The Economics of the Biopharmaceutical Industry

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Abstract and Keywords

This article summarizes the literature, and considers the issue of paying for research and development. It reviews research and development costs, regulation, productivity and incentives for innovation. It discusses market demand and pricing, effects of insurance, reimbursement regulation, alternatives to patents, and generics. Further, it reviews trends in promotion, regulation of promotion and its effects. It discusses global issues, including differential pricing and R&D for neglected diseases. The focus is on the US, as the home of the largest number of multinational pharmaceutical and smaller biotech companies. This article notes the important differences in regulatory and reimbursement systems in other countries. Finally it suggests that although there is large and growing literature on the pharmaceutical industry that has produced valuable information, important issues remain for future research.

Keywords: research and development, generics, pharmaceutical, reimbursement, productivity

22.1 Introduction: Key Characteristics of Biopharmaceuticals[1]

SPENDING on biopharmaceuticals has grown rapidly over the last two decades. This spending growth reflects technological advances that contribute significantly to human health but also pose novel challenges for policymakers. The US research-based biopharmaceutical industry invests 15–17 percent of sales in R&D, and the R&D cost of bringing a new compound to market is estimated at over $1bn. (DiMasi and Grabowski 2007). This research intensity underlies many of the unique features of this industry. First, regulation of the safety and efficacy of new drugs entails high costs, benefits and policy debate about the appropriate extent and structure of regulation. Second, the biopharmaceutical firm's cost structure has high, globally joint, fixed costs of R&D and low marginal costs of production. Patents are thus essential to enable innovator firms to recoup their R&D investments. But patents operate by limiting competition and enabling innovator firms to charge prices above marginal cost. Defining appropriate prices and patent terms, including criteria for post-patent generic entry, is problematic. The high price-marginal cost margin also creates strong incentives for promotion that has sometimes been viewed as inappropriate. (p. 521) Alternatives to patents have been proposed (prizes, patent-buyouts, etc.) but all have implementation challenges.

Third, on the demand side consumer price sensitivity is undermined by physician prescribing, acting as agents for consumers who cannot readily evaluate the benefits and risks of pharmaceuticals, and by pervasive insurance coverage, to protect consumers against financial risk. Inelastic demand creates incentives for firms to charge higher prices than they would if consumers were informed decision-makers and faced full prices. To address the information asymmetries and insurance-induced distortions, private and public insurers in the US and other countries use a range of strategies to control patient and supplier moral hazard, including tiered formularies and patient cost sharing in the US and price or reimbursement controls in other countries. These third party payer controls significantly affect drug pricing, rates of uptake or diffusion of new products, the nature of competition between firms and ultimately profitability and incentives for R&D to supply new medicines.

Fourth, the global nature of pharmaceutical R&D raises issues of appropriate cross-national price differentials and cost sharing. National regulators have incentives to free-ride, driving domestic prices to country-specific marginal cost, leaving others to pay for the joint costs of R&D. The long R&D lead times—on average roughly twelve years from drug discovery to product approval—make the incentives for short run free-riding by individual countries particularly acute because negative effects will be delayed for years and hard to attribute. While the principle of differential pricing between the richest and poorest nations is widely accepted, consensus breaks down on appropriate price levels and differentials, particularly for middle-income countries with emerging middle classes but large poor populations. In practice, the ability of pharmaceutical firms to price

discriminate is undermined by government policies that regulate domestic prices by referencing foreign prices, adoption of most-favored-nation clauses, and legalization of drug importation (also called parallel trade or international exhaustion of patent rights). These cross-national price spillovers in turn create incentives for firms to delay or not launch new drugs in low price markets, if these low prices would undermine potentially higher prices in other markets. Thus the design of each country's price regulatory system affects not only its prices and availability of drugs but also availability in other countries through price spillovers in the short run, and through R&D incentives in the long run.

Structurally, the on-patent phase of most pharmaceuticals can be viewed as oligopolistic with differentiated competitor products in the short run. In the longer run, the appropriate model for a therapeutic class is monopolistic competition, with generic entry on patent-expired older molecules and dynamic competition from newer, improved products as new therapeutic pathways are discovered. Despite high costs of drug discovery, over the last two decades thousands of small firms have been created around new R&D technologies or products. Many have exited as products fail, but new entry of firms and products continues to occur.

Although the biopharmaceutical industry is heavily regulated, the economic rationale for regulation is not structural barriers to competition. Rather, market access regulation is a response to imperfect and/or asymmetric information of consumers and (p. 522) physicians in evaluating the safety and efficacy of new products. Price and/or reimbursement regulations are a response to patents and insurancerelated moral hazard. To the extent that market power exists, it is due in part to government-granted monopoly implied by patents. Both positive and normative analysis of product differentiation and pricing must take into account heterogeneity in patients' response to different drugs, and the roles of physician prescribing and third party payment as key determinants of demand elasticities. In this context, drawing welfare conclusions about optimal levels of R&D and product variety is complex. Most analysis to date and most discussion here is therefore positive rather than normative.

The structure of this chapter is as follows. Section 22.2 reviews R&D costs, regulation, productivity and incentives for innovation. Section 22.3 discusses market demand and pricing, effects of insurance, reimbursement regulation, alternatives to patents, and generics. Section 22.4 reviews trends in promotion, regulation of promotion and its effects. Section 22.5 discusses global issues, including differential pricing and R&D for neglected diseases. Section 22.6 concludes. The focus is on the US, as the largest single market (North America accounted for 45.9 percent of global pharmaceutical sales in 2007, compared to 31.1 percent for Europe) and the home of the largest number of multinational pharmaceutical and smaller biotech companies. Important differences in other countries' regulatory and reimbursement systems are noted, to the extent possible.

22.2 R&D: Technology, Regulation, and Costs

22.2.1 Technology

The pharmaceutical industry grew out of the chemical industry. Advances in basic science, medicine, and microbiology have enabled new generations of medicines to treat previously untreated diseases—for example, antiulcerants in the 1980s, antidepressants, and lipid lowering drugs (statins) in the 1990s, recombinant proteins and monoclonal antibodies more recently. The nature and potential of pharmaceutical R&D was revolutionized in the 1990s by advances in microbiology, informatics, genomics, and other sciences that are still evolving. Many of the basic science breakthroughs occurred in academic labs, often with government funding. In the US, the 1983 Bayh-Dole Act facilitated the commercialization of these discoveries, by enabling the transfer of IP rights to the private parties responsible for the innovation, subject to residual rights retained by government. This process continually spawns new start-up firms, which usually obtain venture capital and other private and public equity financing. Many are acquired by larger companies, seeking to acquire the new technologies and products. The most successful survive to become midsize and ultimately large biotech firms, such as Genentech, (p. 523) Amgen, Gilead, etc. Thus the biotech revolution has revolutionized drug discovery and transformed industry structure.

22.2.2 Regulation of R&D and Market Access

Although the methods of drug discovery have changed, the process still proceeds through stages of lead identification, preclinical laboratory and animal testing, followed by small scale human trials to establish safety and proof of concept and ultimately large human clinical trials, often in thousands of patients, to prove safety and efficacy prior to drug approval. This process, culminating in drug approval, is regulated in the US by the Food and Drug Administration (FDA), by the European Medicines Evaluation Agency (EMEA) in Europe and by similar agencies in other countries that have evolved in similar ways. In the US, the 1938 Food, Drug and Cosmetics Act required any firm seeking to market a new chemical entity (NCE) to file a new drug application (NDA) to demonstrate that the drug was safe for use as suggested by the proposed labeling. The FDA had 180 days to reject the NDA. This Act also established jurisdiction over drug advertising and requirements that patients obtain a prescription from a physician in order to obtain retail drugs.

The 1962 Kefauver-Harris Amendments laid the ground rules of current FDA regulation. These Amendments strengthened safety requirements; added the requirement that drugs show proof of efficacy, usually by double blind, randomized controlled trials of the drug relative to placebo; removed the 180 day time limit within which the FDA could reject an

NDA; extended FDA oversight of clinical testing and manufacturing; and restricted manufacturers' promotion to approved indications. Basic requirements for promotional materials include that they cannot be false or misleading; they must provide a fair balance of risks and benefits; and they must provide a “brief summary” of contraindications, side effects and effectiveness. The 2007 Amendments further strengthened the FDA's authority to grant conditional or restricted approval, subject to specified risk evaluation and monitoring systems.

The economic rationale for requiring pre-market proof of safety is that manufacturers may face suboptimal incentives to provide risk information to consumers in the absence of regulatory requirements. The requirement for pre-market proof of efficacy has been more controversial, given the high cost and launch delays associated with doing large Phase III trials required to establish efficacy and/or detect remote risks in subpopulations. The economic rationale for efficacy requirements is that imperfect information may prevent physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and other associated costs, and possibly excessive product differentiation that undermines price competition. Firms may have incentives to exaggerate benefits and downplay risks in their promotion, given the high price-marginal cost margins. Moreover, setting standards and evaluating clinical trial evidence of efficacy and safety requires expertise and is a public good that can arguably be provided most efficiently by a single expert agency.

(p. 524) However, these pre-launch requirements for safety and efficacy also add significantly to the cost and delay of launching new drugs, raising concerns over barriers to entry and forgone benefits for consumers. Subsequent legislation has addressed some of these cost-increasing effects of the 1962 Amendments. The Orphan Drug Act of 1983 increased “pull and push subsidies” for drugs that receive orphan status (defined as conditions that affect less than 200,000 individuals in the US), including market exclusivity for seven years and a 50 percent tax credit for expenses accrued through clinical testing. Between 1983 and 1998, the number of orphan drugs increased five-fold, while the number of non-orphan drugs increased less than two-fold (Lichtenberg and Waldfogel 2003).

To accelerate FDA review of regulatory filings, under the Prescription Drug User Fee Act (PDUFA) of 1993[2] and subsequent renewals, pharmaceutical firms pay user fees that are used to fund additional FDA reviewers.[3] These user fees now account for about 50 percent of total processing costs at the FDA (US FDA 2005). The Priority Review system provides a six month target review time for new drugs that target unmet medical need, whereas “standard review” drugs have target review time of ten months. Fast Track status to further accelerate the approval of novel drugs that are “intended for the treatment of a serious or life-threatening condition” and “demonstrate the potential to address unmet medical needs for the condition” (US FDA 1997). Fast Track has reduced overall development times by approximately 2.5 years (Tufts Center for the Study of Drug Development 2003).

Harmonization of requirements of the US FDA and parallel agencies in the EU and Japan has enabled companies to prepare a common dossier, typically based on trials done in multiple countries, although some country-specific variations remain—for example, the EMEA typically requires comparison relative to current treatment rather than placebo and Japan requires trials on Japanese nationals—and each agency makes its own approval decision based on its evaluation of risks vs. benefits.

22.2.3 R&D Costs

The cost of developing an approved new medical entity (NME), measured as a discounted present value at launch, grew from $138 million in the 1970s to $802 MILLION in 2001 and over $1bn in 2007 (DiMasi and Grabowski 2007). This high cost per NME reflects three main factors: high input costs of discovery research, animal and human trials; high failure rates, including the great majority of preclinical candidates and over four out of five compounds that enter human trials; and the eight-twelve years required, (p. 525) such that roughly half of the total cost per NME is forgone interest or capitalization cost. Although this capitalization cost is not an out-of-pocket expense to firms, it is an opportunity cost that must be returned to investors in order to attract capital.

Several factors have contributed to this growth in cost per NME and, inversely, to the implied declining R&D productivity. Clinical trial costs have risen, due to larger and longer trials, more procedures and higher cost per participant (DiMasi, Hansen, and Grabowski 2003). These trends reflect many factors, including: longer trials for drugs targeted at chronic diseases; higher costs of medical care and testing due to new medical technologies; higher failure rates on compounds that address novel targets (Aghazadeh, Boschwitz, Beever, and Arnould 2005); collection of economic data to satisfy payer demands for cost-effectiveness data; and heightened regulatory concerns to detect remote risks. Whether or not regulatory standards have increased is hard to distinguish from underlying changes in circumstances. As patents have expired on prior innovations, many of the mass, primary care diseases can be treated reasonably well with cheap generics, hence regulators and payers may require either high benefits or minimal risks on new drugs. Innovator firms have shifted R&D towards diseases with few existing treatment options, which are typically more complex, with less well understood biological pathways, such as Alzheimer's, cancer, obesity, and rheumatoid arthritis. Failure rates on drugs with novel mechanisms are higher than on drugs that address well-established targets, reflecting both safety and efficacy failures that sometimes are only manifest in the large scale, Phase III trials. Many of the successful innovative products are biologics, discovered by biotechnology firms. Despite rising R&D investments, large pharmaceutical firms have been unable to generate internally new drugs to replace their patent-expiring older drugs. Although large firms have aggressively acquired and inlicensed new products and technologies from biotech firms, many have seen dramatic declines in market capitalizations, and some consolidation.

22.2.4 Empirical Evidence on Costs and Benefits of Regulation

Measuring the costs and benefits of regulation requires identifying the counterfactual against which to compare actual experience. Early studies used intertemporal and cross-national comparators, which both require strong *ceteris paribus* assumptions. With that caveat, studies generally concluded that the 1962 Amendments, which raised safety standards and added efficacy requirements, increased costs for firms, added to delay in drug approval, and possibly reduced competition (for example, Grabowski, Vernon, and Thomas 1978). Peltzman's (1973) study of both benefits and costs of the 1962 Amendments concluded that the benefits were minimal and were far outweighed by the costs due to fewer new drugs. However, the methods and conclusions have been questioned (for example, Temin 1979). In particular, ascribing the 1960s decline in NCEs entirely to regulation, rather than to a short-term hiatus in scientific opportunities, may overstate the costs and understate the safety improvements of the 1962 Amendments.

(p. 526) Several recent studies have examined the benefits and costs of the priority review policy introduced by PDUFA in 1992. The User Fee and Priority Review systems have clearly reduced review time: Between 1993 and 2003 the median time to approval for “priority” drugs declined from 14.9 to 6.7 months, while review times for “standard” products only decreased from 27.2 to 23.1 months (Okie 2005). At issue is whether faster review led to approval of more risky products, and hence contributed to increased post-launch adverse drug reactions and some recalls. Olson (2004a) finds that post-launch reports of adverse drug reactions were more likely for drugs that the FDA rates as “priority,” but that these safety costs were outweighed by the benefits of a faster launch due to priority review, assuming Lichtenberg's (2002) estimate of gain in life expectancy due to new drugs. However, costs may be under-estimated, given subsequent evidence of under-reporting of adverse events through the FDA's postmarketing surveillance mechanisms (Brewer and Colditz 1999; Bennett, Nebeker, et al. 2005). By contrast, the General Accounting Office (US GAO 2002b) found that drug withdrawals rates differed insignificantly between the period before and after the PDUFA; however, this study did not control for other factors that may have influenced drug withdrawals rates. Philipson, Berndt, Gottschalk and Sun (2008) consider the speed-safety trade-off induced by PDUFA and conclude that net welfare effects were significantly positive.

While accelerating regulatory review plausibly has positive net effects, provided it remains adequately resourced, reducing the duration of Phase III trials raises more fundamental trade-offs between risk reduction and prompt access to new drugs. Whether this trade-off should be framed more rigorously in terms of net expected QALYs gained is a fundamental question that has not been widely addressed. However, significant progress is underway on trying to improve the trade-off by initially restricting launch to more controlled environments and by supplementing pre-launch randomized controlled trials with post-launch observational evidence. The 2007 FDA Amendments Act authorized the FDA to condition approval on risk evaluation and mitigation strategies, such as post-launch monitoring requirements through patient registries and approvals

limited to patient sub-groups with greatest medical need. Such restrictions may increase FDA willingness to approve new drugs earlier. In addition, advances in statistical methods for analyzing claims and other data from routine care, to adjust for possible non-random assignment of patients to different treatments, offers a potentially rich and relatively cheap source of information that could supplement clinical trial data, providing larger sample sizes, detail on subpopulations and evidence on long term effects without delaying access to new drugs. Such approaches are critical to efficiently detect rare safety issues and identify subpopulations at risk for adverse effects or non-response. Over time, accumulation of evidence and understanding of heterogeneity in patient response to drugs, based on genetic and other biomarkers, should eventually enhance the safety and efficacy of approved drugs, reduce R&D failure rates and costs, and advance the goal of "personalized medicine."

Although charges that the FDA is "captured" by the industry are common in popular media, standard economic models of producer vs. consumer capture of the regulatory process appear to be less relevant than current events and crises in explaining the shifting (p. 527) regulatory emphasis between safety and speed to market. For example, public and Congressional concerns focused on speeding up access to new drugs in the 1980s and 1990s, partly in response to the AIDS crisis. More recently, post-launch evidence on risks of some widely used drugs, including the COX-2 inhibitors for arthritis and pain (notably rofecoxib (Vioxx) and valdecoxib (Bextra)), the SNRI antidepressants and others have led to a range of proposals and initiatives to enhance regulation of safety. Some argue that an effective oversight board should be independent of the FDA as the approving agency (for example, Okie 2005) to avoid industry capture. On the other hand, given the FDA's limited resources and vast responsibilities, there is a strong case for coordination of pre- and post-launch monitoring to take advantage of expertise and economies of scale in reviewing data and assuring consistency.

22.2.5 Regulation vs. Markets vs. Tort Liability

Some have argued that consumers should be permitted to make their own evaluations of risks vs. benefits based on phase II trials (Madden 2004).[4] However, phase II trials are small, designed to provide proof of concept and preliminary dose-ranging evidence of safety and efficacy in select patient sub-groups. Such trials lack the statistical power to provide credible results for general decision-making. A specialized agency such as the FDA accumulates expertise and provides a public good in evaluating the evidence on safety and efficacy, including requiring that minimum standards and reasonable trade-offs be met as a condition of launch. Such information would be under-provided in a free market regime and cannot be efficiently assessed from the personal experience of individual physicians or even health plans, both of which have more limited information and expertise than the FDA and may be imperfect agents, given their financial stakes, respectively, in prescribing and controlling drug spending.

The expanded range of drug therapy and growth of insurance coverage have increased the social benefit of having a regulatory agency review and establish minimum standards for marketed drugs. When consumers paid out-of-pocket and few drugs were available, the main benefit of a regulatory requirement for efficacy was to protect consumers from wastefully spending their own money on useless drugs. Given the expansion in number and complexity of drugs available, with many consumers taking multiple prescriptions for chronic diseases, the information burden of staying informed and the potential cost of being misinformed have increased, as has the potential for adverse drug reactions and interactions. The growth of insurance coverage has also undermined individual consumer's financial incentives to avoid wasteful spending on drugs that are of low or only minor benefit. These trends increase the public good case for a regulatory agency such as the FDA to establish minimum standards of safety, efficacy, and quality as a condition of market access. Similar arguments might also be applied to limit reimbursement to approved indications, (p. 528) as occurs in most countries with national or social insurance systems. By contrast, in the US both Medicare and private health plans so far generally reimburse for off-label use, provided it is supported by published studies as listed in medical compendia.

A related question is the optimal role of tort liability, given regulation. The FDA is an expert agency that relies on internal specialists and external advisory panels comprised of medical and statistical experts who review and evaluate comprehensive data on risks and benefits. Their decisions should in theory be better informed, more consistent across drugs and more able to balance societal risks and benefits than the untrained juries that decide tort claims. Moreover, tort claims focus on adverse outcome to an identified patient, who may have had competing medical and lifestyle risk factors, rather than average effects for patients at large. For example, if the FDA decided that a 1 percent risk of an adverse outcome from a drug was acceptable in view of its benefits, how does a jury decide whether an individual patient's adverse event is within this 1 percent, in which case the firm should not be liable, or lies outside the 1 percent, in which case the drug may be less safe than expected and the firm should be liable? More generally, notions of a “defective product” under strict product liability or “negligent product design” in a negligence claim, are problematic when applied to drugs for which it may be prohibitively costly to identify patients at risk of adverse response. Unclear standards lead to erratic and unpredictable liability rulings, in which case incentives for safety are likely to be excessive (Craswell and Calfee 1986). Moreover, tort decisions made ex post, after a drug has been on the market, are at risk of applying new information retroactively, holding a firm liable for a rare adverse effect that only emerges after widespread or long-term use of the drug, which could not reasonably have been foreseen without undue costs and delay of pre-launch testing that would deprive other patients of access. However the Supreme Court recently struck down the claim of pre-emption, that the FDA's regulatory approval protects companies against liability when the agency's instructions are followed, because the FDA has not expressly been given pre-emption by Congress.[5]

22.3 Industry Structure, Competition, Pricing, and Price Regulation

22.3.1 Industry Structure and Competition

The pharmaceutical industry is structurally competitive, with relatively low overall concentration and continual entry of new firms and products. Patents constitute a government-granted barrier to generic competition for the term of the patent, in order to enable innovators to recoup R&D investments. However, over time firms are subject to both intermolecular and intra-molecular competition. Specifically, dynamic (p. 529) competition exploits and pushes scientific advance, such that within each therapeutic class there are typically several similar but differentiated, competing compounds that are ultimately challenged by generics and by dynamic competition from new, improved originator products. Number of competitor compounds in a class depends on the size of the market (Acemoglu and Linn 2004) but successive entry occurs increasingly rapidly. The period of market exclusivity of first entrants to a new therapeutic class fell from 10.2 years in the 1970s to 1.2 years in the late 1990s (DiMasi and Paquette 2004).

Price competition between on-patent brands (intermolecular) is muted by two institutional characteristics: physician prescribing and insurance coverage. Theory suggests that the separation of prescribing from consumption reduces demand elasticity if physicians are imperfectly informed about drug prices and/or are imperfect agents for patients (assuming no payer controls). The limited evidence from the UK and Germany suggests that placing physicians at risk for drug spending through indicative budgets increases price sensitivity, mainly through greater use of generics, but may also lead to inappropriate rationing.[6]

More fundamentally, insurance coverage undermines patients' price-sensitivity, hence makes the demand facing manufacturers more price-inelastic. This creates incentives for firms to charge higher prices and patients to use more (and/or more costly) drugs, unless payers adopt controls. Consumer cost-sharing can mitigate this tendency for insurance to induce producer and consumer moral hazard, but only by reducing financial protection for patients, which may have undesirable efficiency and equity effects unless cost-sharing is appropriately income-adjusted.

To counteract this price-increasing tendency of insurance, both private and public insurers use a range of strategies to either encourage competition or constrain prices directly. In fact, the structure of insurance reimbursement has become the major determinant of competition and pricing strategies for pharmaceuticals. Conclusions on the extent and nature of price competition may therefore be specific to particular insurance arrangements, as are estimates of demand elasticity.

22.3.2 Pricing and Reimbursement in the US

In the US, private insurers and pharmacy benefit managers (PBMs) establish three- or four-tier formularies of preferred drugs, with higher co-payments for higher tiers—for example, $5 for a generic, $25 for a preferred brand, $45 for a non-preferred brand and 25 percent co-insurance for the fourth tier. The tiered co-payments shift utilization towards drugs on lower tiers. This ability to shift market share enables PBMs to negotiate price discounts from manufacturers in return for preferred formulary placement. (p. 530) Medicare (the public program for seniors) added Part D to provide outpatient drug coverage under the Medicare Modernization Act (2003). Seniors can choose among private prescription drug plans (PDPs) that are similar to PBMs and use similar formulary structures to negotiate drug price discounts. Under the “non-interference” clause of the Medicare Modernization Act, the federal government is barred from negotiating drug prices, although this may change. Thus formulary design, whereby PBMs, PDPs, and other payers induce competitive discounting, is the main mechanism for constraining prices on pharmacy-dispensed outpatient drugs in the US. Discounts are confidential in order to preserve competitive incentives. Although comprehensive evidence on effects of formularies on drug prices is unavailable, theory and anecdotal evidence suggest that competitive discounting is effective in therapeutic classes with several, closely substitutable drugs, but that it is less effective in specialty classes, including most biologics, where clinical differences between drugs limit payers' ability to constrain physician/patient choices.

Competitive price discounting has also been constrained by the “best price” provision for Medicaid, the public program for certain low income groups. Under the 1990 Omnibus and Reconciliation Act, originator drugs must give Medicaid the lower of (a) the “best price” offered to any non-federal purchaser or (b) a 15.1 percent discount off AMP (the average manufacturer price to the retail sector), plus an “excess-inflation” rebate for price increases greater than the CPI (to deter firms from raising AMP in response to the best price provision). For 2003, the combined effect of these mandatory discounts resulted in an average 31.4 percent discount for Medicaid, relative to AMP (CBO 2005b). By tying Medicaid rebates to discounts given to private payers, the Medicaid best price provision limits the ability of manufacturers to price discriminate, which led to a decline in discounts to private payers (GAO 1993; CBO 1996). The MMA explicitly exempted discounts granted to Medicare PDPs from the Medicaid Best Price provision, to encourage deep discounts to PDPs. Duggan and Scott Morton (2006) found that drugs with larger Medicaid market share had larger price increases.[7]

Many cancer drugs and other biologics that require infusion in a physician's office are reimbursed under Medicare Part B or the medical benefit of private plans. Since 2005 Medicare pays physicians the manufacturer's volume-weighted Average Sales Price (ASP), plus 6 percent to cover storage and handling. This reimbursement approach creates perverse incentives for physicians to prefer high-priced products and hence for manufacturers to compete by charging high rather than lower prices (Danzon, Wilensky,

and Means 2005). This system will also undermine potential savings from follow-on biologics, unless such follow-on products are classified under the same reimbursement code as the originator product, in which case firms may have an incentive to discount to physicians, which would in turn reduce subsequent calculations of ASPs.

(p. 531) 22.3.3 Price Regulation and Competition Ex-US

In most industrialized countries with universal national health insurance schemes, the government (or a surrogate) regulates prices or reimbursement for drugs as for other medical services. Price controls generally only apply if the product is reimbursed, consistent with the view that pharmaceutical price regulation is fundamentally an insurance strategy to control potential supplier pricing moral hazard. Patient co-payments are often modest and invariant to the drug price. Firms thus have little incentive to price below the regulated price except for sales to hospitals, where tendering is common and prices are reportedly often below regulated prices.

The theoretically optimal insurance/reimbursement contract for drugs must deter both insurance-induced over-use by patients and excessive prices by manufacturers, while paying prices sufficient to reward appropriate R&D, taking into account the global scope of pharmaceutical sales. Models by Lackdawalla and Sood 2005, Garber and Romer (2006), Jena and Phillipson (2008), and Danzon, Towse and Ferrandiz (2011) address some of these issues. An important conclusion is that patient cost sharing alone cannot simultaneously provide optimal incentives for efficient use of drugs, control of patient moral hazard and optimal provider incentives for R&D. In addition, given the global nature of pharmaceutical utilization, creating optimal R&D incentives require appropriate price differentials across countries (Danzon and Towse 2003; Danzon, Towse and Ferrandiz 2011). In practice, many countries also regulate conditions of patient access and total drug spending.

In regulating drug price and/or reimbursement, most countries use some form of either *internal* or *external* benchmarking (for more detail see Danzon and Keuffel 2007, Danzon 2011).[8]

Internal benchmarking. This compares the price of the new drug to prices of otherdrugs in the same class, with potential mark-ups for improved efficacy, side effect profile or convenience, and sometimes for local production. An extreme variant of internal benchmarking is *Reference Price (RP) Reimbursement*. Generic RP clusters products based on the same compound, and is widely used for off-patent products. Therapeutic RP, as implemented in Germany, the Netherlands, and New Zealand, clusters products with the same or similar mode of action and/or same indication. All products in an RP group are reimbursed at the same reference price, which is usually based on a low priced product within the group. If manufacturers charge prices above the RP, the patient must pay the difference, and in practice prices usually converge to the reference price.

Internal benchmarking and, in particular, reference price reimbursement systems, differ in stringency, depending on whether reimbursement groups are broadly defined, regardless of differences in efficacy, dosing convenience and formulations, and patent (p. 532) status. In particular, if therapeutic reference groups disregard patent status, patent expiry on the oldest compound in a class can reduce reimbursement for later on-patent products in the group to the price of a cheap generic, effectively truncating patent life for late entrants unless patients recognize and are willing to pay surcharges for product improvements. Such reimbursement systems would significantly reduce incentives for R&D for later entrants and improved formulations of existing drugs, if applied in major pharmaceutical markets such as the US. Whether this would be welfare-enhancing, by eliminating wasteful R&D, or welfare-reducing, by eliminating potentially cost-effective new drugs and reducing competition, is probably context-specific and cannot be predicted a priori.

External benchmarking. External benchmarking caps the price of the new drug incountry A to that same drug's mean, median or minimum price in specified comparator countries. For example, Italy uses an average European price, Canada uses the median of seven countries, etc. Thus external benchmarking limits the manufacturer's ability to price discriminate across countries. In cases where relatively high price countries reference lower price countries, theory and evidence suggest that such policies lead manufacturers to seek higher prices in low-price countries and delay or forgo launch, particularly in small markets, until higher prices have been established in the referencing countries (Danzon, Wang, and Wang 2005; Kyle 2005; Lanjouw 2005; Danzon and Epstein 2009). Parallel trade, which is legal in the EU, similarly creates incentives for manufacturers to seek higher prices as a condition of launch in lower-price EU markets, unless such trade can be deterred through supply limits and other mechanisms.

External referencing by high-price countries thus imposes a welfare loss in lower-price, referenced countries, contributing to launch lags and non-launch and/or higher prices. More generally, regulatory systems that induce price convergence across countries are likely to reduce social welfare. This assumes that price discrimination is welfare-increasing, compared to uniform pricing for pharmaceuticals, because utilization declines under uniform pricing as low-income countries and sub-groups drop out of the market (Danzon and Towse 2003, 2005; Jack and Lanjouw 2003). Moreover, Ramsey pricing principles suggest that differential pricing also contributes to dynamic efficiency (Ramsey 1927; Baumol and Bradford 1970). Recent use of MFN clauses by some middle income countries and US proposals to legalize commercial drug importation from a broad group of countries could, if implemented, have serious negative effects on price and availability of drugs in referenced countries. Thus whereas the welfare effects of country-specific price regulation are ambiguous a priori, assuming regulators internalize (most of) the costs and benefits, welfare effects are clearly negative from regulatory systems that attempt to control one country's prices by referencing prices or importing drugs from other countries.

Drug Budgets and Expenditure Controls. Some countries have augmented price/reimbursement controls with expenditure caps on total drug spending to a target percent of health care spending—for example, France and Italy. Over-runs are recouped by price cuts or mandatory rebates from companies and/or drug classes that exceed allowed targets and/or allowed promotion guidelines.

(p. 533) 22.3.4 Cost-effectiveness Requirements for Reimbursement

Evaluation of the comparative effectiveness and cost-effectiveness of a new drug relative to current treatment is a condition of reimbursement in Australia, Canada, and the UK (for most drugs) and an input to price and/or reimbursement negotiations in many other countries. Drug cost generally includes any offsets in other medical costs, and sometimes other societal costs such as care-giver time. Outcomes measures and decision rules differ across countries. For example, the UK National Institute for Clinical Excellence (NICE) generally uses cost per quality adjusted life year (QALY). Although the CE review process is usually separate from the price control process, if any, applying a CE threshold effectively constrains the price that can be charged for a new drug, given its relative efficacy and cost of comparator treatment. Regulating prices indirectly through a review of cost-effectiveness is in theory consistent with principles of efficient resource allocation (Danzon, Towse and Ferrandiz 2011), in contrast to other criteria used to regulate drug prices. However, many theoretical and practical details of implementation remain unresolved, including: appropriate measurement of benefits, particularly for life-threatening treatments such as cancer; appropriate thresholds; and how to adapt decisions post-launch, as more data on costs and outcomes accumulate.

22.3.5 Evidence of Effects of Price Regulation

Estimating effects of drug price regulation is confounded by the heterogeneity of such systems and by other unobservable country-specific characteristics. Estimates of cross-national drug prices indexes vary significantly, depending on the time period, sample of drugs, the price index methodology, consumption weights and exchange rates. Many price comparisons have been biased by focusing on small, non-random samples of branded drugs only, and have not used standard index number methods (for example, GAO 1992, 1994). The exclusive focus on branded drugs tends to bias comparisons in favor of countries with strict price regulation, because more regulated markets have traditionally had lower brand prices but smaller generic market shares and higher generic prices. Overall, countries that use direct price controls do not consistently have lower prices than countries that use other indirect means to constrain prices (Danzon and Chao, 2000a and 2000b; Danzon and Furukawa 2003, 2006, 2008). Drug price differences among industrialized countries are roughly consistent with differences in per capita income, which may be consistent with optimal differential pricing (see section 22.4 below).

Although theory suggests that drug price regulation may affect prices, launch timing and R&D, measuring such effects for specific price control regimes is problematic, because each country's regulations are different, often multidimensional and change over time. For example, Germany adopted RP for some classes starting in 1989, but new (p. 534) patented drugs were excluded from 1996 to 2004. Germany also had variants of physician drug budgets, intermittent price controls on non-referenced drugs, and changing requirements for pharmacies to substitute generics. Moreover, the effects of RP or other regulatory strategies on R&D depend on the adopting country's share of global sales, because R&D incentives depend on global expected revenues. In particular, effects of regulatory regimes on R&D have so far probably been modest, compared to the likely effects if the US were to adopt, say, therapeutic RP, given the large US share of global revenues and its low-priced generics (Danzon and Ketcham 2004).

The early literature on RP is summarized in Lopez-Casasnovas and Puig-Junoy 2000. Early evidence from Germany confirmed that brand drugs generally dropped their prices when RP was introduced. However, both theory and evidence suggest that dynamic price competition over time was weak, because firms have no incentive to reduce prices below the RP, unless other provisions make pharmacists price sensitive (Danzon and Ketcham 2004). Although RP has been compared to premium support subsidies for insurance, this analogy is imperfect because unlike premium support subsidies, RP is not risk-adjusted for patients and RP may have significant R&D effects.

22.3.6 Generics

After patent expiration of the originator brand, entry of generics can lead to intense price competition and significant savings for payers/consumers, depending on critical regulatory and reimbursement details. In the US, generics now account for almost seventy percent of all prescriptions but only about 16 percent of sales, due to their low prices. Although US prices for on-patent drugs are on average 20–40 percent higher in the US than in other industrialized countries, US generic prices are lower (Danzon and Furukawa 2008), due to US regulatory and reimbursement conditions that align to promote intense price competition. First, the 1984 Hatch-Waxman Patent Term Restoration and Generic Competition Act established the Abbreviated New Drug Application (ANDA) process, which permits generic approval on proof of same active ingredient and bioequivalence to the originator, without new clinical trials. The generic can simply reference the originator's safety and efficacy data, once its five-year data exclusivity has lapsed.[9] Moreover, the Bolar Amendment permits generic companies to start work before expiry of the originator's patents, so generics can enter promptly once patents expire or are successfully challenged (see below). Thus the Hatch-Waxman Act dramatically reduced the time and cost required for generic entry and, by requiring bioequivalence, established clinical conditions necessary for substitutability.

Second, all states have established default substitution rules that allow pharmacists to substitute a bioequivalent generic for the originator brand, even if the physician prescribes the brand, unless the physician specifically notes “brand required.” This substitution rule makes the pharmacist the decision-maker with respect to whether and which generic to (p. 535) dispense, subject to patient acceptance.[10] Since US generics are required to be bioequivalent, quality can be assumed and price is key to pharmacy choice. Public and private payers typically reimburse pharmacies a fixed amount (Maximum Allowable Cost, or MAC), regardless of which generically equivalent product is dispensed, and the MAC is based on the price of a low-price generic. Pharmacies capture the margin between their MAC reimbursement and their acquisition cost. Pharmacies therefore have strong incentives to dispense the cheapest generics, which in turn creates incentives for generic suppliers to compete on price. Generic price competition has been intensified by the consolidation of retail pharmacies into large national chains, such as Walgreens or Rite-Aid, which purchase at corporate levels. Similarly, independent pharmacies purchase through group purchasing organizations. Generic suppliers compete for the business of these high-volume customers through low prices, broad product range and prompt availability of new generics. Brand image is irrelevant for FDA-approved generics that are certified bioequivalent. Thus in the US generics companies do not invest in sales force, promotion or brand.

Finally, most health plans create strong financial incentives for patients to accept generics by placing generics on the lowest formulary tier, with a $0-$10 co-pay, while off-patent brands are on the third or fourth tier with a $40-$50 co-pay or not covered. This co-pay spread has increased over time and has contributed to generic share growth.

Whereas generics in the US are pharmacy-driven, unbranded, and cheap, generic markets in many EU and Latin American countries were traditionally physician-driven. Generics in physician-driven markets tend to be branded, heavily promoted and higher priced. These high-price, branded generics survive in markets that lack the regulatory and reimbursement conditions for price-competitive generics, specifically: bioequivalence; pharmacy substitution as the default rule; financial incentives for pharmacies to substitute low-price generics; and patient incentives to accept generics. Until recently, many European countries authorized pharmacy substitution only if the physician prescribed by generic name, which is uncommon. Moreover, countries that regulate drug prices traditionally also regulated pharmacy dispensing margins as a percent of the drug price, which creates perverse incentives for pharmacists to prefer higher priced products, even if they are authorized to substitute. Moreover, patient co-payments are often invariant to the price of the drug dispensed. In such contexts, generic companies behave like originator products, detailing their brand to physician decision-makers, competing on brand rather than price, which results in relatively high generic prices and often low generic shares (Danzon and Furukawa 2011). Several EU countries have recently changed their regulations, to encourage generic uptake and reduce generic

prices. For example, German sickness funds now negotiate discounts directly from generic suppliers, and pharmacies must dispense these preferred generics.

Many middle and lower income countries that were late in adopting the World Trade Organization's Trade Related Intellectual Property (TRIP) regime grandfathered existing “copy products” that claim “similarity” but have not demonstrated bioequivalence to (p. 536) the originator product. Since quality is uncertain, generic substitution by pharmacies is generally not authorized (although it may occur in practice), and generics market to physicians, competing on brand as a surrogate for reliability, rather than price. The unfortunate result is that many middle and low income countries have relatively high generic prices (Danzon and Furukawa 2008) and uncertain generic quality.

Incentives for early generic entry are greater in the US than in other countries because of the Hatch-Waxman provision, that a generic that successfully challenges the originator's patents (a paragraph IV filing), rather than waiting for the patents to expire, obtains 180 days' exclusivity as the sole generic in the market. Since the sole generic can gain significant market share and profits while shadow-pricing the brand, generic companies invest aggressively in challenging brand patents. Originator firms often issue “authorized generics” to compete during this 180-day exclusivity period. Patent challenges have spawned extensive litigation between generic and originator firms. The circumstances in which originators can legally settle with generic challengers and, more generally, optimal incentives for patent challenges, remain important issues.

Originator brands' options in responding to post-patent generic entry depends on regulatory rules and the nature of competition. In the US pharmacy-driven generic market, originator strategies to produce their own generics have been unsuccessful (other than authorized generics during the exclusivity period) because originator firms lack the major generic firms' large portfolio of products and low costs, which are essential for competing for pharmacy customers.[11] Other originator strategies include: shifting patients to a follow-on formulation (usually a delayed release version of the original drug) or a related product (such as a single isomer version); raising price to the price-inelastic brand-loyal segment (Frank and Salkever 1992); or switching the drug to over-the-counter status, if it can be shown to be safe and effective under patient self-medication.

Empirical studies of generic entry have shown, not surprisingly, that generic prices are inversely related to number of generic competitors (Grabowski and Vernon 1992); generic entry is more likely for compounds with large markets (measured by pre-expiry brand revenue), chronic disease markets (price sensitive patients) and oral-solid (pill) form (Scott Morton 1999; Scott Morton 2000). Caves, Whinston, and Hurwitz (1991) found that total volume did not increase after patent expiration, presumably because the positive effect of lower price is offset by the elimination of promotion at patent expiry, as substitutability erodes the promoter's return on investment. Scott Morton 2000 finds no significant generic deterrent effect of incumbent advertising via detailing or journal

advertising from two-three years prior to generic entry. This is unsurprising, given that such advertising targets physicians, whereas pharmacists make the generic substitution decision, in response to price and other financial incentives.

For biologics, the manufacturing process involves live organisms and complex processes. The abbreviated approval process, that simply requires bioequivalence and referencing of the originator's clinical trials, is therefore not available to generic biologics. (p. 537) Rather than require complete de novo clinical trials, the EMEA has adopted guidelines for an abbreviated approval pathway for follow-on biologics that relates requirements to product-specific complexity, and a similar approach was authorized in 2010 for the US. The expected outcome is that follow-on biologics will have some, albeit reduced clinical trial requirements and, in the US, originator biologics will receive a 12-year data exclusivity period compared to the five years for chemical drugs, although both types receive ten years in the EMEA. Follow-on biologics will also have higher manufacturing costs than most chemical drugs and may not be treated as substitutable by payers. Thus originator biologics are unlikely to face the almost certain and complete generic erosion faced by originator chemical drugs in the US. Moreover, whether follow-on biologics yield significant savings to payers/patients will depend on whether they are coded as substitutable by payers and by confidence of physicians and patients, which may take time. In the US, given the current perverse reimbursement incentives for dispensing physicians to prefer more costly drugs, significant savings from follow-on biologics are unlikely unless these reimbursement rules are changed to encourage use of cheaper products, given comparable quality.

22.3.7 Profitability and Rates of Return

The pharmaceutical industry is widely perceived to earn excessive profits. Accurate measurement of pharmaceutical profits has no easy solution. Available accounting data treat R&D as a current expense that offsets current, country-specific revenues, rather than as an investment in a long-lived intangible asset that may generate revenues in global markets over a ten-twenty-year product life. Adjusting accounting data to treat R&D and promotion as investments reduced accounting rates of return to levels comparable to other industries (Clarkson 1996).

As an alternative approach, Caves, Whinston, and Hurwitz (1991) estimated the Lerner index, proxied by the ratio of the price of originator drugs relative to generic prices (a proxy for marginal cost), at roughly five. However, this price-marginal cost estimate at patent expiry overstates the average Lerner index over the life-cycle because prices of originator drugs rise in the US and marginal costs decline with time since launch. More fundamentally, a one-year Lerner index based on short-run marginal production cost in one country is both theoretically and empirically inadequate as a measure of profit for global products with high and long-lived R&D investments.

A third—and conceptually more correct approach—measures the rate of return on investment in a cohort of drugs, using discounted cash flow estimates of costs and returns. Grabowski and Vernon 1990 and Grabowski et al. 2002 estimate the return on R&D for new drugs introduced in the 1970s, early 1980s and 1990s, respectively. Market sales data are used to estimate the net present value of sales over a twenty-year product life of global sales. Comparing this NPV of net revenues to the estimated average capitalized cost of R&D per NCE, at launch, Grabowski and Vernon conclude that the 1970s drug cohort on average earned a return roughly equal to its cost of capital, whereas the (p. 538) 1980s and 1990s cohorts show a small, positive excess return. The returns distribution is consistently highly skewed, with only the top 30 percent of drugs covering the average R&D cost. This extreme result would be mitigated if the distribution of revenues were compared to the distribution of R&D costs, rather than to a single mean R&D cost per NCE, but the overall conclusion of skewed return distribution would probably remain.

This evidence that pharmaceutical R&D investments on average earn a roughly normal rate-of-return is consistent with the theoretical prediction that, if the expected return on R&D exceeded the cost of capital, competitive entry would occur until the excess expected profit is eliminated. Such competitive adjustments are neither instantaneous nor perfect, due to the long lead times and unpredictable outcomes of R&D, and unpredictable competitive and regulatory conditions. But given the evidence of extensive competitive entry to exploit R&D opportunities, dynamic competition should reduce *expected* profits to competitive levels. This suggests that in designing policy, regulators should focus less on short run profitability measures and more on whether the resulting rate of R&D yields a level and mix of new drugs that is socially optimal. The current trend of payers to demand evidence of cost-effectiveness relative to existing drugs as a condition for reimbursement, reinforces incentives for manufacturers to target R&D towards innovative therapies and away from imitative drugs. Given R&D uncertainties, ex post realizations will still yield some “me-too” drugs, and some of these have value as a competitive constraint and in improving therapies for some subsets of patients.

22.3.8 Industry Structure and Productivity: Regulation or Technology?

Several early studies (for example, Grabowski 1976, Grabowski and Vernon 1978, Temin 1979, and Thomas 1990) concluded that regulation-induced increases in R&D cost and risk created scale economies that resulted in concentration of innovation in large firms and exit of smaller firms.

However, since the 1980s and 1990s the biotechnology revolution has apparently eliminated any advantages of size in drug discovery and shifted the balance of power in the industry to smaller firms that create innovation. Large firms have continued to grow mainly by acquiring such biotechnology firms or their products, and by large horizontal mergers with other medium and large firms. In the 1990s firms often rationalized

horizontal mergers on grounds of economies of scale and scope in R&D, but the empirical evidence does not support claims for gains from mergers on average, after controlling for the condition of firms that chose to merge (Danzon, Epstein, and Nicholson 2007). Larger firms' experience does have some advantage in conducting complex phase III trials for regulatory approval (Danzon, Nicholson, and Pereira 2005). In theory, smaller firms can purchase such expertise through contract research, sales and manufacturing organizations and/or by hiring experienced personnel from larger firms. A growing number of biotechnology firms have grown to be fully-integrated firms. Thus increased (p. 539) regulatory requirements over the last two decades do not appear to have harmed small firms, and technological change has certainly benefited them. Moreover, competition for promising products developed by smaller discovery firms is strong and prices paid for such products have risen over the last decade, reflecting the shifting of bargaining power from large to smaller firms (Longman 2004; Longman 2006).

Theory might suggest that the high rate of new start-ups in this industry reflects excessive entry as firms compete for profits in a differentiated products oligopoly, and that such entry is welfare reducing due to the repeated initial costs associated with achieving reasonable scale. However, the great majority of new start-ups are formed around new technologies, which face great scientific uncertainty that can only resolved by preclinical and clinical testing that takes time. The rate of discovery of new technologies is driven in part by public funding of basic research and the incentives to commercialize such research that results from patent regimes and reimbursement rules, and possibly by favorable tax treatment of R&D, especially for orphan drugs. Whether or not public funding to basic research is excessive or suboptimal is an important subject for research. Thus in the current environment it does not appear that regulation of market access or endogenous investments in sunk R&D costs are major contributors to excessive product differentiation or monopoly power, with the possible exception of orphan drugs that by design receive five years of market exclusivity.

However, it is plausible that health insurance coverage for modestly differentiated on-patent drugs, when cheap generics are available for off-patent, therapeutic substitutes, contributes to product differentiation through slightly differentiated molecules and new formulations. Whether insurance structures in the US create incentives for excessive product differentiation, including extensions and new formulations, and whether this reduces cross-price demand elasticities are important subjects for future research.

22.3.9 Alternatives to Patents

The potential welfare losses entailed by patents have led to several proposed alternative mechanisms to create incentives for innovation, including direct government grants (“push” mechanisms) and government-funded prizes or rewards (“pull” mechanisms). Grants raise issues of determining optimal levels and allocation of funding, and maintaining grantees' incentives. Prizes avoid grantee performance issues but still pose huge valuation and implementation challenges, since the true social value of

pharmaceuticals may not be known until several years after launch, as additional safety and efficacy data accrue for the initial and possibly additional indications. Measuring and valuing the health gain is also problematic. Of course it may be argued that a regulator's value estimates may be no more inaccurate than the prices that result under the patent system, given distortions due to insurance, promotion etc. Hollis 2005 argues that therapeutic value could be measured in incremental qualityadjusted (p. 540) life years (QALYs), with volume determined annually based on actual sales by competitive suppliers. Whether such a system would be superior to a patent system with prices indirectly regulated based on incremental QALYs gained (Danzon et al. 2011) or other approaches to constraining the distorting effects of insurance is an important area for future research.

22.4 Promotion

22.4.1 Regulation

The 1962 FDA Act, with subsequent Amendments, establishes the foundation for regulation of promotion in the US, subject to the US constitutional protection of freedom of speech, which includes commercial speech. The 1962 Act restricts promotional claims to facts established in clinical trials; requires that risks as well as benefits be described in brief summary; and excludes promotion of unapproved indications. The FDA's 1997 Guidance relaxed the requirement that the full product label, which includes all known risks, be displayed in broadcast ads. Rather, the requirement for a brief summary of risks and benefits could be provided by giving a website, a toll free number, or reference to a print ad with the full label, in addition to advice to “see your physician.” These changes were deemed to reflect the ways in which consumers obtain information from modern media. In its oversight of promotion, as for its other activities, the FDA is required by statute to consider risks and benefits to patients. Costs and, in particular, whether promotion leads to unnecessary spending, is beyond the FDA's purview. The 1997 FDAMA permitted companies to inform physicians of potential unapproved (“off-label”) uses of drugs through the distribution of peer reviewed journals.

By contrast, many other countries are more restrictive in regulating pharmaceutical promotion, on grounds of unnecessary costs and possibly that any constitutional protections of freedom of speech have been more narrowly interpreted. Countries that regulate prices often include limits or deterrents to promotion. The UK Pharmaceutical Price Regulatory Scheme (PPRS) limits the promotional expenditure that companies can deduct as a cost in calculating their return on capital. Germany's global drug budget, in effect from 1993–2001, placed the pharmaceutical industry at financial risk for budget over-runs, second in line after physicians, in order to discourage promotion. France penalizes “excessive” promotion, both directly through fines for exceeding allowed

promotion limits and indirectly through penalties for over-shooting allowed sales limits. Samples are a significant component of promotion in the US, while some other countries prohibit samples; even where there is no prohibition, samples have less value to patients in countries where all patients are insured with low co-payments.

Most countries restrict DTCA to so-called “help seeking” ads, which inform consumers about the availability of treatment for a health condition but do not mention a specific product. The exception is New Zealand, which also has a commitment to (p. 541) freedom of commercial speech. New Zealand has no constraining statute that requires DTCA to present a “fair balance” between risks and benefits. Survey results indicate that between 82–90 percent of individuals recall benefits information in DTCA in both the US and New Zealand, but only 20–27 percent recall risk information in New Zealand compared to 81–89 percent recall for risks in the US (Hoek, Gendall, and Calfee 2004).

22.4.2 Trends in Promotion

Promotion by manufacturers is an important mechanism whereby physicians, consumers and payers learn about drugs. Promotion in the US as a percent of sales grew from 14.1 percent in 1996 to 17.1 percent in 2003 (Berndt 2005).[12] This promotion spending estimate is downward biased due to omitting promotion-related components of pre- and post-launch clinical trials, but is also is upward biased because almost two-thirds reflects free samples distributed to physicians for patient use. Samples are valued at a retail price, which significantly exceeds the economic cost of sampling to manufacturers.[13] Ignoring samples, the largest components of promotional spending are physician and hospital detailing, direct to consumer advertising, and medical journal advertising, but relative shares differ significantly across drugs.

Direct to consumer advertising (DTCA) grew rapidly, prior to and following the 1997 FDA reinterpretation of the guidelines for broadcast DTCA (Palumbo and Mullins 2002; Berndt 2005). The 1997 FDA Guidance increased the share of DTCA that is broadcast, from under 30 percent prior to 1997 to almost two-thirds in 2002 (Rosenthal, Berndt, et al. 2002, 2003). DTCA tends to be concentrated on the leading drugs in a class, and on therapeutic classes that are particularly amenable to patient awareness and choice, such as antidepressants, antihistamines, antihyperlipidemics, and antiulcerants. The industry has recently adopted voluntary promotion guidelines that, among other things, allow only those gifts to physicians that benefit patients, and limit DTCA within the first year post-launch of a new product, to enable education of physicians about new products, and as a precaution against unanticipated adverse effects.

Pharmaceutical promotion is also changing in response to the growth of managed drug benefits. The implementation of drug formularies shifts power from physician-patients to payers who design formularies. Recent cuts in pharmaceutical sales forces partly reflects this shift in influence from physicians to payers, who are more interested in evidence of comparative effectiveness and cost-effectiveness (Elixhauser, Luce, and Steiner 1995;

(p. 542) Neumann 2004). Other factors contributing to cuts in sales force include: belief that the “medical representative arms race” had hit diminishing returns; patent expiration on many high volume products; and shift of new product approvals towards specialty products that require smaller sales forces.

Currently the US lags other countries in the use of comparative and/or cost-effectiveness as an input to reimbursement decisions. Recent increases in public funding for comparative research may change this, although so far there is no link to reimbursement. Greater focus on evidence-based comparative effectiveness may shift industry's promotion focus from detailing and DTCA towards investment in documenting health outcomes, comparative-, and cost-effectiveness.

22.4.3 Evidence on Effects of Pharmaceutical Promotion

The pharmaceutical industry's large expenditure on advertising is controversial, with policy concern over both magnitude and form. The economic literature outlines the issues and provides some evidence, but data availability has limited empirical studies and basic questions remain unresolved. The economic rationale is that promotion can provide information to physicians and consumers about the benefits and risks of drugs, which is necessary for appropriate help-seeking, prescribing, and compliance. Critics contend that much promotion is designed to persuade rather than inform; that it increases product differentiation, brand loyalty, market power, and prices; and that it leads to inappropriate use, including use of high-price, on-patent drugs when cheap generics would be equally effective.

Promotion studies pre-1997. An early proponent of the anti-competitive hypothesis,Walker 1971 argued that large promotion expenditure raises entry barriers and increases market power, by requiring new entrants to make large outlays in order to attract awareness of new products. The alternative view is that advertising may enhance competition by facilitating the introduction of new products and new firms. Telser 1975 found that new entry into a therapeutic class is positively related to promotional intensity. However, causal relationships remain questionable. Leffler 1981 finds that selling effort is related to the number of new products introduced in a class, and concludes that pharmaceutical advertising is at least partly informative. However, repeated advertising of established pharmaceutical products more likely accomplishes “reminder” and “habit-formation” purposes. Thus pharmaceutical advertising is clearly multidimensional and net effects on competition, information and appropriate usage may differ, depending on the circumstances. Berndt et al. (1995) find that promotional stocks of detailing, journal advertising, and DTCA (pre-1997) significantly affect industry-level demand for antiulcerants, but with diminishing returns, again suggesting the importance of reminder or loyalty-building promotion.

Promotion studies post-1997. The growth of DTCA has shifted the focus and the complexity of empirical studies of promotion, with important data and empirical challenges. One major empirical challenge is that DTCA is endogenously determined and just one (p. 543) of several types of promotion a firm may use. Ignoring the endogeneity of DTCA and its correlation with other (often unobserved) forms of promotion and managed-care contracting can lead to biased estimates of the impact of DTCA. Second, estimates of effects of promotion spending must take into account lagged and future impacts of information stocks, as physicians form prescribing habits and patients tend to stay with a particular brand for chronic medications, once they have found a drug that works for them. Third, the net effect of one firm's promotion depends on competitors' strategic responses.

Drawing welfare conclusions from the empirical evidence is particularly problematic. The economic/marketing literature generally views advertising that expands aggregate category sales as more likely to be informative, and hence welfare-enhancing, whereas advertising that simply changes market shares without affecting aggregate use is more likely to be wasteful (for a discussion see Berndt 2005; Kravitz, Epstein et al. 2005). However, in the case of heavily insured pharmaceuticals, for which consumers pay only a small fraction of the cost out-of-pocket, it is possible that even category-expanding effects could reflect unnecessary use (and/or unnecessarily costly use), even though such purchases are well-informed and rational for individual consumers, given their insurance coverage.

With these caveats, some of the main findings from the recent literature are reviewed here (for a more detailed review, see Berndt 2005). The study of promotion in the anti-histamine and antiviral categories by Narayanan et al. (2004) acknowledges the complex market environment by including data on DTCA, detailing, pricing, and other medical spending as alternative marketing mechanisms; measuring both the short and long run effects of promotion; and estimating cross-firm elasticities. All marketing mix variables are modeled as endogenous. This study finds that, of the four marketing variables, only DTCA has a positive but small effect on aggregate category sales. Each product's own DTCA also positively affects its own brand sales, but interaction effects with other brands' DTCA are negative. Own DTCA and detailing appear to be complements, rather than substitutes. The estimated return on investment is lower for DTCA than for detailing, suggesting that firms might gain by reallocating marketing budgets away from DTCA and towards detailing. This study has limited therapeutic scope and significant data limitations, but it does illustrate the importance of including the full marketing mix and controlling for endogeneity of the marketing variables.[14]

In contrast to the Narayanan et al. (2005) paper, other studies suggest that DTCA has a greater effect on category sales than on individual brand sales. Rosenthal and Berndt (2003) (p. 544) conclude that DTCA has a significant positive impact on class sales, with an average elasticity of roughly.1, but they find no evidence that detailing or DTCA affects product-specific market shares, controlling for product sampling.[15] The authors emphasize that failure to find brand-specific effects could reflect learning or unmeasured

longer term effects. Wosinska 2002 finds that DTCA for the cholesterol reducing medications (statins) positively affects brand share only if the brand had preferred formulary status. Similarly, Iizuka and Jin (2005b) find that DTCA increases total category sales, but brand-specific share is only significantly shifted by physician promotion such as detailing and journal publications. The authors conclude that a product should hold at least 58 percent market share of its therapeutic category sales in order to recoup DTCA investment. In fact, they find that 69 percent of DTCA spending is on drugs with at least a 60 percent market share. They also find that DTCA increases the number of doctor visits at which a drug is prescribed (Iizuka and Jin 2005a), with some differences between patient types in their responsiveness to DTCA (young vs. elderly; private vs. public insurance). Donohue and Berndt 2004 find that DTCA has no significant effect on choice of product, but that it does motivate individuals to visit the physician. These findings are supported by a randomized control trial by Kravitz et al. (2005), in which standardized patients (who were not sick, but were scripted with dialog to feign depression or adjustment disorder) asked unsuspecting blinded physicians for either no medication, a generic drug or a specific brand. Patients who requested a drug were significantly more likely to receive a drug, but not necessarily the suggested drug. Even if such findings could be generalized, they do not necessarily support conclusions about appropriateness of DTCA, which would also require data on costs and medical outcomes.

International Comparisons. Cross-national evidence on effects of promotion are limited, in part because data on promotion spending is limited and sometimes inconsistent across countries. For example, the content of a detail visit to a physician can be very different, depending on time spent, messaging allowed, whether sampling is permitted, etc. Berndt, Danzon, and Kruse (2007) provide some evidence on cross-national differences in promotion and in diffusion of new drugs.

22.5 Drugs for Developing Countries

Patents create the potential for static efficiency loss, if prices to consumers exceed marginal cost and result in suboptimal consumption. In most industrialized countries with comprehensive insurance coverage, this patent-induced tendency for under-consumption is roughly offset by an insurance-induced tendency for overconsumption. However, in many middle and most low income countries (LICs), insurance coverage is (p. 545) minimal and patients pay out-of-pocket for drugs. This raises concerns that requiring these countries to adopt standard, twenty-year product patents, under the WTO TRIPs provisions, may lead to unaffordable drug prices and suboptimal drug consumption.[16]

In theory, patents need not lead to high prices in markets/countries where patent holders perceive that demand is highly price-elastic, due to consumers' limited ability or willingness to pay. Thus for globally marketed drugs, price discrimination across countries should enable firms to recoup their R&D investments by pricing above marginal cost in high income countries while pricing close to marginal cost in LICs.[17] In practice, price differentials between high and lower income countries vary less than in proportion to average per capita income, hence prices are relatively unaffordable in middle and low income countries (MLICs), especially for the poorest sub-groups in these countries. These relatively high prices in MLICs may in part reflect firms' perceived inability to maintain price differentials between countries, due to external referencing and parallel trade. They may also reflect an optimal pricing strategy of targeting only the high income sub-groups, due to inability to maintain price differentials within countries, (Mulcahy and Towse 2011). Flynn et al. (2009) show that a single price monopolist would rationally charge a high price, relative to mean per capita income, in countries with highly skewed distribution of income, and that welfare losses are potentially large. Regulatory structures that protect differential pricing within as well as between countries would encourage lower pricing to low-income populations. Compulsory licensing has also been suggested (e.g. Flynn et al. 2009) and is authorized under TRIPs under certain conditions. However, whether compulsory licensing of generic producers would achieve marginal cost pricing depends on market conditions. Even marginal cost prices may be unaffordable to the poorest sub-groups, in which case additional tax-financed subsidies may be appropriate. Such subsidies exist for vaccines, through the Global Alliance for Vaccines and Immunization (GAVI) and for some HIV-AIDs drugs, but not for most other drugs.

For drugs to treat diseases that occur only in developing countries, patents are an ineffective mechanism to stimulate R&D, because these consumers' ability to pay is insufficient to recoup R&D investments. Recent “push” subsidy initiatives include public private partnerships that combine government and philanthropic funds with private industry expertise and resources, to address diseases such as malaria (Medicines for Malaria Venture), tuberculosis (the Global Alliance for TB), an AIDs vaccine (the International AIDs Vaccine Initiative, IAVI), and others (Kremer 2002). “Pull” subsidies include the Advance Market Commitment (AMC) approach, which would guarantee

purchase of vaccines that meet specified conditions at pre-specified prices. Pneumococcal vaccine has been selected as the first vaccine target. Thanks to these public-private partnerships, significant progress has been made, with several promising drug and vaccine candidates in late stage development.

(p. 546) 22.6 Conclusions

The R&D intensity of biopharmaceuticals, their high cost and non-obvious risks and benefits has led to patents, extensive regulation of market access, promotion and pricing, and insurance coverage. These features in turn radically affect supply and demand, pricing, competition and market structure of the biopharmaceutical industry. Theoretical and empirical research has shed some light on the effects of various components of regulation but many important questions remain for future research. These include the optimal structure of market access regulation, including safety and efficacy trade-offs and integration of pre-launch clinical trial data with post-launch observational data; effectiveness and costs of promotion and promotion regulation; optimal structure of regulation and competition to constrain prices, including price differentials across and within countries; optimal patent and data exclusivities (or alternative regimes); pricing and reimbursement for biologics, in particular, physician-dispensed cancer and other drugs, for which current Medicare reimbursement systems create perverse incentives in the US and other countries debate appropriate pricing and financing systems. Generics have delivered enormous savings to consumers/payers in countries, such as the US, with regulation and reimbursement regimes that encourage generic price competition. Achieving substantial savings from follow-on biologics will require changes in current regulatory and reimbursement systems.

In summary, although there is a large and growing literature on the pharmaceutical industry that has produced valuable information and useful lessons learned, important issues remain for future research. Economic models from other industries require significant adaptation to fit this industry's peculiar characteristics—in particular, high rates of R&D and technical change, hard-to-measure but potentially life-affecting effects, patents, insurance, and physicians, consumers, payers and pharmacists as potential customers. This industry remains a fertile area for future research.

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Notes:

(1) The terms “biopharmaceuticals” and “pharmaceuticals” are used interchangeably to include both traditional pharmaceuticals and biologics, except where explicitly noted.

(2) This has subsequently been renewed three times as part of the Food and Drug Administration Modernization Act (1997) and subsequent legislation.

(3) The fee for review of data related to product approval was $767,400 for applications with new clinical data, $383,700 for supplemental applications or those with no new clinical data (for fiscal year 2006). There is also a fee for each manufacturing facility ($264,000) and an annual fee for the right to market products ($42,130) (FDA 2005a).

(4) Post-launch efficacy trials would be required with results posted on the internet, for consumers to make their own evaluations (Madden 2004).

(5) *Wyeth vs. Levine* (2009).

(6) From 1993–2001, Germany had a drug spending limit with over-runs in principle to be repaid partly by physicians and the pharmaceutical industry. Physicians responded by reducing prescription volume and switching to cheaper drugs (Munnich and Sullivan 1994), and by referring patients to hospitals that were exempt from the spending limit (Schulenburg et al. 1994).

(7) As a proxy for price to private payers, they use the average price paid by Medicaid, which is a percent of a list price. They report that, in a limited sample of drugs, the log of this price is highly correlated with the log of a better measure of transactions price to private payers.

(8) Although some countries, including Italy, have attempted to base prices on costs, this approach is not widely used because accurate measurement of costs is problematic, particularly for R&D. R&D cost occurs over many years, should in principle include the cost of failures and forgone interest, and is largely a joint cost that must be allocated across global markets. In practice, cost-based price regulation has relied on transfer pricing rules which were designed for tax purposes, not price regulation.

(9) The EU allows ten years of data exclusivity (Kuhlik 2004).

(10) Substitution is not permitted on a few drugs for which any slight change in patient response could be critical.

(11) The major exception is Novartis, whose Sandoz generic division is a broad scale and global generic producer.

(12) For 2003, the reported promotion spending in the US is less than the spending on R&D of $34.5 billion (PhRMA 2005); however, this country-specific measure of R&D-to-sales is imprecise for multinational firms with global sales but R&D concentrated in at most a few countries.

(13) The opportunity cost of samples to firms lies between the marginal production cost and the actual ex-manufacturer selling price, which is the forgone manufacturer revenue had the patient paid for the drug.

(14) Narayanan et al. rely on three sets of instruments for price, DTCA and detailing. Price is instrumented with the pharmaceutical PPI interacted with product dummy variables as well as lagged (3 years total) PPI interacted with product dummies (36 instruments for 12 product categories). DTCA is instrumented with the PPI for television, radio and print advertising. Detailing was instrumented with employment data.

(15) Instruments include a quadratic of the drug's remaining patent life, a post-1997 time trend and the monthly cost of TV advertising.

(16) See Article 31 ⟨http://www.wto.org/english/tratop_e/trips_e/t_agm3_e.htm⟩.

(17) For a discussion of these issues, see for example Malueg and Schwartz 1994; Danzon 1997; Dumoulin 2001; Maskus 2001; Scherer and Watal 2002; Danzon and Towse 2003, 2005, 2009); Jack and Lanjouw 2003, Danzon, Towse and Ferrandiz (2011).

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