The Regulation of Drug Prices: Lessons from Recent Empirical Advances

Luca Maini[†]

In most countries around the world, governments have established mechanisms to regulate the prices of both branded and generic prescription drugs. The choice of mechanism can affect prices, spending, and access to pharmaceutical products. Hence, drug price regulation has important implications for public policy and welfare. Until recently, only a few empirical studies examined the interaction between drug price regulation and market outcomes. However, this topic has garnered considerable attention in the last few years, both because of the availability of novel data and growing discontent about rising pharmaceutical spending. In this chapter, I review the theoretical basis for price regulation of drugs and discuss existing empirical evidence on the effect of different approaches to price regulation on drug prices, government spending, and access to pharmaceutical products.

Drug prices are regulated for two reasons. First, governments are the largest buyers of prescription drugs in most countries. Even in countries where the government does not purchase drugs directly, it often indirectly subsidizes their acquisition (for example, through regulated marketplaces like Medicare Part D or health exchanges in the United States). Hence, governments have a vested interest in determining drug prices.

Second, drug markets are characterized by several frictions that can potentially prevent the achievement of an efficient equilibrium. The most critical friction is the monopoly power granted to manufacturers of branded drugs through patents and market exclusivity. Monopoly power is particularly problematic in the pharmaceutical market because prescriptions are usually subsidized by insurance. As a result, demand for drugs is highly inelastic, allowing firms to charge high markups and limit access to drugs in the absence of countervailing forces.[1] In this context, regulation that aims to lower prices can promote a more efficient equilibrium in the market.

On the other hand, it is essential to remember that drug manufacturers are granted temporary monopoly power to incentivize the costly R&D investments necessary to bring drugs to market.

[†] This manuscript is the author's English version of a chapter originally written in Italian and published as: Luca Maini, "La regolamentazione dei prezzi dei farmaci: lezioni da recenti avanzamenti empirici," in *Il prezzo dei farmaci*, a cura di Fabio Pammolli, Bologna: Società editrice il Mulino, 2024.

[1] Monopoly power is not the only source of friction. Other potential issues that I will not discuss in this chapter include agency problems, which arise because physicians often play a role in drug choice (Dickstein 2017); imperfect information about the effect of drugs (Crawford and Shum 2005); and behavioral biases that may lead to suboptimal use of prescription drugs (Baicker et al. 2015).

Moreover, lower prices occasionally lead to drug shortages when demand increases unexpectedly or when a negative supply shock occurs. Hence, the objective of regulation cannot simply be to lower prices as much as possible but rather to strike a balance between expanding access and promoting future innovation and robust supply lines.

Governments that intervene in drug markets usually take one of three approaches. First, governments can set up regulated marketplaces to incentivize competition among firms and promote lower prices. For example, a few countries around the world (e.g., Italy, Sweden, Denmark, and Brazil, among others) organize periodic procurement auctions to determine the preferred supplier of generic drugs. Second, they can directly negotiate prescription drug prices. When this happens, governments assume a role similar to that of a private buyer in a firm-to-firm transaction. However, since the government is generally a monopsonistic buyer, it can wield significant bargaining power and extract lower prices than a private payer. Third, they can codify rules to set prices based on non-market criteria. Common examples of these rules include (i) cost-plus regulation, (ii) pricing based on health technology assessments or cost-effectiveness analysis, sometimes referred to as value-based pricing, and (iii) reference pricing, which consists of setting a drug's price based on the price of that same drug in other markets. I also note that the use of one approach does not preclude the use of another one. For example, health technology assessments and reference pricing are often used as a starting point for direct negotiations.

This chapter is divided into three sections. In the first section, I present a simple model where patients choose drugs whose acquisition cost is subsidized by the government. I show how this setting can lead to higher-than-optimal prices when firms have market power, thus motivating the need for price regulation. I then discuss empirical evidence comparing prices across regulated and unregulated markets. In the second section, I examine the two main competing approaches to direct price regulation used around the world. Under the first approach, governments set prices using objective benchmarks based on either cost or value data. Under the second approach, governments set prices using the prices of the same product in other markets. Finally, in the third and last section, I conclude with some thoughts on the fundamental trade-offs governments must consider when designing drug price regulation.

1. Why and when is government intervention necessary?

In this section, I present a simple model to describe the strategic entry and pricing choices of both branded and generic manufacturers and discuss the circumstances and frictions that might lead the market toward an inefficient equilibrium in the absence of government intervention. I then conclude the section by presenting some basic evidence supporting the model's predictions.

1.1 A theoretical framework for competition and regulation in drug markets

To model competition and regulation in the pharmaceutical market, I consider a single-agent, two-step model of entry and price-setting. In the model, a drug manufacturer chooses first

whether to invest a fixed cost to enter a drug market. Later, if the firm decides to invest, it sells its drug to patients covered by insurance.

The fixed cost of entry can be interpreted as an R&D cost in the case of branded manufacturers who are developing novel products, or it can be interpreted as the cost of filing a generic drug marketing application and setting up a production line for a generic manufacturer. Hence, the model can describe the choices of both branded and generic manufacturers, with only a small additional tweak to the price-setting stage. Branded manufacturers, who are granted temporary exclusivity when their product is approved, will act as monopolistic firms. Conversely, manufacturers of generic drugs will play a quantity-setting game with other manufacturers who are also selling the same product.

Since the model's implications for branded and generic manufacturers are slightly different, I will analyze them separately, starting with branded manufacturers.

A model of R&D and drug marketing

A monopolistic firm chooses whether to invest a fixed cost C to develop a new drug. I assume for simplicity that the investment is always successful.

If the firm invests, then it sells the new drug to patients. I assume that the drug is covered by insurance. Patients who purchase the drug pay a fraction α of its price p_d, while insurance covers the rest. Hence, in the absence of price controls, the firm chooses p_d to maximize profits:

$$p_d = \arg\max_p p \times D(\alpha p) \,. \tag{1}$$

The solution to the problem stated in equation (1) is

$$p_d = -\frac{D(\alpha p_d)}{\alpha D'(\alpha p_d)} \tag{2}$$

Under this structure, the firm earns profits $\Pi(p_d) = p_d \times D(\alpha p_d)$, and will choose to develop the new drug if and only if $\Pi(p_d) \geq C$.

From the point of view of society, however, developing a new drug is optimal only if the total welfare it generates exceeds its development cost. The standard way to measure welfare is as the total consumer surplus generated by all patients that receive it, which can be expressed as the area under the inverse demand curve:

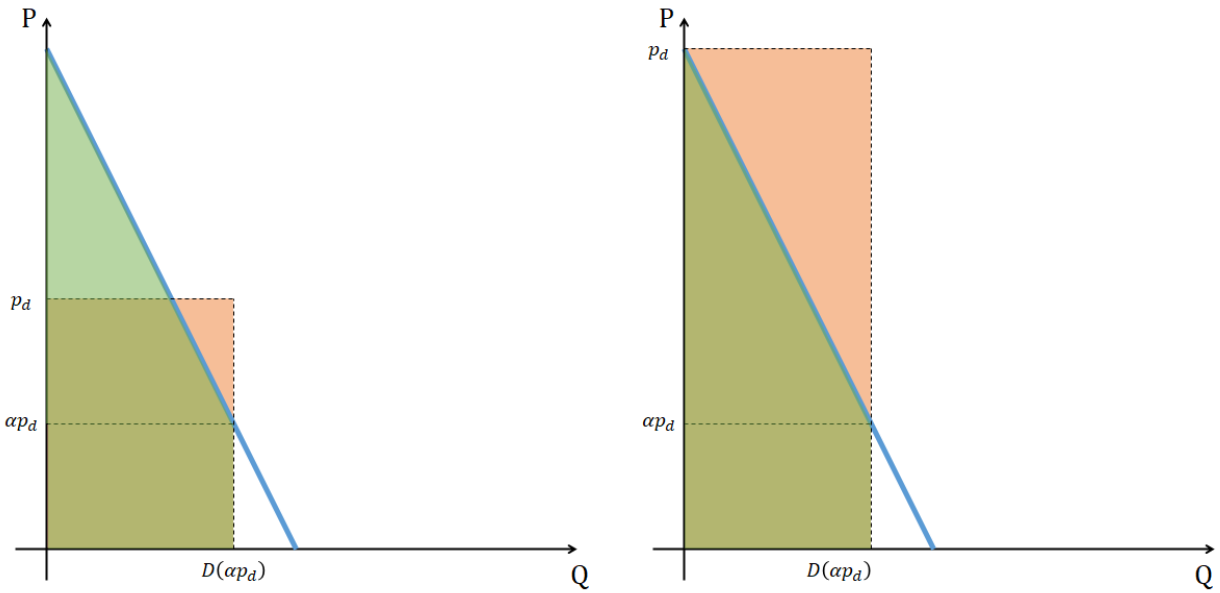
$$W(p_d) = \int_0^{D(\alpha p_d)} D^{-1}(r)\mathrm{d}r.$$

In a market without insurance, patients will only purchase the drug if its price matches or is below its clinical value. Therefore, firms can never set a price above the value of the drug, and profits cannot exceed total welfare. Under these conditions, only drugs whose total welfare exceeds development costs will reach the market. Moreover, because firms generally cannot capture all the consumer surplus they generate, some drugs that should be developed never reach the market.

However, in markets with insurance, firms can charge above value because patients do not bear the entire cost of the drug—a phenomenon called moral hazard. Moral hazard implies that some patients will use drugs whose benefits are eclipsed by their price.

Figure 1 shows an example of what optimal prices, patient choices, welfare, and firm profits could look like under different values of α. In the figure, the green triangle represents consumer surplus that the firm does not capture through profits, while the orange triangle represents the part of firm profits that exceeds consumer surplus, which exists because of moral hazard.

For high values of α (panel A), only a small number of the patients who use the drug receive benefits lower than its price. In this scenario, the drug generates a small net welfare loss from moral hazard but large net welfare gains through residual consumer surplus. Hence, total welfare is greater than firm profits, and developing the drug is optimal from the point of view of society.



A. Optimal price with $\alpha = 0.5$

B. Optimal price with $\alpha = 0.25$

However, for low values of α (panel B), the firm will set a much higher price. As a result, the number of patients for whom the drug price exceeds its benefits can be substantially higher, and firm profits could exceed total welfare. In this situation, firms may greenlight R&D spending for new drugs whose benefits don't justify their development cost.

This misalignment of private incentives and welfare justifies government intervention to impose price caps and realign R&D incentives. However, three caveats must be noted. First, higher-than-optimal prices will occur only if patient cost-sharing is low enough. This may be the case in many countries with universal health insurance, but it will not necessarily happen in all instances. Second, while I have modeled the drug manufacturer as a monopolist—for convenience—in practice, even manufacturers of branded drugs compete with manufacturers of other treatments for patients with similar medical conditions. Competition of this kind, if properly managed, will result in lower prices and mitigate the need for government intervention. Third, even in cases where cost-sharing is very low or non-existent, determining the optimal price is not straightforward. Governments may set prices that are too low, resulting in underinvestment in drug development.

A model of entry and competition among generic manufacturers

A slightly modified version of this model can also provide insights into competition and regulation in markets with generic drugs, where C can now be interpreted as the cost to file a generic drug application plus the cost of setting up a production line. To model competition between generic firms, I extend the model to have multiple firms, each making a simultaneous entry decision. This is followed by a Cournot quantity-setting problem where all firms that decided to enter compete by simultaneously choosing quantities. Prices then adjust in equilibrium.

The problem of the representative firm becomes

$$\max_{q_d} p(q_d, q_{-d}) \times q_d$$

where q_{-d} represents the total quantity produced by its $N-1$ other competitors. For the sake of simplicity and to illustrate how the equilibrium changes with the number of firms, let us assume that demand is linear and of the form $Q(p_d) = A - \alpha B \times p_d$. Then, under the additional assumption that all firms are identical, the equilibrium quantity becomes the well-known Cournot solution:

$$q_d = \frac{A}{N+1}$$

Since each firm produces the same amount, the total quantity is $Q = q_d + q_{-d} = N \times q_d$, and the equilibrium price is $p_d = \frac{A}{\alpha B \times (N+1)}$, and profits for each firm are $\Pi_d = \frac{A^2}{\frac{1}{\alpha B} \times (N+1)^2}$.

The profit function can be used to determine the equilibrium number of firms. Since firms will only enter if they expect to make positive profits, N is pinned down by the condition $\Pi_d \geq C$, which implies

$$N = \frac{A}{\sqrt{C \times \alpha B}} - 1.$$

With this value for N, the equilibrium price would be $p_d = \sqrt{\frac{C}{\alpha B}}$.

If, instead, the government were to impose a price cap $\bar{p} < p_d$, fewer firms would enter the market. To find out how many, I can use the restriction on positive profits again, but this time using the price cap and the total quantity demanded implied by the price cap. The restriction implies

$$\frac{(A - \alpha B \times \bar{p})}{N} \times \bar{p} \geq C$$

or,

$$N = \frac{(A - \alpha B \times \bar{p}) \times \bar{p}}{C}.$$

For values of $\bar{p} \leq \sqrt{\frac{C}{\alpha B}}$, the expression above leads to fewer firms, each producing more units. In a static model, this represents a superior equilibrium: prices are lower, so more patients can access the drug.

However, this simple model does not account for fluctuations and production issues that often affect drug markets. When fewer firms produce the same drug, supply may be slower to react to market changes, such as unexpected surges in demand or plant closures that lead to temporarily reduced supply. This happens because firms need time to adjust production capacity and because lower prices (which imply lower profits from immediately filling the gap in the market) may reduce their incentives to do so in a timely manner. Hence, generic markets with price controls may be more likely to suffer from temporary drug shortages. The takeaway from this model is that government intervention in generic markets can be beneficial if markets are stable, but risky if demand or supply are prone to unexpected fluctuations.

1.2. Empirical evidence on the effect of government intervention on drug prices

The simple model described in the previous section provides both a rationale for government intervention in the pricing of pharmaceutical products and a warning about the potential downsides of overreach. On the one hand, without price caps, moral hazard can lead to higher-than-optimal prices that distort innovation incentives and result in outsized spending for payers. On the other hand, interventions that result in lower-than-optimal prices can lead to underinvestment in innovation and drug shortages.

Impact of government intervention on prices

In markets for branded drugs, the success of price regulation will depend on setting the right price level. Unfortunately, the model cannot provide exact guidance on the optimal level of prices since they depend on primitives—like the total welfare generated by a new drug, the level of coinsurance, and the cost of drug development—which are hard to estimate empirically. As a result, the available empirical evidence is limited to documenting that government intervention generally leads to lower prices without taking a stand on their optimality.

The extent to which government intervention lowers prices, however, is unclear. Early studies by the U.S. General Accounting Office (GAO) found that U.S. drug prices were, on average, 32% higher than in Canada and 60% higher than in the United Kingdom (Comptroller General of the United States 1992). Later works used different methodologies and found much smaller differences in quantity-weighted price indexes across the U.S. and eight other countries (Canada, Germany, France, Italy, Japan, the U.K., Switzerland, and Sweden). However, U.S. prices were still higher than those in non-US countries (Danzon and Kim 1998; Danzon and Chao 2000).

Cross-country comparisons are difficult because not all drugs are sold in all countries, so comparisons must be made on subsets of all available drugs. Moreover, countries differ in many more ways than just government regulation. Countries with different incomes and health needs will naturally pay different prices for the same drug, even under equivalent procurement systems.

In recent years, two papers have exploited within-country variation to document price differences between unregulated markets and markets where the government intervenes in drug procurement. Dubois, Lefouili, and Straub (2021) examine drug procurement rules in several low- and middle-income countries (the Philippines, Serbia, Tunisia, India, Senegal, and South Africa) and find that centralized, government-run procurement systems obtain lower prices than decentralized procurement systems. They exploit both cross-country variation and within-country variation in countries that use multiple procurement systems and find that government procurement leads to a 15% average reduction in price. Levy and Ippolito (2021) examines variation in the prices of branded drugs across various segments of the U.S. market. Interestingly, the lowest U.S. prices are those obtained by the Department of Veterans Affairs (V.A.), which is the only government agency with the ability to negotiate prices directly. The paper finds that V.A. prices were roughly 20% to 30% lower than U.S. commercial prices from 2010 to 2019.

It is also worth mentioning that evidence looking exclusively at generic markets is much more mixed. A recent cross-national comparison of generic prices across the U.S., UK, Canada, and Australia shows that generic drug prices are higher in U.S. markets with four or fewer suppliers, roughly equivalent in markets with five or six suppliers, and lower when the number of suppliers is seven or more (Ganapati and McKibbin, 2023). This suggests that competition may be more effective than the government at keeping prices down when market sizes are large enough to support many suppliers.

Impact of government intervention on access and shortages

A parallel strand of empirical evidence has also long established a relationship between the existence of price regulation and launch delays of new drugs (see, e.g., Kyle 2007; Danzon and Epstein 2012; Cockburn, Lanjouw, and Schankerman 2016). However, the mechanisms that generate this relationship are not usually easy to identify. Some delays may be linked not to the

existence of price regulation itself but rather to the spillover effects that regulation sometimes generates across countries (see, e.g., Ridley, 2005; and Kyle and Ridley, 2007, on the impact of price transparency, or Chaudhuri et al. 2006, on the impact of increased patent protection in India).[2]

A possible direct link between price regulation and launch delays could arise because pharmaceutical markets rely on global suppliers that market the same product in many different countries. In these instances, a capacity-constrained supplier will prioritize entry in markets where prices are higher. In these cases, rather than absolute price levels, it is the price differential across countries that matters. This constraint is why vaccines diffused much faster in higher-income countries during the COVID pandemic when vaccine production struggled to match demand in the months immediately following marketing approval.

Finally, empirical evidence has also suggested that lower prices are associated with more severe and prolonged drug shortages. Yurukoglu, Liebman, and Ridley (2017) show that a price-lowering reform of U.S. drugs administered by physicians in offices and hospitals increased the frequency of drug shortages. They explain the link by arguing that lower markups lead to diminished entry, as well as lower incentives to invest in capacity and production reliability for existing suppliers. In Europe, where shortages are common, such a link has been suggested (see, e.g., Pauwels et al. 2014), though it has not been conclusively proved.

2. Approaches to drug regulation

In the previous section, I introduced a general model to discuss price regulation and its possible role in shaping drug market outcomes. Of course, how a government regulates prices is just as important as deciding whether to use regulation at all. In this section, I present some common approaches to price regulation and discuss what theoretical and empirical evidence suggests about their strengths and shortcomings.

Broadly speaking, one can categorize approaches to drug regulation into two categories. The first category, which I call market-based approaches, consists of exploiting market forces to set prices. Examples of these approaches include procurement auctions (which are primarily relevant for generic drugs) and regulated marketplaces, where drug manufacturers and private payers operate in a competitive environment but must adhere to government-dictated parameters.

The second category, which I call rule-based approaches, consists of setting drug prices through the use of statutory formulas, which are generally not based on competitive forces but instead rely on external data such as measures of value from clinical trials or health technology assessments, or prices of similar products, or from similar markets.

[2] I return to this topic in section 3.2. when discussing reference pricing.

1.1 Market-Based approaches

In most cases, market-based approaches to price regulation consist of setting up government-regulated marketplaces for drug prices. Regulation of this kind can have multiple goals. In most cases, governments use regulation to promote competition among firms to reduce prices and spending. In other instances, however, the main objective might be to ensure that patients receive a minimum level of coverage.

In Europe, regulated marketplaces are most prominently used in the procurement of generic drugs. These auctions are usually run separately at the product level, where a product is defined as the specific combination of active ingredient (or molecule), strength, form of administration (e.g., pill vs. injection), and sometimes even package size. Manufacturers submit bids for each pay period, and the firm with the lowest bid is granted preferred status throughout the pay period. Preferred status usually entails mandatory dispensing of the manufacturer's product at the pharmacy unless the product is out of stock or the physician explicitly requests a different manufacturer's product.

While auctions are an effective way to promote price competition, the scope of drug procurement auctions is limited for three reasons. First, auctions can only be effective in the procurement of generics because branded drugs are not necessarily substitutable with one another. Conferring preferred status to a different branded drug in each period can significantly disrupt patient care.

Second, the repeated nature of these auctions can lead firms to adopt dynamic bidding strategies that can push equilibrium prices away from the optimal static equilibrium—occasionally even veering into tacit collusion territory. Janssen (2022) looks at evidence of this behavior in Swedish procurement auctions for generic drugs. The paper focuses on markets with three or fewer bidders and documents the existence of price cycles consisting of alternating bids, where firms take turns submitting a high bid and a low bid in consecutive periods. Under a model where patients exhibit a degree of inertia and are, therefore, slow to switch products, alternating bids allow manufacturers to retain a fraction of consumers when they lose the auction and extract higher profits from them.

Third, the auction structure generates significant demand uncertainty for participating firms. To bid effectively, firms must have enough capacity to fulfill demand if they win the auction. However, expanding capacity can be damaging if the firm does not win the auction. To account for the fact that the winning firm may not have the capacity to supply the entire market, auctions usually allow other bidders to participate in the market, selling at the higher price they bid. While this ensures a steady supply of each product, it also diminishes the competitive incentives that firms face. Consistent with this idea, Hauschultz and Munk-Nielsen (2020) document the existence of price cycles in Danish generic drug procurement auctions. Their evidence shows that the winning bid in many markets follows repeating cycles of significant and sudden price hikes followed by a slow undercutting phase. They argue that firms may face a trade-off between low pricing and winning a large fraction of the market, and pricing high and earning a higher markup from a smaller fraction of patients. When the winning bid

becomes too low, many firms will switch to submitting high bids, leading to an upward shift in the equilibrium winning bid and restarting the cycle.

Given this evidence, it might be tempting to dismiss procurement auctions as a regulatory mechanism and instead let generic manufacturers compete in an unregulated setting. After all, the previously mentioned evidence from (Ganapati and McKibbin 2023) suggests this approach works well enough in the United States. However, there are limitations to this approach as well. In the early 2010s, several papers pointed out that U.S. generic prices had been growing, reversing a secular trend going back to the 1980s (see, e.g., Berndt, Conti, and Murphy 2017). It was later discovered that collusion between a few firms had significantly contributed to this trend change. Recent estimates suggest that collusion between U.S. generic manufacturers led to an average price increase of up to 166% in affected markets and contributed between $5 and $12 billion in excess drug spending between 2013 and 2015 (Clark et al. 2022; Cuddy 2020; Starc and Wollmann 2025).

Occasionally, regulated marketplaces also impose restrictions on what private insurance providers must cover. For example, in Medicare Part D—a privately administered, government-subsidized prescription drug insurance market for adults over 65 in the United States—insurance providers are required to cover all drugs in six protected drug classes of essential medications (antidepressants, antipsychotics, anticonvulsants, immunosuppressants for treatment of transplant rejection, antineoplastics, and antiretrovirals). This kind of regulation, which is meant to protect patients, can have a negative impact on spending. Under normal circumstances, insurance providers would negotiate prices with drug manufacturers and be able to extract price concessions by threatening a drug with coverage exclusion. Coverage mandates eliminate this threat and put outsized bargaining power in the hands of the manufacturer, leading to higher prices. Recent empirical evidence confirms this intuition by showing that the introduction of Medicare Part D led to higher spending in protected classes relative to non-protected classes (Yarbrough 2020).

I conclude this section by mentioning another mechanism that can be considered market-based: direct government negotiations. Importantly, I distinguish between a rule-based government-set price (which I will discuss in the next section) and a government-led negotiation. In the latter case, the government relies on a negotiating unit that essentially plays the role of the private payer in a business-to-business transaction. The main difference is that the government is the sole procurer of drugs for the entire market (or for a specific market segment) and, therefore, can wield significant bargaining power and extract much lower prices than a private payer. This distinction is occasionally hard to see in practice because most governments that negotiate drug prices also rely on rule-based approaches (for example, Italy negotiates the price of drugs but also often relies on External Reference Pricing). As a result, it is often hard to disentangle the role of government negotiations from that of the rules used as part of the negotiation. Nonetheless, the distinction is important. For example, the U.S. government regulates drug prices using formulas that closely resemble European reference pricing rules. However, the price that the government references is negotiated by several decentralized

payers, which usually results in higher benchmarks than their European counterparts. In this case, the reason prices are higher in the U.S. is not necessarily the lack of regulation but rather the fact that the government is precluded from negotiating.

1.2 Rule-based approaches to drug regulation

In contrast to market-based approaches, rule-based approaches to price regulation consist of setting price caps constructed using formulas or models. Conceptually, the main difference with market-based approaches is that in market-based approaches, prices are not fixed but set in a competitive bargaining equilibrium. In regulated marketplaces, firms still compete against one another, albeit in an environment with additional government-imposed constraints. In the case of direct negotiations, firms negotiate against the government, but the outcome still reflects a competitive bargaining equilibrium, with a final price that—at least in theory—should reflect competitive forces such as the value of a drug and the availability of alternative treatments. Conversely, prices set through rule-based regulation generally do not reflect competitive equilibria, though they often try to approximate them by using data on primitives that affect equilibria, like drug value or cost. However, rules often use partial data, which implies that different rules will be appropriate in different contexts. For example, cost-plus regulation does not consider the added benefits generated by a drug and usually best approximates equilibria in generic markets, where firms compete aggressively on price and earn very thin margins regardless of drug value.

Most governments use some rule to set prices, or at least as an informative criterion in the price-setting process. I distinguish between two broad groups of rules. The first group of rules consists of setting prices based on cost or clinical value data. The second group of rules consists of using the prices in other markets.

3.1 Rules based on cost or value data

One of the complications in pricing new drugs is that when a drug first arrives on the market, there is relatively scant information about its clinical value. Clinical trials used for approval provide an unbiased estimate of effectiveness but are conducted under ideal conditions, with patient monitoring ensuring perfect adherence. Moreover, the sample size of most clinical trials is usually too small to reliably identify side effects.

To learn more about a drug's value, many governments conduct more sophisticated evaluations of clinical trial data (often called Health Technology Assessments, or HTAs) before approving a drug for reimbursement. Sometimes, HTAs are used to determine the cost of a drug to a patient. Drugs that represent a significant improvement over existing therapies will receive lower copays, while drugs that don't offer substantial additional benefits will be placed in more expensive reimbursement tiers.

Occasionally, HTAs form the basis of drug pricing as well. The most prominent example is the value-based pricing approach used by the National Institute for Health and Care Excellence

(NICE) in the U.K. NICE conducts cost-effectiveness analyses that estimate the incremental value of new drugs from clinical trial data and statistical models of disease progression in a population. This value is then converted to a monetary figure by applying a conversion rate between Quality-Adjusted Life Years (QALYs, the unit of measure for drug value) and pounds. In most instances, NICE uses £30,000 as the conversion rate (Devlin and Parkin 2004; McCabe et al. 2008; Dakin et al. 2015).

Other European countries, like France, also use this approach in conjunction with other rules. The idea of using value-based pricing has also been raised in the United States, where a private company called ICER (Institute for Clinical and Economic Review) runs evaluations of new drugs similar to those of NICE (Institute for Clinical and Economic Review 2020). However, no formal attempt at introducing value-based pricing has yet been put forward by the government.

Cost-based regulation for pharmaceutical products is less common because the marginal cost of production of drugs is often minimal, so cost-based regulation would drastically reduce prices and cut into profits, ultimately harming R&D incentives. The approach could work for generic drugs, however. India used cost as a basis for the price of essential medications until 2013 (Motkuri and Mishra 2020). In the U.S., a recently founded online retailer of generic drugs uses cost-plus pricing to set prices, and researchers have argued that this strategy could lead to considerable savings if it were adopted by the government as well (Lalani, Kesselheim, and Rome, 2022). Finally, cost-plus regulation has been recently proposed in the U.S. as a solution for bringing down the price of biologic drugs by researchers and policymakers who do not believe biosimilars to be a viable mechanism for competition (Trusheim et al. 2019).

Three caveats apply to regulation based on value or cost data. First, these rules require a lot of data and sophisticated modeling to develop a reasonable benchmark. This is especially true of value-based approaches, which should ideally include considerations such as long-term savings from early interventions and offsets from alternative care.

Second, the accuracy of the resulting benchmark will inevitably depend on the accuracy of the data. This can be problematic for drugs that have just been approved, where the only available data comes from clinical trials. While most clinical trials generally provide a reasonable estimate of efficacy, their limited sample size usually implies that safety data is less accurate. Moreover, there are at least three reasons to believe clinical trials may misrepresent real-world outcomes (Rothwell 2005). First, patients in clinical trials are monitored to ensure perfect adherence, whereas patients often skip doses in the real world. Evidence from diabetes drugs shows that partial adherence can lead to a significant drop in the effectiveness of drugs (Carls et al. 2017). Second, patients who select into clinical trials may not be a representative sample. Drug manufacturers often exclude at-risk populations, like children and pregnant women. Moreover, evidence shows that the composition of clinical trial patients is often different from the composition of the population as a whole, both because some demographic segments are harder to recruit (Alsan et al. 2024) and because patients who select into clinical trials may have specific

disease characteristics (Hamilton et al., 2023). Third, the availability of drugs may lead to behavioral changes in the real world but not in clinical trials, where patient behavior is monitored. In some instances, e.g., with drugs that treat or prevent infectious diseases, behavioral changes may spill over to populations that do not use the treatment. For example, recent evidence on the introduction of PrEP in the U.S. (a method to prevent HIV infection with a nearly 100% success rate) shows no evidence of a decline in HIV infection rates and argues that this is due to an increase in risky behavior by individuals who do not use the drug (Beheshti et al. 2025).

Finally, these approaches tend to impose additional costs on pharmaceutical companies, both in terms of information disclosure requirements and because governments often require data specific to their population, which implies the need to run additional clinical trials.

3.2 Rules based on external benchmarks

A second approach to price regulation involves using external benchmarks based on market outcomes—almost always observed prices in other markets. This class of rules is usually called reference pricing.

The most commonly applied form of reference pricing around the world is External (or International) Reference Pricing (ERP), which is the practice of using a drug's price abroad to determine a price cap or a benchmark for further negotiations. In contrast to value-based rules, the appeal of reference pricing is often its simplicity. However, ERP also carries a high potential for market distortion. Prices are endogenous equilibrium outcomes. Therefore, rules that reference those prices will affect them by distorting the incentives of the firms that set them. In particular, firms will be incentivized to increase prices in lower-income markets and sometimes even delay the introduction of new drugs to minimize the effect of reference pricing from higher-income countries.

Mounting empirical evidence shows that the distortions generated by reference pricing can be immense. Maini and Pammolli (2023) show that ERP rules result in up to a year of additional delay in the introduction of novel drugs in lower-income European countries. Moreover, while ERP is usually justified as a cost-saving measure, it is not clear that it is particularly effective at achieving this goal. Dubois, Gandhi, and Vasserman (2022) simulate U.S. adoption of reference pricing with Canada and find that the policy would lead to negligible savings, instead resulting in significantly higher prices in Canada.

In the U.S., both Medicare Part B and Medicaid rely on formulas that reference U.S. commercial prices to set reimbursements for drugs prescribed to their beneficiaries. These formulas closely resemble ERP rules in place outside the U.S. Research on U.S. reference rules confirms the results obtained with European data. Extensive research on Medicaid—a program that covers low-income Americans— and Medicare—which covers Americans over 65—repeatedly shows that drug manufacturers respond to drug reimbursement rules by adjusting their pricing

strategy, ultimately leading to higher prices for U.S. non-government payers (Scott Morton 1997; Duggan and Scott Morton 2006; Ridley and Lee 2020; Feng et al. 2023).

3. Conclusion: Is there a one-size-fits-all approach?

Regulation must weigh different incentives, and there is likely no one-size-fits-all approach that will work for all drugs and all countries. As governments weigh which approach fits their needs best, there are two considerations that they should take into account.

First, lower prices can improve access to existing drugs and ease the burden on government spending, but may hurt dynamic incentives to develop new molecules and lower manufacturers' incentives to scale up capacity, increasing the likelihood of drug shortages. The balance of these two forces will depend on each government's objectives and the types of drugs being regulated. Since innovation is undertaken primarily with profits from high-income countries in mind, lower prices in low- and middle-income countries (LMICs) will probably have a secondary effect on innovation unless higher-income countries reference them through a mechanism such as ERP. Higher-income countries also usually have higher budgets, which allow them to absorb higher spending while providing drugs to patients at favorable cost-sharing rates, mitigating the negative effect of high prices on access.

There are exceptions, though. Recently, the introduction of a new generation of Hep-C drugs, like Sovaldi and Harvoni, put a heavy strain on the budget of even the wealthiest nations due to a relatively rare combination of a high price tag and a large eligible population. A peculiarity of the new generation Hep-C drugs is that their high price was justified by clinical value and savings that would be realized over several years.

Managing spending on high-cost, high-efficacy drugs will be a crucial challenge as a wave of revolutionary gene therapies emerges from the R&D pipelines and reaches the market. As these therapies represent cures for previously untreatable hereditary conditions, they will be both expensive and highly effective. Healthcare systems worldwide, especially in high-income countries, must figure out how to balance access to these therapies with price tags that provide the correct incentives for future innovation.

A potential solution lies in innovative contract solutions. For example, in the case of high-cost Hep-C drugs, governments could have delayed payment over several years by diluting the payment over time. Alternatively, they could have signed a flat fee contract where firms are not paid based on quantity supplied (see, e.g., Auty, Shafer, and Griffith 2021, on a subscription contract signed by the state of Louisiana with Asegua Therapeutics).

The second consideration is the trade-off between price-setting rules based on objective benchmarks and reference pricing regulation that could generate costly spillovers across markets.

The main downside of objective benchmarks lies in the difficulty of assessing a drug's value. An accurate measurement of a drug's value would incorporate its clinical benefits and any spillover effects on other related healthcare costs (such as savings from reduced hospitalizations). These evaluations can be complicated and costly, which creates an incentive for governments to simply copy prices in other markets. However, doing so changes the strategic incentives of firms and often leads to unwanted consequences in the form of higher prices and delayed launches in referenced markets.

These negative effects are most prominent when high-income countries reference the price in low-income countries. When reference pricing leads to higher prices, this will damage vulnerable patients who struggle to access the drug. When reference pricing leads to delays, the damage is even greater. Not only will patients be unable to access the drug, but manufacturers will also lose revenue, which in turn can negatively impact innovation incentives.

The presence of these damaging spillovers, coupled with the fact that high-income countries generally have the capability and resources to evaluate drugs objectively, suggests that these policies should be abandoned, except maybe in the case of low-income countries referencing high-income countries. While this type of reference can also create negative spillovers, these spillovers will be small. For example, if a lower-income European country like Romania referenced the price in a high-income country like Germany, drug manufacturers would still be incentivized to increase the price in Germany to extract some extra surplus from Romania. However, this incentive is likely negligible since Romania (and lower-income countries in general) represents a small fraction of a company's sales. Hence, reference pricing can be a useful shortcut to price setting that saves valuable resources for lower-income countries without the ability to evaluate drugs.

References

Alsan, Marcella, Maya Durvasula, Harsh Gupta, Joshua Schwartzstein, and Heidi Williams. 2024. "Representation and Extrapolation: Evidence from Clinical Trials." *The Quarterly Journal of Economics* 139 (1): 575–635. https://doi.org/10.1093/qje/qjad036.

Auty, Samantha G., Paul R. Shafer, and Kevin N. Griffith. 2021. "Medicaid Subscription-Based Payment Models and Implications for Access to Hepatitis C Medications." *JAMA Health Forum* 2 (8): e212291. https://doi.org/10.1001/jamahealthforum.2021.2291.

Baicker, Katherine, Sendhil Mullainathan, and Joshua Schwartzstein. 2015. "Behavioral Hazard in Health Insurance." *The Quarterly Journal of Economics* 130 (4): 1623–67. https://doi.org/10.1093/qje/qjv029.

Beheshti, David, Johnny Huynh, and Eilam Nir. 2025. "Why Doesn't Clinical Efficacy Translate into Real-World Impact? Evidence from PrEP." Unpublished manuscript.

Berndt, Ernst R., Rena M. Conti, and Stephen J. Murphy. 2017. "The Landscape of US Generic Prescription Drug Markets, 2004-2016." Working Paper 23640. Working Paper Series. National Bureau of Economic Research, July. https://doi.org/10.3386/w23640.

Carls, Ginger S., Edward Tuttle, Ruo-Ding Tan, et al. 2017. "Understanding the Gap Between Efficacy in Randomized Controlled Trials and Effectiveness in Real-World Use of GLP-1 RA and DPP-4 Therapies in Patients With Type 2 Diabetes." *Diabetes Care* 40 (11): 1469–78. https://doi.org/10.2337/dc16-2725.

Chaudhuri, Shubham, Pinelopi K. Goldberg, and Panle Jia. 2006. "Estimating the Effects of Global Patent Protection in Pharmaceuticals: A Case Study of Quinolones in India." *American Economic Review* 96 (5): 1477–514. https://doi.org/10.1257/aer.96.5.1477.

Clark, Robert, Christopher Fabiilli, and Laura Lasio. 2022. "Collusion in the US Generic Drug Industry." *International Journal of Industrial Organization* 85: 102878. https://doi.org/10.1016/j.ijindorg.2022.102878.

Cockburn, Iain M., Jean O. Lanjouw, and Mark Schankerman. 2016. "Patents and the Global Diffusion of New Drugs." *American Economic Review* 106 (1): 136–64. https://doi.org/10.1257/aer.20141482.

Comptroller General of the United States. 1992. *Prescription Drugs: Companies Typically Charge More in the United States than in Canada*. GAO/HRD-92-110. General Accounting Office. Washington, DC.: U.S.

Crawford, Gregory S., and Matthew Shum. 2005. "Uncertainty and Learning in Pharmaceutical Demand." *Econometrica* 73 (4): 1137–73. https://doi.org/10.1111/j.1468-0262.2005.00612.x.

Cuddy, Emily. 2020. "Competition and Collusion in the Generic Drug Market." Unpublished manuscript.

Dakin, Helen, Nancy Devlin, Yan Feng, Nigel Rice, Phill O'Neill, and David Parkin. 2015. "The Influence of Cost-Effectiveness and Other Factors on Nice Decisions." *Health Economics* 24 (10): 1256–71. https://doi.org/10.1002/hec.3086.

Danzon, Patricia M., and Li-Wei Chao. 2000. "Cross-National Price Differences for Pharmaceuticals: How Large, and Why?" *Journal of Health Economics* 19 (2): 159–95. https://doi.org/10.1016/S0167-6296(99)00039-9.

Danzon, Patricia M., and Andrew J. Epstein. 2012. "Effects of Regulation on Drug Launch and Pricing in Interdependent Markets." *Advances in Health Economics and Health Services Research* 23: 35–71. http://www.nber.org/papers/w14041.pdf.

Danzon, Patricia M., and J. D. Kim. 1998. "International Price Comparisons for Pharmaceuticals. Measurement and Policy Issues." *PharmacoEconomics* 14 Suppl 1: 115–28. https://doi.org/10.2165/00019053-199814001-00014.

Devlin, Nancy, and David Parkin. 2004. "Does NICE Have a Cost-Effectiveness Threshold and What Other Factors Influence Its Decisions? A Binary Choice Analysis." *Health Economics* 13 (5): 437–52. https://doi.org/10.1002/hec.864.

Dickstein, Michael. 2017. *Physician vs. Patient Incentives in Prescription Drug Choice*.

Dubois, Pierre, Ashvin Gandhi, and Shoshana Vasserman. 2022. "Bargaining and International Reference Pricing in the Pharmaceutical Industry." Working Paper 30053. Working Paper Series. National Bureau of Economic Research, May. https://doi.org/10.3386/w30053.

Dubois, Pierre, Yassine Lefouili, and Stéphane Straub. 2021. "Pooled Procurement of Drugs in Low and Middle Income Countries." *European Economic Review* 132 (February): 103655. https://doi.org/10.1016/j.euroecorev.2021.103655.

Duggan, Mark, and Fiona M. Scott Morton. 2006. "The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing." *Quarterly Journal of Economics* 121 (1): 1–30. https://doi.org/10.1162/qjec.2006.121.1.1.

Feng, Josh, Thomas Hwang, and Luca Maini. 2023. "Profiting from Most-Favored Customer Procurement Rules: Evidence from Medicaid." *American Economic Journal: Economic Policy* 15 (2): 166–97.

Ganapati, Sharat, and Rebecca McKibbin. 2023. "Markups and Fixed Costs in Generic and Off-Patent Pharmaceutical Markets." *The Review of Economics and Statistics* 105 (6): 1606–14. https://doi.org/10.1162/rest_a_01130.

Hamilton, Bart, Brian McManus, Juan Pantano, and Justin Trogdon. 2023. *Dynamic Treatment Choices and Selection into RCTs: Evidence from Prostate Cancer*.

Hauschultz, Frederik Plum, and Anders Munk-Nielsen. 2020. "Markups on Drop-Downs: Prominence in Pharmaceutical Markets∗." MPRA Paper. December 1. https://mpra.ub.uni-muenchen.de/104582/.

Institute for Clinical and Economic Review. 2020. *A Guide to ICER's Methods for Health Technology Assessment*. https://icer.org/wp-content/uploads/2021/01/ICER_HTA_Guide_102720.pdf.

Janssen, Aljoscha. 2022. "Price Dynamics of Swedish Pharmaceuticals." *Quantitative Marketing and Economics* 20 (4): 313–51. https://doi.org/10.1007/s11129-022-09257-2.

Kyle, Margaret K. 2007. "Pharmaceutical Price Controls and Entry Strategies." *Review of Economics and Statistics* 89 (February): 88–99. https://doi.org/10.1162/rest.89.1.88.

Kyle, Margaret K., and David B. Ridley. 2007. "Would Greater Transparency And Uniformity Of Health Care Prices Benefit Poor Patients?" *Health Affairs* 26 (5): 1384–91. https://doi.org/10.1377/hlthaff.26.5.1384.

Lalani, Hussain S., Aaron S. Kesselheim, and Benjamin N. Rome. 2022. "Potential Medicare Part D Savings on Generic Drugs From the Mark Cuban Cost Plus Drug Company." *Annals of Internal Medicine* 175 (7): 1053–55. https://doi.org/10.7326/M22-0756.

Levy, Joseph, and Benedic Ippolito. 2021. "Branded Price Variation in the United States Drug Market, 2010 to 2019." *Value in Health* 24 (9): 1237–40. https://doi.org/10.1016/j.jval.2021.04.1272.

Maini, Luca, and Fabio Pammolli. 2023. "Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market." *American Economic Journal: Microeconomics* 15 (2): 345–83. https://doi.org/10.1257/mic.20210053.

McCabe, Christopher, Karl Claxton, and Anthony J. Culyer. 2008. "The NICE Cost-Effectiveness Threshold: What It Is and What That Means." *PharmacoEconomics* (New Zealand) 26 (9): 733–44. https://doi.org/10.2165/00019053-200826090-00004.

Motkuri, Venkatanarayana, and Rudra Narayan Mishra. 2020. "Pharmaceutical Market and Drug Price Policy in India." *Review of Development and Change* 25 (1): 30–53. https://doi.org/10.1177/0972266120929146.

Pauwels, Kim, Isabelle Huys, Minne Casteels, and Steven Simoens. 2014. "Drug Shortages in European Countries: A Trade-off between Market Attractiveness and Cost Containment?" *BMC Health Services Research* 14 (1): 438. https://doi.org/10.1186/1472-6963-14-438.

Ridley, David B. 2005. "Price Differentiation and Transparency in the Global Pharmaceutical Marketplace." *PharmacoEconomics* 23 (7): 651–58. https://doi.org/10.2165/00019053-200523070-00002.

Ridley, David B., and Chung-Ying Lee. 2020. "Does Medicare Reimbursement Drive Up Drug Launch Prices?" *The Review of Economics and Statistics* 102 (5): 980–93. https://doi.org/10.1162/rest_a_00849.

Rothwell, Peter M. 2005. "External Validity of Randomised Controlled Trials: 'To Whom Do the Results of This Trial Apply?'" *Lancet (London, England)* 365 (9453): 82–93. https://doi.org/10.1016/S0140-6736(04)17670-8.

Scott Morton, Fiona M. 1997. "The Interaction between a Most-Favored-Customer Clause and Price Dispersion: An Empirical Examination of the Medicaid Rebate Rules of 1990." *Journal of Economics & Management Strategy* 6 (1): 151–74. https://doi.org/10.1111/j.1430-9134.1997.00151.x.

Starc, Amanda, and Thomas G. Wollmann. 2025. "Does Entry Remedy Collusion? Evidence from the Generic Prescription Drug Cartel." *American Economic Review* 115 (5): 1400–1438. https://doi.org/10.1257/aer.20220276.

Trusheim, Mark R., Preston Atteberry, Jennifer A. Ohn, and Peter B. Bach. 2019. "Biologics Are Natural Monopolies (Part 2): A Proposal For Post- Exclusivity Price Regulation Of Biologics." *Health Affairs Forefront (Blog)*, April 15. https://www.healthaffairs.org/do/10.1377/forefront.20190405.839549/full/.

Yarbrough, Courtney R. 2020. "How Protected Classes in Medicare Part D Influence U.S. Drug Sales, Utilization, and Price." *Health Economics* 29 (5): 608–23. https://doi.org/10.1002/hec.4006.

Yurukoglu, Ali, Eli Liebman, and David B. Ridley. 2017. "The Role of Government Reimbursement in Drug Shortages." *American Economic Journal: Economic Policy* 9 (2): 348–82. https://doi.org/10.1257/pol.20160035.