMRs, varying by indication or patient subgroups, there is a single price established for the entire market, illustrating the practical difficulty of indication-based pricing linked to value.

Cost-effectiveness thresholds. An approach that avoids haggling directly over price instead has payers exercise their power to refuse insurance coverage. For the reasons discussed above, in most health systems, insurance reduces the price elasticity of patients, and prescribers are unaware of or insensitive to the price of drugs. If manufacturers are free to set price, full reimbursement of all drugs is inefficient and impossible from a budgetary standpoint. Payers can therefore choose to limit coverage by reimbursing only those products whose prices are less than the payer's willingness-to-pay for a health improvement.

The United Kingdom and Germany both use cost-effectiveness evaluations as the main policy instrument to address price. Manufacturers can freely set prices of their products in the United Kingdom; these products are subject to cost-effectiveness evaluation by the National Institute for Clinical Excellence (NICE), which decides whether to recommend a product for reimbursement by the National Health Service. Germany allows the manufacturer to establish a price at the time the product is launched, and six months later, evaluates whether the

country will reimburse the product at that price or at the price of a competing product. Of course, the manufacturer determines its price in the shadow of the reimbursement decision.

Given a manufacturer's chosen price, a health technology assessment evaluates the product's cost per quality-adjusted life year (QALY) and determines whether the product should be reimbursed. A QALY is based on a combination of life expectancy and quality of life, where quality of life is measured on a scale from zero to one, from death to perfect health. The calculated QALY for a given drug can vary across countries depending on the data and methods used. This willingness-to-pay can be explicitly announced, or governments can provide guidance on a range of thresholds. Prices are not negotiated directly with payers, but manufacturers anticipate the need to adjust price in response to cost-effectiveness thresholds.

The health technology assessment (like that done for value-based pricing) is a large information burden. Cost-effectiveness policies also require consensus on the value of a statistical life. Allowing for different valuations by disease or target population is theoretically possible, but may be difficult to justify politically. Thresholds used in practice vary by country; the King's Fund in the United Kingdom estimates that the incremental cost-effectiveness ratio threshold in the United Kingdom is lower than that used in Ireland and the Netherlands, for example (Collins 2020).

The case of Ocrevus (ocrelizumab) illustrates the variation in health technology assessments across countries, with implications for price, reimbursement, and access. The French assessment concluded that it offered moderate therapeutic benefits for primary progressive multiple sclerosis (PPMS) and minor benefits for relapsing-remitting multiple sclerosis (RRMS), and the drug is reimbursed for both. The German assessment also determined minor benefits for RRMS, but found the evidence insufficient for PPMS. In the United Kingdom, the National Institute for Clinical Excellence has recommended it for PPMS, but only for RRMS if another treatment is contraindicated or unsuitable. Each country may put different weight on the strength of the evidence, value some patient subsets more than others, choose different comparator products, or focus on different clinical outcomes.

These policy choices, with their varied informational and administrative burdens, have implications for the speed of access to new drugs. Manufacturers launch new products in Germany almost immediately after obtaining market authorization. The administrative steps in countries like France, Italy, and Spain contribute to months-long delays of product launch. It is certainly possible that the negotiation process could be streamlined or accelerated. However, launch delays can also be strategic, as discussed below.

Other factors. Other criteria are also factors in negotiations over price or the level of reimbursement. Paris and Belloni (2013) provide an excellent description of how different OECD countries approach this. For example, some governments may reward manufacturers for investing in research and development or manufacturing locally. Orphan drugs, which treat small patient populations, may be subject to different reimbursement rules. Often, both price and quantities are negotiated

simultaneously. For example, firms may commit to price reductions if volumes exceed a certain level. In assessments that consider more than clinical performance, payers must consider what offsetting costs or benefits to account for. A therapy that reduces absenteeism or increases productivity generates social benefits, but may not reduce costs directly incurred by the health system. Valuing such benefits may then favor treatments for younger patients, rather than the elderly. Increasingly, countries are experimenting with alternative approaches, such as those described later in this paper.

Pricing Benchmarks and Parallel Trade

In well-functioning markets, prices convey information. Government interventions in drug pricing often use other prices as benchmarks, as a complement to the procedures discussed above. These comparisons can be to other drugs that treat the same condition, or to the price of the same drug in other markets. These two types of "reference pricing" have very different effects, however. Governments can also allow for prices in other countries to affect local prices through policies on parallel trade or reimportation.

Internal reference pricing. Internal reference pricing establishes a new product's reimbursement level as equal to that of a competing product, or reference product, within the same country. In some countries, manufacturers are free to set a higher price, but patients must then pay the premium over the reference product price. This has some similarities to tiered formulary pricing in the US context. It introduces some price sensitivity and allows the market to reward quality. For example, if patients value an improvement in dosing (for example, once a week instead of daily, or an oral formulation instead of injection) or have a strong preference for branded products over generics, then manufacturers should arrive at a price that reflects that valuation. However, the efficiency of this policy relies on how well-informed patients and prescribers are about the clinical characteristics of competing products and on the appropriate choice of a reference product.

Experiences with the use of internal reference pricing vary across countries. While Brekke, Holmas, and Straume (2011) and Kaiser et al. (2014) find that its introduction in Norway and Denmark increased the use of generic substitutes and lowered average prices, the policy led to higher patient co-payments and an increase in the price of off-patent products in Portugal (Costa and Santos 2022). Depending on how the reference price is calculated, the effects are theoretically ambiguous (Miraldo 2009). Because these policies have the potential to affect revenues—and in particular, the distribution of revenues between innovative and generic products, or through rewards to quality—they could also affect innovation incentives. However, isolating the effect of a single country's adoption of such a policy on global investment is a challenge.

External reference pricing. In contrast, external reference pricing compares the price of a drug to the same product in other countries. Many European countries

use some form of this policy. For example, in 2012, the Netherlands limited the price of a new drug to be no more than the average in Belgium, France, Germany, and the United Kingdom.[1]

An economic justification for this benchmarking could be that if the referenced countries have useful health technology assessments of a new product and that information is reflected in their prices, there is no need for another country to perform one—it can instead rely on the information generated by other payers. This is an argument for coordination on a single health technology assessment. Because external reference pricing is often used alongside a country's own health technology assessment, another economic argument is that it is like a meta-analysis of comparative studies, filtered through pricing. However, the price in the reference country is likely to be a function of more than just the health technology assessment. Finally, small countries may reference prices in larger markets to counteract their lower bargaining power with manufacturers—but small markets like Belgium, Denmark, and Ireland are often referenced by larger countries. As implemented, therefore, the main motivation for external reference pricing seems to be the perception of fairness: why should a country pay higher prices than its neighbors?

An important argument against external reference pricing is that it creates incentives for strategic launching of new products to the detriment of countries with relatively low prices, if those countries are used as external references. If markets were completely independent and manufacturers faced no supply constraints, pharmaceutical firms should be willing to sell at any price that covers their marginal costs and country-specific fixed costs. However, most drugs are not launched immediately in every country, or even all developed markets. In addition to the bureaucratic delays associated with pricing and reimbursement, there is an incentive for manufacturers to delay launch (or never launch) in referenced countries that negotiate low prices. Because the price in a referenced country affects the price in the referencing countries, manufacturers favor faster launch in countries with higher prices. In practice, those are often the richest countries; these strategic launch delays are costly to those with lower income levels and whose prices are referenced (Kyle 2007; Maini and Pammolli 2023).

Parallel trade in pharmaceuticals (or reimportation, as it is sometimes called in the United States) creates similar incentives. If permitted, drugs sold in other countries at a lower price can be imported to compete with local products. This arbitrage of cross-country price differences makes launch in low price markets less attractive, along with other consequences like shortages (Kyle 2011). Both external reference pricing and parallel trade limit the ability of firms to price discriminate across countries. However, economists often see price discrimination as a relatively efficient outcome, particularly if access to new products in poorer countries is important.

Neither external reference pricing nor parallel trade has entirely eliminated cross-national price differences. Importantly, prices are not simply a function of

[1] For details, see Figure E.3 of Maini and Pammolli (2023).

GDP per capita, but reflect the policy choices, preferences, and bargaining power of countries. For example, injectable semaglutide (Ozempic) was priced at $83 in France, but $103 in Germany; in tablet form (Rybelsus), it was $203 in the Netherlands, compared to $103 in Sweden (Amin et al. 2023). Launch delays and access are also stark. Of the drugs approved by the European Medicines Agency from 2019 to 2022, 88 percent were available in Germany by early 2024, but less than 20 percent for the Baltics and Romania (EFPIA 2024).

Can the United States Import Similar Policies?

While governments are the main health payers in other developed countries, the private sector has a larger role in the United States, and drug coverage is not universal. In other developed countries, most patients face approximately the same price for a drug. In the decentralized US system, however, the same drug may be sold at very different prices to different buyers. Pharmacy benefit managers or the insurance companies who use them negotiate pharmaceutical prices with manufacturers. While no pharmacy benefit manager is a monopsonist, they do control access to large patient populations, and they are not price-takers (Guardado 2024). Manufacturers negotiate both price and reimbursement (or formulary placement) with pharmacy benefit managers. As with government payers, it is important that pharmacy benefit managers act as good agents for patients. One critical difference with national payers is that even if US patients face switching costs in changing insurers, residents of a country are less likely to "vote with their feet" by moving abroad if dissatisfied with pharmaceutical pricing and access. That is, pharmacy benefit managers face some competition and may lose market share if they refuse to cover an important drug. A second important difference is that pharmacy benefit managers try to maximize profits, not social welfare. The influence of any single pharmacy benefit manager on the level and direction of innovation is limited, but they also may not realize the long-run benefits of innovation to the same extent as a government payer. For example, the benefits of a childhood vaccine accrue to a government payer over an individual's entire life, in the form of reduced illness and associated healthcare costs. But that individual is unlikely to be the client of the pharmacy benefit manager over their entire lives, nor is the pharmacy benefit manager necessarily sensitive to the reduction in associated healthcare costs.

The US federal government is also a major payer, but its interventions in drug pricing until recently were limited. While the Department of Veterans Affairs can negotiate directly, it is a very small share of government spending on drugs. The price Medicaid pays is linked to that in the private sector, but not negotiated directly. The 2003 Medicare Modernization Act barred the federal government from bargaining over prices for drugs reimbursed under Medicare Part D. Instead, the private sector (insurers who offer Medicare Part D and pharmacy benefit manager) takes that role.

This has recently changed. The Inflation Reduction Act of 2022 introduced the Medicare Drug Price Negotiation Program, which establishes a Maximum Fair Price (MFP) on single source products with large shares of Medicare spending whose active ingredients were first approved at least seven years ago (or eleven in the case of biologics). Prominent health economists argue that this negotiation should be based on value, linking prices to measures of clinical and economic benefits (Conti, Frank, and Gruber 2021). As adopted, however, the law mandates price discounts based on the number of years since US launch. Many unintended consequences may result due to strategic responses by manufacturers. For example, although a limited patent term generally encourages firms to launch as quickly as possible, some have suggested that that firms may avoid launching early in a single indication to avoid triggering the "clock" for Medicare negotiations (Patterson, Motyka, and O'Brien 2024). Mandatory price discounts in advance of generic or biosimilar entry have the effect of reducing the incentives for that entry, which usually responds to the size of a drug's revenues (Danzon and Chao 2000). Firms may also have more incentive to "product hop," which refers to the introduction of a new version of an existing drug prior to patent expiration. Long a concern to competition authorities (Federal Trade Commission 2022), this can lead to substitution away from the product subject to Medicare negotiation and towards a more expensive product, reducing the expected cost savings from the policy. A crucial point is that in contrast to most of the countries discussed above, the United States is a big enough market for its policy choices to "move the needle" on research and development investment. Total spending on pharmaceuticals in the United States is almost four times higher than in China, five times higher than in Japan, and ten times higher than in Germany (IQVIA Institute 2024). The balancing of static and dynamic effects is therefore more important than in the case of a country the size of Belgium or Ireland. An explicit policy goal to reduce total spending is likely to reduce investment, and imperfect assessments of value (for example, through erroneous assumptions used in a health technology assessment or discounts that are independent of value) may distort it. The magnitude of these effects is the subject of intense debate.

The incentives created by the United States historically have allowed smaller markets to free ride, at least to some extent. This has prompted proposals to link US prices to those in other markets. Reimportation of drugs from Canada or other developed markets has been proposed, but not yet implemented, at the federal level. In 2019, the Trump administration proposed creating pathways for reimportation of pharmaceuticals (FDA 2019). Some states have moved in this direction, including Florida and several states in the Northeast. Their legal authority to do so has been challenged, but the US Food and Drug Administration approved a plan to allow reimportation in early 2024. The consequences of parallel trade in Europe suggest that reduced access to new drugs in Canada is a serious risk. Canada would also likely take steps to limit export in order to protect access for Canadian patients. The relative size of the Canadian market (approximately one-tenth that of the United States) implies that even if every product were reimported into the US market, the change in the overall US price level would be small (Kyle 2011).

Tying US prices to prices in other countries—that is, external reference pricing—is also a policy proposal with bipartisan support. Though not implemented, the Medicare Most Favored Nation pilot program would have capped prices at the lowest paid by other countries with at least 60 percent of US GDP per capita (Centers for Medicare & Medicaid Services 2021). An optimistic take on this applies the ideas of Grossman and Lai (2008), whose model predicts that prices in other countries would increase (as would research and development and firm profits) as a result of this linkage. Industry trade groups strongly oppose this policy, though, suggesting that manufacturers expect a negative effect on firm profits.

A less optimistic assessment of external reference pricing considers the European experience. As noted above, external reference pricing like this would induce a number of strategic responses from other stakeholders. These include delayed launch and/or supply limitations to lower-price markets, as well as efforts to make products less comparable across countries (Kyle 2007, 2011; Maini and Pammolli 2023). Another response is similar to the approach taken by pharmacy benefit managers, who negotiate secret rebates with manufacturers. That is, the true price paid by pharmacy benefit managers is not easily observed; there is a list price, but the rebate or discount offered by the manufacturer is not public. Some European countries also use hidden rebates. For example, the use of France as a reference by other countries ultimately led to agreements between manufacturers and the government to establish a public price as well as secret rebates paid by manufacturers back to the government (Kanavos et al. 2017). This allows the official price (that which is referenced by other countries) to be higher, like the list price in the United States, than what is in fact paid. These nonpublic prices have prompted calls for greater price transparency, but the effects of increased transparency here are ambiguous. When (true) prices are secret, a manufacturer can more easily lower its price in a country, because it sees no negative consequences from having that secret price referenced by other countries. In concentrated markets, transparent prices could also facilitate collusion by manufacturers. However, nonpublic prices make economic assessments much more challenging.

The evidence suggests that US adoption of reimportation or external reference pricing would have only modest effects on US drug prices (but would probably reduce access or price transparency in other countries). Negotiating prices paid by Medicare has larger potential effects on the level of US prices, depending on what criteria are used. Importantly, unlike pricing interventions in most countries, this policy could also have large effects on global research and development due to the size of the US market. Numerous studies have shown that research and development responds to increases in market size that result from US government purchases or mandates without price controls, though the innovation is not necessarily socially valuable (Finkelstein 2004; Dranove, Garthwaite, and Hermosilla 2022). The new Medicare policy could, in theory, better align profits with social welfare than the current system and improve incentives. However, as discussed previously, reliable health technology assessments are essential for this purpose. The effects also depend on how private payers respond.

Alternative Approaches

Many stakeholders, both in the United States and other countries, are unhappy with the drug pricing status quo. Payers face budgetary challenges that are most acute when arguably the most valuable therapies reach the market. Sovaldi (sobosfivir) in 2013 is an example: launched at an initial price tag in excess of $80,000 in the United States, it was a large advance in treatment (indeed curing) hepatitis C (HCV). While it was cost-effective even at its list price, the size of the potential patient population caused an abrupt increase in expenditures by payers on treating HCV. Although both private payers in the United States and public payers elsewhere negotiated substantially lower prices, the impact on pharmaceutical spending was nevertheless large. Iyengar et al. (2016) calculated that providing Sovaldi or similar antivirals to all patients with HCV would amount to an increase of more than 10 percent of total pharmaceutical spending in 30 countries studied; for some countries, treating all HCV patients would require doubling total spending on drugs. In the United States, public programs also saw an large increase in outlays. Medicare spent $8.2 billion (before rebates) on HCV treatments in the 18 months after Sovaldi's launch, six times more than spending on HCV previously. The recent introduction of effective treatments for obesity for a larger potential population could strain public budgets even more. According to Deese, Gruber, and Cummings (2024), "[u]nder reasonable assumptions and at current prices, making this class of drugs available to all obese Americans could eventually cost over $1 trillion per year."

Some countries are considering or experimenting with alternatives to the regulatory approaches outlined above. Many of these rely primarily on patents as the policy tool for creating innovation incentives. More significant departures from the status quo would involve ex ante commitments (that is, before a treatment has been developed).

Contracting before Innovation

In general, countries face a trade-off between providing incentives for innovation through high prices and providing access to that innovation. As discussed above, the many frictions in establishing drug prices and ensuring appropriate use—whether in the United States or other developed countries—yield profits that are not aligned with social value, distorting incentives. De-linking rewards for innovation from high-margin sales, and instead using fixed payments for successful innovation, is an attempt to avoid this trade-off.

Kremer and Williams (2010) suggest experimentation with alternatives to intellectual property rights, including prizes or advance market commitments (AMCs). These mechanisms have payers announcing a reward for developing a treatment meeting specified criteria, and have many appealing features. Because price is not negotiated after the product reaches the market, the manufacturer faces a reduced risk of hold-up, and funders have more certainty about budgets. There is no need to ration treatments to patients, as was the case for hepatitis C drugs, or for

manufacturers to encourage inappropriate use. While the patent system is a blunt policy tool, as the length of protection is not a function of therapeutic value or importance and prices may be hard to predict, a prize system provides much clearer innovation incentives.

One prominent example of an advance market commitment is the Gates Foundation's $1.5 billion pilot financing for pneumococcus vaccines in 2009. More recently, Operation Warp Speed used AMCs for the development of COVID-19 vaccines (Slaoui and Hepburn 2020). Evaluations of these provide valuable lessons for their design and deployment going forward. In particular, both required a number of assumptions, with considerable uncertainty at the time funds were committed, and some of which were criticized afterwards (GAVI 2021; D'Souza et al. 2024). Indeed, this informational burden probably best explains why AMCs are rare. Concerns over the challenges of implementing AMCs or prizes have also been a factor in the failure to adopt the Medical Innovation Prize Fund Act, proposed by Senator Bernie Sanders (I-Vermont) many times.

The use of prizes or advance market commitments also suffers from the same risk of international free-riding as the status quo. In theory, contributions to financing a prize or AMC could be linked to GDP per capita. However, could funders credibly commit to denying access to a resulting treatment to countries that did not contribute?

Contracting after Innovation

Policy changes that leave the patent system largely in place are likely to be easier to implement, because trade agreements such as the Trade-Related Aspects of Intellectual Property Rights Agreement require that signatories provide a minimum level of protection for intellectual property. Patents align private and social value when profits are linked to therapeutic quality and need. Price regulations (or limiting quantities sold through access restrictions) that break this link distort innovation incentives as well as consumption in the short run.

As an alternative to negotiations or "take-it-or-leave-it" offers, auctions are commonly used in government procurement. Indeed, many payers use procurement auctions like this for markets with intramolecular competition. In the United States, for example, the Department of Veteran's Affairs and Group Purchasing Organizations use competitive bidding to procure supply of generic drugs. For on-patent products, this approach is feasible when there are several molecularly distinct treatments that are nevertheless reasonably close substitutes. This is the case for many vaccines, but rarely observed for other situations of intermolecular competition.

In theory, the manufacturer of an on-patent product could itself auction off access to its treatment, or to the associated intellectual property. Kremer (1998) proposes the uses of patent buyouts, using auctions to elicit information about the value of the treatment. In Kremer's proposal, the government would put the intellectual property in the public domain. Manufacturers may be hesitant to participate in patent buyouts if there is uncertainty about the ability to enforce intellectual

property rights in other countries where there was no buyout; organizing a global patent buyout presents the same challenges as international funding of prizes. While the Biden administration recently pressured the National Institutes of Health to exercise "march-in" rights (Department of Health and Human Services 2023), even these are rarely exercised, and I am aware of no government buyout of a pharmaceutical patent.

At least two incremental adjustments to existing pricing approaches could be welcomed both by industry and by payers. Sood et al. (2018) provide an overview of the so-called Netflix model, subscription pricing, or all-you-can eat pricing. In this scenario, there is a fixed payment to the manufacturer for supplying any quantity demanded at zero price (or close to). It is similar, therefore, to buying the patent rights for some period of time; the difference with a patent buyout is that the buyer does not put the intellectual property in the public domain. This approach provides greater certainty for planning budgets, both for payers and for manufacturers. The payment could be staggered over several years, in order to smooth outlays. Because the manufacturer's profit does not depend on the number of units sold, there is reduced incentive to market the product or encourage its use in patients who are unlikely to benefit from it. The payer also should seek to maximize patient access.

The imperfect information at the time of a drug's launch is the same for subscription pricing as for the more traditional approaches described above. While a multi-year agreement provides certainty to both parties, it also makes adjustments to either the arrival of new information or the arrival of new competitors more difficult. This contract also limits the incentive for a manufacturer to disseminate information—while marketing is often criticized, it can play an important role in educating both physicians and patients about the existence of treatments. Manufacturers may also have less interest in finding new therapeutic uses, or improved formulations, if they expect no increase in profits under the subscription model.

Australia implemented this approach in 2015, paying $766 million to four manufacturers of hepatitis C treatments for unlimited access to these drugs over five years. Analysis of the Australian experience suggests that access increased, with a per-patient cost well below the estimated price that would result from negotiations. The Medicaid programs of some US states, including Louisiana and Washington, also negotiated subscription pricing for HCV. Their experiences illustrate that while access has improved, pricing is not the only barrier (Conti, Frank, and Gruber 2021). For example, screening patients who need treatment is itself a challenge. Neither state achieved their initial goals for the number of patients treated.

Pay-for-performance, outcomes-based, or risk-sharing contracts[2] are another potential improvement over traditional pricing. Instead of linking price to therapeutic value demonstrated in trials or studies available at the time a drug is brought to market, these contracts link payments to the realization of *future* clinical milestones or other metrics. The importance of information revealed after market

[2] Many other terms are used for these arrangements; see Towse, Garrison, and Puig-Peiró (2011) for more details.

approval is clear. Prasad et al. (2013) conclude that "[t]he reversal of established medical practice is common and occurs across all classes of medical practice." Many follow-up studies of oncology treatments, which are increasingly approved based on secondary or surrogate endpoints, do not confirm the benefits suggested by earlier clinical trial results (Prasad et al. 2013; Haslam et al. 2021; Mooghali et al. 2024). Boyle et al. (2021) find that "real world data" currently provided on the use of cancer drugs are too sparse or of too little quality to be of use in reimbursement decisions.

The appeal of pay-for-performance contracts is obvious to economists. If well-designed, they address the imperfect information available at launch, but do not delay access while additional information is produced; they buttress incentives for manufacturers to develop treatments with demonstrable gains to patients; and they reduce incentives for manufacturers to encourage the use of a drug in patients who are unlikely to benefit. Better performing drugs generate higher profits, which sends the correct signals for investment in innovation.

Of course, the details in risk-sharing contracts matter. Barros (2011) argues that over-treatment of patients is a risk, and that welfare effects are ambiguous, for the specific contract he models. Contracts that are theoretically well-specified may be impossible to write in practice. Indeed, there is substantial heterogeneity in contract design, to the extent such information is available. (In a survey of the literature on outcomes-based contracts from 2000 to 2019, Antonanzas et al. (2019) note a lack of transparency.) The performance measure can be at the level of an individual patient or more aggregated. While they have the advantage of allowing earlier access despite a lack of complete information about therapeutic value, both parties must agree on appropriate outcome measures. It must be possible to monitor performance, as well as confounding factors that might affect that measure. For example, if a patient adjusts behavior in response to the belief that a drug is effective, that behavioral response could interfere with the measured performance.

In 2002, the United Kingdom's National Health Service established a risk-sharing scheme for four multiple sclerosis treatments that were deemed not cost-effective. Under this program, 5000 patients were monitored over a ten-year period. The agreement was that the manufacturer of a drug that failed to achieve the benefits suggested by initial clinical trials would reimburse the NHS. Initial results were disappointing, and illustrated the difficulties in monitoring patient outcomes (Boggild et al. 2009). However, later results confirmed that the treatments were cost-effective, and are recommended by NICE (National Institute for Health and Care Excellence 2018). Other examples of risk-sharing include the cancer treatment Velcade (bortezomib) in the United Kingdom and Rasilez (aliskiren) for hypertension in Italy (Garrison et al. 2013).

The challenges of negotiating these contracts have hindered their adoption. Payers may also be reluctant because the evidence on the results of pay-for-performance contracts is scant (Antonanzas et al. 2019). Neumann et al. (2011) also point to a lack of data infrastructure and difficulties

in measurement. The absence of a national patient registry and fragmented payers may also hamper their use in the United States. Advances in technologies that enable real-time monitoring of patient compliance and outcomes should reduce the costs of implementing pay-for-performance, if privacy concerns can be overcome.

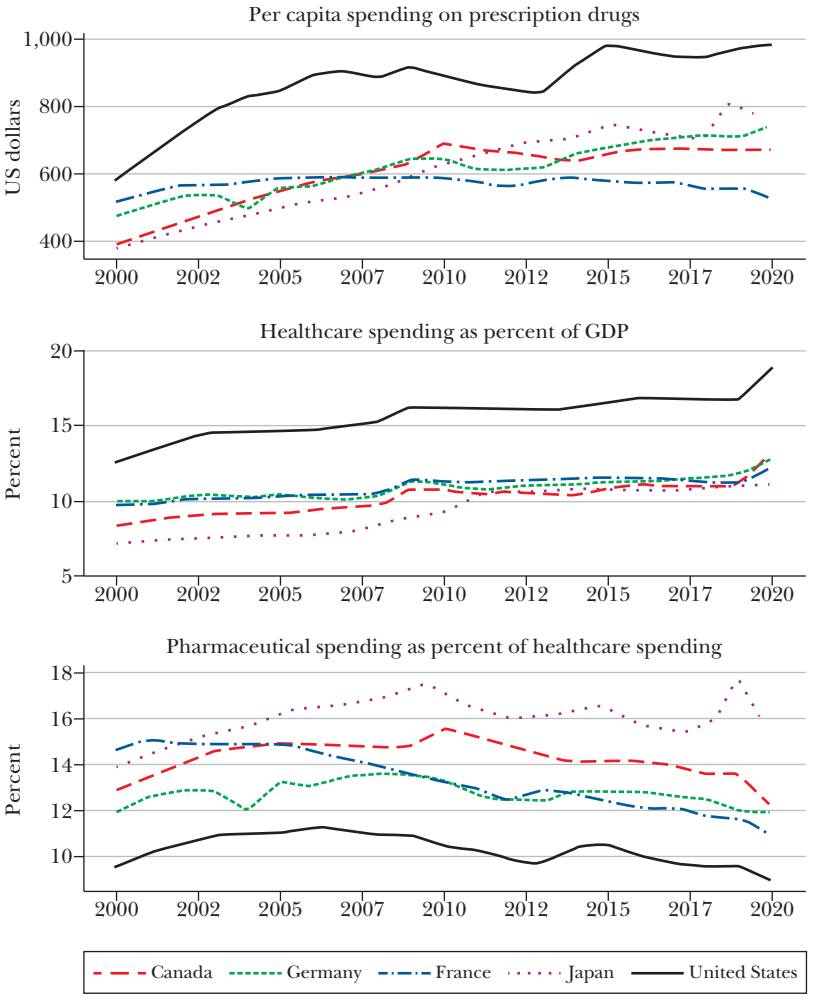
Recent surveys by consulting firms in the United States suggest interest in and adoption of outcomes-based contracts (Chatterjee et al. 2017; Avalere 2023). An increase in the use of risk-sharing contracts, both in the United States and elsewhere, is also noted in Carlson, Chen, and Garrison (2017), Yu et al. (2017), and Piatkiewicz, Traulsen, and Holm-Larsen (2018). However, there is little public documentation of the outcomes of these arrangements. In particular, we lack systematic evidence on whether the cost-savings or health improvements realized offset the difficulties of negotiating them.

The Broader Context of Pharmaceutical Spending

Despite the attention drug prices receive, pharmaceuticals do not seem to be a major driver of healthcare cost increases overall, in the United States or other high-income countries. Drugs are but one input into the broader healthcare production function. The top panel of Figure 2, based on OECD data, shows that per capita spending on prescription drugs is indeed much higher in the United States than in other high-income countries—though this gap is smaller than that for drug prices, as shown in Figure 1. However, US spending on health overall is also much higher: as the second panel of Figure 2 illustrates, health care spending is almost 18 percent of GDP in the United States, but closer to 11–12 percent in Canada, France, Germany, and Japan. The share of pharmaceuticals within health spending is, in fact, lowest in the United States. While healthcare spending as a percent of GDP was essentially unchanged during the pre-pandemic period from 2015 to 2019, the share of pharmaceuticals in that spending declined.

One interpretation is that the prices of other healthcare goods and services in the United States are relatively more expensive than pharmaceuticals. For example, a recent survey of physician salaries across countries in 2021 reported an average of $316,000 in the United States versus $183,000, $138,000 and $98,000 in Germany, the United Kingdom, and France, respectively (Medscape 2021). Similarly, according to OECD Health Statistics, the average salary for hospital nurses in the United States in 2018 was $77,760, versus $56,157 in Canada, $55,302 in Germany, $42,925 in the United Kingdom, $42,099 in Japan, and $41,713 in France. The United States has higher GDP per capita than other countries, and cost-effectiveness thresholds based on the value of a statistical life will naturally allow for a higher US price than in Germany, for example. If a pharmaceutical treatment substitutes for another type of care (for example, surgery) or reduces the use of other interventions that are more expensive in the United States, then the system savings associated with pharmaceuticals are also higher. Given the other prices in the system of US healthcare,

Figure 2
Pharmaceutical and Healthcare Spending, Selected Countries



Source: OECD Data Explorer.
Note: Spending on prescription drugs is reported in the OECD Data Explorer as expenditures on "Pharmaceuticals and other medical non-durable goods." Per capita spending is in PPP-adjusted constant US dollars.

perhaps drug prices are not exceptionally high. Put another way, the market for pharmaceuticals may not be more problematic than other inputs, and interventions in the market for one input may introduce unexpected distortions.

Information asymmetries and other market imperfections can result in distorted prices, and therefore research and development incentives. Intervention by governments can, in theory, address these problems. But the fundamental challenge of valuing new treatments remains. To payers, the costs are visible and

immediate; the benefits may accrue over a long period of time. Government payers may introduce distortions by breaking the link between social value and profits. Prior research has identified distortions resulting from Medicaid drug pricing policies; for example, see Duggan and Scott Morton (2006) and Alpert, Duggan, and Hellerstein (2013). This is particularly a risk when budgets are strained by high demand for a novel product: it may be difficult to distinguish between products with high demand because they yield therapeutically important results from those with high demand due to moral hazard or well-organized patient advocates. Denying coverage can also be politically fraught. After the National Institute for Clinical Excellence recommended against reimbursement of several cancer drugs, the United Kingdom established the Cancer Drug Fund to pay for them in response to patient outcry and legal challenges (Aggarwal, Ginsburg, and Fojo 2014). Subsequent analyses generally conclude that this funding did not provide value to UK cancer patients (Aggarwal et al. 2017). Similar political pressures may influence Medicare decisions in the United States, where warnings about "death panels"[3]—committees of bureaucrats who determine whether patients will have access to care—have long resonated.

Generic drug competition in the United States is generally robust, with rapid entry and price declines following patent expiration. This is exactly what economic theory predicts: high profits are competed away when barriers to entry are reduced and products are undifferentiated. Margins on many generic products are very small (so small that manufacturer exit has created shortages, particularly in some markets for injectable products). Indeed, as noted in the introduction, generic prices in the United States are lower than in peer countries. The high prices paid by US consumers during the limited patent term are at least somewhat offset by the benefits of low prices later on.

The General Accounting Office estimated that the average profit margin of the largest drug companies was 15–20 percent from 2006 to 2015, versus 4–9 percent across the largest 500 firms (Government Accountability Office 2017). The Congressional Budget Office reported that US-based publicly traded pharmaceutical firms spent an average of more than 19 percent of net revenues on research and development between 2000 and 2019, much higher than the average of 3 percent for the S&P Total Market Index and even above other innovative sectors like software and semiconductors (Congressional Budget Office 2021). Industry lobbyists sometimes justify drug prices by pointing to these large research and development expenses. Those investments are made with the expectation of future profits; they should not be a justification after the fact. However, policies that lower expected profits reduce research and development spending, and by extension, innovation (Acemoglu and Linn 2004; Filson 2012; Blume-Kohout and Sood 2013; Dubois et al. 2015). The size and importance of the US market make such policy changes much more significant than in most other countries. We have little evidence on the value of the marginal research and development that is sacrificed, though Dranove, Garthwaite,

[3] Sarah Palin, former Republican Vice Presidential candidate, first used this term during the debate over the Affordable Care Act.

and Hermosilla (2022) and Finkelstein (2004) suggest that increases to expected market size induced by policy changes in the United States did not trigger scientifically novel innovation. Policies that target the rewards to more innovative products through longer exclusivity, such as for orphan drugs, or through faster regulatory approval, such as the US Food and Drug Administration's breakthrough therapy designation, appear to have been more successful in this regard (Yin 2008; Chandra et al. 2024).

Firms themselves may have difficulty identifying which products are likely to be the most profitable. Not only do they face technical risk during the process of drug development, but they also face market risk if a product completes clinical trials. Wouters, McKee, and Luyten (2020) find no correlation between the research and development costs associated with specific products and their prices. Reports by consulting firms find that new drug launches often fail to meet analysts' expectations (McKinsey & Company 2013; Deloitte Center for Health Solutions 2020), with poor formulary placement or formulary exclusions as an explanation in many cases. Greater clarity from payers could reduce this uncertainty, and allow firms to direct their efforts more efficiently.

To achieve better outcomes than in the current system, policymakers must focus on more than reducing the average price paid or total spending. Accepting higher prices on effective drugs (offset by reducing the rewards to ineffective therapies), and valuing long-run benefits accrued over time, should result in more efficient use and innovation incentives. Unlike many other health innovations, pharmaceuticals have low transportation costs, are easy to adopt and deliver, and see large price reductions within 10–15 years of introduction. Their potential in treating diseases like Alzheimer's, obesity, and others justifies at least maintaining, if not increasing, incentives for investment. The informational and political challenges are nontrivial, however. Addressing some of the frictions or imperfections described here should also increase efficiency.

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