Regulation of Price and Reimbursement for Pharmaceuticals

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Abstract and Keywords

This article reviews, first, the rationale for price regulation of on-patent pharmaceuticals and then models of optimal regulatory structure. It then describes the main regulatory prototypes for on-patent drugs and the empirical evidence on their effects. This is followed by a review of regulatory and reimbursement regimes for generics and evidence of their effects. Finally, international regulation of promotion is addressed. The concluding section reviews major unanswered research questions.

Keywords: price regulation, on-patent pharmaceuticals, drug price, regulatory structure, reimbursement regulation, generic drugs, promotion

MOST industrialized countries have a comprehensive national or social health insurance system that covers pharmaceuticals with at most modest consumer cost-sharing. In such contexts, price regulation is best understood as a response by public insurers to “supplier moral hazard,” that is, the tendency for insurance to lead to higher prices. When consumers are heavily insured, producers of patented products face highly inelastic demand and hence incentives to charge higher prices than would occur in the absence of insurance, unless payers intervene. Physician prescribers, acting as good agents for patients, are also indifferent to prices unless they are at risk for the cost of the drugs they prescribe, but this is a blunt instrument and is rarely used. In such contexts, regulation of prices and other reimbursement controls are in theory a potentially efficient response by payers to insurance-induced producer moral hazard, which can lead to excessive prices, excessive costs of insurance, and excessive investment in research and development (R&D) compared with levels that would result from patents alone.[1]

Payer concern to control drug prices also reflects the desire to make drugs widely available to patients at a cost that is affordable to government budgets (p. 267) and ultimately to taxpayers. Given the cost structure of pharmaceuticals, which includes high globally joint, sunk costs of R&D and production capacity and relatively low country-specific marginal costs, governments have incentives to seek to pay prices that are sufficient to cover only their country-specific costs, free-riding on other countries to pay the joint costs of R&D. Such strategies may be rational for all countries in the short term, because any negative effects on the supply of new drugs take years to emerge and are hard to attribute to specific countries or policies. Even in the long term, countries that account for only a small fraction of global demand may rationally seek to pay prices sufficient to cover only their country-specific costs, since their behavior has minimal effect on global R&D incentives. How actual regulation strategies and resulting price levels reflect welfare-enhancing attempts to constrain insurance-induced moral hazard versus free-rider incentives to pay only marginal costs is an important question.[2]

Pharmaceutical prices are also regulated in some middle- and lower-income countries (MLICs) that lack comprehensive insurance and its price-increasing effects. Such countries may regulate prices as part of an industrial policy to control imported products and encourage domestic production or local firms. Governments also regulate prices to make drugs more affordable to their citizens. In the absence of regulation, drug prices tend to be high relative to per capita income in MLICs, for several reasons. First, multinational companies may be concerned that charging low prices in lower-income countries may undermine prices in higher-income countries through parallel trade and external referencing. Second, highly skewed income distributions in many MLICs may contribute to high prices relative to average per capita income (Flynn et al. 2009). Third, weak regulation of product quality contributes to competition on brand and undermines price competition (Danzon et al. 2011a). The practical effects and welfare implications of price regulation in self-pay markets are not addressed here but are important issues for future research.

Although price/reimbursement regulation can potentially be welfare enhancing in the context of insurance-induced inelastic demand interacting with patents, the optimal structure of such regulation is not simple. Optimal insurance protection and optimal price/reimbursement regulation for drugs should ideally assure appropriate financial protection and drug use for patients while constraining pricing moral hazard by firms and providing incentives for R&D that are consistent with dynamic efficiency. In practice, price regulatory regimes differ across countries but typically use one or both of two criteria for setting prices. First, “internal referencing” sets as benchmarks for new drug prices the prices of similar products in the same country, with possible mark-ups for superior efficacy, safety, or convenience. Reference price reimbursement (which sets a uniform reimbursement for all products in designated categories) and indirect price regulation through requirements to meet cost-effectiveness thresholds can be viewed as special cases (p. 268) of internal referencing. Second, “external referencing” (also called international referencing) sets as benchmarks the prices of the same product in other countries and includes most-favored-nation requirements as a special case. As discussed

later, the internal referencing approach, implemented indirectly through limits on the allowable incremental cost-effectiveness ratio (ICER), can be designed to achieve price levels that appropriately reward innovation and reflect each country's willingness to pay individually and collectively across countries; external referencing, in contrast, tends to undermine appropriate price differences and is not structured to achieve static or dynamic efficiency.

Whereas pricing of on-patent and originator (research-based, potentially patentable) drugs has been the focus of most regulation and most academic studies of regulation, the growing share of generics in pharmaceutical consumption has focused attention on appropriate regulatory regimes to promote generic entry, uptake, and pricing once patents expire. Generics are unpatented and in most industrialized countries are required by regulation to be bioequivalent to the originator product. In theory, competition should drive prices down to marginal cost and this would be efficient. The literature on generics in the United States (Grabowski and Vernon 1992; Frank and Salkever 1992, 1997; Saha et al. 2006) shows that generic entry and uptake are rapid, and aggressive price competition assures low prices. By contrast, generic entry and uptake have traditionally been slower and generic prices higher in many other countries, including those that regulate generic and originator prices (Danzon and Chao 2000; Danzon and Furukawa 2005, 2008). Several major industrialized countries have recently changed their regulatory systems to promote generics. Analyses of these changes provide valuable evidence and increase our understanding of the effects of different regulatory and reimbursement rules for off-patent pharmaceuticals (see Danzon and Furukawa 2011 and references therein).

This chapter, reviews, first, the rationale for price regulation of on-patent pharmaceuticals and then models of optimal regulatory structure. The next section describes the main regulatory prototypes for on-patent drugs and the empirical evidence on their effects. This is followed by a review of regulatory and reimbursement regimes for generics and evidence of their effects. Finally, international regulation of promotion is addressed. The concluding section reviews major unanswered research questions.

The Economic Rationale for Price and Reimbursement Regulation

Regulation of pharmaceutical prices is a priori anomalous, from the perspective of standard industrial economics, because the pharmaceutical industry is structurally competitive. Patents, which are the main source of market power, are a (p. 269) government-granted protection against copies for a limited term; they are intended to permit pricing above marginal cost in order to recoup R&D investment. Moreover, on-patent compounds usually face competition from other, differentiated but similar compounds to treat the same condition. An innovative product in a new therapeutic class

may experience some period as a sole-in-class supplier, but such exclusivity periods have shrunk over time, because the rapid diffusion of scientific knowledge has eroded first-mover advantages in R&D and multiple firms typically race to enter new classes.[3] Concentration within the industry is relatively low overall. Although concentration within specific therapeutic categories is greater, the market is contestable, as evidenced by the continual formation of new firms and the growing share of new products discovered by relatively recent entrants to the industry. Therefore natural or patent-based monopoly is not a sufficient rationale for regulation of drug prices.[4]

Two features of pharmaceutical markets potentially exacerbate the market power granted by patents. First, if physician prescribers are uninformed about drug prices and are not themselves at risk or otherwise motivated to be cost conscious, their demand may be price inelastic. But if consumers were price sensitive, then physicians as their agents would have reason to also be price sensitive. Second, and more fundamentally, extensive insurance coverage undermines consumer price sensitivity, such that neither patients nor physicians acting as their agents have incentives to be price sensitive. By making the demand facing manufacturers highly inelastic, insurance creates incentives for higher prices than would result from patents alone, in the absence of payer controls. Patient co-payments can mitigate the insurance effect, but because co-payments reduce financial protection and may discourage appropriate drug use, in practice most public and private insurance plans include only very modest co-payments, often unrelated to the price of the drug and with a catastrophic limit on the patient's annual out-of-pocket spending.[5]

To counteract this price-increasing tendency of insurance, both private and public insurers limit the prices that they pay for all insured services including drugs, physician visits, and hospital visits. In the United States, private insurers or pharmacy benefit managers negotiate discounts off manufacturer list prices (p. 270) as a condition of preferred formulary placement, which increases the elasticity of demand. Among public insurers, Medicare Part D is implemented by private plans and uses similar negotiated discounts, while Medicaid, the Veteran's Administration, and other federal programs mandate discounts off list prices (see chapter 8). However, list prices are unconstrained, which plausibly contributes to the relatively high drug prices, including higher post-launch price increases, in the United States compared with other countries.

In contrast to the United States, most other industrialized countries have either a universal national health insurance scheme or a system of mandatory, regulated social insurance funds. Such national or social insurance systems control reimbursed prices for all covered services, including physician and hospital services as well as drugs, in order to control supplier moral hazard. Consistent with this view of pharmaceutical price regulation as an insurance strategy to control supplier moral hazard, price regulation in most countries applies only to drugs that are reimbursed by the public health plan. A drug may be marketed without getting price approval (once registration requirements are met) if the manufacturer does not seek insurance coverage for the drug. The fact that manufacturers rarely choose to price freely and thereby forego reimbursement for their

drugs confirms that expected profits are higher with insurance coverage and regulated prices, compared to free pricing without reimbursement.

In addition to the price-increasing effect, insurance also incentivizes promotion, because price-cost margins tend to be higher on insured products and patients and physicians have incentives to use more drugs or unnecessarily expensive drugs in the absence of payer constraints. Many countries therefore supplement their price controls with controls on total pharmaceutical expenditures ("drug budgets"), implemented by various mechanisms, that constrain utilization volume and penalize above-target manufacturer promotion or above-target physician prescribing. Therefore, although price and reimbursement regulation is initially focused on supply and constrains reimbursed prices, implementation often includes demand-focused strategies to constrain volume.

Theory of Optimal Price and Reimbursement Regulation

Models of optimal price regulation presuppose certain assumptions about manufacturer pricing strategies. These are discussed first, before the models of optimal regulation are presented.

(p. 271) Manufacturer Pricing Incentives

Assuming that on-patent products have some market power due to the interaction of patents and third-party payment, simple models of monopoly pricing predict that, in the absence of constraints, firms will set prices based inversely on demand elasticity and will price discriminate between markets that differ in elasticity if segmentation is feasible. Most industrialized countries with national health insurance systems permit only one price within the country, making the country the natural unit for market segmentation and price discrimination.

International trade in on-patent drugs is constrained by market access regulations and, in some countries, by the traditional patent rule of "national exhaustion" of patent rights, which authorizes a patent holder to block importation of a patented product by an unlicensed third party. In theory, under national exhaustion a patent holder can price discriminate across countries and block price arbitrage by third-party importers (parallel trade). Under World Trade Organization (WTO) patent rules, countries may opt for "international exhaustion," whereby the patent holder exhausts its right to block importation once it launches the drug in another country. The European Union (EU) has adopted the principle of international exhaustion within the EU, permitting importation (parallel trade) between EU countries but not from outside the EU.

Price discrimination is also constrained by price regulatory schemes that use external referencing. External referencing and parallel trade thus creates incentives for firms to strategically adjust launch prices and launch timing to reduce external price spillovers. The practical and welfare implications of these policies are discussed later in this chapter.

Optimal Price Regulation for On-Patent Pharmaceuticals

Standard models of price regulation for natural monopolies are inappropriate for pharmaceuticals, for which the issue is market power due to insurance, not natural monopoly. Standard models of optimal insurance contracts are also inadequate because they focus on structuring consumer co-payments to optimally balance financial protection and incentives for overuse (e.g., Pauly 1968; Zeckhauser 1971; Ma and Riordan 2002; also see chapters 11 and 12 in this volume). Recent evidence suggests that for many effective drugs, especially those that can reduce use of other medical services, optimal patient cost-sharing may be quite low (see chapter 12). Optimal financial protection also typically includes an annual catastrophic cap, after which all drugs are “free” to patients. Therefore, the cost-sharing levels that are necessary to induce optimal use and provide optimal financial protection for patients may offer minimal constraint on manufacturer pricing, especially for potentially expensive drugs and those that are used (p. 272) chronically by patients with multiple prescriptions, who typically reach full coverage early in the year.

Optimal provider cost-sharing has been analyzed for physician and hospital services (e.g., Ellis and McGuire 1990). For pharmaceuticals, physician drug budgets (hard or indicative spending limits) have sometimes been applied to general practitioners (GPs) in Germany and the United Kingdom (see later discussion), but such caps are likely to be blunt instruments and could lead to cream-skimming unless the limits are risk-adjusted to reflect the illness profile of each physician's patient pool. Similarly, placing pharmaceutical companies at financial risk for exceeding expenditure limits is a crude instrument compared with product-specific price and utilization controls.

Models of optimal pricing for pharmaceuticals must consider both optimal use of existing drugs (static efficiency) and optimal investment in R&D (dynamic efficiency), which requires that producers capture the consumer surplus generated by new drugs. A series of papers (Garber et al. 2006; Jena and Philipson 2008; Lakdawalla and Sood 2006, 2009) have explored the potential for using insurance to achieve both static and dynamic efficiency in a single country without price regulation. To achieve static efficiency, these models propose to set the patient's co-payment equal to marginal cost and let consumers determine utilization. Payers make a top-up payment to manufacturers such that the manufacturer captures the entire social surplus at this level of use, as required for dynamic efficiency.[6]

Garber et al. (2006) examined the optimal percentage of price for co-insurance and incentives for innovation when the monopoly firm sets its profit-maximizing price without constraint. Lowering the co-insurance rate encourages use but also makes demand more inelastic and therefore leads firms to charge higher prices. Garber et al. showed that if the monopoly price is unconstrained, the co-insurance rate that is optimal for static efficiency may result in monopoly profits that exceed consumer surplus. They concluded that limits on monopoly pricing may be necessary to avoid excessive incentives for innovation but did not address how to set such limits.

Lakdawalla and Sood (2006, 2009) argued that a subsidized but optional public insurance program can achieve both static and dynamic efficiency with unregulated manufacturer prices and consumer choice of drugs. Like Garber et al. (2006), they proposed setting the consumer co-payment equal to the manufacturer's marginal cost, assuming that consumer choice will achieve static efficiency. To achieve dynamic efficiency, the insurer would top up the patient co-payment to the manufacturer's price. Although the manufacturer's price is unregulated, they assumed that the public payer can observe and use as a benchmark the price the firm charges to uninsured patients (p_m). The public payer is assumed to deter manufacturers from charging a higher price by imposing a surcharge on co-payments if (p. 273) the public price exceeds p_m. Although this is a theoretically elegant solution, several key assumptions are problematic in practice. First, marginal cost for pharmaceuticals is conceptually ambiguous, is hard to measure, and varies over the product life cycle. For example, is the marginal cost that of producing an additional pill, expanding treatment to an additional indication, or entering another country? Marginal cost differs across these margins, implying very different levels of patient cost-sharing and payer top-up payments. Second, these papers ignore the fact that optimal financial protection for patients may require a catastrophic cap, in which case cost-sharing plays little or no role in utilization decisions and provides no constraint on manufacturer pricing. This is plausibly the norm for some chronic medications and most expensive drugs, including biologics. Third, in most industrialized countries with universal insurance, there is no uninsured market that reveals the uninsured monopoly price, in which case the public payer requires some other benchmark to determine optimal top-up payments. Finally, if raising funds to pay the top-up payments entails a significant deadweight cost of raising taxes, second-best principles apply. Optimal static efficiency then requires setting utilization such that marginal benefit equals long-run marginal cost, including the top-up payment, not short-run marginal cost. This would be consistent with the second-best principles underlying patents for other industries.

Jena and Philipson (2008) discussed the relationship between average cost-effectiveness, consumer and producer surplus, and incentives for innovation. They showed that a reduction in price that increases utilization may increase static efficiency but may increase or decrease the *ex post* or endogenous ICER, depending on how incremental benefit changes along the demand curve. They did not consider use of an exogenous ICER

threshold to indirectly set price, or the exogenous constraint of utilization to the efficient level at that price, to achieve dynamic efficiency.

Danzon et al. (2011b) proposed a mechanism for setting optimal price levels within each country, as well as optimal price differentials across countries, for countries with comprehensive insurance coverage. Specifically, payers in countries with comprehensive insurance should regulate prices indirectly by defining their willingness to pay for health gain in terms of a threshold ICER, based on their citizens' willingness to pay taxes to fund the health budget. Health gain can be measured in terms of quality-adjusted life years (QALYs) or another outcome measure.[7] Making reimbursement for drugs, devices, and other technologies contingent on meeting this ICER threshold constrains the price that a firm can charge, given a drug's incremental effectiveness relative to existing treatments. Drugs that provide more incremental effectiveness can charge higher prices. Thus, this is a form of value-based pricing (VBP). Payers should define patient eligibility and utilization protocols such that all patients for whom the drug is cost-effective at the price set by the manufacturer have access. Modest (p. 274) co-payments may be used to raise funds and deter excess demand, but these are not intended to ration use, which is done by eligibility rules and protocols, as is the norm for expensive drugs and procedures in most countries.[8] Under this approach, prices in each country reflect its willingness to pay for health gain, and utilization should be second-best efficient.[9] The firm captures the full consumer surplus at this optimal utilization, as required for dynamic efficiency. If all countries with comprehensive insurance adopted this approach, prices would differ between countries based on their willingness to pay, and aggregate demand across all countries would reflect global willingness to pay, providing appropriate global incentives for R&D.

Optimal Price Differentials Across Countries

Price Discrimination Models

Several papers have addressed the welfare implications of price discrimination versus uniform pricing of pharmaceuticals in the context of national versus international exhaustion of patent rights. These analyses (e.g., Malueg and Schwartz 1994) showed that under plausible assumptions about demand dispersion across countries, price discrimination yields higher utilization and improves static efficiency compared to uniform pricing. More recently, Szymanski and Valletti (2005), Valletti (2006), and Valletti and Szymanski (2006) introduced endogenous R&D and addressed dynamic as well as static efficiency. They modeled product quality as a function of the level of R&D investment and showed that permitting price discrimination leads to higher R&D investment and quality, compared with uniform pricing.

Although the assumption that product quality is a continuous function of R&D investment does not capture the discrete nature of pharmaceutical R&D with regulatory requirements for safety and efficacy, nevertheless these models suggest that price discrimination is likely to stimulate more R&D and more new drugs, in addition to ensuring greater access to existing drugs. They suggest that price discrimination is plausibly superior to uniform pricing for both static and dynamic efficiency, but they do not address optimal price levels or optimal cross-national price differentials.

Ramsey Pricing

Ramsey (1927), Baumol and Bradford (1970), Braeutigam (1984), and others outlined a theoretical foundation for second-best pricing to maximize social welfare (p. 275) in a context in which firms incur significant fixed costs and must break even or meet some other target profit level (“Ramsey-optimal pricing”). Several papers have applied this theory to optimal price differentials across countries to recoup the fixed costs of pharmaceutical R&D. Danzon (1997) and Danzon and Towse (2003) showed that, with competitive entry, the cross-national price differentials set voluntarily by a profit-maximizing manufacturer would be Ramsey optimal and would be inversely related to per capita income, assuming that true demand elasticities (before insurance) are inversely related to per capita income. Jack and Lanjouw (2005) argued that price differentials should exceed Ramsey-optimal price (ROP) differentials if high-income countries have altruistic concerns for low-income countries.[10] Barros and Martinez-Giralt (2008) modeled the impact of insurance coverage on ROP prices in the context of an overall constraint on the manufacturer's profit. Insurance coverage tends to increase the prices a country pays, but because manufacturer revenues also increase, all prices may be reduced to satisfy the ROP budget constraint, assuming that a superregulator imposes such a constraint.

These ROP models address optimal price differentials across countries for a given, exogenously determined level of R&D, but they do not address setting absolute price levels to achieve the optimal level of endogenous R&D. These issues were addressed by the mechanism proposed in Danzon et al. (2011b), which is designed to simultaneously

achieve optimal country-specific price levels and optimal cross-national price differentials for dynamic efficiency. The authors discussed how their model differs from the ROP approach.

In MLICs that lack comprehensive insurance coverage, most patients pay out of pocket for drugs. The distorting effects of insurance are thus avoided, and the case for price regulation to constrain insurance-induced pricing moral hazard does not apply. In theory, manufacturer incentives to price discriminate between and within countries, together with competition between therapeutic and generic substitutes, could result in prices that are affordable, given per capita income. However, in practice prices in these countries are high relative to average per capita income (Danzon et al. 2011a). Flynn et al. (2009) showed that skewed income distributions in many MLICs create incentives for monopolist firms to charge prices that are unaffordable to most patients. In fact, originator drugs usually face competition from copy products and generics, but quality uncertainty leads to competition on brand rather than price. Common distribution channels preclude price discrimination within the retail sector, where most patients buy drugs. Thus, the market failures and possible policy responses are different in these self-pay markets than in countries with comprehensive insurance. Optimal policy in such contexts remains an important subject for future research.

(p. 276) Price Regulation Prototypes for On-Patent Products and Evidence of Effects

Systems for regulating pharmaceutical prices usually require approval of the drug's launch price as a condition of reimbursement. Post-launch price increases also require approval, and price decreases may be mandated. Most countries use one or both of two criteria in setting prices: (1) Internal referencing or benchmarking compares the price of the new drug to the price of one or more established drugs in the same class, with potential mark-ups for improved outcomes and other factors. Reference price reimbursement and cost-effectiveness analysis (CEA) review are important special cases of internal benchmarking. (2) External referencing caps the price of a specific new drug in a specific country to an average, median, or minimum price of the same drug in selected other countries. Other, less frequently used criteria include regulation of prices based on cost and regulation of profit or return on capital. Global budgets and other expenditure limits are increasingly superimposed on various forms of price regulation to constrain company promotion or influence physician prescribing toward the use of fewer or less costly drugs.

Empirical analysis of the effects of different regulatory systems would ideally use difference-in-differences methodology, which would compare prices and other outcome measures before and after the adoption of a specific policy in one or more countries, relative to the change over the same time period in appropriate comparison countries. In

practice, such analysis is rarely possible, because many countries adopt multiple policies simultaneously, and each country's variant of each prototype is unique and continually evolving, reflecting both short-term responses to fiscal and political pressures and structural changes intended to improve efficiency. Given the diversity within each prototype, in addition to different methodologies used by different studies, it is unsurprising that investigations of the effects of regulatory regimes have reached mixed conclusions. For previous reviews, see Kanavos (2001), Puig-Junoy (2005), Sood et al. (2008) and sources therein.

The following sections describe the design and rationale for each prototype and summarize the evidence on effects.

Internal Benchmarking

Under internal benchmarking, the starting point for pricing a new drug is the price of one or more comparator drugs in the same class. Regulators increasingly require the innovator firm to provide health outcomes data to support claims (p. 277) of superior value—safety, efficacy, or convenience features—relative to the comparator products. Because the incremental benefits may depend on the specific indication and category of patients treated, the final negotiated outcome is often a price and a designated category of patients eligible for reimbursement. An additional step may determine the reimbursement percentage and its complement, the patient's co-insurance percentage. The reimbursed share may vary from 100 percent, for drugs to treat serious conditions, to zero for “lifestyle” drugs. In most countries other than the United States, patient cost-sharing is usually modest and is either covered by supplementary insurance or subject to a low annual cap. From an economic welfare perspective, internal benchmarking may be rationalized as an attempt to imitate well-informed markets, which would constrain the price of a new product to the price of close substitute products except to the extent that the new product has superior characteristics for which informed consumers would pay a premium. This of course presupposes that the prices of comparator drugs accurately reflect consumers/taxpayers’ willingness to pay for health gain (see earlier discussion).

France illustrates a highly structured variant of this approach that combines internal benchmarking, informal use of pharmacoeconomics and comparative effectiveness analysis, external referencing, and budget caps with price-volume offsets. The regulatory structure is negotiated by the pharmaceutical industry and the government every five years. Under the current system, the Transparency Commission first assesses the drug's clinical value or medical importance (Service Medical Rendu, or SMR): does it treat a life-threatening or a lifestyle condition? This determines whether the drug will be reimbursed and, if so, at what level of coverage and implied cost-sharing.[11] The Economic Committee then evaluates the drug's incremental value relative to existing drugs (Amelioration du Service Medical Rendu, or ASMR) by indication or patient subgroup or both, the expected budget impact, and the drug's average price in the top five EU markets, to arrive at a negotiated price. If actual sales after launch at this price exceed the target budget, a

payback or price reduction may be required. Firms thus face post-launch volume-price offsets that are intended to discourage promotion of a drug beyond its approved indications. Because price reductions in France can reduce a product's price in other countries via parallel trade and external referencing, the French government has occasionally permitted the target price to be achieved through a two-part price, including a market price at “international” levels plus a rebate to the government to achieve the target price for France.

(p. 278) Reference Price Reimbursement

Reference price reimbursement (often called reference pricing, hereafter RP) is a special case of internal benchmarking. Under this model, products are clustered for reimbursement based on either the same compound (generic RP, or GRP) or different compounds with a similar mode of action or the same indication (therapeutic RP, or TRP). All products in a group are reimbursed at the same price per daily dose. This reference price (RP) is set at the price of the lowest or a relatively low-priced product in the group. Manufacturers may charge prices above the RP, but patients must pay any excess. In practice, manufacturers typically drop their prices to the RP, suggesting that demand is highly elastic when patients must pay out of pocket.

Germany initiated RP in 1989, but in 1996 new on-patent products were exempted and RP was applied primarily to off-patent drugs until 2005, when “jumbo” TRP was applied to on-patent drugs in classes with at least one generic. The Netherlands and New Zealand have had comprehensive TRP systems since the early 1990s, including most drugs except innovative, first-in-class products until competitors enter. Several other countries and provinces (Australia, British Columbia, Italy at certain times) have applied TRP to specific therapeutic classes in which the drugs are considered highly substitutable for most patients.[12]

Because TRP limits reimbursement but not the manufacturer's price, it is sometimes considered less constraining than price regulation. In practice, TRP may be more constraining on new-product prices than price regulation with internal benchmarking, for several reasons. First, whereas internal benchmarking permits a mark-up for a new drug that can demonstrate superiority over established products in the class, classification of new drugs under TRP is usually done without extensive pharmacoeconomic analysis; rather, a new drug with the same mechanism of action is assumed to be equivalent to existing drugs and receives the same reimbursement per defined daily dose (DDD) unless it can show sufficient differentiation to warrant a new class. Second, TRP systems typically cluster on-patent together with off-patent compounds based on mechanism of action or indication but without regard to patent status. If the RP is based on the cheapest product in the cluster, reimbursement for all products drops to generic levels once generic entry occurs for the oldest compound in the cluster, effectively truncating patent life for the newer products unless patients are willing to pay surcharges. The

magnitude of this potential patent-truncating effect is greater, the broader the definition of reimbursement clusters and the more price-competitive the generic market.

Compared to TRP, a much larger number of countries have adopted GRP, which sets a single reimbursement for all products within a molecule or molecule-formulation. Because GRP usually applies only to generically equivalent products, (p. 279) any resulting product substitution is unlikely to affect patient care. Similarly, because GRP usually applies after patent expiry, expected effects on R&D are modest, except that GRP systems that apply the same RP per daily dose to all formulations of a molecule may discourage investment in new formulations of existing compounds, such as delayed release and other convenience-enhancing formulations that are often launched just prior to patent expiry on the original formulation. GRP as a strategy for realizing savings in generic markets is discussed later.

RP reimbursement systems have been extensively studied, with focus on effects on price levels (both short-term response and dynamic effects over time), patient care and outcomes, and incentives for R&D. Because countries' RP systems differ in important design details—including whether the system is TRP with on-patent drugs included or just GRP applied to off-patent compounds, breadth of classes, and how the RP is set—effects are not expected to be the same across countries, and this is confirmed by the evidence. Moreover, most countries have adopted RP as one of many price or expenditure controls, which complicates the identification of the effects of RP alone. The early and more recent literatures on RP systems were summarized by Lopez-Casasnovas and Puig-Junoy (2000) and by Galizzi et al. (2011), respectively. Puig-Junoy (2010) reviewed the literature on effects of GRP and other forms of generic price regulation (see later discussion).

Both theory and most of the evidence show that drugs that are initially priced above the RP (usually originators) will drop their prices to the RP or lose significant market share, as expected if demand is highly elastic when patients must pay out of pocket. Stargardt (2010) described the German experience of atorvastatin (Lipitor), which maintained its price above the RP and experienced a share decline from 33.2 percent to 6.0 percent of statin prescriptions. However, theory suggests that drugs priced below the RP may increase price to the RP and dynamic price competition over time may be weak, because firms have no incentive to reduce prices below the RP unless other provisions incentivize price sensitivity on the part of patients, physicians, or, in the case of generics, pharmacists.[13] Incentives for price competition may also depend on market structure. For example, Zweifel and Crivelli (1996) analyzed firms' response to RP in the context of duopoly, whereas RP often applies to classes with multiple products including generics, in which case oligopoly or monopolistic competition models may be more relevant. RP appears to have had significantly greater negative effects on prices and availability of new drugs in New Zealand than in the Netherlands or Germany (Danzon and Ketcham (p. 280) 2004). This is unsurprising, because the New Zealand regulatory agency explicitly required new entrants to accept a price below the established RP as a condition

of reimbursement, thereby reducing the RP for all existing drugs in the class, and New Zealand used broader classes than Germany or the Netherlands.

The effect of TRP on patient care in theory depends on manufacturers' pricing response and the breadth of classes. If all manufacturers drop their prices to the RP, so that patients face no additional surcharges, drug choice and patient outcomes should be unaffected.[14] However, if some manufacturers maintain their prices above the RP so that patients using these drugs face significant surcharges, some patients may switch to lower-priced drugs that are less suited to their condition, and others may remain on the surcharged product but be less than fully compliant, with potentially adverse effects on health outcomes and possibly other costs. Stargardt (2010) documented both types of response to the Lipitor surcharge in Germany. Similarly, adverse health effects have been documented in British Columbia, where several studies found that some manufacturers maintained their prices (Galizzi et al. 2011). Manufacturers are more likely to retain prices above the RP in contexts in which lowering of the price could have spillover effects in other markets. This applies in Canada, where intermediary arbitrage presumably prevents manufacturers from maintaining different prices in different provinces. Similarly, some manufacturers may prefer to retain a high price and lose market share in Germany, to avoid undermining potentially higher prices in other EU countries that reference Germany. Thus, the risks of adverse short-run effects of TRP on patients are greater the more broadly TRP classes are defined, the more comprehensive the TRP system (to include classes in which different compounds are imperfect substitutes for some patients), and the greater the potential spillovers from the RP market to prices in other countries and provinces.

The effects of TRP on incentives for R&D are theoretically complex. In theory, TRP reduces incentives in invest in R&D for follow-on products, new formulations, or expanded indications of existing drugs if effective patent life for late entrants is truncated by generic entry in the older molecules or formulations, which reduces the RP and hence cuts reimbursement to generic levels before patent expiry on more recent entrants. Whether incentives for investing in novel therapies would increase depends on reimbursement rules for first-in-class products. Whether any such R&D reduction would be welfare enhancing, by eliminating wasteful R&D and product proliferation, or welfare reducing, by reducing potentially cost-effective entry and competition, is probably context specific. In theory, such negative effects might be mitigated by permitting review of comparative effectiveness and cost-effectiveness of new entrants to established drug classes, to permit a reimbursement mark-up if a new drug or formulation can demonstrate cost-effectiveness at the higher price. Drummond et al. (2010) discussed the merits of such a mixed system, with full CEA review for novel drugs but RP for drugs that **(p. 281)** are clearly similar to existing drugs, thereby realizing some of the administrative savings of RP compared with CEA.

In practice, because firms' incentives for R&D depend on global expected revenues, the effects of TRP are not expected to be large if it is adopted only in markets that account for a small share of global sales, which is the case so far. The effects of TRP on R&D

incentives would be much greater if it were adopted by the United States, which accounts for almost 40 percent of global revenues and has relatively low-priced generics, implying very low TRP reimbursement levels once generics enter a cluster (Danzon and Ketcham 2004).

Cost-Effectiveness Review and Indirect Value-Based Price Regulation

Many countries use comparative outcomes data as one input to reimbursement and pricing decisions that involve internal benchmarking. An increasing number of countries, including Australia, Canada, New Zealand, and the United Kingdom, have dedicated bodies that conduct formal CEA review of some or all new drugs as a condition of reimbursement by national health systems. Such CEA review may be administratively separate from pricing review. For example, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) reviews cost-effectiveness of drugs and other technologies that are expected to have major health or budgetary impact, relative to current treatment, using a standardized methodology. Costs include not only the price of the drug but also any associated medical costs or cost offsets. Benefits are measured in QALYs. NICE has traditionally used a threshold ICER of £20,000 to £30,000, but higher thresholds have been recognized for certain end-of-life conditions (see chapter 13). Canada's Common Drug Review (CDR) program also reviews costs, effectiveness, and cost-effectiveness and makes recommendations for coverage under provincial drug plans. In 2004 Germany established an expert body (the IQWiG) to review clinical effectiveness and now cost-effectiveness.

As discussed in the previous section, establishing an ICER limit as a condition of reimbursement implies an indirect constraint on the price of a drug, given its effectiveness relative to current treatment. This indirect regulation of price through an ICER threshold can in theory be more consistent with principles of static and dynamic efficiency than regulation using ad hoc internal benchmarking, RP reimbursement, or external referencing, provided that the threshold ICER reflects societal willingness to pay for health gain. In contrast to broad TRP systems, this ICER approach permits the more effective drugs in a class to charge higher prices, commensurate with their incremental health gain relative to less effective drugs. Moreover, the focus of the ICER approach on measuring incremental health gain, although probably imperfect, is likely to improve methodologies for outcomes measurement over time. This approach also implies consistent (p. 282) standards across drug classes, as required for efficient allocation of health budgets to achieve maximum health gain. By permitting manufacturers to charge prices commensurate with incremental health gains, this approach also creates appropriate incentives for R&D. Of course, such an approach is only as sound as the data, methods, and judgments used in implementation.

The rapidly growing literature on theoretical foundations, empirical measurement of outcomes, and appropriate cost-effectiveness thresholds and the increasing adoption of this approach are discussed in detail in chapter 13. Major issues are briefly summarized

here. One concern is the cost and availability of data. The available data at launch are from controlled, clinical trials, which may not accurately reflect the costs or effects of a drug in actual usage in broad patient populations. Updating the CEA with data from post-launch clinical experience is possible but potentially costly and less accurate due to nonrandom treatment assignments. Nevertheless, integrating pre-launch and post-launch data is likely to become the norm as available databases and statistical techniques improve.

A second challenge is setting the payer-specific ICER thresholds or willingness to pay for health gain, which could vary by condition or context. Setting appropriate thresholds is conceptually and politically challenging. Claxton et al. (2008) argued that such thresholds should be determined empirically, based on analysis of QALYs gained from current health spending. This approach is simpler because it takes the health budget as given, but it begs the question of whether the health budget appropriately reflects societal willingness to pay for health.

Third, any ICER threshold implies a maximum price at which a drug of given effectiveness is cost-effective, but that drug would be even more cost-effective and have lower budget impact at a lower price. Claxton et al. (2008) argued for setting the price below the maximum consistent with the ICER, to permit the health budget to capture some social gain from innovation prior to patent expiry. However, in theory this creates suboptimal incentives for dynamic efficiency, which requires that manufacturers capture the full social gain from any innovation (Jena and Philipson 2007), assuming patent terms are optimal. Given these challenges in measuring QALYs and setting ICER thresholds, it is unsurprising that most countries use CEA evaluation as one among several criteria for controlling prices and expenditures.

In 2010 the UK government proposed adopting a system of value-based price control by the Department of Health, separate from the (modified) review of CEA by NICE. Because the CEA review by NICE already implies an indirect, value-based constraint on price, it remains to be seen whether adoption of a formal value-based pricing (VBP) regulation will lead to major change. Key issues are whether the VBP will constrain price below the maximum level permissible under the ICER, whether the VBP will be applied only at launch or adjusted to changes in evidence or in prices of comparator drugs, and administrative costs and delays.

(p. 283) External Referencing

Whereas internal referencing and its variants seek to imitate price competition by benchmarking new drugs to prices of comparator, established products, external referencing regulates the domestic price of a new drug so that it is equivalent to the price of the same drug in a set of other countries, thereby limiting the manufacturer's ability to price discriminate across countries. External referencing has been adopted in an increasing number of countries, often as a supplement to other controls. Usually

countries reference other countries with roughly similar incomes and price levels, but widely varying practices exist. For example, Italy has used an average European price; Canada references the median price in seven countries for pricing of novel products but uses internal referencing for “me-too” products; the Netherlands uses external referencing to four EU countries in setting the RP for their TRP system; and Greece uses the lowest price in specified comparator countries. Brazil references the lowest EU price to set its private sector prices but requires a 26 percent discount off this private price for sales to the public sector, which primarily serves lower-income patients. An extreme and rarely used variant of external referencing is a most-favored-nation approach, whereby one country demands the lowest price a manufacturer has granted to any other country.[15]

Modeling a firm's profit-maximizing response to external referencing is complex because in practice linkages are multidimensional, both direct and indirect and often partial, depending on whether the formulas refer to a mean, median, or minimum price in the referenced countries. However, when faced with a significant probability of linkage between several countries, such that price discrimination is not possible, theory predicts that a manufacturer will seek to launch within a narrow price band in linked countries and may rationally prefer to delay launch or not launch at all in countries that cannot or will not pay this price, particularly those countries with small markets relative to potentially higher-priced, larger markets. Such strategic pricing and launch delays are particularly likely within the EU, where external referencing to other EU countries is very common.

Parallel trade, which is legal within the EU, in theory induces strategic responses similar to those seen with external referencing, but with important differences.[16] Whereas external referencing automatically affects the price for all units sold, manufacturers are usually able to limit parallel exports by supply restrictions or dual pricing, so that in practice parallel trade accounts for only a fraction of a product's sales even in relatively high-priced EU countries that are subject to parallel importing, such as the United Kingdom or Sweden.

(p. 284) In theory, the welfare effects of external referencing and parallel trade are more negative than those observed with price regulation by internal referencing, because external referencing induces potentially negative effects—launch delays, non-launch, and price increases—in the referenced countries, in addition to any effects in the country adopting it. In particular, if higher-income countries reference lower-income countries, this tends to raise prices and reduce access in the lower-income countries. The relevant theoretical literature includes broader analyses of welfare effects of price discrimination versus uniform pricing and generally supports price discrimination. Although empirical evidence confirms that parallel trade and external referencing as currently practiced within the EU have so far not led to uniform prices, this finding does not undermine the theoretical conclusion that, to the extent that regulatory policies undermine price discrimination and contribute to uniform pricing, they are likely to reduce static efficiency by raising prices and reducing access and use of drugs in lower-income

countries, compared with other regulatory approaches (e.g., VBP) that support differential pricing across countries.

Several empirical studies have confirmed that external referencing contributes to launch delay and non-launch of new drugs, especially in lower-price markets in the EU (Danzon et al. 2005; Kyle 2006, 2007; Lanjouw 2005; Danzon and Epstein 2009). Danzon and Epstein (2009) also found evidence that external referencing raises launch prices in the referenced countries. Some of the observed effects may be attributable to parallel trade risk, but available data make this hard to quantify, and theoretical effects are uncertain. Kanavos and Costa-Font (2004, 2005) found limited savings for payers from parallel trade, with traders capturing most of the rents, and little evidence that parallel importation caused price convergence in Europe between 1997 and 2002. One exception was the study by Ganslandt and Maskus (2004), who estimated a 12 to 19 percent reduction in the ex-manufacturer price in Sweden for drugs subject to parallel imports. Given the small size of the Swedish market, this result cannot necessarily be generalized to other, larger importing markets. Kyle (2008) showed that manufacturers may also respond to parallel trade risk by modifying formulations and dosing.

Drug Budgets and Expenditure Controls

Despite price and reimbursement controls, drug spending may continue to grow as a result of increased prescription volume and upgrading from older, cheaper drugs to newer, higher-priced drugs. Most countries that initially controlled only price have added other measures to limit total reimbursed drug expenditures. These limits are usually enforced by putting pharmaceutical firms or physicians at risk for overruns.[17]

(p. 285) From 1993 to 2001, Germany had a national drug budget or limit on outpatient drug expenditures that was set initially at the 1991 spending level and updated modestly over time. Any overrun was to be repaid in part from the budget for physicians’ services and in part by price cuts from the pharmaceutical industry the following year. Physicians responded by reducing the number of prescriptions and switching to cheaper drugs, notably to generics, leading to a 16 percent reduction in drug spending during the first year of the budget (Munnich and Sullivan 1994) and only modest increases thereafter. Schulenburg and Schoffski (1994) reported that physicians also increased patient referrals to specialists and hospitals, which were exempt from the drug budget. Germany's aggregate drug budget was abolished in 2003, because enforcing the repayment of overruns was practically and politically problematic. Most regions in Germany subsequently adopted physician-specific budgets, adjusted by specialty and patient mix, usually with warnings rather than strict financial penalties for overruns. Similarly, GP fundholders in the United Kingdom in the 1990s had target drug budgets and were permitted to plough back any “savings” into other practice expenses, but they were not at financial risk for overruns. Such soft budgets were associated with increased generic prescribing by fundholding GPs relative to non-fundholding GPs.

Although the evidence from Germany (and, to a lesser extent, the United Kingdom) suggests that placing physicians at notional risk encourages cost-conscious prescribing and reduces drug spending, this approach has potential disadvantages and has not been widely adopted. Physician-specific budgets with incentives to encourage therapeutic substitution may lead to cream-skimming of patients or inappropriate prescribing if such budgets are not appropriately risk-adjusted to reflect the disease profile of each physician's patient roster. If cost savings are obtained mainly from generic substitution, this can be achieved by authorizing and incentivizing such substitution by pharmacists (unless the physician explicitly requires the brand), as discussed later. More generally, “silo budgets” that place budget limits by medical service category undermine incentives for efficient substitution, where increased use of drugs might have offsetting savings and reduce overall medical costs.

More common than drug budgets with physicians at risk are drug expenditure limits that put pharmaceutical firms at risk via price-volume offsets. For example, France has a limit on total drug spending that is allocated across companies, and sometimes by particular therapeutic classes or products. Overruns are recouped by price cuts or rebates on companies/products that exceed budget targets. Similarly, Italy limits drug spending to a specified percentage of health spending, and overruns have been recouped by price cuts in major therapeutic classes. Company-specific and product-specific revenue limits in theory reduce incentives for firms to encourage drug use beyond the level deemed appropriate in setting the budget target. Aggregate company limits may also undermine incentives for R&D, depending on how revenue limits are expanded to accommodate the launch of new drugs. The effects of such limits remain an important subject for future research.

(p. 286) Regulating Prices Based on Costs

Setting prices based on cost of production (including a transfer price to incorporate R&D) has prima facie appeal and has been used in a few countries, including Italy and China in the early 1990s. Standard efficiency problems apply; that is, setting prices based on costs may undermine incentives for production efficiency or create incentives for “X-inefficiency” or intentional padding of real or reported costs that are passed through by the regulatory formula. For pharmaceuticals, these standard distortions are exacerbated by the difficulty of accurately measuring the cost of product-specific R&D, given that this cost accrues over many years and includes many associated failures and foregone interest over the development period (DiMasi et al. 2003). Standard accounting systems are not designed to capture costs that accrue across multiple years. Moreover, there are no consensus rules for allocating these globally joint R&D costs across countries and over the economic life of the product. If transfer pricing rules can be manipulated by regulators and firms, this approach may lead to particularly arbitrary and politically influenced prices. Unsurprisingly, most countries have moved away from this approach.

A variant of cost-based reimbursement exists in the US Medicare Part B program, which pays physicians for the drugs they purchase and dispense, including most cancer drugs and other infused biologics. Prior to 2005, Medicare Part B paid dispensing physicians 95 percent of the Average Wholesale Price (AWP), a list price set by manufacturers. Because physicians captured the margin between AWP and their acquisition cost, manufacturers could increase physicians' financial incentives to use their drugs by discounting the acquisition price. Such discounting was reportedly extensive (General Accounting Office 2001), but physicians rather than payers captured the savings from price competition. Since 2006, Medicare Part B has reimbursed for physician-dispensed drugs based on their acquisition cost, estimated as the manufacturer's volume-weighted Average Sales Price (ASP), inclusive of all discounts, plus a 6 percent margin. This cost-based reimbursement system creates incentives for manufacturers to set high prices, undermines their incentives to offer discounts, and encourages physicians to use higher-priced drugs on which they get a larger absolute margin (Danzon et al. 2005; Danzon and Taylor 2010).

Rate of Return on Capital Regulation

The United Kingdom's Pharmaceutical Price Regulation Scheme (PPRS) is unique among industrialized countries in that it regulates a firm's rate of return on capital (ROC) from all sales to the UK National Health Service, leaving the firm free to set the launch prices of individual drugs (subject to the constraint of NICE review). Post-launch price increases require approval, and allowable expenses for promotion and other purposes are limited to prevent expense padding. The allowed rate (p. 287) of return has been 19 to 21 percent on an historical cost-accounting basis, with a "margin of tolerance" of up to 29 percent, beyond which excesses must be repaid directly or through lower prices the following year. Conversely, if a firm's ROC falls to less than 15 percent, it may seek price increases. Companies may substitute a return-on-sales formula. The PPRS is renegotiated every five years between the research-based pharmaceutical industry and the government. These reviews have usually resulted in price cuts.

Standard theoretical analyses of ROC regulation predicted excessive capital investment relative to labor and hence reduced total factor productivity (Averch and Johnson 1962); however, these predictions hold only under restrictive assumptions (Joskow 1974). In a study of the effects of input-based regulatory schemes in the United Kingdom, France, and Italy on labor productivity and total factor productivity, Danzon and Percy (2000) found that although the rate of growth of capital and labor in the UK pharmaceutical industry was high in comparison with other UK industries and relative to pharmaceuticals in other countries, it was not biased toward capital relative to labor. Overall, the United Kingdom experienced relatively high total factor productivity growth, compared with other regulated and unregulated countries. Empirical analysis of the effects of the PPRS on prices is not feasible, because it has been in effect too long to permit before-and-after

studies, and comparison to other countries raises issues of confounding effects, including exchange rate changes.

In a 2007 review of the PPRS, the UK Office of Fair Trading concluded that the ROC constraint had rarely been binding on prices and that it had failed to incentivize innovative R&D because the allowed ROC was the same regardless of the value or incremental health gain of a drug. The OFT therefore recommended that the country move to a system of VBP (Office of Fair Trading 2007). In 2010, the UK government outlined proposals to move toward VBP controls at launch, with more limited power for NICE in determining access to new drugs. As argued earlier, the ICER constraint applied by NICE already indirectly implies a limit on launch prices that resembles a VBP approach. However, the proposed new approach would explicitly empower the government to negotiate prices at launch and enable price changes after launch (e.g., if new data on efficacy is developed). It remains to be seen how these and other details will be implemented.

Other Effects of Price Regulation

In addition to the evidence on effects of particular forms of regulation previously noted, price regulation in general may have effects on competition, drug utilization and static efficiency, location of investments, and overall incentives for R&D and dynamic efficiency. General tendencies are noted here, with country-specific effects depending on the particular regulatory regime.

(p. 288) Competition

Although the regulated price sets a ceiling rather than a floor on actual price, firms generally have no competitive incentive to price below the regulated price, because neither patients nor physicians have incentives to prefer cheaper products (except in some cases of RP reimbursement). Therefore firms attempt to obtain the highest price the regulator will permit, and price competition is typically not a feature of such markets at the ex-manufacturer or the retail level.

One exception to the conclusion that price regulation eliminates price competition occurs in contexts where physicians dispense the drugs that they prescribe, as was the case traditionally in Japan and Korea and remains the norm in hospitals in China. Physician dispensing enables physicians to profit from the margin between the regulated reimbursement price and their acquisition cost. Manufacturers therefore compete by discounting the acquisition price to increase the physician's margin and incentivize use of their drug. The Japanese government audits acquisition prices biannually and reduces the reimbursement price to leave only a 1 to 2 percent margin, which triggers another round of competitive price cuts. Thus, by revising the reimbursement price to reflect the market price, Japan's payers take advantage of the price competition such that reimbursement prices generally decline over a drug's life cycle in Japan.[18]

Utilization

Utilization and static efficiency under price regulation regimes depend on features other than the patient's response to cost-sharing, which is typically modest and unrelated to drug prices, except for lifestyle drugs. Utilization and price may be inversely related empirically, because regulators consider budget impact in approving price and through explicit expenditure targets and volume-price offsets that reduce manufacturers' incentives to promote use beyond approved indications.

Production and R&D

Internal benchmarking systems in several EU countries historically granted mark-ups for local production despite the 1989 EU Transparency Directive, which requires that regulations be neutral with respect to country of origin. Such biased regulation might have created incentives for nonoptimal location of manufacturing plants, or for an excessive number of plants, if these excessive production costs were "offset" by higher prices (Danzon and Percy 2000). In practice, these regulatory distortions have been reduced over time, and since the late 1990s many (p. 289) companies have consolidated manufacturing facilities as part of postmerger integration and other cost reduction initiatives, so that regulation-induced excessive production facilities are probably now minimal.

Conversely, the pharmaceutical industry sometimes argues that low and unpredictable regulated prices discourage local investment in R&D. In theory, price regulation could reduce R&D due to both the incentive effect of lower expected profits and the financing effect of lower retained earnings. It is empirically true that most R&D facilities are located in countries with relatively free pricing, mainly the United States, United Kingdom, Switzerland, and Germany. However, the causal relationship is unclear. In theory, given the potentially global market for innovative drugs and extensive in- and out-licensing networks that enable small firms to reach global markets regardless of their location, there is no necessary connection between domestic price levels and firms' location of R&D facilities. For discovery research, casual evidence suggests that access to world-class scientific research and a pool of skilled human capital are key factors in the location of drug discovery sites, as evidenced by the proliferation of R&D units of both US and foreign firms near Boston and in California in the United States. For clinical trials, location is motivated by cost, patient access, regulatory considerations, and marketing considerations. In particular, the low cost of medical care and large pools of untreated patients are attracting an increasing fraction of clinical trials to emerging markets, whereas the need to engage with key physicians and regulators retains trials in the major mature markets of North America and Europe. As both national and local governments increasingly offer tax subsidies to try to attract pharmaceutical and biotechnology R&D, the importance of financial versus other factors in R&D location becomes a fruitful area for further research.

The overall level of R&D investment can be significantly affected by the level and structure of price regulation, depending on whether it is adopted in countries that represent a significant share of global pharmaceutical sales. Small countries may be able to free-ride on contributing to R&D, with negligible impact on global incentives for R&D and the flow of new drugs, whereas similar policies adopted in larger markets would have significant impacts. Vernon (2005) and Giaccotto et al. (2005) concluded that direct price regulation has reduced pharmaceutical prices and R&D. These papers did not address whether the resulting R&D levels are suboptimal. As argued earlier, if comprehensive insurance without any constraints on prices could lead to excessive prices and excessive incentives for R&D, the finding that regulation reduces prices and R&D leaves unanswered the question of whether such effects reduce or increase welfare.

Conclusions on Price Regulation

Optimal price regulatory systems should in principle reflect societal willingness to pay for incremental health gain. In practice, internal referencing systems could approximate this objective provided that (1) the comparator drug's price (p. 290) is based on societal willingness to pay and (2) the incremental value of the new drug is accurately estimated and incorporated into the allowed price. In practice, comparator prices are often the result of arbitrary historical factors, and allowed mark-ups for innovation are roughly set. Nevertheless, such internal referencing approaches are theoretically superior to external referencing systems, which are not structured to reward innovation and pay prices that reflect willingness to pay for health gain. External referencing also limits appropriate cross-national price differences and imposes welfare losses on referenced countries through higher prices and launch lags.

Regulation of Generics

Generic entry after patent expiry should in theory be potentially profitable for generic producers, who can largely free-ride on the R&D and marketing investments made by originator firms. Generics can also offer significant savings to payers and consumers, provided that generics compete on price but are of comparable quality. In fact, countries have adopted different regulatory and reimbursement strategies in regard to generics, and generic entry, shares, and relative prices show major cross-national differences. In 2009 in the United States, generics accounted for approximately 70 percent of prescriptions but less than 20 percent of sales value, because generic prices are relatively low. Although generic volume shares are lower in most other countries than in the United States, generic shares of sales value are sometimes higher, reflecting higher generic prices, both absolutely and in relation to originator prices, than in the United States (Danzon and Furukawa 2011).

Countries differ in their patent extension and data exclusivity provisions and in regulations governing generic entry. Although the WTO requires member countries to recognize a basic 20-year patent term, provisions vary for patent term extension and supplementary protection to compensate originators for patent term lost during the lengthy R&D and regulatory approval process, which can take 10 to 12 years. For example, the US Hatch-Waxman Act of 1984 provided for up to 5 years of patent restoration, to a maximum of 14 years after launch.[19] The Act also established an Abbreviated New Drug Application (ANDA) pathway for generics whereby generic drugs can be approved based on proof of bioequivalence to the originator drug, with reference to the originator's clinical trial data rather than performing new clinical trials. The Hatch-Waxman Act granted originator drugs five years of data exclusivity (from launch of the new chemical entity), during which (p. 291) time generics may not reference their data.[20] The Bolar Amendment to the Hatch-Waxman Act permits generic companies to start their development work before expiry of the originator patents, thereby enabling generics to launch promptly once originator patents expire or are successfully challenged. Some EU countries and many MLICs have been slower to adopt bioequivalence requirements for generics, which likely has reduced acceptance of generics by physicians and patients and slowed the adoption pharmacy substitution provisions.[21]

Given the value of patent protection, originator firms have incentives to engage in strategic filing of additional patents on ancillary product features, so as to extend the effective patent period. The United States is unique in that it incentivizes generic firms to challenge originator patents by granting a 180-day market exclusivity to the first generic firm to file a complete ANDA and successfully challenge all outstanding originator patents (a so-called paragraph IV filing), rather than simply waiting for patents to expire. This 180-day market exclusivity period can be lucrative, because the sole generic can capture substantial market share at a price modestly below the originator price. Such paragraph IV challenges have become increasingly common, often leading to settlements between the originator and one or more generic challengers. Whether this structure of permitting early challenges but rewarding them with an exclusivity period is on balance procompetitive or anticompetitive remains an empirical question.

The US ANDA process for approval of generics does not apply to biologics, which therefore have not faced competition from generics. In 2010 the Food and Drug Administration (FDA) was authorized to establish an abbreviated approval pathway for biosimilars, with details to be determined. The expectation is that biosimilars will be required to perform some clinical trials to establish safety and efficacy, because of concerns that bioequivalence cannot be readily established for biologics, which are based on living organisms. The data exclusivity period for biologics was set at 12 years, thereby assuring a longer period of protection against generic competition for biologics than for chemical drugs. Whether this longer period appropriately or inappropriately biases protection in favor of biologics is an empirical question. The European Medicines Agency has established an approval pathway for several types of biosimilars, and in contrast to

the FDA, it provides a consistent, 10-year data exclusivity period for both chemical and biologic drugs.

In addition to regulations governing generic entry, regulations governing pharmacy substitution, generic reimbursement, and patient cost-sharing are critical to providing incentives for generic uptake and price competition and contribute to differences in generic markets across countries. In the United States during the 1980s, all states repealed antisubstitution laws, thereby authorizing pharmacists to substitute bioequivalent generics unless the physician specifically requires the brand. In addition, all major public and private health plans have adopted reimbursement rules for pharmacists that incentivize them to choose cheaper generics. **(p. 292)** Typically, pharmacists are paid a fixed dispensing fee (e.g., $2) that is independent of the price of the drug, plus a fixed reimbursement based on the molecule-formulation (the Maximum Allowable Cost, or MAC, which is similar to a reference price), regardless of which generically equivalent form of the prescribed drug they dispense, including the originator. Pharmacies thus capture any margin between the MAC and the acquisition cost of the product they dispense. This creates an incentive for generic firms to compete by discounting to pharmacies. Payers periodically audit generic acquisition prices and revise the MAC downward, thereby capturing the savings from generic competition, which leads to further discounting by generics. Payers structure patient co-payments such that the co-pay on a generic is less than $10, compared with more than $45 for the originator brand; as a result, most patients accept generics. This regulatory and reimbursement structure creates a pharmacy-driven generic market in which generics are accepted as being of equivalent quality and competition focuses on price to the price-sensitive pharmacy decision maker. Patients, physicians, and payers play no role in choosing one generic over another. Because brand conveys no market advantage, almost all US generics are unbranded, that is, marketed under the molecule or International Nonproprietary Name (INN).

The regimes in the United Kingdom and in Canada resemble that of the United States in having pharmacy-driven generic markets, but with some important differences. In particular, Canadian provinces have traditionally regulated generic prices to a fixed percentage of the originator price. This regulated price has become a floor as well as a ceiling on list prices for generics (Anis et al. 2003). Because pharmacies are decision makers, competition takes the form of off-invoice discounts, which have largely been captured by pharmacists rather than payers. This may change under recent reform proposals (e.g. Ontario Ministry of Health and Long Term Care).

By contrast, pharmacists in most EU countries and middle-income countries have traditionally had less authority and less financial incentive to substitute generics. In some countries, pharmacy substitution has been permitted only where the physician prescribed by INN, which is uncommon except in the United Kingdom. Moreover, countries that regulate manufacturer prices usually also regulate distribution margins, to assure regulated public prices to payers. Even where the pharmacist's percentage margin is digressive, the absolute margin is typically higher on higher-priced products,

undermining pharmacy incentives to substitute cheaper generics or parallel imports. Patient cost-sharing is typically independent of product price, except for surcharges under RP reimbursement. In such contexts, generic markets are mainly physician driven; generics compete on brand rather than price, and generic brands are detailed to physicians just like originator brands. Because no potential decision maker—physician, patient, or pharmacist—is motivated to be price sensitive, generic prices are typically higher, relative to originator prices, in physician-driven generic markets than in pharmacy-driven generic markets (Danzon and Furukawa 2011). Several studies have confirmed that regulation of generic prices (p. 293) tends to undermine generic price competition (Anis et al. 2003; Danzon and Chao 2000; Puig-Junoy 2010).

Most major EU markets (except the United Kingdom, the Netherlands, and Sweden) were traditionally physician-driven, branded generic markets. GRP was the main policy used to encourage competition in off-patent products, but with limited success. Germany adopted GRP in 1989, and many other countries, including France, Italy, and Spain, adopted variants of RP in the 1990s and early 2000s. As described earlier, because the RP caps reimbursement for all products in a cluster, leaving the patient to pay any excess of price over RP, the optimal strategy for most manufacturers is to drop their price to the RP (unless such price cuts would erode prices in other countries through external referencing or parallel trade). However, RP systems create no incentive for manufacturers to price at less than the initial RP if pharmacists receive higher margins on higher-priced products and patient co-payments are unaffected. Therefore GRP systems in general have not created incentives for dynamic price competition below the initial RP.[22] Since the early 2000s, most of these countries have adopted additional measures to mandate or encourage generic substitution, in an attempt to reduce generic prices and expand generic uptake. The impact of these reforms was reported by Danzon and Furukawa (2011).

Latin American markets were traditionally a variant on the physician-driven, branded generic model with the additional element that, because of late adoption of patents or weak enforcement or both, most generics are “similares” or copies that claim equivalence to the originator but have not met regulatory tests for bioequivalence. Many MLICs have established regulatory pathways for true generics that show bioequivalence, but similares have not been phased out. Pharmacy substitution is not legally authorized, although in practice many patients obtain drugs without a prescription, in which case substitution can occur de facto at the option of the pharmacist or the patient. Competition tends to be on brand rather than price, resulting in relatively high generic prices (Danzon and Furukawa 2011; Danzon et al. 2011a). Japan and other Asian countries where physicians have traditionally dispensed drugs have also had slow generic uptake, partly because physicians earn more on higher-priced products.

Empirical research on generic entry and price competition initially focused on the US market. Several studies showed that generic entry is related to market size (Scott Morton 1999; Saha et al. 2006) and that generic prices are inversely related to number of generic competitors (Grabowski and Vernon 1992; Saha et al. 2006). These studies have not

recognized the role of pharmacies as key decision makers in US generic markets. For example, several papers hypothesized that originator firms may use promotion to deter generic penetration but found no effects, which (p. 294) is unsurprising in a market where pharmacists decide which generically equivalent product to dispense and are motivated by price rather than brand.

A growing literature has documented differences across countries in generic markets and changes over time, including both originator and generic strategies. Hudson (2000) examined generic entry and erosion of brand shares in the United States, United Kingdom, Germany, and Japan, using data from the early 1990s that predated the recent changes in all these markets. Hollis (2003) examined anticompetitive effects of strategic licensing of brand-controlled “pseudogenerics” in Canada, which was found to deter generic entry. Incentives for originator-authorized generics appear to exist in countries with branded generic markets but not in the price-competitive, pharmacy-driven US generic market, except during the 180-day exclusivity period, when authorized generics are common (Danzon and Furukawa 2011).

Magazzini et al. (2004) examined generic entry in the United States, United Kingdom, Germany, and France using sales data from July 1987 through December 1998 on major molecules with patent expiry dates between 1986 and 1996. They concluded that market share of licensed products (defined as products launched within three years of patent expiry) was negatively related to unbranded generic market share, whereas the number of different brand names had a positive effect. Possible reasons for these apparently contradictory findings were not explored. Appelt (2009) provided evidence of originator licensing strategies prior to patent expiry and branded generics’ use of trademarks to enhance brand competition in Germany's branded generic market. These strategies likely became less viable after 2007 with the growth of competitive tendering for generics by sickness funds, which focuses on price rather than brand.[23] Moreno-Torres et al. (2009) provided detailed evidence on generic entry in Spain. Ghislandi et al. (2005) and Garattini and Ghislandi (2006) discussed recent changes in Italy.

Danzon and Furukawa (2011) studied generic entry, shares, and prices across 12 different countries over the period 1998–2009, focusing on differences between pharmacy-driven versus physician-driven generic markets, which in turn involve competition on price among unbranded generics versus competition on brand by branded generics. The study also examined effects of originator defense strategies, in particular licensing of competing branded products and launching of new formulations. Theory suggests that licensing of competing branded products may be effective in physician-driven, branded markets but not in pharmacy-driven, unbranded markets. Launching and switching of patients to new formulations before patent expiry on older formulations is potentially a rational strategy in both market types, depending on reimbursement rules, cost, and feasibility. The evidence confirms that generic price competition is greater in pharmacy-driven (p. 295) markets than in physician-driven markets, provided that pharmacies face financial incentives to prefer cheaper products. As predicted, branded generics, which predominate in physician-driven markets, are less price competitive than

unbranded generics, which predominate in pharmacy-driven markets. Consistent with previous evidence, generic entry is related to market size, but market size does not explain the differences across countries in number of generic competitors, either in total or per presentation, suggesting that margins also differ across countries. Launching of new formulations is a successful originator defense strategy in the United States but not in other countries, plausibly because reimbursement systems that use internal referencing or RP do not reward such strategies.

Experience with follow-on biologics and biosimilars is too recent and sparse to afford conclusions, and the extent of uptake and price competition is likely to be context and product specific. Whereas small-molecule generics are oral products and typically are dispensed through retail pharmacies, most biologics are large-molecule drugs that must be taken by infusion in a hospital or in a physician's office. Therefore provider reimbursement rules are critical to incentives for uptake. In the United States, biologics are typically dispensed in physicians’ offices. Since 2005, Medicare has paid dispensing physicians 6 percent of the manufacturer's Average Sales Price (ASP) as a dispensing fee, which creates incentives to prefer higher-priced products. The 2010 Patient Protection and Affordable Care Act provided that, although biosimilars will have a separate reimbursement code from the originator, the dispensing physician's 6 percent margin will be based on the originator's ASP, in order to preserve neutral incentives. Nevertheless, price competition is expected to be weaker for biosimilars than for pharmacy-dispensed small-molecule generics due to these neutral financial incentives, lack of bioequivalence, and higher costs resulting in fewer competitors. Therefore, biosimilars are not expected to generate the same savings for payers and patients as chemical generics do.

International Regulation of Promotion

High margins of price over marginal cost for pharmaceuticals create strong incentives for promotion. Several countries therefore limit promotion directly or include in their price regulation systems features that discourage promotion. The UK PPRS limits the promotional expenditure that can be deducted as a cost in calculating the net rate of return. Germany's 1993 global drug budget placed the pharmaceutical industry at financial risk for a second tier of budget overrun, after physicians. France penalizes “excessive” promotion, both directly and indirectly through penalties for overshooting target sales limits. Some countries prohibit samples, and many countries limit the number of detail visits per year per physician. Most (p. 296) countries reimburse only for approved indications, whereas most US payers reimburse for unapproved uses that are documented in published compendia.

Most countries restrict direct-to-consumer advertising (DTCA) to so-called “help-seeking” ads, which inform consumers about a specific health condition and the availability of treatment for that condition. The only country other than the United States that permits DTCA that names a specific product to treat a condition is New Zealand. New Zealand has a strict freedom of commercial speech commitment, and it has no constraining statute that requires DTCA to present a “fair balance” between risks and benefits. Survey results indicate that between 82 and 90 percent of individuals recall benefits information in DTCA in both the United States and New Zealand, but only 20 to 27 percent recall risk information in New Zealand, compared with 81 to 89 percent in the United States (Hoek et al. 2004).

Information on regulatory limits on promotion and their effects is much more limited than for prices, in part because data on promotion spending is more limited and less informative across countries. For example, the content of a visit by a detail representative to a physician can be very different depending on time spent, messaging allowed, whether sampling is permitted, and so on. Berndt et al. (2007) provided some evidence on cross-national differences in promotion and diffusion of new drugs. This remains an important area for future research.

Conclusions and Future Research

Regulation of price and reimbursement for pharmaceuticals differs from price regulation in other industries in that the rationale for regulation arises out of insurance and its effects on demand elasticity. Outside the United States, most public insurers adopt supply-side policies, limiting price or reimbursement or both as a condition of reimbursement in order to control supplier pricing moral hazard, while setting patient co-payments at modest levels independent of prices to ensure affordability. In theory,

optimal price regulatory systems would constrain prices indirectly, based on a product's incremental value and the country's willingness to pay for innovation. In practice, price regulatory systems that use ICER review or internal referencing, or both, only roughly approximate this ideal at best. By contrast, regulation based on external referencing has no basis in optimal resource allocation, constrains optimal cross-national price differences, and imposes welfare losses on referenced countries due to higher prices and launch delays.

Progress has been made in measuring effects of regulatory systems. Conclusions are usually tentative, because classifying countries based on regulatory prototypes ignores important differences in each country's system and most countries adopt multiple control strategies simultaneously, making identification of marginal effects difficult. Therefore within-country, longitudinal approaches may be preferable to (p. 297) cross-national approaches, if other time-varying factors can be adequately controlled. Moreover, effects on R&D are confounded by the fact that incentives for pharmaceutical R&D depend on global revenues. Understanding effects of different regulatory systems remains an important subject for future research, including effects on prices, utilization, patient outcomes, and firm R&D incentives.

Regulation of promotion is still a relatively uncharted territory, with many remaining questions. Empirical issues are particularly challenging, given the number of promotional channels that are simultaneously determined and interdependence between competitor strategies in oligopolistic markets. Both positive and normative welfare analyses remain to be developed.

Optimal demand-side incentives also warrant further consideration and study. The literature on value-based insurance design, which emphasizes low patient cost-sharing in order to encourage appropriate use of drugs that may substitute for more costly services (see chapter 12), does not consider the effect of low patient cost-sharing on drug prices. Nevertheless, the focus of this literature on financial protection aspects of patient cost-sharing highlights the importance of using other approaches to constrain prices. Physician cost-sharing for drugs is an area that has not been addressed in theoretical analysis, although empirical evidence of the German and UK experience suggests significant effects. Analysis of provider risk-sharing in other contexts suggests that it can lead to undesirable cream-skimming if budget parameters cannot be appropriately risk-adjusted to reflect differences in each provider's patient characteristics. “Silo budgeting” with specific spending limits on individual medical services—drugs, hospitals, physicians—can also undermine incentives for cost-effective substitution between medical services. Integrating optimal patient and physician risk-sharing into regulatory systems for setting drug prices and utilization is an important issue for future research.

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Notes:

(1.) Efficient incentives for innovation also depend on optimal patent structure and subsidies (Garber et al. 2006), which are beyond the scope of this chapter.

(2.) Addressing this question empirically is problematic in the absence of exogenous measures of optimal levels of prices and R&D expenditures.

(3.) DiMasi and Paquette (2004) reported that entry of follow-on compounds reduced the market exclusivity period of first entrants in a new therapeutic class from 10.2 years in the 1970s to 1.2 years in the late 1990s.

(4.) Although the industry is characterized by high fixed costs, models in which firms endogenously choose sunk costs, in the form of either R&D or promotion, to retain competitive advantage and deter competition or entry (Sutton 1991) have been refuted by the entry of hundreds of small firms over the last two decades.

(5.) For example, in Sweden the maximum co-payment for chronic medications is 200 euros over a 12-month period; in effect, most patients taking chronic medications have “free drugs” (Drummond et al. 2010).

(6.) As Garber et al. (2006) and Jena and Philipson (2008) pointed out, these models ignore issues of optimal public funding of R&D, incremental R&D for which late entrants get excessive returns, and optimal patent length and breadth.

(7.) Social benefits other than health gain could in theory also be included but in practice may be more difficult to implement.

(8.) For example, see Drummond et al. (2010).

(9.) This assumes that in the steady state the prices of current therapies that are being referenced when constructing the ICER are based on the value they provide.

(10.) They did not consider alternative mechanisms for delivering subsidies to low-income countries.

(11.) Coverage by the basic Social Security system may vary from 100 percent for life-saving drugs to 30 percent for largely discretionary drugs. However, the great majority of the French population have supplementary, mutuelle insurance that covers their cost-sharing, so the high co-insurance on basic coverage has little constraining effect on pricing.

(12.) Pharmacy benefit managers in the United States rarely use TRP, preferring the tiered formularies, which are more flexible in permitting price differences between drugs in the same therapeutic class, especially between on-patent and off-patent drugs.

(13.) Germany has at times waived the patient co-payments for products priced lower than the RP. Physician drug budgets may also encourage physicians to prefer cheaper products. For generics, if pharmacy substitution is permitted and reimbursement creates incentives to prefer cheaper products, this can stimulate price competition below the RP (Danzon and Furukawa 2011). The fact that since 2006 German sickfunds have chosen to contract directly with generic suppliers, using competitive tenders to obtain lower prices than those available through the RP system, confirms the weak competitive effects under RP.

(14.) This assumes that in the absence of TRP price is equal to reimbursement and patient cost-sharing is low.

(15.) The Pan American Health Organization (PAHO) has used this approach in purchasing vaccines.

(16.) Parallel trade is also called commercial drug importation (or simply drug importation). Some analyses refer to international exhaustion of patent rights, which has the effect of legalizing parallel trade.

(17.) Aggregate spending limits are usually historically based. Physician-specific spending limits may be adjusted by specialty. Product-specific limits for new drugs are based on expected volume given approved indications.

(18.) The regulation of new drug prices in Japan starts with prices of existing drugs, with mark-ups provided for innovation or incremental value (in theory). The resulting internal benchmark price is averaged with an external benchmark, calculated as the average list prices in four major markets (the United States, United Kingdom, France, and Germany). This partially offsets the downward pressure on new drug prices that could otherwise result from internal benchmarking to existing drugs with declining prices.

(19.) In 1993 the EU adopted a Supplementary Protection Certificate (SPC) of up to five years.

(20.) See chapter 7 for more detail on patents and on data and market exclusivities.

(21.) For example, generics were defined by law in France only in 1996.

(22.) In Germany physician drug budgets and the waiving of patient co-payments for use of drugs priced below the RP has created some incentive for generics to price below the RP.

(23.) Since 2007, German sickness funds have contracted directly with generic companies to become preferred generic suppliers in return for discounts. This is expected to transform the German generic market from branded and physician driven to unbranded and payer driven.

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